

Cardiac glycosides

Plant-derived drugs that block the sodium-potassium pump in heart muscle, making each contraction stronger while slowing conduction through the atrioventricular node. Digoxin is the surviving member, and its narrow safety margin is the whole story.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/cardiac-glycosides>

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Quick revision

One Liner: Cardiac glycosides reversibly block the myocardial sodium-potassium ATPase pump, so sodium builds up inside the cell, calcium follows it in and contraction strengthens; at the same time a vagal effect slows conduction through the atrioventricular node - and because the gap between a useful concentration and a toxic one is so small, recognising toxicity is as examinable as the mechanism.

1. Digoxin reversibly inhibits the myocardial sodium-potassium ATPase pump, raising intracellular sodium and driving an influx of calcium that strengthens contraction. [1]
2. Digoxin also acts on the atrioventricular node by stimulating the parasympathetic nervous system, a vagomimetic effect that slows conduction and reduces heart rate. [1]
3. Those two actions explain its two uses: stronger contraction for symptomatic heart failure, and slower nodal conduction for rate control in atrial fibrillation. [1]
4. Cardiac glycosides are natural compounds built from a steroid ring, a lactone ring and a sugar, found in plants and in some amphibians. [2]
5. Digoxin comes from the foxglove *Digitalis lanata*; oleander and toad-derived bufalin are other cardioactive steroids, and ouabain comes from plants of the genus *Acokanthera*. [2]
6. Oral bioavailability is around 75%, roughly 13% of a dose is metabolised, and the rest is excreted by the kidneys in direct proportion to the glomerular filtration rate. [1]
7. The half-life is 36 to 48 hours in healthy adults and is significantly prolonged in renal failure, which is why kidney function dominates safe use. [1]
8. The described therapeutic serum range is 0.8 to 2 nanograms per millilitre, with a lower target of 0.5 to 0.9 recommended for heart failure by 2013 ACC Foundation and AHA guidance. [1]
9. Hypokalaemia, hypomagnesaemia and hypercalcaemia all increase susceptibility to digoxin's effects, and loop diuretics are a common route to the low potassium that does it. [1]
10. Yellow or green tinted vision, called xanthopsia, is the classic visual sign of digoxin toxicity, alongside nausea, vomiting and loss of appetite. [1]
11. At toxic levels digoxin becomes proarrhythmic and can produce almost any arrhythmia; bidirectional ventricular tachycardia is pathognomonic and premature ventricular complexes are the most common. [2][1]
12. Acute toxicity causes a high serum potassium because the pump is blocked, whereas chronic toxicity often occurs on a background of low potassium from diuretics. [2]
13. The digoxin effect on the electrocardiogram is a downsloping, scooped ST segment sometimes called the reverse tick, with a shortened QT interval and a lengthened PR interval. [1]
14. Digoxin immune Fab, made from sheep antibody fragments, binds digoxin with an affinity greater than that of the cardiac receptor and is the first-line treatment for severe, life-threatening toxicity. [3]
15. Intravenous calcium is contraindicated in a person taking digoxin, on the theoretical concern of an irreversible non-contractile state described as stone heart. [2]
16. Amiodarone can produce a notable rise in digoxin concentrations, potentially doubling them, and quinidine may significantly increase them as well. [4][1]

