

Non-dihydropyridine calcium channel blockers

Verapamil and diltiazem, the rate-limiting half of the calcium channel blocker class: they suppress sinoatrial and atrioventricular nodal conduction and myocardial contractility, which is what makes them useful in supraventricular arrhythmia and hazardous alongside a beta blocker.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/non-dihydropyridine-calcium-channel-blockers>

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Quick revision

One Liner: Verapamil and diltiazem block the same L-type channel as the dihydropyridines but act where it matters for rhythm: the sinoatrial and atrioventricular nodes and the myocardium - so they control rate, and combining them with a beta blocker stacks two drugs on the same conduction pathway.

1. The group contains two agents: verapamil, a phenylalkylamine, and diltiazem, a benzothiazepine. [1]
2. They exert inhibitory effects on the sinoatrial and atrioventricular nodes, slowing cardiac conduction and contractility. [1]
3. Approved uses include hypertension, conversion and prophylaxis of paroxysmal supraventricular tachycardia, atrial fibrillation and flutter, and chronic stable and vasospastic angina. [1]
4. Combining them with a beta blocker increases the likelihood of bradycardia, heart block or acute decompensated heart failure. [2]
5. Even topical ophthalmic timolol can contribute, because systemic absorption is enough to add to atrioventricular nodal suppression. [2]
6. They are contraindicated in heart failure with reduced ejection fraction, second- or third-degree atrioventricular block, severe hypotension and sick sinus syndrome. [1]
7. Atrial fibrillation or flutter with an accessory pathway is a further contraindication for both agents. [2][3]
8. Constipation is the classic verapamil complaint; gingival hyperplasia and peripheral oedema also occur. [2]
9. Diltiazem commonly causes peripheral oedema, bradycardia, dizziness, headache and fatigue. [3]
10. Both drugs inhibit CYP3A, so they raise concentrations of ciclosporin, statins, benzodiazepines, buspirone and sildenafil. [1]
11. Both also inhibit P-glycoprotein, which raises digoxin, dabigatran, colchicine and immunosuppressant levels. [1][2]
12. Patients starting either drug need liver function tests, blood pressure, heart rate and electrocardiogram monitoring. [1]
13. Verapamil is a first-line prophylactic for cluster headache and an option in hypertrophic cardiomyopathy where a beta blocker cannot be used. [2]
14. Hypotension and bradycardia dominate poisoning with this group, and hyperglycaemia marks severity. [1]

Overview

1. Calcium channel blockers bind L-type voltage-gated calcium channels in the heart, vascular smooth muscle and pancreas, and the class splits into two categories on the basis of their primary physiological effects. The non-dihydropyridines are the cardiac half of that split: verapamil, classified as a phenylalkylamine, and diltiazem, classified as a benzothiazepine. [1]
2. Their defining action is inhibition of the sinoatrial and atrioventricular nodes, which slows cardiac conduction and reduces contractility. That property lets them treat hypertension, reduce myocardial oxygen demand and control the ventricular rate in tachydysrhythmias - the last of which the vascular-selective dihydropyridines cannot do. [1]
3. Diltiazem illustrates how the two halves of the effect combine. It relaxes vascular smooth muscle and reduces peripheral vascular resistance to lower blood pressure, and it acts as a negative inotrope and negative chronotrope, so

myocardial oxygen demand falls through reduced rate and pressure while coronary dilation increases supply. Notably, the fall in blood pressure is proportionate to the starting pressure, so normotensive individuals see only a modest drop. [3]

4. The same nodal action creates the class's hazards. These agents are contraindicated in heart failure with reduced ejection fraction, second- or third-degree atrioventricular block, severe hypotension and sick sinus syndrome, and their combination with a beta blocker stacks two negative chronotropic and inotropic influences on the same tissue. They are also enzyme inhibitors in their own right, which makes their interaction profile broader than that of the dihydropyridines. [1][2]

Classification and drug examples

Intro: A subclass of two, and the useful split is the chemical family each belongs to, because that tracks the difference in how strongly each suppresses conduction and contractility relative to its vasodilator effect.

