

Nitrates

Drugs that release nitric oxide inside the blood vessel wall, relaxing smooth muscle. They act most strongly on veins, which lowers the volume of blood returning to the heart and so lowers the work the heart has to do - the basis of their use in angina.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/nitrates>

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Quick revision

One Liner: Nitrates are converted to nitric oxide, which switches on guanylyl cyclase and raises cyclic GMP inside vascular smooth muscle so the vessel relaxes; the effect is greatest in the veins, so preload falls, cardiac work falls and angina eases - and the two things that ruin nitrate therapy are tolerance, which needs a daily nitrate-free interval, and combination with a PDE5 inhibitor, which can drop the blood pressure catastrophically.

1. Nitrates release nitric oxide, the endothelium-derived relaxing factor, which activates guanylyl cyclase and converts guanosine triphosphate into cyclic GMP. [1][2]
2. Rising cyclic GMP activates cGMP-dependent protein kinases, which reduce calcium availability and switch off myosin light chain kinase, so vascular smooth muscle relaxes. [2]
3. Nitrates dilate venous capacitance vessels, arterioles and coronary arteries, but the maximal effect is on the venous capacitance vessels. [2]
4. Venodilation pools blood in the venous system and reduces preload - the volume of blood returning to and filling the heart - which lowers cardiac work and relieves anginal symptoms. [1]
5. Reduced preload lowers myocardial oxygen demand, while coronary dilation improves perfusion, so supply and demand move in the helpful direction together. [2]
6. Sublingual glyceryl trinitrate starts working in one to three minutes with a maximum effect at about five minutes, and its half-life is only two to three minutes. [1]
7. Isosorbide dinitrate undergoes extensive first-pass metabolism in the liver, so its oral bioavailability is around 20% and its elimination half-life is about one hour. [2]
8. Isosorbide mononitrate escapes the first-pass effect, so oral bioavailability is 100% and the elimination half-life is five to six hours - which is what makes it the once-daily prophylactic option. [2]
9. Tolerance can develop within as little as 12 to 24 hours of continuous exposure, after which the clinical effect fades. [2][3]
10. Preventing tolerance requires a daily nitrate-free interval, described as at least 10 to 12 hours; continuous intravenous infusion is a recognised way to induce tolerance. [2][1]
11. Headache affects more than 10% of patients and can be severe, throbbing and persistent; hypotension, orthostatic symptoms, flushing, reflex tachycardia and syncope follow from the vasodilation. [2][1]
12. Concurrent use with a phosphodiesterase-5 inhibitor such as sildenafil, vardenafil or tadalafil is absolutely contraindicated because the combination can cause life-threatening hypotension. [1][2]
13. Riociguat, a soluble guanylate cyclase stimulator, is contraindicated with nitrates for the same reason - both raise cyclic GMP and the effects stack. [2]
14. Right ventricular infarction is a contraindication, because a preload-dependent right ventricle can be tipped into profound hypotension and cardiogenic shock. [1][2]
15. Hypertrophic cardiomyopathy is also listed as an absolute contraindication to nitrate therapy. [2][3]
16. Methaemoglobinaemia is a rare complication, arising when nitrate ions released during metabolism oxidise haemoglobin; methylene blue can act as an antidote. [2]

