

Dihydropyridine calcium channel blockers

L-type calcium channel blockers that act almost entirely on vascular smooth muscle rather than the myocardium, producing vasodilation, reflex tachycardia and the peripheral oedema that most often limits their dose.

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Quick revision

One Liner: Dihydropyridines block L-type calcium channels in vascular smooth muscle, so at therapeutic doses they are peripheral vasodilators with minimal direct myocardial effect - which is why they lower blood pressure and relieve angina but also cause flushing, headache and peripheral oedema.

1. Calcium channel blockers bind L-type voltage-gated calcium channels in the heart, vascular smooth muscle and pancreas, and split into dihydropyridine and non-dihydropyridine groups. [1]
2. Dihydropyridines exert minimal direct effects on the myocardium and act primarily as peripheral vasodilators at therapeutic doses. [1]
3. Most members of the group end in -pine, including amlodipine, felodipine, nisoldipine and nicardipine. [1]
4. Their approved cardiovascular uses are hypertension, coronary artery disease and chronic stable angina. [1]
5. Off-label uses across the calcium channel blocker class include migraine prophylaxis, Raynaud phenomenon, pulmonary hypertension, anal fissures and high-altitude pulmonary oedema. [1]
6. Peripheral oedema is the characteristic adverse effect and may appear within the first few weeks of starting treatment. [1]
7. The oedema arises because selective arteriolar dilation raises intracapillary pressure and drives fluid into the interstitial space. [4]
8. Mistaking that oedema for a new condition and adding a diuretic is a classic prescribing cascade. [2][4]
9. Lightheadedness, flushing and headache complete the vasodilatory adverse effect picture. [1]
10. Reflex tachycardia follows the fall in peripheral resistance, and immediate-release nifedipine was notorious for it. [4][3]
11. The class is extensively metabolised by CYP3A4, so inhibitors, inducers and grapefruit juice all matter. [1]
12. Nimodipine is the outlier: its use is restricted primarily to cerebral vasospasm following subarachnoid haemorrhage. [5]
13. Gingival hyperplasia is a recognised effect of several members and is usually reversible on stopping the drug. [4][3]
14. In overdose, mild to moderate ingestion may cause reflex tachycardia, but receptor selectivity can be lost in severe poisoning, producing bradycardia instead. [1]

Overview

1. Calcium channel blockers work by blocking the inward movement of calcium through L-type voltage-gated channels found in the heart, vascular smooth muscle and pancreas. The class divides into two groups with different physiological emphases, and the dihydropyridines are the vascular half of that split: at therapeutic doses they exert minimal direct effects on the myocardium and behave as peripheral vasodilators. [1]
2. At the cellular level the sequence is well defined. Calcium entering vascular smooth muscle through L-type channels binds calmodulin, which activates myosin light-chain kinase; that enzyme phosphorylates the myosin light chain and the muscle contracts, narrowing the vessel and raising resistance and pressure. Blocking the initial influx interrupts the chain at its first step, so the muscle relaxes and the vessel dilates. [2][4]
3. Clinically this makes the group useful in hypertension, coronary artery disease and chronic stable angina, with a

long tail of off-label roles across the wider calcium channel blocker class including migraine prophylaxis, Raynaud phenomenon, pulmonary hypertension, anal fissures and high-altitude pulmonary oedema. In angina the benefit comes largely from afterload reduction lowering myocardial oxygen demand, and in vasospastic angina from relieving coronary spasm directly. [1][2]

4. The characteristic adverse effects follow from the same vasodilation: lightheadedness, flushing, headaches and peripheral oedema, the last of which may appear within the first two to three weeks. The oedema is worth understanding precisely, because it is a redistribution of fluid into the interstitium driven by raised intracapillary pressure, not fluid overload - and treating it as though it were leads to one of the best-documented prescribing cascades in cardiovascular medicine. [1][4]

Classification and drug examples

Intro: Members are grouped here by the role they actually occupy in practice, because the pharmacology is largely shared: long-acting antihypertensives, agents whose formulation defines their use, and one agent reserved for the cerebral circulation.