Overview

1. Cardiac glycosides are naturally occurring compounds built from a steroid ring, a lactone ring and a sugar, found in a range of plants and in some amphibians. Digoxin, extracted from the foxglove *Digitalis lanata*, is the member that became a medicine. William Withering first used foxglove for oedema in 1775, digoxin itself was isolated in 1930, and the drug is still prescribed today despite the arrival of safer alternatives. [2]
2. The pharmacology rests on a single molecular action with two clinical consequences. Reversible inhibition of the myocardial sodium-potassium ATPase pump raises intracellular sodium, which drives calcium into the cell and makes each contraction stronger. Separately, digoxin stimulates the parasympathetic nervous system to act on the atrioventricular node, prolonging its refractory period and slowing conduction through it. Stronger contraction serves heart failure; slower nodal conduction serves rate control in atrial fibrillation. [1]
3. What makes this class distinctive is not the mechanism but the margin. Digoxin has a narrow therapeutic window, is excreted by the kidneys in proportion to the glomerular filtration rate, and has a half-life of a day and a half or more that lengthens further when renal function falls. Concentration is also not the whole story, because low potassium, low magnesium and high calcium all raise susceptibility, so a stable patient can become toxic without any change in what they are taking. [1]
4. The consequence is that toxicity recognition is examined as heavily as the mechanism. Nausea, appetite loss, confusion and yellow-green vision are the systemic clues; almost any arrhythmia is possible, with bidirectional ventricular tachycardia the pathognomonic one. Management combines supportive care and electrolyte correction with a specific antidote, digoxin immune Fab, and one memorable prohibition: intravenous calcium is contraindicated in a digitalised patient. [1][2][3]

Classification and drug examples

Intro: Only one cardiac glycoside is in routine therapeutic use, so the useful division is between the medicine and the other cardioactive steroids that appear in clinical practice as poisonings rather than prescriptions. They share the same mechanism and produce the same toxidrome.

1. Name: The therapeutic glycoside - digoxin

1. Note: The only cardiac glycoside in ordinary prescribing use. It is licensed for chronic atrial fibrillation and symptomatic heart failure, but the reference literature describes it as reserved as a backup option when first-line agents are ineffective.

Name: Digoxin

Digitalis

Route: Oral/IV

Note: Derived from the foxglove *Digitalis lanata*. Reversibly inhibits the myocardial sodium-potassium ATPase pump and exerts a vagomimetic effect on the atrioventricular node. Oral bioavailability is about 75%, the volume of distribution is roughly 475 to 500 litres, and elimination is renal in proportion to the glomerular filtration rate. [1][2] [1]

2. Name: Other cardioactive steroids - encountered as poisonings

2. Note: Naturally occurring glycosides that are not prescribed but which reach clinical attention through ingestion or exposure. They share the steroid-lactone-sugar structure and the same sodium-potassium ATPase mechanism, so they produce the same picture as digoxin overdose.

1. Name: Oleander glycosides

Nerium oleander

1. Route: Ingestion - not a therapeutic agent

1. Note: Oleander is named among the plant sources of cardioactive steroids, and ingestion produces cardiac glycoside toxicity. [2]

2. Name: Bufalin

Toad venom steroid

2. Route: Ingestion or exposure - not a therapeutic agent

2. Note: A cardioactive steroid present in toads of the class Amphibia, listed alongside the plant glycosides as a cause of the same toxidrome. [2]

3. Name: Ouabain

3. Route: Not in routine therapeutic use

3. Note: Obtained from plants of the genus *Acokanthera* and named among the naturally occurring cardiac glycosides. [2] [2]

Mechanism of action

Summary: Cardiac glycosides reversibly block the sodium-potassium ATPase pump in cardiac muscle. Sodium accumulates inside the cell, sodium-calcium exchange brings calcium in instead of removing it, and the extra calcium strengthens contraction. A separate parasympathetic action on the atrioventricular node prolongs its refractory period and slows conduction, so rate falls while force rises.

Target: Myocardial sodium-potassium ATPase, plus a vagomimetic action on the atrioventricular node

1. Step: 1

1. Title: The sodium-potassium pump normally resets the cell

1. Detail: This membrane pump exports sodium and imports potassium after each beat, maintaining the ionic gradients on which excitation and relaxation depend. [1][2]

2. Step: 2

2. Title: The glycoside binds and reversibly blocks it

2. Detail: With the pump inhibited, sodium is no longer removed efficiently and intracellular sodium concentration rises. [1]

3. Step: 3

3. Title: Sodium-calcium exchange brings calcium in

3. Detail: The exchanger that normally uses the inward sodium gradient to expel calcium works less effectively, so calcium accumulates inside the cell. [1][2]

4. Step: 4

4. Title: More calcium means a stronger contraction

4. Detail: The additional intracellular calcium enhances contractility, which is the positive inotropic effect that underlies the heart failure indication. [1]