Overview

1. Nitrates are among the oldest cardiovascular drugs still in daily use, and their pharmacology is unusually clean. Each of them is a source of nitric oxide, the molecule the endothelium itself releases to relax the vessels it lines. Once released, nitric oxide activates guanylyl cyclase, which converts guanosine triphosphate into cyclic GMP. Cyclic GMP then activates protein kinases that reduce the calcium available to the contractile machinery and inactivate myosin light chain kinase, and the smooth muscle relaxes. [1][2]
2. Where that relaxation happens is what makes nitrates antianginal drugs rather than simply antihypertensive ones. They dilate venous capacitance vessels, arterioles and coronary arteries, but the effect is maximal on the veins. Blood pools in the venous system, so less returns to the heart; that fall in preload reduces the work the heart must do and with it the oxygen the myocardium needs. Coronary dilation improves the supply side at the same time, which is why the anginal symptom settles. [2][1]
3. The clinical division within the class is about time course rather than mechanism. Glyceryl trinitrate given under the tongue acts within one to three minutes and disappears within minutes, which suits the acute attack. Isosorbide dinitrate is heavily metabolised by the liver on first pass, and isosorbide mononitrate avoids that step altogether, giving it a longer half-life and a prophylactic role. Transdermal glyceryl trinitrate patches are reserved for prophylaxis rather than for rescue. [1][2]
4. Two problems dominate the safe use of the class. The first is tolerance: effect can be lost within 12 to 24 hours of continuous exposure, so a daily nitrate-free interval is built into treatment rather than being optional. The second is the interaction with drugs that act on the same cyclic GMP pathway. Phosphodiesterase-5 inhibitors prevent cyclic GMP being broken down and riociguat stimulates the enzyme that makes it, so either combination can produce hypotension described as life-threatening. [2][1][3]

Classification and drug examples

Intro: All therapeutic nitrates share one mechanism, so the class is divided by how fast a preparation acts and how long it lasts. That, in turn, is decided by the molecule and by the route - specifically, by whether the preparation has to survive a pass through the liver before reaching the circulation.

1. Name: Short-acting nitrate for the acute attack

1. Note: Fast onset, very short duration, and formulated to bypass hepatic first-pass metabolism. This is the rescue preparation, used when symptoms are present or immediately before a predictable trigger.

Name: Glyceryl trinitrate

1. Nitroglycerin

2. GTN

Route: Sublingual/IV/Transdermal

Note: Sublingual tablets act in one to three minutes with maximum effect at about five minutes, and the mean half-life is two to three minutes. An intravenous infusion is used in emergency and intensive care settings, transdermal ointment is absorbed over five to ten minutes, and transdermal patches are reserved for prophylaxis only. [1] [1]

2. Name: Long-acting nitrates for prevention

2. Note: Oral preparations intended to prevent angina rather than to abort an attack in progress. Their pharmacokinetic differences come down to the hepatic first-pass effect, and both are excreted mainly by the kidney as glucuronide derivatives without requiring dose adjustment in renal or hepatic dysfunction.

1. Name: Isosorbide dinitrate

ISDN

1. Route: Oral/Sublingual

1. Note: Undergoes an extensive first-pass effect that reduces oral bioavailability to about 20%, with an elimination half-life of roughly one hour. Licensed for prevention or treatment of angina pectoris - though not for the acute episode - and for congestive heart failure. The sublingual route, which avoids first-pass metabolism, is preferred when a rapid

effect is wanted. [2]

2. Name: Isosorbide mononitrate

ISMN

2. Route: Oral

2. Note: Does not undergo the first-pass effect, so oral bioavailability is 100% and the elimination half-life is five to six hours. Licensed for chronic angina pectoris, and for prevention of variceal haemorrhage in combination with a beta blocker. Sustained-release tablets are available. [2] [2]

Mechanism of action

Summary: A nitrate is a nitric oxide delivery vehicle. Nitric oxide activates guanylyl cyclase in vascular smooth muscle, cyclic GMP accumulates, cGMP-dependent protein kinases lower intracellular calcium and inactivate myosin light chain kinase, and the vessel relaxes - most of all on the venous side, which is what makes the preload fall.

Target: Soluble guanylyl cyclase in vascular smooth muscle, reached by nitric oxide released from the drug

1. Step: 1

1. Title: The drug releases nitric oxide

1. Detail: Organic nitrates are metabolised in the vessel wall to nitric oxide, the same endothelium-derived relaxing factor the body uses to regulate vascular tone. The drug is effectively substituting for an endogenous signal. [2][1]

2. Step: 2

2. Title: Nitric oxide switches on guanylyl cyclase

2. Detail: The enzyme converts guanosine triphosphate into cyclic guanosine monophosphate, so cyclic GMP concentrations inside the smooth muscle cell rise. [1][2]

3. Step: 3

3. Title: Cyclic GMP relaxes the muscle

3. Detail: Cyclic GMP activates cGMP-dependent protein kinases, which inhibit calcium release and deactivate myosin light chain kinase. Without calcium-driven myosin activation the contractile apparatus cannot maintain tone, so the vessel dilates. [2]