1. Name: Long-acting oral antihypertensives

1. Note: The everyday members of the group, used for hypertension, coronary artery disease and chronic stable angina.

1. Name: Amlodipine

Amlodipine besylate

1. Route: Oral

1. Note: Available as oral tablets. Reduces afterload, which lowers myocardial oxygen demand in stable angina, and relieves vasospastic angina by blocking coronary spasm. Terminal elimination half-life is long, supporting once-daily use. [1][2]

2. Name: Felodipine

2. Route: Oral

2. Note: Supplied as an extended-release tablet. Selectively dilates arterioles with no effect on venous vessels, and clinical trials have not shown a negative inotropic effect. [1][4]

3. Name: Nisoldipine

3. Route: Oral

3. Note: Supplied as an extended-release oral tablet. [1] [1]

2. Name: Agents whose formulation shapes their use

2. Note: Members whose immediate-release and extended-release or injectable forms behave differently enough that the formulation is part of the clinical decision.

1. Name: Nifedipine

1. Route: Oral

1. Note: Immediate-release preparations act within minutes and provoked reflex sympathetic activation; extended-release preparations give a sustained effect across the day with fewer adverse effects and are preferred in chronic stable angina. [3]

2. Name: Nicardipine

2. Route: Oral/IV

2. Note: Available in oral capsules and in injectable formulations, which is what allows it to be used where a parenteral dihydropyridine is wanted. [1] [1]

3. Name: Agent reserved for the cerebral circulation

3. Note: A dihydropyridine whose indication sits outside routine blood pressure management altogether.

Name: Nimodipine

Route: Oral/IV

Note: A second-generation dihydropyridine originally developed for systemic hypertension whose current use is

restricted primarily to the prevention and treatment of cerebral vasospasm after subarachnoid haemorrhage. [5] [5]

Mechanism of action

Summary: Dihydropyridines block L-type voltage-gated calcium channels in vascular smooth muscle, preventing the calcium influx that initiates contraction, so arterioles dilate, peripheral resistance falls and blood pressure falls, with little direct effect on the myocardium at therapeutic doses.

Target: L-type voltage-gated calcium channels in vascular smooth muscle

Cidal Static: ion channel blocker

Kill Kinetics: vascular-selective at therapeutic doses

1. Step: 1

1. Title: Calcium entry starts vascular contraction

1. Detail: Contraction begins when calcium enters the smooth muscle cell through voltage-dependent L-type channels, and calcium-induced calcium release from the sarcoplasmic reticulum amplifies the signal. [2]

2. Step: 2

2. Title: Calcium activates the contractile machinery

2. Detail: Cytosolic calcium binds calmodulin, which activates myosin light-chain kinase; that enzyme phosphorylates the myosin light chain, the myosin head attaches to actin, and the muscle contracts. [2][4]

3. Step: 3

3. Title: The drug blocks the initial influx

3. Detail: Blocking the voltage-dependent L-type channel prevents that first calcium entry, so cytosolic calcium falls and vascular smooth muscle relaxes. [2][4]

4. Step: 4

4. Title: Peripheral resistance and blood pressure fall

4. Detail: Reduced vascular smooth muscle contractility produces vasodilation, a decrease in peripheral vascular resistance and a decrease in systemic blood pressure. [4][3]

5. Step: 5

5. Title: The myocardium is largely spared

5. Detail: At therapeutic doses these agents have minimal direct effects on the myocardium, which is what makes them vascular-selective rather than rate-limiting. [1]

6. Step: 6

6. Title: Afterload reduction relieves angina

6. Detail: Lower afterload reduces myocardial oxygen demand at any level of exertion, and blocking coronary spasm restores flow in vasospastic angina. [2]

7. Step: 7

7. Title: Baroreflex activation answers the fall in pressure

7. Detail: Because resistance falls without a direct negative inotropic effect, a compensatory reflex increase in heart rate follows, most sharply when vasodilation is rapid. [4][3]

8. Step: 8

8. Title: Arteriolar selectivity produces the oedema

8. Detail: Dilating arterioles without a matching effect on the venous side raises intracapillary pressure, so fluid extravasates into the interstitial space. [4]