1. Name: Phenylalkylamine

1. Note: The most cardiac-weighted member of the calcium channel blocker class, with the fullest set of supraventricular arrhythmia indications and the broadest interaction profile.

Name: Verapamil

Route: Oral/IV

Note: Approved for chronic stable, vasospastic and unstable angina, hypertension as add-on therapy, prophylaxis of paroxysmal supraventricular tachycardia, supraventricular tachycardia, and atrial flutter and fibrillation. It is a CYP3A4 substrate and a P-glycoprotein inhibitor, and norverapamil is its principal active metabolite. [2] [1]

2. Name: Benzothiazepine

2. Note: Shares the nodal action but combines it with potent coronary dilation, and carries a similarly broad set of arrhythmia and angina indications.

Name: Diltiazem

Route: Oral/IV

Note: Approved for atrial arrhythmia including atrial fibrillation with a rapid ventricular rate, hypertension, paroxysmal supraventricular tachycardia, chronic stable angina and angina due to coronary artery spasm. It is a CYP3A4 inhibitor and a P-glycoprotein inhibitor, and desacetyl diltiazem, its metabolite, also contributes to coronary vasodilation. [3] [1]

Mechanism of action

Summary: Verapamil and diltiazem block L-type voltage-gated calcium channels with an emphasis on cardiac tissue, inhibiting the sinoatrial and atrioventricular nodes so conduction slows and contractility falls, while also relaxing vascular smooth muscle to reduce peripheral resistance.

Target: L-type voltage-gated calcium channels in the sinoatrial and atrioventricular nodes, myocardium and vascular smooth muscle

Cidal Static: ion channel blocker

Kill Kinetics: rate-limiting and negatively inotropic

1. Step: 1

1. Title: Calcium entry drives nodal depolarisation and myocardial contraction

1. Detail: Calcium moves inward through L-type voltage-gated channels in the heart, vascular smooth muscle and pancreas; in nodal tissue that current is what sets the pace of depolarisation. [1]

2. Step: 2

2. Title: The drug blocks that inward movement in cardiac tissue

2. Detail: Diltiazem inhibits the inflow of calcium ions into cardiac muscle during depolarisation, and reduced intracellular calcium follows. [3]

3. Step: 3

3. Title: Nodal conduction slows

3. Detail: Inhibitory effects on the sinoatrial and atrioventricular nodes slow cardiac conduction, which is what allows control of the rate in tachydysrhythmias. [1]
4. Step: 4
4. Title: Contractility falls
4. Detail: The same blockade produces a negative inotropic effect, reducing the force of contraction alongside the reduction in rate. [1][3]
5. Step: 5
5. Title: Vascular smooth muscle also relaxes
5. Detail: Reduced intracellular calcium relaxes vascular smooth muscle, producing arterial vasodilation and a fall in peripheral vascular resistance and blood pressure that is proportionate to the starting pressure. [3]
6. Step: 6
6. Title: Oxygen demand falls while supply rises
6. Detail: Reduced heart rate and blood pressure lower myocardial oxygen demand, while potent dilation of epicardial and subendocardial coronary arteries increases supply - together increasing exercise tolerance in angina. [3]
7. Step: 7
7. Title: The same mechanism becomes the hazard
7. Detail: Because the drugs suppress the nodes and the myocardium, they can worsen or create arrhythmias such as extrasystole and atrioventricular block, and their effects add to those of any other agent that slows conduction. [3]