4. Step: 4

4. Title: Veins respond more than arteries

4. Detail: Venous capacitance vessels, arterioles and coronary arteries all dilate, but the maximal effect is venous. Blood is held in the venous compartment instead of returning to the heart. [2]

5. Step: 5

5. Title: Preload falls and cardiac work falls with it

5. Detail: Less blood returning to the heart means less stretch on the ventricle before contraction. Cardiac work drops, myocardial oxygen demand drops, and the mismatch between oxygen supply and demand that causes anginal pain narrows. [1][2]

6. Step: 6

6. Title: Coronary dilation adds to the supply side

6. Detail: Dilation of the coronary arteries increases coronary perfusion, so nitrates improve supply as well as reducing demand. This is also the basis of their off-label use in coronary artery spasm. [2][1]

7. Step: 7

7. Title: Continuous exposure blunts the response

7. Detail: Effect can be lost within 12 to 24 hours of uninterrupted exposure. This is tolerance, and the counter-measure is a daily interval without the drug rather than a larger amount of it. [2][3]

8. Step: 8

8. Title: The same pathway explains the dangerous interactions

8. Detail: Phosphodiesterase-5 inhibitors prevent the breakdown of cyclic GMP and riociguat stimulates soluble guanylate cyclase. Either one, added to a nitrate, amplifies the same signal and can cause life-threatening

hypotension. [2][1]

Major clinical uses

1. Drug: Glyceryl trinitrate

1. Indication: Acute relief of an anginal attack, and acute prophylaxis of angina pectoris secondary to coronary artery disease

1. Line: first-line

1. Note: This is the licensed use. Sublingual administration is the standard route for it because of the one- to three-minute onset. [1]

2. Drug: Glyceryl trinitrate

2. Indication: Off-label roles in hypertensive urgency and emergency, coronary artery spasm, angina related to cocaine use, congestive heart failure, chronic anal fissure, and reduction of radial artery spasm during coronary angiography

2. Line: alternative

2. Note: The intravenous preparation is the one used in emergency and intensive care settings, with real-time blood pressure monitoring during administration. [1]

3. Drug: Isosorbide dinitrate

3. Indication: Prevention or treatment of angina pectoris, though not for the acute episode, and treatment of congestive heart failure

3. Line: targeted

3. Note: A short-acting sublingual form exists for when a faster onset is required, because that route escapes hepatic first-pass metabolism. [2]

4. Drug: Isosorbide mononitrate

4. Indication: Chronic angina pectoris, and prevention of variceal haemorrhage in combination with a beta blocker

4. Line: targeted

4. Note: Complete oral bioavailability and a five- to six-hour half-life make it the more predictable long-acting oral option. [2]

5. Drug: Isosorbide dinitrate with hydralazine

5. Indication: Heart failure, as a fixed-dose combination approved for use in African American patients

5. Line: targeted

5. Note: The nitrate contributes venodilation and the hydralazine component contributes arterial dilation; the combination is a distinct licensed product rather than an ad hoc pairing. [2]

6. Drug: Isosorbide (dinitrate or mononitrate)

6. Indication: Off-label use in achalasia and diffuse oesophageal spasm

6. Line: alternative

6. Note: Smooth muscle relaxation is not confined to blood vessels, which is what makes an oesophageal indication possible. [2]

Pharmacokinetics

1. Drug: Glyceryl trinitrate

1. Route: Sublingual/IV/Transdermal

1. Absorption: Sublingual onset in one to three minutes with maximum effect at about five minutes; transdermal ointment absorbed over five to ten minutes

1. Metabolism: Rapid metabolism in the liver

1. Elimination: Cleared so rapidly that no serum level monitoring is available

1. Half Life: Mean of approximately two to three minutes

1. Dose Adjust: Real-time blood pressure monitoring accompanies intravenous use; transdermal patches are reserved for prophylaxis only [1]