5. Step: 5

5. Title: A separate vagal action slows the atrioventricular node

5. Detail: Stimulation of the parasympathetic nervous system prolongs the refractory period of the atrioventricular node and slows electrical conduction through it, which lowers the ventricular rate in atrial fibrillation. [1]

6. Step: 6

6. Title: The electrocardiogram records both effects

6. Detail: Long-term use produces a shortened QT interval, a prolonged PR interval and T wave flattening or inversion, with downsloping scooped ST segments described as the reverse tick appearance. [1]

7. Step: 7

7. Title: Beyond the therapeutic range the same mechanism causes arrhythmia

7. Detail: Increased cell excitability and a less negative resting potential generate afterdepolarisations and aftercontractions, so the drug becomes proarrhythmic and can produce ventricular tachyarrhythmias and ectopy. [2][1]

8. Step: 8

8. Title: Potassium competes for the same pump

8. Detail: Hypokalaemia, hypomagnesaemia and hypercalcaemia are each described as increasing susceptibility to digoxin's effects, so a given serum concentration can be tolerated at one electrolyte state and toxic at another. [1][2]

Major clinical uses

1. Drug: Digoxin
 1. Indication: Rate control in chronic atrial fibrillation
 1. Line: alternative
 1. Note: A licensed indication, but used when conventional first-line rate-controlling therapies have not worked; current practice treats digoxin as a backup option. [1]
2. Drug: Digoxin
 2. Indication: Symptomatic heart failure, particularly heart failure with reduced ejection fraction where the left ventricular ejection fraction is 40% or below
 2. Line: alternative
 2. Note: The benefit here is symptomatic rather than a substitute for prognostic therapy, and the drug sits behind first-line heart failure agents. [1]
3. Drug: Digoxin
 3. Indication: Off-label use in supraventricular tachycardia, including fetal supraventricular tachyarrhythmia
 3. Line: alternative
 3. Note: Digoxin crosses the placenta and produces similar serum concentrations in mother and newborn, which is what makes a transplacental approach possible. [1]
4. Drug: Digoxin immune Fab
 4. Indication: Severe or life-threatening cardiac glycoside toxicity, including life-threatening dysrhythmias, refractory hyperkalaemia and very high serum concentrations
 4. Line: first-line
 4. Note: Sheep-derived antibody fragments that bind digoxin with an affinity greater than that of the cardiac receptor. Given intravenously over a minimum of 30 minutes, with clinical improvement described within 45 minutes in 50% to 90% of patients. [3][2]
5. Drug: Lidocaine and phenytoin in glycoside toxicity
 5. Indication: Ventricular arrhythmias arising from cardiac glycoside toxicity
 5. Line: targeted
 5. Note: Atropine is described for bradycardia and a short-acting beta blocker for supraventricular tachycardia in this setting; magnesium is not recommended because it may worsen bradycardia and block. [2][1]

Pharmacokinetics

1. Drug: Digoxin
 1. Route: Oral/IV
 1. Absorption: Oral bioavailability approximately 75%, reduced by high-fibre foods
 1. Metabolism: Only about 13% of a dose is metabolised in healthy individuals
 1. Elimination: Excreted by the kidneys in direct proportion to the glomerular filtration rate
 1. Half Life: 36 to 48 hours in healthy adults, significantly prolonged in renal failure
 1. Dose Adjust: Renal impairment, interacting drugs and electrolyte disturbance all shift exposure or sensitivity; volume of distribution is roughly 475 to 500 litres and protein binding about 25% [1]
2. Drug: Digoxin immune Fab
 2. Route: IV
 2. Absorption: Given intravenously as a reconstituted lyophilised powder
 2. Metabolism: Acts by binding digoxin rather than by being metabolised for effect
 2. Elimination: Removes digoxin from receptor binding by shifting the equilibrium away from the cardiac sodium-potassium ATPase
 2. Half Life: Not the governing parameter; clinical improvement is described within 45 minutes in 50% to 90% of