Major clinical uses

1. Drug: Non-dihydropyridines as a group
1. Organism: Not applicable
1. Indication: Hypertension, conversion and prophylaxis of paroxysmal supraventricular tachycardia, atrial fibrillation and flutter, chronic stable angina and vasospastic angina
1. Line: first-line or add-on depending on indication
1. Note: This breadth across rhythm and angina indications is what distinguishes the subclass from the dihydropyridines. [1]
2. Drug: Verapamil
2. Organism: Not applicable
2. Indication: Vasospastic angina
2. Line: first-line
2. Note: Calcium channel blockers including verapamil are recommended as first-line antianginal therapy for vasospastic angina in current guidance; long-acting agents and nitrates are preferred for coronary artery spasm and short-acting agents avoided. [2]
3. Drug: Verapamil
3. Organism: Not applicable
3. Indication: Prophylaxis of cluster headache
3. Line: first-line
3. Note: Recommended as a first-line prophylactic to reduce headache severity and decrease episode frequency during a cluster period. [2]
4. Drug: Verapamil
4. Organism: Not applicable
4. Indication: Symptom control in obstructive or non-obstructive hypertrophic cardiomyopathy
4. Line: second-line
4. Note: Recommended where a beta blocker cannot be used because of adverse reactions, contraindications or lack of response. [2]
5. Drug: Diltiazem

- 5. Organism: Not applicable
- 5. Indication: Atrial arrhythmia, including atrial fibrillation with a rapid ventricular rate
- 5. Line: first-line
- 5. Note: Non-dihydropyridines and beta blockers are the standard therapies for rate control in atrial fibrillation, which is why the choice between them, rather than their combination, is usually the question. [3][2]
- 6. Drug: Diltiazem
- 6. Organism: Not applicable
- 6. Indication: Chronic stable angina and angina due to coronary artery spasm
- 6. Line: first-line
- 6. Note: Increases exercise tolerance by reducing myocardial oxygen demand and by dilating epicardial and subendocardial coronary arteries. [3]
- 7. Drug: Diltiazem
- 7. Organism: Not applicable
- 7. Indication: Off-label roles including anal fissure, migraine prophylaxis and selected pulmonary hypertension
- 7. Line: off-label
- 7. Note: The pulmonary hypertension role is confined to group 1 patients with a positive vasoreactivity test. [3]

Pharmacokinetics

- 1. Drug: Verapamil
- 1. Route: Oral/IV
- 1. Absorption: More than nine-tenths of an oral dose is absorbed, but extensive first-pass hepatic metabolism reduces absolute bioavailability to roughly a quarter to a third
- 1. Csf Penetration: Verapamil and norverapamil are detectable in cerebrospinal fluid at low concentrations after repeated dosing
- 1. Metabolism: Extensive hepatic metabolism by CYP3A, producing norverapamil as the principal active metabolite; verapamil also inhibits P-glycoprotein
- 1. Elimination: Mostly as metabolites in urine, with a smaller share in faeces and very little unchanged
- 1. Half Life: A few hours after a single immediate-release dose, longer with repeated dosing and with extended-release formulations, and longer still in severe hepatic impairment
- 1. Dose Adjust: Hepatic impairment reduces metabolism, prolongs half-life and decreases clearance [2]
- 2. Drug: Diltiazem
- 2. Route: Oral/IV
- 2. Absorption: Well absorbed from the gastrointestinal tract with extensive first-pass metabolism, giving a bioavailability of roughly two-fifths; immediate-release tablets act within the first hour
- 2. Csf Penetration: Not a defining feature of this agent
- 2. Metabolism: Metabolised by the cytochrome P450 system and is itself a CYP3A4 inhibitor; desacetyl diltiazem contributes to coronary vasodilation
- 2. Elimination: Extensively metabolised, with only a small fraction of unchanged drug appearing in urine
- 2. Half Life: A few hours after administration
- 2. Dose Adjust: Pharmacokinetics vary significantly between brands and formulations, so the specific package insert governs [3]
- 1. Calcium channel blockers are readily absorbed orally but many have low bioavailability because of hepatic first-pass metabolism mediated primarily by CYP3A4; they are highly protein-bound and are excreted renally after metabolism. [1]
- 2. In repeated dosing or overdose the hepatic enzymes responsible become saturated, reducing first-pass effects and increasing absorption of active drug, which lengthens the effective half-life alongside any modified-release formulation. [1]

