

ACE inhibitors

Competitive inhibitors of angiotensin-converting enzyme that lower blood pressure and limit adverse cardiac and renal remodelling, defined clinically by the bradykinin-mediated cough, angio-oedema, hyperkalaemia and an absolute contraindication in pregnancy.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/ace-inhibitors>

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Quick revision

One Liner: ACE inhibitors competitively block the conversion of angiotensin I to angiotensin II, so vasoconstriction and aldosterone secretion both fall - and because the same enzyme also degrades bradykinin, the cough and the angio-oedema come from the mechanism rather than from an allergy.

1. Mechanism: competitive inhibition of angiotensin-converting enzyme, which blocks conversion of angiotensin I to angiotensin II and reduces aldosterone secretion. [1]
2. Core approved roles are hypertension, heart failure with reduced ejection fraction, chronic kidney disease with albuminuria, and the period after ST-elevation myocardial infarction. [1]
3. Dry cough is reported in 10% to 20% of patients and reflects accumulation of kinins in the lung, not hypersensitivity. [1]
4. Angio-oedema is rare but potentially life-threatening, is also attributed to bradykinin accumulation, and rules the class out permanently once it has happened. [1]
5. Hyperkalaemia (2% to 6%) follows directly from the loss of aldosterone-driven potassium secretion. [1]
6. A slight fall in glomerular filtration rate on starting is expected; a further large fall points to poor renal perfusion and mandates stopping. [1]
7. Contraindicated in the second and third trimesters of pregnancy because of a well-documented fetopathy. [1]
8. Lisinopril and captopril are the only members that are not prodrugs, so they need no hepatic activation. [1]
9. Monitoring means renal function and serum potassium, checked before starting and again when the dose changes. [4]

Overview

1. ACE inhibitors are used to treat and manage hypertension and a range of related cardiovascular conditions, including heart failure with reduced ejection fraction, chronic kidney disease, coronary artery disease and myocardial infarction. Captopril was the first member approved for clinical use, in 1981, and the class is now large enough that most members share a recognisable name ending. [1]
2. Their target sits in the middle of the renin-angiotensin-aldosterone system. Juxtaglomerular cells release renin, renin cleaves liver-derived angiotensinogen to angiotensin I, and angiotensin-converting enzyme - expressed on vascular endothelium and concentrated in the pulmonary circulation - removes two amino acids to generate angiotensin II. Angiotensin II is the principal effector: it constricts arterioles, stimulates aldosterone release from the zona glomerulosa, increases proximal tubular sodium reabsorption, raises sympathetic outflow and triggers vasopressin release. [2]
3. Blocking that one enzyme therefore does two useful things at once. Less angiotensin II means vasodilation and a lower blood pressure; less aldosterone means less sodium and water retention. Because chronic exposure to angiotensin II and aldosterone drives adverse cardiac remodelling, reducing both is also what gives the class its prognostic role rather than a purely haemodynamic one. [1]
4. What defines the class at the bedside is a small set of predictable problems. Dry cough is reported in 10% to 20% of patients, dizziness in 12% to 19%, hypotension in 7% to 11%, raised blood urea nitrogen and creatinine in 2% to 11%,

syncope in 5% to 7% and hyperkalaemia in 2% to 6%. Angio-oedema is far rarer but potentially life-threatening, and pregnancy is an absolute bar. [1]

Classification and drug examples

Intro: The conventional division is by chemical structure - the group attached to the molecule that binds the zinc site of the enzyme - because that grouping also tracks the pharmacokinetic differences students are asked about.

1. Name: Sulphydryl-containing ACE inhibitors

1. Note: Represented in practice by captopril, the first ACE inhibitor approved for clinical use and one of only two members that is not a prodrug.

Name: Captopril

Route: Oral

Note: Active as given, requires multiple daily doses, must be taken on an empty stomach because food reduces absorption, and is the only member described as crossing the blood-brain barrier. [1] [1]

2. Name: Dicarboxylic acid-containing ACE inhibitors

2. Note: By far the largest group, and the one most prescriptions fall into.

1. Name: Lisinopril

1. Route: Oral

1. Note: The other non-prodrug, so it needs no hepatic activation; effectively removed by haemodialysis. [1]

2. Name: Enalapril

Enalaprilat (intravenous active form)

2. Route: Oral or IV

2. Note: A prodrug converted to enalaprilat, which is the only intravenous ACE inhibitor and has a rapid onset of action. [1]