Major clinical uses

1. Drug: Dihydropyridines as a group

1. Organism: Not applicable

1. Indication: Hypertension, coronary artery disease and chronic stable angina

1. Line: first-line or add-on depending on indication

1. Note: These are the approved cardiovascular indications shared across the group; each individual agent has its own approved set. [1]
2. Drug: Amlodipine
2. Organism: Not applicable
2. Indication: Hypertension, stable angina and vasospastic (Prinzmetal) angina
2. Line: first-line
2. Note: Relieves stable angina by afterload reduction and vasospastic angina by blocking coronary spasm; also an effective short-term option in Raynaud phenomenon. [2]
3. Drug: Nifedipine
3. Organism: Not applicable
3. Indication: Chronic stable angina, vasospastic angina and hypertension
3. Line: first-line or second-line depending on indication
3. Note: A long-acting formulation is preferred for chronic stable angina; reflex tachycardia may limit effectiveness, and adding a beta blocker can overcome that limitation. [3]
4. Drug: Felodipine
4. Organism: Not applicable
4. Indication: Essential hypertension
4. Line: first-line
4. Note: Extended-release monotherapy performs comparably to cardioselective beta blockers, thiazide diuretics, ACE inhibitors and other calcium antagonists in mild-to-moderate hypertension, and can be added where severe hypertension has not responded to beta blockers and diuretics. [4]
5. Drug: Nimodipine
5. Organism: Not applicable
5. Indication: Prevention and treatment of cerebral vasospasm following subarachnoid haemorrhage
5. Line: targeted
5. Note: Indicated to improve neurological outcomes by reducing the incidence and severity of ischaemic deficits. [5]
6. Drug: Nifedipine
6. Organism: Not applicable
6. Indication: Off-label roles including Raynaud phenomenon, high-altitude pulmonary oedema, anal fissure and distal ureteric calculi
6. Line: off-label
6. Note: In a network meta-analysis of anal fissure treatments it showed the highest healing rate, working by decreasing anal resting pressure. [3]
7. Drug: Calcium channel blockers as a class
7. Organism: Not applicable
7. Indication: Off-label use in migraine prophylaxis, Raynaud phenomenon, pulmonary hypertension, anal fissures and high-altitude pulmonary oedema
7. Line: off-label
7. Note: The specific agent must be verified against its own approved and off-label profile rather than assumed from the class. [1]

Pharmacokinetics

1. Drug: Amlodipine
1. Route: Oral
1. Absorption: Absolute bioavailability roughly two-thirds to nine-tenths; food does not alter it, and peak plasma concentrations take several hours
1. Csf Penetration: Not a defining feature of this agent

1. Metabolism: Extensively hepatic to inactive metabolites, importantly by CYP3A4 and CYP3A5
1. Elimination: Primarily renal, mostly as metabolites
1. Half Life: Biphasic, with a long terminal elimination phase that supports once-daily use
1. Dose Adjust: Hepatic dysfunction reduces clearance and prolongs the half-life [2]
2. Drug: Felodipine
2. Route: Oral
2. Absorption: Almost completely absorbed, but bioavailability only about a fifth because of extensive first-pass metabolism; grapefruit juice and alcohol both raise concentrations
2. Csf Penetration: Not a defining feature of this agent
2. Metabolism: Hepatic; weakly inhibits CYP3A4 and CYP2D6
2. Elimination: See a current prescribing reference
2. Half Life: See a current prescribing reference
2. Dose Adjust: Avoid concurrent alcohol; extended-release formulation used to smooth exposure [4]
3. Drug: Nifedipine
3. Route: Oral
3. Absorption: Completely absorbed; extended-release tablets plateau after several hours and hold steady across the day, with less fluctuation than the immediate-release capsules
3. Csf Penetration: Not a defining feature of this agent
3. Metabolism: Extensive hepatic metabolism via CYP3A4 to inactive, water-soluble metabolites
3. Elimination: Mostly urinary as inactive metabolites, with the remainder in faeces via biliary excretion
3. Half Life: Short for the immediate-release form; the extended-release form acts across roughly a day
3. Dose Adjust: Hepatic impairment increases bioavailability and prolongs half-life; renal impairment has minimal impact [3]
4. Drug: Nimodipine
4. Route: Oral/IV
4. Absorption: Rapidly absorbed orally, but bioavailability is low because of elevated first-pass metabolism
4. Csf Penetration: Its cerebral action is the basis of its only principal indication
4. Metabolism: Hepatic via CYP3A4
4. Elimination: See a current prescribing reference
4. Half Life: See a current prescribing reference
4. Dose Adjust: CYP3A4 inhibitors raise and inducers lower plasma concentrations; grapefruit juice should be avoided [5]
1. These drugs are readily absorbed orally, but many have low bioavailability because of hepatic first-pass metabolism mediated primarily by CYP3A4; they are highly protein-bound, often with a high volume of distribution, 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; modified-release formulations and that saturation both lengthen the effective half-life. [1]
3. Patients with hepatic impairment often need dosage adjustment, whereas renal impairment generally does not require it, though the specific agent must still be checked. [1]
4. This page gives no dose regimens by design. Doses depend on the agent, the formulation, hepatic function, age and comorbidity, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Peripheral oedema
1. Detail: The characteristic and most common effect, appearing within roughly the first two to three weeks of starting therapy and more frequent at higher doses and in older patients. [1][4]