3. Patients starting either agent should have liver function tests, blood pressure, heart rate and electrocardiogram monitoring, and a baseline metabolic panel is used with diltiazem to track electrolytes and kidney and liver function. [1][3]

4. This page gives no dose regimens by design. Doses depend on the agent, the formulation and brand, the indication, hepatic function and comorbidity, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Constipation

1. Detail: A characteristic complaint with verapamil and listed among the adverse effects of the non-dihydropyridine group generally. [2][1]

2. Effect: Peripheral oedema

2. Detail: Reported with verapamil and among the common adverse effects of diltiazem. [2][3]

3. Effect: Bradycardia

3. Detail: A common effect of diltiazem and a direct consequence of nodal suppression. [3]

4. Effect: Dizziness, headache and fatigue

4. Detail: Common with diltiazem, and fatigue is also reported with verapamil. [3][2]

5. Effect: Orthostatic hypotension and elevated liver enzymes

5. Detail: Listed among the adverse effects of the non-dihydropyridine group. [1]

6. Effect: Gingival hyperplasia and dyspepsia

6. Detail: Both reported with verapamil therapy. [2]

1. Effect: Atrioventricular block and arrhythmia

1. Detail: Because diltiazem treats arrhythmias by suppressing conduction, it can also worsen existing arrhythmias or create new ones such as extrasystole and atrioventricular block.

1. Action: Electrocardiogram monitoring is part of starting either agent, and continuous monitoring accompanies intravenous administration. [3][1]

2. Effect: Severe hypotension and bradycardia

2. Detail: Both are recognised severe reactions with this group and dominate the picture in poisoning, where profound hypotension may be life-threatening.

2. Action: Symptomatic hypotension or bradycardia requires urgent assessment in an emergency setting. [1]

3. Effect: Congestive heart failure

3. Detail: Listed among the severe adverse reactions for this group and among the severe effects of diltiazem specifically.

3. Action: These agents are contraindicated in heart failure with reduced ejection fraction. [1][3]

4. Effect: Hepatotoxicity

4. Detail: Listed among severe reactions to the group, and among the severe adverse effects of diltiazem.

4. Action: Liver function tests are checked when therapy begins. [1][3]

5. Effect: Paralytic ileus and Stevens-Johnson syndrome

5. Detail: Both appear among the more severe adverse reactions attributed to non-dihydropyridine agents.

5. Action: Stop and reassess if a severe cutaneous reaction or obstructive bowel picture develops. [1]

1. Drug: Verapamil

1. Effect: Constipation, gingival hyperplasia and dyspepsia are the characteristic non-cardiac complaints. [2]

2. Drug: Diltiazem

2. Effect: Photo-distributed hyperpigmentation has been described in case reports, and severe effects include myocardial infarction and hepatotoxicity. [3]

3. Drug: Diltiazem with ibrutinib

3. Effect: A fatality has been identified from this interaction: diltiazem is a moderate CYP3A4 inhibitor and ibrutinib a CYP3A4 substrate, so prolonged concurrent administration decreases ibrutinib clearance and results in cardiotoxicity.

[3]

4. Drug: Diltiazem in pregnancy

4. Effect: An alternative agent is recommended for hypertension in pregnancy because adverse fetal effects have been shown in animal studies; where the drug is being continued for hypertrophic cardiomyopathy, additional fetal monitoring is required. [3]