3. Name: Ramipril

3. Route: Oral

3. Note: Widely used for hypertension, heart failure and after myocardial infarction; can be used in patients on dialysis. [1][4]

4. Name: Perindopril

4. Route: Oral

4. Note: A dicarboxylic-group member used in the same indications as the rest of the class. [1]

5. Name: Quinapril

5. Route: Oral

5. Note: A prodrug converted to quinaprilat; may require more frequent dosing because of a lower trough-to-peak ratio. [1]

6. Name: Benazepril

6. Route: Oral

6. Note: A prodrug converted to benazeprilat; also described as needing more frequent dosing than once daily in some patients. [1]

7. Name: Moexipril

7. Route: Oral

7. Note: A prodrug that, like captopril, must be taken on an empty stomach. [1]

8. Name: Trandolapril

8. Route: Oral

8. Note: A further member of the dicarboxylic group. [1] [1]

3. Name: Phosphorus-containing ACE inhibitors

3. Note: A single-member group whose distinguishing feature is its elimination route rather than its potency.

Name: Fosinopril

Route: Oral

Note: A prodrug converted to fosinoprilat and eliminated by both renal and hepatic routes, so it can be used without dose adjustment in renal impairment. [1] [1]

Mechanism of action

Summary: ACE inhibitors are competitive inhibitors of angiotensin-converting enzyme. Blocking the enzyme reduces the formation of angiotensin II, which lowers vasoconstriction and aldosterone secretion; because the same enzyme also degrades bradykinin, kinins accumulate, and that second consequence explains the cough and the angio-oedema.

Target: Angiotensin-converting enzyme on vascular endothelium, expressed predominantly in the pulmonary circulation

1. Step: 1

1. Title: Renin sets the cascade running

1. Detail: Juxtaglomerular cells in the afferent arteriole release renin in response to reduced renal perfusion, reduced sodium and chloride delivery to the macula densa, beta-1 adrenergic stimulation and humoral signals. Renin then cleaves liver-derived angiotensinogen to angiotensin I, a peptide with no known biological activity of its own. [2]

2. Step: 2

2. Title: ACE converts angiotensin I to angiotensin II

2. Detail: Angiotensin-converting enzyme, expressed on the plasma membranes of vascular endothelial cells and concentrated in the pulmonary circulation, removes two amino acids from the C-terminus of angiotensin I to generate the active peptide. [2]

3. Step: 3

3. Title: Competitive inhibition reduces angiotensin II formation

3. Detail: The drug competes with angiotensin I for the enzyme, so less angiotensin II is produced. Angiotensin II is a potent vasoconstrictor, and removing it dilates vessels and lowers blood pressure. [1]

4. Step: 4

4. Title: Aldosterone falls with it

4. Detail: Angiotensin II normally stimulates the adrenal cortex to produce aldosterone, which drives sodium and therefore water reabsorption while potassium and protons are secreted into the urine. Less angiotensin II means less aldosterone, less sodium and water retention - and less urinary potassium loss, which is where the hyperkalaemia comes from. [1]

5. Step: 5

5. Title: Remodelling slows

5. Detail: The combined actions of angiotensin II and aldosterone lead to adverse cardiac remodelling. By reducing the concentrations of both, ACE inhibitors prevent that remodelling, which is the basis of their prognostic rather than merely symptomatic benefit. [1]

6. Step: 6

6. Title: Bradykinin accumulates as a side consequence

6. Detail: Angiotensin-converting enzyme also metabolises bradykinin and other local molecules. Inhibiting the enzyme raises kinin concentrations, and bradykinin induces prominent vasodilation and plasma extravasation into local tissue - the accepted explanation for both the dry cough and, in susceptible individuals, angio-oedema. [1]

Major clinical uses

1. Drug: ACE inhibitors as a class

1. Indication: Heart failure with reduced ejection fraction, and prevention of heart failure in a patient with reduced ejection fraction after myocardial infarction

1. Line: guideline-directed

1. Note: Supported by the American College of Cardiology and the American Heart Association for patients with heart

failure and reduced ejection fraction. [1]

2. Drug: ACE inhibitors as a class

2. Indication: Hypertension in adults and in children over six years old, alone or with other antihypertensives

2. Line: first-line

2. Note: One of the classes recommended for initiating antihypertensive therapy, with the choice shaped by comorbidity and population. [1]