2. Drug: Isosorbide dinitrate
2. Route: Oral/Sublingual
2. Absorption: Extensive first-pass effect in the liver reduces oral bioavailability to about 20%; the sublingual route avoids it
2. Metabolism: Hepatic, with conversion to glucuronide derivatives
2. Elimination: Excreted primarily by the kidney as glucuronide derivatives
2. Half Life: Elimination half-life of about one hour
2. Dose Adjust: No adjustment is required for renal or hepatic dysfunction, but a daily nitrate-free interval is needed to preserve effect [2]
3. Drug: Isosorbide mononitrate
3. Route: Oral
3. Absorption: No first-pass effect, giving 100% bioavailability after oral administration
3. Metabolism: Hepatic conjugation to glucuronide derivatives
3. Elimination: Excreted primarily by the kidney as glucuronide derivatives
3. Half Life: Elimination half-life of five to six hours
3. Dose Adjust: No adjustment is required for renal or hepatic dysfunction; sustained-release preparations still need a drug-free part of the day [2]
1. The route chosen is really a decision about the liver. Preparations that bypass first-pass metabolism act fast and suit rescue treatment; oral preparations that survive it or avoid it altogether suit prevention. [2][1]
2. Tolerance is the defining pharmacokinetic-pharmacodynamic problem of the class: uninterrupted exposure over 12 to 24 hours costs the drug its clinical effect, and a daily nitrate-free interval described as at least 10 to 12 hours is what restores it. [2][3]
3. Continuous intravenous nitrate infusion is a recognised way to generate tolerance, which is why transition to an intermittent oral schedule with long nitrate-free intervals is described. [1]
4. Because glyceryl trinitrate is metabolised so quickly, there is no serum level to follow; monitoring is clinical, using blood pressure and symptom response. [1]
5. Closer observation is described for patients with low blood pressure or heart rate, those on long-term diuretics, older patients with autonomic dysfunction, those taking other vasodilators and those who are volume-depleted. [2]
6. This page gives no dose regimens by design. Amounts, intervals and formulations depend on the indication, the preparation and the individual patient, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Headache
1. Detail: Occurs in more than 10% of patients and is the single most characteristic nitrate effect. With glyceryl trinitrate it can be severe, throbbing and persistent. [2][1]
2. Effect: Hypotension and orthostatic symptoms
2. Detail: A direct extension of the vasodilator action; dizziness, light-headedness and syncope belong to the same picture. [2][1]
3. Effect: Reflex tachycardia
3. Detail: The baroreflex response to a falling blood pressure, reported among the common nitrate effects. [2]
4. Effect: Cutaneous flushing
4. Detail: Dilation of skin vessels, reported alongside the other vasodilator effects. [2]
5. Effect: Nausea and vomiting
5. Detail: Described with both glyceryl trinitrate and isosorbide, along with weakness, palpitations, vertigo and sweating. [1][2]
1. Effect: Life-threatening hypotension with a PDE5 inhibitor or riociguat
1. Detail: Combining a nitrate with sildenafil, vardenafil, tadalafil or riociguat raises cyclic GMP far beyond the intended

level, accentuating the hypotensive effect and precipitating syncope.

1. Action: The combination is listed as an absolute contraindication rather than a caution, and the medication history has to be established before a nitrate is given. [1][2]
2. Effect: Profound hypotension and cardiogenic shock in right ventricular infarction
2. Detail: A right ventricle damaged by infarction depends on filling pressure to sustain output, so the preload reduction that normally helps becomes harmful.
2. Action: Right ventricular infarction is an explicit contraindication; recognising it before giving a nitrate is the safeguard. [1]
3. Effect: Methaemoglobinaemia
3. Detail: A rare complication in which nitrate ions released during metabolism oxidise haemoglobin into methaemoglobin, which cannot carry oxygen normally.
3. Action: Diagnosis requires an arterial or venous blood gas with co-oximetry, and methylene blue can work as an antidote. [2]
4. Effect: Loss of effect through tolerance
4. Detail: Not a toxicity but a safety issue in its own right, because a patient may believe they are protected when the drug has stopped working; it can appear within 12 to 24 hours of continuous exposure.
4. Action: A daily nitrate-free interval is built into treatment, and unexplained loss of symptom control prompts review by the treating clinician. [2][3]
5. Effect: Overdose picture
5. Detail: Excess nitrate produces profound systemic hypotension, heart block with bradycardia, syncope, nausea, vomiting and raised intracranial pressure.
5. Action: Management described includes stopping the drug, passive leg elevation and intravenous fluid, given cautiously where renal failure or heart failure is present. [2]
1. Drug: Glyceryl trinitrate
1. Effect: The severe throbbing headache and the rapid, marked blood pressure fall that follow its speed of onset; phlebotic and haemodynamic effects make real-time blood pressure monitoring standard during intravenous use. [1]
2. Drug: Isosorbide dinitrate
2. Effect: Monday disease - tachycardia, dizziness and headache on re-exposure after a drug-free interval, arising from tolerance built up during continuous therapy. [2]
3. Drug: Isosorbide mononitrate
3. Effect: Its complete bioavailability and longer half-life make sustained exposure easy to achieve, which is precisely why a daily drug-free part of the day matters with it. [2]