Contraindications, precautions and interactions

1. Heart failure with reduced ejection fraction, because of the risk of bradycardia and worsening cardiac output. [1]
 2. Second- or third-degree atrioventricular block, except where a functioning ventricular pacemaker is present. [1][2]
 3. Sick sinus syndrome, except where a functioning artificial pacemaker is present. [1][3]
 4. Severe hypotension or cardiogenic shock. [1][2]
 5. Atrial fibrillation or flutter associated with an accessory bypass tract, as in Wolff-Parkinson-White syndrome. [2][3]
 6. Concomitant intravenous beta blockers. [2][3]
 7. Acute myocardial infarction with pulmonary congestion. [1][3]
 8. Wide complex ventricular tachycardia, for diltiazem. [3]
 9. Severe left ventricular dysfunction, for oral verapamil, and severe heart failure for the intravenous formulation unless it arises from a supraventricular tachycardia responsive to the drug. [2]
 10. Known hypersensitivity to the drug or any component of its formulation. [1][2]
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1. Concurrent use of any other agent that slows cardiac conduction, which can further potentiate atrioventricular block or bradycardia. [3]
 2. Hepatic impairment, which reduces verapamil metabolism, prolongs its half-life and decreases clearance. [2][1]
 3. Renal impairment, where caution is advised and a lower starting dose may be considered even though adjustment is generally not required. [1]
 4. Heart failure with reduced ejection fraction after myocardial infarction, where diltiazem is associated with a higher risk of recurrent heart failure. [3]
 5. Pregnancy, where an alternative agent is recommended for hypertension because of adverse fetal effects in animal studies with diltiazem. [3]
 6. Older patients, in whom these drugs are excreted at a lower rate. [1]
 7. Concurrent alcohol with controlled-release diltiazem, which increases the rate and extent of exposure and is associated with dose-related adverse reactions. [3]
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1. With: Beta blockers
 1. Effect: Both depress atrioventricular nodal conduction and myocardial contractility, so the combination increases the likelihood of bradycardia, heart block or acute decompensated heart failure; even ophthalmic timolol contributes through systemic absorption. [2][4]
 2. With: CYP3A substrates - ciclosporin, statins, benzodiazepines, buspirone, sildenafil
 2. Effect: Verapamil and diltiazem inhibit the CYP3A isoenzyme, raising concentrations of these drugs so that reduced doses of the interacting medicine may be needed. [1]
 3. With: CYP3A4 inhibitors - erythromycin, clarithromycin, azole antifungals, protease inhibitors, cimetidine, grapefruit juice
 3. Effect: Increase plasma concentrations of verapamil by reducing hepatic clearance, raising the risk of bradycardia, hypotension and atrioventricular block. [1][2]
 4. With: CYP3A4 inducers - rifampicin, carbamazepine, oxcarbazepine, phenytoin, nevirapine
 4. Effect: Markedly reduce exposure by accelerating metabolism, which can lead to therapeutic failure. [1][2]
 5. With: Digoxin
 5. Effect: P-glycoprotein inhibition raises digoxin concentrations, so dose adjustment and level monitoring are needed. [2][3]
 6. With: Direct oral anticoagulants - dabigatran, apixaban

6. Effect: P-glycoprotein inhibition raises their systemic levels and increases bleeding risk. [2][3]
7. With: Colchicine and immunosuppressants such as ciclosporin and tacrolimus
7. Effect: Verapamil elevates systemic levels, so therapeutic drug monitoring is required for the immunosuppressants. [2]
8. With: Ibrutinib
8. Effect: Prolonged concurrent administration with diltiazem decreases ibrutinib clearance and results in cardiotoxicity; a fatality has been reported. [3]

Comparison tables

Title: Verapamil and diltiazem side by side

Caption: Two drugs, one subclass, and a set of differences that mostly concern chemistry, metabolism and the specific indications each carries. Actual therapy is governed by a current prescribing reference.