3. Drug: ACE inhibitors as a class

3. Indication: Chronic kidney disease with hypertension, particularly with increased albuminuria

3. Line: first-line

3. Note: Recommended as initial therapy to improve kidney outcomes; KDIGO 2024 supports renin-angiotensin system inhibition in chronic kidney disease with albuminuria regardless of diabetes status. [1]

4. Drug: ACE inhibitors as a class

4. Indication: ST-elevation myocardial infarction, especially anterior infarction, heart failure, or ejection fraction of 40% or less

4. Line: guideline-directed

4. Note: Described as being started within 24 hours of the infarct in this setting. [1]

5. Drug: ACE inhibitors as a class

5. Indication: Hypertension with chronic stable angina where there is left ventricular dysfunction, diabetes mellitus or chronic kidney disease

5. Line: add-on

5. Note: Recommended as part of the regimen rather than as sole therapy in this group. [1]

6. Drug: Ramipril

6. Indication: High blood pressure, heart failure and the period after a heart attack, with prevention of future strokes, heart attacks and kidney problems

6. Line: first-line

6. Note: Available as tablets, capsules and an oral liquid. [4]

7. Drug: Enalapril (as enalaprilat)

7. Indication: Situations needing intravenous renin-angiotensin blockade with a rapid onset, such as hypertensive emergency

7. Line: reserve

7. Note: The only intravenous ACE inhibitor. [1]

8. Drug: Captopril, lisinopril and enalapril

8. Indication: Paediatric hypertension

8. Line: alternative

8. Note: These are the members described as commonly used in children within the class. [1]

Pharmacokinetics

1. Drug: Captopril

1. Route: Oral

1. Absorption: Reduced by food, so it is taken on an empty stomach

1. Csf Penetration: The only ACE inhibitor described as penetrating the blood-brain barrier

1. Metabolism: Not a prodrug - active as given

1. Elimination: Effectively removed by haemodialysis

1. Half Life: The shortest in the class - its label puts the half-life of unchanged captopril at probably less than 2 hours

1. Dose Adjust: Heart failure, salt depletion and renal impairment; requires multiple daily doses [1][6]

2. Drug: Lisinopril

2. Route: Oral

2. Absorption: Peak serum concentrations occur within about 7 hours after an oral dose
2. Metabolism: Not a prodrug - suitable where hepatic conversion is impaired
2. Elimination: Effectively removed by haemodialysis
2. Half Life: An effective half-life of 12 hours on multiple dosing, long enough for once-daily use, and it has no active metabolite
2. Dose Adjust: Heart failure, salt depletion and renal impairment [1][5]
3. Drug: Enalapril
3. Route: Oral or IV
3. Absorption: Oral absorption adequate; the intravenous form bypasses it entirely
3. Metabolism: Prodrug requiring hepatic conversion to enalaprilat
3. Elimination: Effectively removed by haemodialysis
3. Half Life: See prescribing reference
3. Dose Adjust: Heart failure, salt depletion and renal impairment [1]
4. Drug: Ramipril
4. Route: Oral
4. Absorption: Oral, as tablets, capsules or a liquid
4. Metabolism: Requires hepatic conversion to its active form
4. Elimination: Can be used in patients on dialysis
4. Half Life: See prescribing reference
4. Dose Adjust: Heart failure, salt depletion and renal impairment [1][4]
5. Drug: Fosinopril
5. Route: Oral
5. Absorption: Systemic exposure adequate by the oral route
5. Metabolism: Prodrug requiring hepatic conversion to fosinoprilat
5. Elimination: Both renal and hepatic
5. Half Life: See prescribing reference
5. Dose Adjust: No dose adjustment needed for renal impairment, unlike the rest of the class [1]
1. The single most useful pharmacokinetic split in this class is prodrug status. Lisinopril and captopril are active as administered; enalapril, fosinopril, benazepril, quinapril and moexipril must be converted in the liver, which is why a non-prodrug is preferable when hepatic function is impaired. [1]
2. Most members can be given once daily. Captopril needs several doses a day, and benazepril, quinapril and moexipril may need more frequent dosing because of a lower trough-to-peak ratio. [1]
3. Blood tests are taken before starting and again when the dose changes, to check kidney function and potassium. Intercurrent illness with severe diarrhoea or vomiting is a recognised trigger for temporarily withholding the drug, and is a point patients are specifically counselled on. [4]
4. Withholding renin-angiotensin system inhibitors before non-cardiac surgery has been reported to reduce intraoperative hypotension and acute kidney injury, with non-significant effects on mortality and major adverse cardiovascular events. [1]
5. This page gives no dose regimens by design. Doses depend on indication, renal function, volume status, age and the other drugs in use, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Dry cough
1. Detail: Reported in 10% to 20% of patients, typically beginning between one week and six months after initiation. Resolution usually follows 1 to 4 days after stopping but can take up to a month. There is also an increased propensity to bronchospasm. [1]
2. Effect: Dizziness