patients

2. Dose Adjust: The infusion is described as being given over a minimum of 30 minutes, with the number of vials calculated from serum concentration and body weight [3]
1. Digoxin crosses the blood-brain barrier and the placenta, producing similar serum concentrations in mother and newborn. [1]
2. The described therapeutic serum range is 0.8 to 2 nanograms per millilitre, while 2013 ACC Foundation and AHA guidance recommends 0.5 to 0.9 for heart failure; risk rises above about 2, and above roughly 2.4 is regarded as toxic. [1][2]
3. Blood for a digoxin concentration is taken at least six to eight hours after the last dose, because the very large volume of distribution means an early sample reflects drug still moving into tissue rather than drug at its site of action. [1][2]
4. Concentrations do not always correlate with the severity of poisoning, so the clinical picture and the electrocardiogram carry weight alongside the number. [2]
5. After the antidote has been given, assays cannot separate free from bound drug, so an accurate concentration requires waiting about three weeks. [3]
6. Concentrations are described as being checked a week after starting treatment and regularly thereafter, alongside electrocardiograms, renal function and electrolytes. [1]
7. This page gives no dose regimens by design. Amounts depend on indication, renal function, body size, interacting drugs and measured concentrations, and belong in a prescribing reference used by the treating clinician.

Adverse effects

1. Effect: Gastrointestinal upset
 1. Detail: Nausea, vomiting and loss of appetite are the mild early symptoms and are often the first sign that concentrations have drifted too high. [1][2]
2. Effect: Visual disturbance
 2. Detail: Colour vision changes with a yellow or green tint, known as xanthopsia, together with photophobia, photopsia and reduced acuity. [1][2]
3. Effect: Neurological and general symptoms
 3. Detail: Confusion and weakness occur, and chronic toxicity produces lethargy, delirium and generalised weakness; headache, malaise and insomnia are also described. [1][2]
4. Effect: Bradycardia
 4. Detail: A predictable extension of the vagomimetic slowing of atrioventricular conduction, and amplified by beta blockers, calcium channel blockers and ivabradine. [1]
1. Effect: Proarrhythmia
 1. Detail: At toxic levels digoxin can produce almost every type of arrhythmia, including premature ventricular complexes as the most common, non-paroxysmal junctional tachycardia, ventricular fibrillation, sinoatrial and atrioventricular block, and bidirectional ventricular tachycardia as the pathognomonic rhythm.
 1. Action: Continuous cardiac monitoring with serial electrocardiograms; digoxin immune Fab is first-line for dysrhythmias caused by suspected toxicity. [2][1]
2. Effect: Hyperkalaemia in acute toxicity
 2. Detail: A significant marker of severity. In one study of acute ingestion, a serum potassium above 5.5 milliequivalents per litre predicted 100% mortality, 5.0 to 5.5 was associated with 50% mortality, and below 5.0 with none.
 2. Action: Life-threatening hyperkalaemia is treated with glucose and insulin; intravenous calcium is contraindicated in this setting. [2][1]
3. Effect: Toxicity precipitated by electrolyte change alone
 3. Detail: Hypokalaemia, hypomagnesaemia and hypercalcaemia increase susceptibility, so a patient on an unchanged prescription can become toxic after starting a loop diuretic or losing renal function.

3. Action: Regular electrolyte and renal function monitoring alongside concentration measurement. [1]
4. Effect: Severe glycoside poisoning
4. Detail: Approximately 20% mortality is reported for severe digoxin toxicity, and chronic toxicity from falling clearance is the form seen most often in practice.
4. Action: Supportive care with hydration and electrolyte repletion, activated charcoal in acute overdose, and digoxin immune Fab where criteria are met. [2][1]
5. Effect: Adverse effects of the antidote itself
5. Detail: Digoxin immune Fab is associated with hypokalaemia in about 13% of cases - because reactivated pumps move potassium back into cells - heart failure exacerbation in about 13%, worsening atrial fibrillation in about 7%, allergic reactions and serum sickness.
5. Action: Continuous electrocardiographic monitoring with hourly potassium for the first four to six hours, plus renal function, blood pressure and temperature. [3]
1. Drug: Digoxin
1. Effect: The classic triad of gastrointestinal upset, yellow-green visual disturbance and arrhythmia, on a background of a narrow therapeutic index and renal-dependent clearance. [1][2]
2. Drug: Oleander and other plant glycosides
2. Effect: Produce the same toxidrome as digoxin overdose, which is why a glycoside poisoning can present in someone who has never been prescribed the medicine. [2]
3. Drug: Digoxin immune Fab
3. Effect: Hypokalaemia, heart failure exacerbation, worsening atrial fibrillation, allergic reaction and serum sickness, plus assay interference that makes digoxin levels uninterpretable for about three weeks. [3]