1. Key: feature
1. Label: Feature
1. Is Row Header: true
2. Key: verapamil
2. Label: Verapamil
3. Key: diltiazem
3. Label: Diltiazem
1. Feature: Chemical family
1. Verapamil: Phenylalkylamine
1. Diltiazem: Benzothiazepine [1]
2. Feature: Enzyme relationship
2. Verapamil: CYP3A substrate and P-glycoprotein inhibitor
2. Diltiazem: CYP3A4 inhibitor and P-glycoprotein inhibitor [2][3]
3. Feature: Active metabolite
3. Verapamil: Norverapamil, reaching concentrations comparable to the parent drug
3. Diltiazem: Desacetyl diltiazem, which also contributes to coronary vasodilation [2][3]
4. Feature: Distinctive approved uses
4. Verapamil: Angina including unstable, hypertension as add-on, supraventricular tachycardia and its prophylaxis, atrial flutter and fibrillation
4. Diltiazem: Atrial arrhythmia including atrial fibrillation with rapid ventricular rate, hypertension, paroxysmal supraventricular tachycardia, stable and vasospastic angina [2][3]
5. Feature: Notable off-label roles
5. Verapamil: Cluster headache prophylaxis; hypertrophic cardiomyopathy where a beta blocker cannot be used
5. Diltiazem: Anal fissure, migraine prophylaxis, group 1 pulmonary hypertension with positive vasoreactivity [2][3]
6. Feature: Characteristic adverse effect
6. Verapamil: Constipation, with gingival hyperplasia and dyspepsia also reported
6. Diltiazem: Peripheral oedema and bradycardia [2][3]
7. Feature: Notable interaction hazard
7. Verapamil: Raises digoxin, dabigatran, colchicine and immunosuppressant levels
7. Diltiazem: A reported fatality with ibrutinib, and increased bleeding risk with direct oral anticoagulants [2][3]

High-yield exam pearls

1. Pearl: Rate-limiting is the defining word for this pair.
1. Why: Unlike the dihydropyridines, verapamil and diltiazem inhibit the sinoatrial and atrioventricular nodes, slowing conduction and contractility - which is exactly why they appear in the supraventricular arrhythmia indications the

dihydropyridines do not have. [1]

2. Pearl: The beta blocker combination is the single most examinable interaction here.

2. Why: Both drug groups depress atrioventricular nodal conduction and myocardial contractility, so the combination raises the likelihood of bradycardia, heart block or acute decompensated heart failure and should follow a clear indication with close monitoring. [2][4]

3. Pearl: Intravenous beta blockade alongside these agents is a contraindication, not merely a caution.

3. Why: Concomitant intravenous beta blockers are listed among the contraindications for intravenous verapamil and for diltiazem, which is a stronger statement than the general caution about oral combination. [2][3]

4. Pearl: An accessory pathway changes the answer entirely.

4. Why: Atrial fibrillation or flutter associated with a bypass tract, as in Wolff-Parkinson-White syndrome, contraindicates both agents, because nodal blockade can favour conduction down the accessory pathway. [2][3]

5. Pearl: These are enzyme inhibitors as well as substrates.

5. Why: Verapamil and diltiazem inhibit CYP3A and P-glycoprotein, so they raise concentrations of ciclosporin, statins, benzodiazepines, digoxin, dabigatran and colchicine - a two-way interaction profile the dihydropyridines largely lack. [1][2]

6. Pearl: Reduced ejection fraction rules these drugs out.

6. Why: Non-dihydropyridines are contraindicated in heart failure with reduced ejection fraction because of the risk of bradycardia and worsening cardiac output, and diltiazem after myocardial infarction in that group is associated with a higher risk of recurrent heart failure. [1][3]

7. Pearl: Monitoring differs from the dihydropyridines.

7. Why: Patients starting verapamil or diltiazem need liver function tests, blood pressure, heart rate and electrocardiogram monitoring, whereas blood pressure and heart rate are typically sufficient for a dihydropyridine. [1]

8. Pearl: Constipation is not a trivial side effect for verapamil.

8. Why: It is one of the reported adverse effects of the drug, and in severe poisoning paralytic ileus appears among the severe reactions attributed to this group. [2][1]

Common exam traps

1. Trap: "All calcium channel blockers are safe to add to a beta blocker."

1. Correction: Verapamil and diltiazem both depress atrioventricular nodal conduction and contractility, so adding them to a beta blocker increases the likelihood of bradycardia, heart block or acute decompensated heart failure. [2]