2. Effect: Flushing and headache

2. Detail: Direct consequences of vasodilation and among the effects observed in a dose-dependent way in controlled trials. [1][2]

3. Effect: Lightheadedness and dizziness

3. Detail: Follow the fall in blood pressure and are part of the standard vasodilatory picture. [1]

4. Effect: Palpitations from reflex tachycardia

4. Detail: A compensatory response to reduced peripheral resistance, most marked with rapidly acting formulations. [4][3]

5. Effect: Fatigue, nausea, abdominal pain and constipation

5. Detail: Reported across the group and generally dose-independent. [2][4]

6. Effect: Gingival hyperplasia

6. Detail: Occurs through calcium-related overexpression of growth factors driving fibroblast proliferation, is worsened by poor oral hygiene and inflammation, and is usually reversible on stopping the drug. [4][3]

1. Effect: Acute hypotension and syncope

1. Detail: Listed among the more severe adverse events of the dihydropyridine group, which can vary by agent.

1. Action: Blood pressure and heart rate monitoring is generally sufficient for this subclass. [1]

2. Effect: Exacerbated angina and acute myocardial infarction

2. Detail: Recognised among the more severe events; patients with severe coronary artery disease may experience worsening angina after starting therapy.

2. Action: Reassess where angina worsens after initiation rather than escalating the same agent. [1][2]

3. Effect: Drug-induced liver injury

3. Detail: Rare and idiosyncratic; a mixed hepatocellular-cholestatic pattern is typical of amlodipine-induced injury, with recovery some weeks after stopping the drug.

3. Action: Consider the drug as a cause when liver tests become abnormal without another explanation. [2][1]

4. Effect: Severe poisoning

4. Detail: Hypotension and bradycardia dominate calcium channel blocker poisoning; patients may look well initially and then deteriorate rapidly to hypoperfusion and cardiovascular collapse, with hyperglycaemia as a severity marker.

4. Action: Toxicity is managed in an emergency setting with continuous monitoring; this page describes the pattern rather than the treatment protocol. [1]

5. Effect: Severe cutaneous reactions

5. Detail: Erythema multiforme is listed among the severe events for this group, and Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported very infrequently.

5. Action: Stop and reassess if a significant rash develops. [1][3]

1. Drug: Nifedipine

1. Effect: Abrupt discontinuation after prolonged use may lead to rebound hypertension or angina; bowel obstruction during extended-release treatment is rare but possible. [3]

2. Drug: Nimodipine

2. Effect: Acute colonic pseudo-obstruction has been documented with oral use, alongside the expected vasodilatory effects of headache, vertigo, flushing, nausea, diarrhoea, pedal oedema, rash and palpitations. [5]

3. Drug: Felodipine

3. Effect: Peripheral oedema is its commonest clinical adverse effect and becomes more frequent at higher doses and in older patients. [4]