Contraindications, precautions and interactions

1. Acute myocardial infarction. [1]
2. Ventricular fibrillation. [1]
3. Known hypersensitivity to the drug. [1]
4. Pre-excitation syndromes such as Wolff-Parkinson-White syndrome, and states of high sympathetic activity, are listed as situations in which digoxin is contraindicated. [1]
5. Intravenous calcium in a person who is digitalised, on the concern that rapid intravenous calcium can induce severe arrhythmias. [2][1]
1. Renal impairment, which prolongs the half-life and is the usual route to chronic toxicity. [1][2]
2. Bradycardia and atrioventricular block, both listed among the relative contraindications. [1]
3. Hypothyroidism and myocarditis, also named among the relative contraindications. [1]
4. Any electrolyte abnormality, particularly low potassium, low magnesium or high calcium. [1]
5. Concurrent loop diuretic therapy, which frequently supplies the hypokalaemia that amplifies risk. [1]
1. With: Amiodarone
1. Effect: Produces a notable rise in digoxin concentrations, potentially doubling them. [4]
2. With: Quinidine
2. Effect: May significantly increase serum digoxin levels, to the point that a substantial reduction in the digoxin amount is described as necessary. [1]
3. With: Macrolide antibiotics and azole antifungals
3. Effect: Inhibit P-glycoprotein, which can increase intestinal absorption of digoxin and raise its concentration. [1]
4. With: Beta blockers and calcium channel blockers
4. Effect: Potentiate digoxin's effect on atrioventricular conduction, increasing the risk of bradycardia and advanced or complete heart block. [1]
5. With: Class III antiarrhythmics such as sotalolol, dofetilide and dronedarone
5. Effect: Combined use increases arrhythmia risk. [1]

6. With: Ivabradine

6. Effect: Increases the risk of bradycardia when used at the same time as digoxin. [1]

7. With: Loop diuretics

7. Effect: Contribute to hypokalaemia, which amplifies digoxin's effect at any given concentration and therefore the risk of toxicity. [1]

8. With: Intravenous calcium

8. Effect: Given rapidly, calcium can induce severe arrhythmias in a digitalised patient, and its intravenous use is contraindicated. [1][2]

Comparison tables

1. Title: Acute versus chronic cardiac glycoside toxicity

1. Caption: The two presentations differ enough that treating them as one topic causes errors - most obviously about potassium. Management decisions rest with the treating clinician.

1. Key: feature

1. Label: Feature

1. Is Row Header: true

2. Key: acute

2. Label: Acute toxicity

3. Key: chronic

3. Label: Chronic toxicity

1. Feature: Typical setting

1. Acute: Ingestion without prior use, whether intentional or inadvertent

1. Chronic: Decreased clearance, usually renal insufficiency, without any extra dose [2]

2. Feature: Serum potassium

2. Acute: Raised, because the blocked sodium-potassium ATPase cannot return potassium into cells

2. Chronic: Often low, reflecting diuretic use and other contributing factors [2]

3. Feature: Frequency

3. Acute: Less common in clinical practice

3. Chronic: The form that predominates clinically [2]

4. Feature: Dominant symptoms

4. Acute: Prominent gastrointestinal upset with rapidly evolving arrhythmia

4. Chronic: Lethargy, delirium and generalised weakness alongside visual change and arrhythmia [2][1]

2. Title: Interactions that raise digoxin exposure or risk

2. Caption: Most clinically important digoxin interactions work by one of three routes: transporter inhibition, added nodal slowing, or potassium depletion.