2. Trap: "Any calcium channel blocker will control the rate in atrial fibrillation."

2. Correction: Only the non-dihydropyridines act on the nodes. Dihydropyridines have minimal direct myocardial effect at therapeutic doses and tend to provoke reflex tachycardia instead. [1]

3. Trap: "Verapamil is a good choice in heart failure with reduced ejection fraction."

3. Correction: Non-dihydropyridines are contraindicated there because of the risk of bradycardia and worsening cardiac output, and severe left ventricular dysfunction is listed as a contraindication for oral verapamil. [1][2]

4. Trap: "Rate control is rate control, whatever the underlying rhythm."

4. Correction: Atrial fibrillation or flutter associated with an accessory bypass tract contraindicates both agents, so the presence of pre-excitation changes the choice of drug entirely. [2][3]

5. Trap: "Drug interactions with this group are the same as with amlodipine."

5. Correction: Verapamil and diltiazem inhibit CYP3A and P-glycoprotein as well as being metabolised by CYP3A4, so they raise concentrations of other drugs rather than only having their own concentrations raised. [1]

6. Trap: "Peripheral oedema is a dihydropyridine problem only."

6. Correction: Peripheral oedema is reported with verapamil and is among the common adverse effects of diltiazem as well, even though it is more characteristic of the dihydropyridines. [2][3]

Self-test questions

1. Question: How do non-dihydropyridine calcium channel blockers differ in action from the dihydropyridines?

1. They act only on pancreatic beta cells
2. They exert inhibitory effects on the sinoatrial and atrioventricular nodes, slowing cardiac conduction and contractility
3. They block beta-1 adrenergic receptors rather than calcium channels
4. They dilate arterioles with no cardiac effect at all

1. Explanation: Both groups bind L-type voltage-gated calcium channels, but the non-dihydropyridines inhibit the sinoatrial and atrioventricular nodes, slowing conduction and contractility. That property allows them to treat hypertension, reduce oxygen demand and control the rate of tachydysrhythmias. [1]

2. Question: Why is combining verapamil with a beta blocker approached cautiously?

1. The two drugs chemically inactivate one another in the gut
2. Both depress atrioventricular nodal conduction and myocardial contractility, so bradycardia, heart block or acute decompensated heart failure become more likely
3. The combination causes uncontrollable reflex tachycardia
4. Beta blockers prevent verapamil from being absorbed

2. Explanation: Their effects add on the same two properties. The combination should be prescribed only with a clear indication and close monitoring, particularly where conduction disease or left ventricular dysfunction is present, and even systemically absorbed ophthalmic timolol can contribute. [2]

3. Question: Which of these is a contraindication shared by verapamil and diltiazem?

1. Atrial fibrillation or flutter associated with an accessory bypass tract
2. Chronic stable angina
3. Essential hypertension
4. Paroxysmal supraventricular tachycardia

3. Explanation: Atrial fibrillation or flutter associated with an accessory bypass tract, as in Wolff-Parkinson-White syndrome, is a contraindication for both drugs. The other three options are approved indications rather than contraindications. [2][3]

4. Question: Which two drugs make up this subclass, and to which chemical families do they belong?

1. Amlodipine, a phenylalkylamine, and nifedipine, a benzothiazepine
2. Verapamil, a phenylalkylamine, and diltiazem, a benzothiazepine
3. Diltiazem, a dihydropyridine, and verapamil, a benzodiazepine
4. Nimodipine and nicardipine, both phenylalkylamines

4. Explanation: The non-dihydropyridines are verapamil, classified as a phenylalkylamine, and diltiazem, classified as a benzothiazepine. The dihydropyridines are the separate group whose members mostly end in -pine. [1]

5. Question: Why do these two agents cause more drug interactions than most dihydropyridines?

1. They are excreted unchanged in bile and displace other drugs there
2. They inhibit CYP3A and P-glycoprotein as well as being metabolised by CYP3A4
3. They irreversibly bind plasma albumin
4. They induce every major cytochrome enzyme