4. Drug: Amlodipine

4. Effect: Oedema, dizziness, flushing and palpitations were observed in a dose-dependent manner in controlled clinical trials. [2]

Contraindications, precautions and interactions

1. Known hypersensitivity to the drug or to any component of its formulation. [1][2]
2. Severe hypotension. [1]
3. Cardiogenic shock, where the heart already cannot pump effectively and further inhibition of calcium influx worsens it. [2]
4. Acute myocardial infarction with pulmonary congestion. [1]
 1. Severe aortic stenosis, where vasodilation can precipitate ventricular collapse and dysfunction. [2]
 2. Unstable angina, where a reflex rise in contractility raises myocardial oxygen demand and can worsen ischaemia. [2]
 3. Heart failure, where pulmonary oedema, breathlessness and dyspnoea may follow. [2]
 4. Hepatic impairment, where reduced metabolism prolongs the half-life and raises plasma concentrations, so a lower starting dose is considered. [1][2]
 5. Renal impairment, where caution is still advised even though dose adjustment is generally not required. [1]
 6. Older patients, in whom excretion is slower and peripheral oedema is more frequent. [1][4]
1. With: CYP3A4 inhibitors - azole antifungals, macrolides such as clarithromycin and erythromycin, protease inhibitors, cimetidine
 1. Effect: Raise plasma concentrations; coadministration of amlodipine with clarithromycin or erythromycin has been reported to increase the risk of hypotension and acute kidney injury. [1][2]
2. With: Grapefruit juice
 2. Effect: Inhibits intestinal CYP3A4, roughly doubling nifedipine exposure and raising felodipine and nimodipine concentrations, so it should be avoided. [3][4][5]
3. With: CYP3A4 inducers - carbamazepine, oxcarbazepine, phenytoin, nevirapine, rifampicin, St John's wort
 3. Effect: Accelerate metabolism and reduce plasma concentrations, risking loss of therapeutic effect. [1][3]
4. With: High-dose statins
 4. Effect: Amlodipine used with high statin doses carries an increased risk of myopathy and rhabdomyolysis. [2]
5. With: Alcohol, with felodipine
 5. Effect: Significantly increases absorption, raising peak concentration and shortening the time to peak, so concurrent use should be avoided. [4]
6. With: Digoxin, with nifedipine
 6. Effect: Isolated reports of elevated serum digoxin concentrations, so levels are monitored around initiation, adjustment or discontinuation. [3]

Comparison tables

1. Title: Dihydropyridines set against the non-dihydropyridines
 1. Caption: The two halves of the calcium channel blocker class share a target and diverge on tissue selectivity, which then decides almost everything clinical. Actual therapy is governed by a current prescribing reference.
 1. Key: feature
 1. Label: Feature
 1. Is Row Header: true
 2. Key: dhp
 2. Label: Dihydropyridines
 3. Key: nondhp
 3. Label: Non-dihydropyridines
 1. Feature: Principal site of action
 1. Dhp: Vascular smooth muscle; minimal direct myocardial effect at therapeutic doses
 1. Nondhp: Sinoatrial and atrioventricular nodes, slowing conduction and contractility [1]
 2. Feature: Effect on heart rate