Contraindications, precautions and interactions

1. Concurrent use of a phosphodiesterase-5 inhibitor such as sildenafil, vardenafil or tadalafil. [1][2]
2. Concurrent use of riociguat, a soluble guanylate cyclase stimulator. [2]
3. Right ventricular infarction. [1][2]
4. Hypertrophic cardiomyopathy. [2][3]
5. Known allergy to nitrates, although a genuine allergic reaction is described as extremely rare. [2][1]
6. Raised intracranial pressure and severe anaemia, both listed as contraindications to glyceryl trinitrate. [1]
1. Low baseline blood pressure or heart rate, where the vasodilator effect has less margin. [2]
2. Long-term diuretic therapy and volume depletion, both of which magnify the preload reduction. [2][3]
3. Older patients with autonomic dysfunction, in whom the reflex compensation for a falling blood pressure is impaired. [2]
4. Concurrent treatment with other vasodilators, where hypotensive effects add together. [2]
5. Pregnancy, listed among the situations warranting caution with nitrate therapy. [3]
6. Uninterrupted dosing schedules, which are the setting in which tolerance develops and effect is silently lost. [2]

1. With: Phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil)
 1. Effect: Accentuate the hypotensive effect of nitrates and can precipitate syncope; the combined rise in cyclic GMP is described as producing life-threatening hypotension. [1][2]
2. With: Riociguat
 2. Effect: Stimulates soluble guanylate cyclase, so cyclic GMP rises from both directions at once and life-threatening hypotension can result. [2]
3. With: Other vasodilators and antihypertensive drugs
 3. Effect: Additive lowering of blood pressure, which is why closer observation is described when they are combined with a nitrate. [2]
4. With: Diuretics
 4. Effect: Long-term diuretic use is listed among the situations calling for closer monitoring, because volume depletion deepens the fall in preload. [2]
5. With: Beta blockers
 5. Effect: A deliberate pairing rather than a hazard in one setting: isosorbide mononitrate is licensed with a beta blocker for prevention of variceal haemorrhage. [2]
6. With: Hydralazine
 6. Effect: Also a deliberate combination - a fixed-dose product of isosorbide dinitrate with hydralazine hydrochloride is approved for heart failure in African American patients. [2]

Comparison tables

1. Title: Glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate
 1. Caption: One mechanism, three time courses. Actual choice of preparation is governed by a current prescribing reference and the treating clinician.
 1. Key: drug
 1. Label: Drug
 1. Is Row Header: true
 2. Key: first_pass
 2. Label: First-pass effect and bioavailability
 3. Key: half_life
 3. Label: Half-life
 4. Key: role
 4. Label: Role
 1. Drug: Glyceryl trinitrate
 1. First Pass: Bypassed by sublingual, transdermal and intravenous routes; rapidly metabolised by the liver
 1. Half Life: Approximately two to three minutes
 1. Role: Acute relief and acute prophylaxis of angina; intravenous use in emergency settings; patches for prophylaxis only [1]
 2. Drug: Isosorbide dinitrate
 2. First Pass: Extensive first-pass effect; oral bioavailability about 20%, avoided by the sublingual route
 2. Half Life: About one hour
 2. Role: Prevention or treatment of angina but not the acute attack; congestive heart failure [2]
 3. Drug: Isosorbide mononitrate
 3. First Pass: No first-pass effect; oral bioavailability 100%
 3. Half Life: Five to six hours
 3. Role: Chronic angina; prevention of variceal haemorrhage alongside a beta blocker [2]
2. Title: Absolute contraindications and the reason behind each
 2. Caption: Each entry follows from the mechanism rather than from an idiosyncratic reaction, which is why they are

worth learning as a set.