5. Explanation: Verapamil and diltiazem inhibit the CYP3A isoenzyme, raising concentrations of ciclosporin, statins, benzodiazepines, buspirone and sildenafil, and they inhibit P-glycoprotein, which raises digoxin, dabigatran and colchicine levels among others. [1][2]

6. Question: What monitoring is described for a patient starting diltiazem or verapamil?

1. Blood pressure alone
2. Liver function tests, blood pressure, heart rate and electrocardiogram monitoring
3. No monitoring is required
4. Only a serum potassium measurement

6. Explanation: Those initiating diltiazem or verapamil should undergo liver function tests, blood pressure monitoring, heart rate assessment and electrocardiogram monitoring. For a dihydropyridine, monitoring blood pressure and heart rate is typically sufficient. [1]

7. Question: Which adverse effect is particularly associated with verapamil?

1. Constipation
2. Irreversible hearing loss
3. Photosensitivity rash
4. Hyperkalaemia

7. Explanation: Constipation is among the adverse effects reported with verapamil therapy, alongside fatigue, dyspepsia, gingival hyperplasia, hypotension and peripheral oedema. Paralytic ileus also appears among the severe reactions reported for this group. [2][1]

8. Question: Which off-label use is verapamil recommended for as first-line prophylaxis?

1. Cluster headache
2. Rheumatoid arthritis
3. Peptic ulcer disease
4. Obstructive sleep apnoea

8. Explanation: Verapamil is recommended as a first-line prophylactic agent to reduce headache severity and decrease episode frequency during a cluster period. It is also used off-label in hypertrophic cardiomyopathy where a beta blocker cannot be used. [2]

Frequently asked questions

1. Question: Why can these drugs control heart rate when amlodipine cannot?

1. Answer: Because they act on the sinoatrial and atrioventricular nodes, slowing conduction and contractility. The dihydropyridines have minimal direct myocardial effect at therapeutic doses and behave as peripheral vasodilators instead. [1]

2. Question: Is it ever acceptable to give one of these with a beta blocker?

2. Answer: They can be prescribed together, but only with a clear indication and close monitoring, because both depress atrioventricular nodal conduction and contractility and the combination raises the risk of bradycardia, heart block or acute decompensated heart failure. Concomitant intravenous beta blockade is a contraindication rather than a caution. [2][3]

3. Question: Why are these agents avoided in heart failure with reduced ejection fraction?

3. Answer: Because their negative inotropic and chronotropic effects risk bradycardia and worsening cardiac output. That is a listed contraindication for the subclass, and after myocardial infarction in this group diltiazem has been associated with a higher risk of recurrent heart failure. [1][3]

4. Question: Why does an accessory pathway change the choice of drug?

4. Answer: Atrial fibrillation or flutter associated with a bypass tract, such as in Wolff-Parkinson-White syndrome, is a listed contraindication for both verapamil and diltiazem, so a nodal-blocking agent is not the answer in that rhythm. [2][3]

5. Question: Why do these two drugs cause so many interactions?

5. Answer: They are metabolised by CYP3A4 and also inhibit CYP3A and P-glycoprotein themselves. That means their own levels can be raised or lowered by other drugs, and they raise the levels of ciclosporin, statins, benzodiazepines, digoxin, dabigatran and colchicine among others. [1][2]

6. Question: What monitoring is expected when someone starts verapamil or diltiazem?

6. Answer: Liver function tests, blood pressure, heart rate and electrocardiogram monitoring. Diltiazem given intravenously for an arrhythmia also requires continuous blood pressure and electrocardiogram monitoring during administration. [1][3]

7. Question: What happens in an overdose of this group?

7. Answer: Hypotension and bradycardia are the primary features, and they arise from peripheral vasodilation with reduced cardiac contractility. Patients may appear well initially and then deteriorate rapidly, and conduction may be impaired with atrioventricular abnormalities, complete heart block or idioventricular rhythms. [1]

References

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