1. Key: drug

1. Label: Interacting drug

1. Is Row Header: true

2. Key: route

2. Label: How it acts

3. Key: consequence

3. Label: Consequence

1. Drug: Amiodarone

1. Route: Raises digoxin concentration

1. Consequence: Concentrations can potentially double, so toxicity risk rises sharply [4]

2. Drug: Quinidine

2. Route: Raises digoxin concentration

2. Consequence: Serum levels may increase significantly, with a substantial reduction in digoxin described as necessary [1]
3. Drug: Macrolides and azole antifungals
3. Route: Inhibit P-glycoprotein
3. Consequence: Increased intestinal absorption and higher digoxin levels [1]
4. Drug: Beta blockers, calcium channel blockers, ivabradine
4. Route: Added slowing of rate and nodal conduction
4. Consequence: Bradycardia and advanced or complete heart block [1]
5. Drug: Loop diuretics
5. Route: Deplete potassium
5. Consequence: Hypokalaemia increases sensitivity to digoxin at an unchanged concentration [1]
6. Drug: Intravenous calcium
6. Route: Adds calcium to an already calcium-loaded myocyte
6. Consequence: Contraindicated; rapid intravenous administration can induce severe arrhythmias [1][2]

High-yield exam pearls

1. Pearl: One blocked pump produces both of digoxin's effects.
1. Why: Inhibiting the sodium-potassium ATPase raises intracellular sodium, which drives calcium in through sodium-calcium exchange and increases contractility. The separate vagomimetic action prolongs the refractory period of the atrioventricular node and slows the rate. [1]
2. Pearl: Potassium is digoxin's competitor, which is why low potassium is dangerous.
2. Why: Hypokalaemia, hypomagnesaemia and hypercalcaemia all increase susceptibility to digoxin's effects, and loop diuretics frequently supply the hypokalaemia. A concentration that was safe yesterday can be toxic once potassium falls. [1]
3. Pearl: Acute and chronic toxicity move potassium in opposite directions.
3. Why: Acute poisoning causes hyperkalaemia because the sodium-potassium pump is blocked and potassium cannot be moved back into cells; chronic toxicity often presents with hypokalaemia, because diuretics and other factors created the low potassium that precipitated it. [2]
4. Pearl: Bidirectional ventricular tachycardia is the giveaway rhythm.
4. Why: It is described as pathognomonic for cardiac glycoside toxicity, with the QRS axis alternating from beat to beat. Atrial tachycardia in a patient on digoxin is also highly suggestive. [2][1]
5. Pearl: The digoxin effect on the electrocardiogram is not the same as digoxin toxicity.
5. Why: Scooped, downsloping ST segments with a short QT interval and a long PR interval are the expected trace in someone taking the drug at therapeutic concentration. Toxicity is diagnosed from arrhythmia, symptoms and biochemistry, not from that repolarisation pattern alone. [1]
6. Pearl: The serum level is helpful but is not the diagnosis.
6. Why: Toxicity risk rises above about 2 nanograms per millilitre, yet it can occur at lower concentrations when risk factors are present, and serum levels do not always correlate with the severity of poisoning. Sampling is also timing-dependent because of the very large volume of distribution. [1][2]
7. Pearl: Calcium is the drug to withhold, not to give.
7. Why: Intravenous calcium is contraindicated in a digitalised patient. Rapid intravenous calcium can induce severe arrhythmias, and the classical concern is an irreversible non-contractile state described as stone heart, although clinical studies have questioned that risk. [2][1]
8. Pearl: After the antidote, the digoxin level stops meaning anything.
8. Why: Laboratory assays cannot distinguish free digoxin from digoxin bound to the antibody fragment, so measured concentrations read falsely high; accurate levels require waiting about three weeks after digoxin immune Fab has been given. [3]