2. Detail: Reported in 12% to 19% of patients, and mitigated by maintaining adequate volume status and avoiding concomitant diuretic therapy. The first dose is the most likely to provoke it. [1][4]
3. Effect: Hypotension
3. Detail: Reported in 7% to 11% of patients and more common where baseline renin concentrations are high. Repleting fluids and stopping a diuretic before starting therapy minimises hypotensive episodes. [1]
4. Effect: Raised blood urea nitrogen and creatinine
4. Detail: Reported in 2% to 11% of patients. A slight reduction in glomerular filtration rate is common on initiation and is not by itself a reason to stop. [1]
5. Effect: Syncope
5. Detail: Reported in 5% to 7% of patients, and part of the same haemodynamic picture as the dizziness and hypotension. [1]
6. Effect: Hyperkalaemia
6. Detail: Reported in 2% to 6% of patients. Comorbidities that reduce kidney function, and medications that cause potassium retention, both increase the risk. [1]
1. Effect: Angio-oedema
1. Detail: A rare but potentially life-threatening reaction with episodic swelling of the face, lips and upper airway. Excessive accumulation of bradykinin in susceptible individuals is the proposed mechanism, and variants near the bradykinin receptor B2 gene have been associated with it.
1. Action: The primary treatment is discontinuation of ACE inhibitor therapy; airway compromise can require endotracheal intubation, and the class is avoided afterwards. [1]
2. Effect: Marked decline in renal function
2. Detail: Patients with heart failure, chronic kidney disease or bilateral renal artery stenosis and poor renal perfusion can suffer a further reduction in glomerular filtration rate beyond the expected small fall.
2. Action: This pattern mandates discontinuation of ACE inhibitor therapy rather than dose reduction. [1]
3. Effect: Fetal toxicity
3. Detail: Drugs inhibiting the renin-angiotensin system correlate with oligohydramnios, decreased fetal renal function, anuria, renal failure, skull hypoplasia and death. The fetal kidney is the site of the problem: low-pressure fetal haemodynamics are easily disrupted when angiotensin II falls.
3. Action: The class is contraindicated in pregnancy, and pregnancy status is checked before and during therapy. [1]
4. Effect: Rare haematological reactions
4. Detail: Anaemia, neutropenia, agranulocytosis and thrombocytopenia are described as rare adverse effects of the class.
4. Action: A full blood count with differential is used to look for them where the clinical picture suggests it. [1]
1. Drug: Captopril
1. Effect: The only ACE inhibitor to penetrate the blood-brain barrier, with confusion and lethargy as the corresponding features in toxicity. [1]
2. Drug: ACE inhibitors as a class
2. Effect: Post-marketing surveillance reports significant adverse events in fewer than one percent of patients, including anaphylactoid reactions, eosinophilic pneumonitis, hyponatraemia, intestinal angio-oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis. [1]

Contraindications, precautions and interactions

1. Pregnancy, because of teratogenic effects including oligohydramnios, decreased fetal renal function, anuria, renal failure, skull hypoplasia and death. [1]
2. Angio-oedema related to previous ACE inhibitor treatment, and idiopathic or hereditary angio-oedema. [1]
3. Hypersensitivity to any ACE inhibitor or to a component of the formulation, with cross-reactivity between members to be considered. [1]

4. Current use of aliskiren in a patient with diabetes mellitus. [1]

1. Abnormal renal function. Where renal function is abnormal but stable, close monitoring is required; if it starts to decline, the clinician should discontinue the ACE inhibitor. [1]

2. Aortic valve stenosis, where afterload reduction can lead to severe hypotension. [1]

3. Hypovolaemia and dehydration, which these drugs can worsen; initiation is also avoided in an older patient who is dehydrated. [1]

4. Heart failure already treated with a high dose of a loop diuretic, where profound first-dose hypotension may occur. [1]