- 2. Dhp: Tends to provoke reflex tachycardia
- 2. Nondhp: Slows the rate; bradycardia and atrioventricular block are recognised risks [1][4]
- 3. Feature: Approved cardiovascular uses
- 3. Dhp: Hypertension, coronary artery disease, chronic stable angina
- 3. Nondhp: Hypertension, supraventricular tachycardia, atrial fibrillation and flutter, chronic stable and vasospastic angina [1]
- 4. Feature: Characteristic adverse effects
- 4. Dhp: Peripheral oedema, flushing, headache, lightheadedness
- 4. Nondhp: Constipation, orthostatic hypotension, dizziness, fatigue [1]
- 5. Feature: Use with a beta blocker
- 5. Dhp: A beta blocker can be added to offset reflex tachycardia in angina
- 5. Nondhp: Combination raises the risk of bradycardia and heart block [3][1]
- 6. Feature: Metabolism
- 6. Dhp: Extensive hepatic metabolism, primarily CYP3A4
- 6. Nondhp: Extensive hepatic metabolism, and verapamil and diltiazem themselves inhibit CYP3A [1]
- 2. Title: Members of the dihydropyridine group and what defines each
- 2. Caption: Shared pharmacology, different roles. Choice of agent follows the indication and the formulation available.
- 1. Key: drug
- 1. Label: Drug
- 1. Is Row Header: true
- 2. Key: forms
- 2. Label: Available forms
- 3. Key: defining
- 3. Label: Defining feature
- 1. Drug: Amlodipine
- 1. Forms: Oral tablets
- 1. Defining: Long terminal half-life supporting once-daily use; broad role in hypertension and angina [1][2]
- 2. Drug: Felodipine
- 2. Forms: Extended-release oral tablet
- 2. Defining: Dilates arterioles selectively with no venous effect and no demonstrated negative inotropic effect [1][4]
- 3. Drug: Nifedipine
- 3. Forms: Immediate-release and extended-release
- 3. Defining: Formulation dictates behaviour; the immediate-release form provoked reflex sympathetic activation [3]
- 4. Drug: Nicardipine
- 4. Forms: Oral capsules and injectable
- 4. Defining: The member available in a parenteral formulation [1]
- 5. Drug: Nisoldipine
- 5. Forms: Extended-release oral tablet
- 5. Defining: Supplied only in an extended-release oral form [1]
- 6. Drug: Nimodipine
- 6. Forms: Oral and intravenous
- 6. Defining: Restricted primarily to cerebral vasospasm after subarachnoid haemorrhage [5]

High-yield exam pearls

- 1. Pearl: Vascular selectivity is the whole identity of this subclass.
- 1. Why: Dihydropyridines exert minimal direct effects on the myocardium and act as peripheral vasodilators at therapeutic doses, which is precisely what separates them from verapamil and diltiazem. [1]

2. Pearl: The oedema is not fluid overload.
2. Why: Selective arteriolar dilation raises intracapillary pressure and pushes fluid into the interstitium, so the oedema is a redistribution phenomenon rather than a sign of retained salt and water - which is why a diuretic is the wrong reflex. [4][1]
3. Pearl: Adding an ACE inhibitor or angiotensin receptor blocker can prevent the oedema.
3. Why: Because those agents dilate the post-capillary side as well, they relieve the pressure gradient that drives fluid out, which makes them a rational partner rather than a diuretic. [4]
4. Pearl: Reflex tachycardia is a feature, not a coincidence.
4. Why: A fall in peripheral resistance triggers a compensatory rise in heart rate; that is why immediate-release nifedipine produced palpitations and flushing and why extended-release formulations replaced it, and why a beta blocker can be added in angina. [3][4]
5. Pearl: Nimodipine is a dihydropyridine used for the brain, not the blood pressure.
5. Why: It was developed for systemic hypertension but its current use is restricted primarily to preventing and treating cerebral vasospasm after subarachnoid haemorrhage, where it improves neurological outcomes. [5]
6. Pearl: CYP3A4 is the interaction hub for the entire class.
6. Why: These drugs are extensively metabolised by CYP3A4, so azole antifungals, macrolides, protease inhibitors and grapefruit juice raise concentrations while carbamazepine, phenytoin and rifampicin lower them. [1]
7. Pearl: Hyperglycaemia in a calcium channel blocker overdose is a severity marker.
7. Why: Pancreatic beta-islet cells depend on calcium influx through L-type channels to release insulin, so blockade reduces insulin release; the resulting hyperglycaemia has been considered a prognostic indicator of toxicity severity. [1]
8. Pearl: Selectivity is lost in severe overdose.
8. Why: Dihydropyridines in mild-to-moderate overdose may cause reflex tachycardia, but in severe poisoning receptor selectivity is lost and bradycardia appears - so a slow pulse does not exclude a dihydropyridine. [1]