Common exam traps

1. Trap: "Digoxin improves survival in heart failure, so it is a first-line drug."
1. Correction: The reference literature describes digoxin as reserved as a backup option in current practice, used when first-line agents are ineffective. Its licensed place is symptomatic management, particularly where the left ventricular ejection fraction is 40% or below. [1]
2. Trap: "Hyperkalaemia rules out digoxin toxicity because digoxin causes low potassium."
2. Correction: The relationship runs both ways. A high potassium is a significant marker of acute toxicity, while chronic toxicity typically arises against a low potassium caused by diuretics and reduced clearance. [1][2]
3. Trap: "Digoxin is a good choice for atrial fibrillation in Wolff-Parkinson-White syndrome."
3. Correction: Pre-excitation syndromes are listed among the situations in which digoxin is contraindicated, and Wolff-Parkinson-White syndrome appears among its relative contraindications. [1]
4. Trap: "Give calcium for the hyperkalaemia of digoxin poisoning, as in any other hyperkalaemia."
4. Correction: Intravenous calcium is contraindicated in people taking digoxin. Life-threatening hyperkalaemia in this setting is managed with glucose and insulin, and the definitive treatment for severe toxicity is digoxin immune Fab. [2][1]
5. Trap: "Magnesium helps in digoxin toxicity the way it helps in torsades."
5. Correction: In cardiac glycoside toxicity magnesium is not recommended, because it may worsen bradycardia and conduction block. That is the opposite of its role in drug-induced torsades de pointes. [2]
6. Trap: "A blood sample any time after the dose gives a usable digoxin level."
6. Correction: Digoxin has a very large volume of distribution, so blood taken too soon reflects drug still in transit rather than drug at the receptor. Sampling is described as taking place at least six to eight hours after the last dose. [1][2]
7. Trap: "Only prescription digoxin can cause glycoside poisoning."
7. Correction: Cardiac glycosides occur naturally in plants such as foxglove and oleander and in some amphibians. Ingestion of those sources produces the same toxidrome as an overdose of the medicine. [2]

Self-test questions

1. Question: How does digoxin increase the force of cardiac contraction?
 1. By stimulating beta-1 adrenergic receptors
 2. By reversibly inhibiting the sodium-potassium ATPase pump, which raises intracellular calcium
 3. By blocking L-type calcium channels
 4. By increasing cyclic AMP through phosphodiesterase inhibition1. Explanation: Digoxin reversibly inhibits the myocardial sodium-potassium ATPase pump. Intracellular sodium rises, which drives an influx of calcium into the heart muscle cell through sodium-calcium exchange, and the extra calcium enhances contractility. [1]
2. Question: How does digoxin slow the ventricular rate in atrial fibrillation?
 1. By blocking sodium channels in the atrium
 2. By direct blockade of the sinoatrial node
 3. By a vagomimetic effect that slows conduction through the atrioventricular node
 4. By shortening the atrial refractory period2. Explanation: Digoxin exerts vagomimetic effects on the atrioventricular node by stimulating the parasympathetic nervous system. This prolongs the node's refractory period, slows electrical conduction through it and therefore reduces the ventricular rate. [1]
3. Question: Which electrolyte disturbances increase susceptibility to digoxin toxicity?
 1. Hypokalaemia, hypomagnesaemia and hypercalcaemia
 2. Hyperkalaemia, hypermagnesaemia and hypocalcaemia
 3. Hyponatraemia alone

4. Hypophosphataemia alone

3. Explanation: Low potassium, low magnesium and high calcium all increase susceptibility to digoxin's effects. Loop diuretics frequently contribute to the hypokalaemia, which is why electrolyte monitoring is part of using the drug safely. [1]

4. Question: Which arrhythmia is described as pathognomonic for cardiac glycoside toxicity?

1. Atrial flutter with two-to-one conduction
2. Bidirectional ventricular tachycardia
3. Wenckebach second-degree heart block
4. Sinus arrhythmia

4. Explanation: Bidirectional ventricular tachycardia, in which the QRS complexes alternate from beat to beat, is described as pathognomonic for toxicity. Premature ventricular complexes are the most common rhythm disturbance, and digoxin can produce almost every type of arrhythmia. [2]