1. Key: situation

1. Label: Situation

1. Is Row Header: true

2. Key: reason

2. Label: Why it matters

1. Situation: PDE5 inhibitor taken concurrently

1. Reason: Blocking cyclic GMP breakdown while a nitrate is generating more of it accentuates hypotension and can precipitate syncope [1][2]

2. Situation: Riociguat taken concurrently

2. Reason: It stimulates soluble guanylate cyclase, so cyclic GMP is driven up by two mechanisms at once, with life-threatening hypotension described [2]

3. Situation: Right ventricular infarction

3. Reason: The damaged right ventricle needs preload to maintain output; removing it can cause profound hypotension and cardiogenic shock [1]

4. Situation: Hypertrophic cardiomyopathy

4. Reason: Listed as an absolute contraindication to nitrate therapy in the reference literature [2][3]

5. Situation: Raised intracranial pressure or severe anaemia

5. Reason: Both are listed contraindications to glyceryl trinitrate [1]

High-yield exam pearls

1. Pearl: Nitrates are venodilators first and everything else second.

1. Why: They dilate venous capacitance vessels, arterioles and coronary arteries, but the maximal effect is venous. That is why preload reduction, rather than afterload reduction or coronary dilation, is the principal way they relieve angina. [2][1]

2. Pearl: The mechanism is a signalling cascade, and every important interaction sits on it.

2. Why: Nitric oxide raises cyclic GMP; PDE5 inhibitors stop cyclic GMP being broken down; riociguat stimulates the same guanylate cyclase that makes it. Combining any of them stacks the same signal and produces life-threatening hypotension. [2][1]

3. Pearl: First-pass metabolism explains the whole mononitrate versus dinitrate distinction.

3. Why: Isosorbide dinitrate is heavily extracted by the liver on first pass, leaving about 20% oral bioavailability and a one-hour half-life; isosorbide mononitrate bypasses that step entirely with 100% bioavailability and a five- to six-hour half-life. [2]

4. Pearl: Sublingual dosing exists to dodge the liver.

4. Why: The sublingual route avoids the first-pass effect, which is why it is preferred when a rapid effect is needed, and why sublingual glyceryl trinitrate works within one to three minutes. [2][1]

5. Pearl: Tolerance is a dosing-schedule problem, not a dose problem.

5. Why: Effect can be lost within 12 to 24 hours of uninterrupted exposure, so the answer is a daily interval without drug rather than more drug. Continuous intravenous infusion is the classic way tolerance is generated. [2][1][3]

6. Pearl: Monday disease is the tolerance story told backwards.

6. Why: It describes tachycardia, dizziness and headache appearing on re-exposure after a drug-free interval, and it is attributed to the tolerance that develops during continuous therapy. [2]

7. Pearl: Right ventricular infarction turns a helpful drug into a dangerous one.

7. Why: An infarcted right ventricle depends on filling pressure to maintain output, so removing preload with a nitrate can cause profound hypotension progressing to cardiogenic shock. [1]

8. Pearl: A blue patient on a nitrate who does not respond to oxygen suggests methaemoglobinaemia.

8. Why: Nitrate ions released during metabolism can oxidise haemoglobin to methaemoglobin. The diagnosis is made

on an arterial or venous blood gas with co-oximetry, and methylene blue is described as an antidote. [2]

Common exam traps

1. Trap: "Nitrates work mainly by dilating the coronary arteries."

1. Correction: Coronary dilation contributes, but the dominant action is venodilation. Blood pools in the venous system, preload falls, cardiac work falls and the anginal symptom eases; arterial and coronary effects are secondary. [1][2]