5. Sarcoidosis, where the drug lowers peripheral ACE concentrations and makes that measurement uninterpretable. [1]

6. Intercurrent illness with severe watery diarrhoea or vomiting, which is a recognised reason for a temporary interruption decided by the prescriber. [4]

1. With: Aliskiren

1. Effect: Two levels of restriction that are easy to conflate. Co-administration with an ACE inhibitor is CONTRAINDICATED in a patient with diabetes; separately, the labels direct that the combination be AVOIDED in renal impairment, taking a glomerular filtration rate below about 60 mL/min as the threshold. The second is an avoidance, not a contraindication. [5]

2. With: Lithium

2. Effect: ACE inhibitors reduce renal lithium clearance, raising the risk of lithium toxicity; lithium concentrations and clinical signs are checked frequently during co-administration. [1]

3. With: Potassium-sparing diuretics, NSAIDs, ciclosporin and anticoagulants

3. Effect: Combination increases hyperkalaemia, hypotension and renal failure risk, and calls for particular precaution. [1]

4. With: Sulfonylureas

4. Effect: Combination in a patient with diabetes may increase the risk of hypoglycaemia, so blood glucose is monitored regularly. [1]

5. With: Azathioprine

5. Effect: Associated with bone marrow suppression including anaemia and leukopenia; full blood counts are monitored for early myelosuppression. [1]

6. With: Allopurinol

6. Effect: Concurrent use may raise the risk of hypersensitivity reactions, so skin rashes and systemic allergic symptoms are watched for. [1]

7. With: Other antihypertensive agents

7. Effect: Toxicity is rare at therapeutic doses but becomes more likely in combination, with hyperkalaemia, hypotension and renal failure the effects that compound. [1]

Comparison tables

Title: What distinguishes each ACE inhibitor

Caption: The class shares one mechanism, so the examinable differences are almost entirely pharmacokinetic. Actual therapy is governed by a prescribing reference and the treating clinician.

1. Key: drug

1. Label: Drug

1. Is Row Header: true

2. Key: prodrug

2. Label: Prodrug?

3. Key: route

3. Label: Route

4. Key: feature

4. Label: Distinguishing feature

1. Drug: Captopril
 1. Prodrug: No - active as given
 1. Route: Oral
 1. Feature: Sulfhydryl group; empty stomach; the shortest half-life in the class, hence multiple daily doses; crosses the blood-brain barrier [1][6]
2. Drug: Lisinopril
 2. Prodrug: No - active as given
 2. Route: Oral
 2. Feature: No active metabolite, and an effective half-life of 12 hours that supports once-daily dosing; suitable where hepatic conversion is impaired [1][5]
3. Drug: Enalapril
 3. Prodrug: Yes - to enalaprilat
 3. Route: Oral or IV
 3. Feature: The only intravenous member, with rapid onset [1]
4. Drug: Ramipril
 4. Prodrug: Yes
 4. Route: Oral
 4. Feature: Tablets, capsules or liquid; usable in patients on dialysis [1][4]
5. Drug: Fosinopril
 5. Prodrug: Yes - to fosinoprilat
 5. Route: Oral
 5. Feature: Dual renal and hepatic elimination; no dose adjustment in renal impairment [1]
6. Drug: Moexipril
 6. Prodrug: Yes
 6. Route: Oral
 6. Feature: Like captopril, absorption falls with food, so it is taken on an empty stomach [1]

High-yield exam pearls

1. Pearl: The cough is bradykinin, not allergy.
 1. Why: Angiotensin-converting enzyme also metabolises bradykinin and other local mediators, so inhibiting it in the lung raises kinin concentrations and irritates the bronchi. That is why an angiotensin receptor blocker, which does not raise bradykinin, is the usual substitute. [1]
2. Pearl: Only two members of the class are not prodrugs.
 2. Why: Lisinopril and captopril are active as given, whereas enalapril, fosinopril, benazepril, quinapril and moexipril require hepatic conversion to enalaprilat, fosinoprilat, benazeprilat, quinaprilat and moexiprilat. A non-prodrug is preferable where liver function is impaired. [1]
3. Pearl: Enalapril is the one with an intravenous form.
 3. Why: Enalaprilat is the only intravenous ACE inhibitor and has a rapid onset of action, which is what makes it useful in hypertensive emergencies; every other member is oral only. [1]
4. Pearl: Fosinopril is the one that leaves by two routes.
 4. Why: It is eliminated both renally and hepatically, so it can be used without dose adjustment in renal impairment - the exception that the rest of the class does not share. [1]
5. Pearl: Captopril is the one that reaches the brain.
 5. Why: It is the only ACE inhibitor described as penetrating the blood-brain barrier, and confusion and lethargy are the corresponding features in toxicity. [1]
6. Pearl: First-dose hypotension is worst on top of a high-dose loop diuretic.
 6. Why: Profound first-dose hypotension may occur when an ACE inhibitor is introduced to a patient with heart failure

who is already on a high dose of a loop diuretic, which is why volume repletion beforehand matters. [1]