Common exam traps

1. Trap: "Peripheral oedema from a dihydropyridine means heart failure or fluid overload."
1. Correction: It reflects fluid redistribution from the intravascular space into the interstitium, driven by selective arteriolar dilation raising intracapillary pressure. [1][4]
2. Trap: "A diuretic is the correct treatment for calcium channel blocker oedema."
2. Correction: Prescribing a diuretic for oedema that is actually drug-induced is a recognised prescribing cascade; the first step is evaluating whether the oedema is drug-related at all. [2][4]
3. Trap: "Dihydropyridines slow the heart like other calcium channel blockers."
3. Correction: They have minimal direct myocardial effect at therapeutic doses and, by lowering peripheral resistance, tend to provoke reflex tachycardia rather than bradycardia. [1][4]
4. Trap: "All dihydropyridines are interchangeable antihypertensives."
4. Correction: Each agent has its own approved indications; nimodipine in particular is restricted primarily to cerebral vasospasm after subarachnoid haemorrhage rather than to routine blood pressure control. [1][5]
5. Trap: "Immediate-release and extended-release nifedipine are equivalent."
5. Correction: The original immediate-release preparations caused rapid vasodilation followed by reflex sympathetic activation with headaches, palpitations and flushing, which is why extended-release preparations with a sustained effect and fewer adverse effects were developed. [3]
6. Trap: "Grapefruit juice is a trivial dietary note."
6. Correction: It inhibits intestinal CYP3A4 and roughly doubles nifedipine exposure, and it raises felodipine and nimodipine concentrations too, so it is a genuine interaction rather than a footnote. [3][4][5]

Self-test questions

1. Question: What distinguishes dihydropyridine calcium channel blockers from the non-dihydropyridines

pharmacologically?

1. They block T-type rather than L-type channels
2. They exert minimal direct effects on the myocardium and act primarily as peripheral vasodilators at therapeutic doses

3. They act on the atrioventricular node while sparing the vasculature
4. They work by blocking beta-1 adrenergic receptors instead of ion channels

1. Explanation: Both groups bind L-type voltage-gated calcium channels, but the dihydropyridines have minimal direct myocardial effect and behave as peripheral vasodilators at therapeutic doses, whereas the non-dihydropyridines inhibit the sinoatrial and atrioventricular nodes and slow conduction and contractility. [1]

2. Question: Why does peripheral oedema occur with dihydropyridines?

1. The kidney retains sodium and water in response to the drug
2. The drug directly damages capillary endothelium
3. Selective arteriolar dilation raises intracapillary pressure and drives fluid into the interstitial space
4. The drug reduces plasma albumin concentration

2. Explanation: These agents selectively dilate arterioles, which increases intracapillary pressure and causes extravasation of fluid into the interstitium. Because the mechanism is redistribution rather than salt and water retention, the oedema does not respond to the reflex of adding a diuretic. [4][1]

3. Question: A patient develops ankle swelling after starting a dihydropyridine and is prescribed a diuretic for it. What has occurred?

1. Appropriate escalation of antihypertensive therapy
2. A prescribing cascade, in which a drug adverse effect is mistaken for a new medical condition
3. Correct management of drug-induced heart failure
4. A recognised strategy for preventing gingival hyperplasia

3. Explanation: A prescribing cascade occurs when the drug-induced oedema is mistaken for a new condition and a diuretic is added to treat it. Evaluating whether the oedema is attributable to an underlying condition or to the drug is the risk mitigation step; an ACE inhibitor or angiotensin receptor blocker can also prevent the oedema. [2][4]

4. Question: Which dihydropyridine is used primarily for cerebral vasospasm after subarachnoid haemorrhage?

1. Amlodipine
2. Felodipine
3. Nimodipine
4. Nisoldipine

4. Explanation: Nimodipine was originally developed to manage systemic hypertension, but its current use is restricted primarily to the prevention and treatment of cerebral vasospasm following subarachnoid haemorrhage, where it reduces the incidence and severity of ischaemic deficits. [5]

5. Question: Why were extended-release nifedipine preparations developed?

1. Because the immediate-release form was not absorbed
2. Because immediate-release preparations caused rapid vasodilation followed by reflex sympathetic activation with headaches, palpitations and flushing
3. Because the immediate-release form caused profound bradycardia
4. Because the extended-release form avoids CYP3A4 metabolism entirely