2. Trap: "Isosorbide dinitrate is the right choice for an attack that is happening now."

2. Correction: Its licensed role is prevention or treatment of angina pectoris but not the acute episode. Rapid relief is the job of a short-acting sublingual preparation, because the sublingual route avoids first-pass metabolism. [2]

3. Trap: "A nitrate patch can simply be left on all the time for continuous protection."

3. Correction: Uninterrupted exposure is exactly what produces tolerance, within as little as 12 to 24 hours. Maintaining effect requires a daily nitrate-free interval described as at least 10 to 12 hours, and transdermal patches are reserved for prophylaxis rather than acute relief. [2][1]

4. Trap: "A patient can take a nitrate as long as they took their erectile dysfunction tablet yesterday."

4. Correction: Concurrent phosphodiesterase-5 inhibitor use is listed as an absolute contraindication, and the timing question is not one a page like this can settle. The interaction produces life-threatening hypotension and the decision belongs to the treating clinician with a current prescribing reference. [1][2]

5. Trap: "Nitrates are safe in every kind of myocardial infarction because they treat ischaemia."

5. Correction: Right ventricular infarction is a specific contraindication. Preload reduction in that setting can cause profound hypotension and cardiogenic shock. [1]

6. Trap: "Headache with a nitrate means an allergy."

6. Correction: Headache is the expected pharmacological consequence of vasodilation and affects more than one in ten patients. True allergy to nitrates is listed separately and is described as extremely rare. [2][1]

Self-test questions

1. Question: Through which second messenger do nitrates relax vascular smooth muscle?

1. Cyclic AMP, via adenylyl cyclase
2. Cyclic GMP, via guanylyl cyclase
3. Inositol trisphosphate, via phospholipase C
4. Diacylglycerol, via protein kinase C

1. Explanation: Nitrates release nitric oxide, which activates guanylyl cyclase. That enzyme converts guanosine triphosphate into cyclic GMP, and the rise in cyclic GMP activates protein kinases that lower calcium availability and inactivate myosin light chain kinase, relaxing the muscle. [1][2]

2. Question: Which vascular bed shows the maximal nitrate effect?

1. Venous capacitance vessels
2. Renal afferent arterioles
3. Pulmonary capillaries
4. Cerebral arteries

2. Explanation: Nitrates dilate venous capacitance vessels, arterioles and coronary arteries, but the maximal effect is seen in the venous capacitance vessels. Pooling blood there reduces preload and therefore myocardial oxygen demand. [2]

3. Question: Why does isosorbide mononitrate have much higher oral bioavailability than isosorbide dinitrate?

1. It is more water-soluble
2. It is given at a higher strength
3. It does not undergo the hepatic first-pass effect
4. It is absorbed through the buccal mucosa only

3. Explanation: Isosorbide dinitrate undergoes an extensive first-pass effect in the liver, which cuts oral bioavailability to

around 20% and leaves an elimination half-life of about one hour. Isosorbide mononitrate does not undergo that first-pass step, so bioavailability after oral administration is 100% and the half-life is five to six hours. [2]

4. Question: How quickly can nitrate tolerance develop, and what prevents it?

1. Over several months; prevented by increasing the dose
2. Within 12 to 24 hours; prevented by a daily nitrate-free interval
3. Only after years of therapy; prevented by adding a diuretic
4. It does not develop with oral formulations

4. Explanation: Tolerance may develop within as little as 12 to 24 hours, with a subsequent loss of clinical effect. A drug-free interval of at least 10 to 12 hours a day is what maintains responsiveness, and continuous intravenous infusion is a recognised route to tolerance. [2][3]

5. Question: Why is a phosphodiesterase-5 inhibitor absolutely contraindicated with a nitrate?

1. Because the PDE5 inhibitor blocks nitric oxide production
2. Because both drugs raise cyclic GMP, and the combination can cause life-threatening hypotension
3. Because the combination causes severe hypertension
4. Because the PDE5 inhibitor prevents nitrate absorption

5. Explanation: Phosphodiesterase-5 inhibitors such as sildenafil, vardenafil and tadalafil accentuate the hypotensive effect of nitrates and can precipitate syncope. The combined rise in cyclic GMP produces hypotension described as life-threatening, which is why the combination is listed as absolutely contraindicated. [1][2]