7. Pearl: An ACE inhibitor makes the serum ACE level in sarcoidosis uninterpretable.

7. Why: The drug lowers ACE concentrations in peripheral blood, so the result cannot be read as a marker of disease activity in a patient taking one. [1]

Common exam traps

1. Trap: "An ACE inhibitor cough means the patient is allergic to the drug."

1. Correction: It is a pharmacological consequence of reduced bradykinin breakdown, not hypersensitivity. It typically appears between one week and six months after starting and usually settles 1 to 4 days after stopping, although it can persist for up to a month. [1]

2. Trap: "Any rise in creatinine after starting means the drug must be stopped."

2. Correction: A slight reduction in glomerular filtration rate is common on initiation. It is the further, larger fall seen with heart failure, chronic kidney disease or bilateral renal artery stenosis and poor renal perfusion that mandates discontinuation. [1]

3. Trap: "A low dose is acceptable in pregnancy."

3. Correction: Drugs that inhibit the renin-angiotensin system are linked to oligohydramnios, reduced fetal renal function, anuria, renal failure, skull hypoplasia and death. They are contraindicated in the second and third trimesters, and a strong association with major malformations has been described for first-trimester exposure. [1]

4. Trap: "Angio-oedema on an ACE inhibitor can be handled by reducing the dose."

4. Correction: The primary treatment is discontinuation of ACE inhibitor therapy, and the class is avoided thereafter. Swelling of the face, lips and upper airway can be severe enough to require endotracheal intubation to secure the airway. [1]

5. Trap: "Hyperkalaemia on an ACE inhibitor is an idiosyncratic reaction."

5. Correction: It is a direct result of the mechanism: blocking angiotensin II removes the stimulus to aldosterone, and without aldosterone-driven secretion potassium accumulates. Reduced kidney function or a potassium-retaining co-prescription raises the risk further. [1]

6. Trap: "ACE inhibitors are the preferred first antihypertensive for every patient."

6. Correction: In the Black population with diabetes mellitus and without chronic kidney disease, initial antihypertensive therapy is described as a thiazide diuretic or a calcium channel blocker rather than an ACE inhibitor or an angiotensin receptor blocker. [1]

Self-test questions

1. Question: Which enzymatic step do ACE inhibitors block?

1. Cleavage of angiotensinogen to angiotensin I by renin
2. Conversion of angiotensin I to angiotensin II by angiotensin-converting enzyme
3. Binding of aldosterone to the mineralocorticoid receptor in the collecting duct
4. Degradation of natriuretic peptides by neprilysin

1. Explanation: ACE inhibitors are competitive inhibitors of angiotensin-converting enzyme and prevent the conversion of angiotensin I to angiotensin II. Renin cleaves angiotensinogen upstream of that step, and the mineralocorticoid receptor and neprilysin are the targets of entirely different classes. [1][2]

2. Question: Why do ACE inhibitors cause a dry cough in a substantial minority of patients?

1. They deposit in bronchial epithelium and cause direct chemical irritation
2. They trigger an IgE-mediated hypersensitivity response in the airway
3. The same enzyme also degrades bradykinin, so inhibiting it raises kinin concentrations in the lung
4. They increase angiotensin II at the AT₂ receptor, which stimulates the cough reflex

2. Explanation: Angiotensin-converting enzyme metabolises bradykinin and other local molecules as well as angiotensin I. Inhibiting the enzyme in the lung increases kinin concentrations and causes bronchial irritation, which is

why the cough is a mechanism effect rather than an allergy, and why it is reported in roughly 10% to 20% of patients. [1]

3. Question: Which two ACE inhibitors are active as administered and require no hepatic conversion?

1. Enalapril and ramipril
2. Lisinopril and captopril
3. Quinapril and benazepril
4. Fosinopril and moexipril

3. Explanation: Lisinopril and captopril are not prodrugs. Enalapril, fosinopril, benazepril, quinapril and moexipril all require hepatic conversion to their active forms, which is why a non-prodrug is preferred in a patient with underlying liver disease. [1]

4. Question: A patient starting an ACE inhibitor develops a rise in serum potassium. What is the mechanistic explanation?