5. Explanation: The original short-acting immediate-release formulations required multiple daily doses and produced rapid vasodilation with reflex sympathetic activation, causing headaches, palpitations and flushing. Extended-release preparations were introduced because they give a sustained antihypertensive effect with fewer adverse effects. [3]

6. Question: Which enzyme dominates the interaction profile of this class?

1. CYP2D6
2. CYP3A4
3. CYP2C19

4. Monoamine oxidase A

6. Explanation: Calcium channel blockers are extensively hepatically metabolised, primarily by CYP3A4, and many have low bioavailability because of that first-pass metabolism. Inhibitors such as azole antifungals, macrolides, protease inhibitors and grapefruit juice raise exposure, while inducers such as carbamazepine, phenytoin and rifampicin lower it. [1]

7. Question: Why does hyperglycaemia occur in significant calcium channel blocker poisoning?

1. The drugs stimulate hepatic gluconeogenesis directly

2. Beta-islet cells depend on calcium influx through L-type channels to release insulin, so blockade reduces insulin release

3. The drugs block intestinal glucose absorption

4. It reflects a stress cortisol response unrelated to the drug

7. Explanation: Pancreatic beta-islet cells depend on calcium influx through L-type calcium channels for insulin release, so blockade reduces insulin secretion and hyperglycaemia follows. It has been considered a prognostic indicator of the severity of toxicity, and the same insulin blockade impairs myocardial glucose uptake. [1]

8. Question: Which statement about heart rate in dihydropyridine overdose is correct?

1. Bradycardia is impossible because these drugs spare the myocardium

2. Reflex tachycardia may occur in mild-to-moderate overdose, but selectivity can be lost in severe poisoning, producing bradycardia

3. Heart rate is unaffected at any dose

4. Tachycardia is seen only in severe poisoning

8. Explanation: Dihydropyridines in mild-to-moderate overdose may cause reflex tachycardia. In severe poisoning, receptor selectivity may be lost, leading to bradycardia, so the pulse alone does not identify which subclass has been taken. [1]

Frequently asked questions

1. Question: Why do these drugs cause swollen ankles?

1. Answer: They selectively dilate arterioles, which raises pressure inside the capillaries and pushes fluid out into the interstitial space. The swelling is a redistribution of fluid rather than fluid overload, which is why it does not behave like the oedema of heart failure. [4][1]

2. Question: Should a diuretic be added for that swelling?

2. Answer: Adding a diuretic for drug-induced oedema is a recognised prescribing cascade. Establishing whether the oedema is caused by the drug is the first step, and an ACE inhibitor or angiotensin receptor blocker can prevent it where the calcium channel blocker is being continued. [2][4]

3. Question: Why do dihydropyridines speed the heart when other calcium channel blockers slow it?

3. Answer: Because they have minimal direct myocardial effect at therapeutic doses. Their fall in peripheral resistance triggers a compensatory baroreflex rise in heart rate, whereas the non-dihydropyridines act directly on the sinoatrial and atrioventricular nodes and slow conduction. [1][4]

4. Question: Why does grapefruit juice matter?

4. Answer: It inhibits intestinal CYP3A4, the enzyme that carries out much of the first-pass metabolism of this class. That roughly doubles nifedipine exposure and raises felodipine and nimodipine concentrations, so it is avoided rather than merely noted. [3][4][5]

5. Question: What is different about nimodipine?

5. Answer: It is a dihydropyridine whose current use is restricted primarily to preventing and treating cerebral vasospasm after subarachnoid haemorrhage, where it is indicated to improve neurological outcomes by reducing the incidence and severity of ischaemic deficits. [5]

6. Question: Is monitoring needed on a dihydropyridine?

6. Answer: For this subclass, monitoring blood pressure and heart rate is typically sufficient, and symptomatic

improvement in angina or maintained blood pressure indicates efficacy. Regular assessment is warranted where the dose is being titrated quickly. [1]

7. Question: Can gingival overgrowth from these drugs be reversed?

7. Answer: Gingival hyperplasia is usually reversible on discontinuation, and good oral hygiene helps prevent it; where it persists despite that, surgical intervention may be needed. [4][2]

References

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