6. Question: Which infarct pattern makes nitrate use particularly hazardous?

1. Anterior left ventricular infarction
2. Lateral wall infarction
3. Right ventricular infarction
4. Old, healed inferior infarction

6. Explanation: In right ventricular infarction, the reduction in preload produced by a nitrate can cause profound hypotension leading to cardiogenic shock. It is listed among the contraindications for that reason. [1]

7. Question: What is Monday disease?

1. A withdrawal syndrome from beta blockers
2. Tachycardia, dizziness and headache on re-exposure to nitrate after a drug-free interval
3. A form of methaemoglobinaemia unique to mononitrates
4. An allergic reaction to nitrate patches

7. Explanation: Monday disease arises from the tolerance that develops during continuous nitrate exposure. After a drug-free interval, re-exposure produces tachycardia, dizziness and headache as the vasodilator response returns. [2]

8. Question: Which rare adverse effect of nitrates is diagnosed with co-oximetry and treated with methylene blue?

1. Methaemoglobinaemia
2. Haemolytic anaemia
3. Agranulocytosis
4. Carbon monoxide poisoning

8. Explanation: Nitrate ions released during metabolism can oxidise haemoglobin into methaemoglobin, which cannot carry oxygen in the normal way. Blood gas analysis with co-oximetry is what confirms it, and methylene blue is the described antidote. [2]

Frequently asked questions

1. Question: How do nitrates relieve angina?

1. Answer: They release nitric oxide, which raises cyclic GMP in vascular smooth muscle and relaxes it. Because the effect is greatest in the veins, less blood returns to the heart, the heart does less work and needs less oxygen. Coronary dilation improves the supply side at the same time. [1][2]

2. Question: Why do nitrates cause headache?

2. Answer: Because the drug dilates blood vessels everywhere, not only in the heart. Headache is the expected consequence, affects more than one in ten people and can be severe and throbbing with fast-acting preparations. It is a pharmacological effect rather than an allergy. [2][1]

3. Question: What is nitrate tolerance and why does a nitrate-free interval fix it?

3. Answer: Tolerance is the loss of clinical effect that follows continuous exposure, and it can appear within 12 to 24 hours. Leaving a part of each day without the drug - described as at least 10 to 12 hours - lets responsiveness return, which is why nitrate schedules are deliberately intermittent rather than round the clock. [2][3]

4. Question: Why can nitrates not be taken with erectile dysfunction medicines?

4. Answer: Those medicines are phosphodiesterase-5 inhibitors. They stop cyclic GMP being broken down while the nitrate is generating more of it, so the vasodilator signal is amplified from both ends. The result can be life-threatening hypotension, which is why the combination is treated as an absolute contraindication. [1][2]

5. Question: What is the difference between isosorbide mononitrate and isosorbide dinitrate?

5. Answer: The liver. Isosorbide dinitrate is heavily extracted on first pass, leaving about 20% of an oral dose available and a half-life of roughly an hour. Isosorbide mononitrate skips that step, so 100% is available and the half-life is five to six hours, making it the steadier preventive option. [2]

6. Question: Why is a nitrate dangerous in right ventricular infarction?

6. Answer: A right ventricle injured by infarction relies on being well filled to push blood through to the lungs. Nitrates work by reducing exactly that filling, so in this specific setting they can cause profound hypotension and cardiogenic shock. [1]

7. Question: Can a long-acting nitrate be used to stop an attack that has already started?

7. Answer: No. Isosorbide dinitrate is licensed for prevention or treatment of angina pectoris but explicitly not for the acute episode, and transdermal glyceryl trinitrate patches are reserved for prophylaxis. Rapid relief comes from a preparation that bypasses the liver and acts within minutes. [2][1]

8. Question: Do nitrates need dose adjustment in kidney or liver disease?

8. Answer: For isosorbide, the reference literature states that no adjustment is required for renal or hepatic dysfunction, since both forms are excreted mainly by the kidney as glucuronide derivatives. That does not remove the need for individual assessment by the treating clinician. [2]

References

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[2] Isosorbide (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK557839/>

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