1. The drug directly blocks the epithelial sodium channel in the collecting duct
2. Reduced angiotensin II means reduced aldosterone, and without aldosterone less potassium is secreted into the urine
3. The drug inhibits the sodium-potassium ATPase in skeletal muscle, releasing intracellular potassium
4. Increased bradykinin drives potassium out of cells into the plasma
4. Explanation: Blocking angiotensin II removes the downstream stimulus to aldosterone secretion. Aldosterone normally drives sodium reabsorption with secretion of potassium and protons into the urine, so its loss allows potassium to accumulate. Reduced kidney function or a potassium-retaining co-prescription increases the risk. [1][2]

5. Question: Which ACE inhibitor is available in an intravenous formulation?

1. Captopril
2. Ramipril
3. Enalapril, given intravenously as enalaprilat
4. Perindopril

5. Explanation: All ACE inhibitors are prescribed orally except enalapril, which can also be given intravenously. Enalaprilat is the only intravenous member of the class and has a rapid onset of action, which is what makes it useful in a hypertensive emergency. [1]

6. Question: Which statement about ACE inhibitors in pregnancy is correct?

1. They are contraindicated in the second and third trimesters because of a documented fetopathy
2. They are the preferred antihypertensive throughout pregnancy
3. They are safe at any stage provided renal function is normal
4. They are contraindicated only in the first trimester

6. Explanation: ACE inhibitors are contraindicated during the second and third trimesters because of a well-documented fetopathy. Reported effects include oligohydramnios, decreased fetal renal function, anuria, renal failure, skull hypoplasia and death, and a strong association with major cardiovascular and neurological malformations has also been described after first-trimester exposure. [1]

7. Question: Why is the serum ACE concentration unhelpful in a patient with suspected sarcoidosis who is already taking an ACE inhibitor?

1. The drug raises serum ACE, producing a falsely positive result
2. The drug lowers ACE concentrations in peripheral blood, so the result cannot be interpreted accurately
3. Sarcoidosis does not affect serum ACE at all
4. The assay cross-reacts with the drug and always fails

7. Explanation: ACE inhibitors potentially lead to low ACE concentrations in peripheral blood samples, so the clinical interpretation of that measurement in a patient with sarcoidosis receiving one of these drugs is not accurate. [1]

Frequently asked questions

1. Question: Why do ACE inhibitors cause a dry cough?

1. Answer: Because angiotensin-converting enzyme does two jobs. As well as making angiotensin II, it breaks down bradykinin. Inhibiting the enzyme lets kinins build up in the lung, and that causes bronchial irritation. It is reported in 10% to 20% of patients and is a mechanism effect, not an allergy. [1]

2. Question: What is usually done when the cough is intolerable?

2. Answer: An angiotensin receptor blocker is the standard alternative, because these agents do not raise bradykinin and have a lower incidence of cough recurrence than restarting an ACE inhibitor. If cough still recurs, a different class entirely is the next step. [1]

3. Question: Why is a small rise in creatinine after starting not automatically a problem?

3. Answer: Reducing angiotensin II relaxes the efferent arteriole, so filtration pressure falls slightly and creatinine drifts up. That small change is expected. What is not expected is a large or continuing fall in filtration, which points to poor renal perfusion and calls for the drug to be stopped. [1]

4. Question: Why are ACE inhibitors banned in pregnancy?

4. Answer: The fetal kidney depends on angiotensin II to maintain filtration at very low pressures. Removing it causes oligohydramnios, anuria and renal failure, and skull hypoplasia and fetal death have been reported. The class is contraindicated in the second and third trimesters, and first-trimester exposure has also been associated with major malformations. [1]

5. Question: What is monitored on an ACE inhibitor?

5. Answer: Renal function - blood urea nitrogen and serum creatinine - and serum potassium, checked before treatment starts and again whenever the dose changes. Blood pressure is recorded routinely to judge response. [1][4]

6. Question: Are ACE inhibitors and angiotensin receptor blockers used together?

6. Answer: No. Combining agents that block the renin-angiotensin system at more than one point increases hypotension, acute renal failure and hyperkalaemia without a corresponding gain, and the combination is not recommended. [3]

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