5. Question: What happens to serum potassium in acute cardiac glycoside poisoning?

1. It falls, because the pump pushes potassium into cells
2. It rises, because inhibition of the sodium-potassium ATPase blocks potassium re-entry into cells
3. It is unchanged
4. It rises only if the patient is also taking a diuretic

5. Explanation: Acute toxicity causes hyperkalaemia through inhibition of the sodium-potassium ATPase. Chronic toxicity is different: it commonly develops in a patient who is already hypokalaemic from diuretic use and reduced clearance. [2]

6. Question: Which visual symptom is classically linked to digoxin toxicity?

1. Sudden painless loss of vision in one eye
2. Yellow or green tinted vision, known as xanthopsia
3. Bitemporal hemianopia
4. Corneal microdeposits

6. Explanation: Colour vision change with a yellow or green tint, called xanthopsia, is typically associated with digoxin toxicity. Photophobia, photopsia and reduced visual acuity are also described, alongside gastrointestinal upset and confusion. [1][2]

7. Question: Why do serum digoxin measurements become unreliable after digoxin immune Fab is given?

1. Because the antidote destroys digoxin so no drug remains
2. Because laboratory assays cannot distinguish free digoxin from digoxin bound to the antibody fragment
3. Because the antidote interferes with the blood-gas analyser
4. Because digoxin is no longer renally excreted

7. Explanation: Assays cannot tell free digoxin from digoxin bound to the Fab fragment, so results read falsely high even though most of the measured drug is bound and cannot reach the cardiac sodium-potassium ATPase. Accurate levels require waiting about three weeks after administration. [3]

8. Question: Which treatment is contraindicated in a patient who is digitalised?

1. Intravenous calcium
2. Activated charcoal
3. Glucose and insulin
4. Atropine

8. Explanation: Intravenous administration of calcium is contraindicated in people taking digoxin, with rapid intravenous calcium capable of inducing severe arrhythmias. Activated charcoal, glucose with insulin for life-threatening hyperkalaemia, and atropine for bradycardia are all described within the management of toxicity. [2][1]

Frequently asked questions

1. Question: What does digoxin actually do to the heart?

1. Answer: Two things. It blocks the sodium-potassium pump in heart muscle, which indirectly raises intracellular calcium and makes each contraction stronger. Separately, it acts through the parasympathetic nervous system on the atrioventricular node, prolonging its refractory period and slowing conduction so the ventricular rate falls. [1]
2. Question: What does a narrow therapeutic index mean in practice here?
2. Answer: It means the concentration that helps and the concentration that harms are close together. Toxicity risk climbs above about 2 nanograms per millilitre, but it can occur below that when risk factors are present, and serum levels do not always match how ill the patient is. [1][2]
3. Question: Why does low potassium make digoxin more dangerous?
3. Answer: Low potassium is described as increasing susceptibility to digoxin's effects, so the same serum concentration produces a bigger effect once potassium falls. Low magnesium and high calcium increase susceptibility too, and loop diuretics are a common source of the low potassium. [1]
4. Question: What are the warning signs of digoxin toxicity?
4. Answer: Nausea, vomiting and loss of appetite come first in the mild picture, together with confusion and weakness. The distinctive visual sign is colour change with a yellow or green tint. On the electrocardiogram, almost any arrhythmia is possible, and bidirectional ventricular tachycardia is the pathognomonic one. [1][2]
5. Question: Why is renal function so important with digoxin?
5. Answer: Only about 13% of a dose is metabolised; the kidneys excrete the rest in direct proportion to the glomerular filtration rate. The half-life of 36 to 48 hours lengthens significantly in renal failure, so declining kidney function raises exposure without any change in prescription. [1]
6. Question: What is digoxin immune Fab?
6. Answer: It is the antidote: sheep-derived antibody fragments that bind digoxin far more tightly than the cardiac receptor does. Binding pulls digoxin away from the sodium-potassium ATPase and reduces cardiotoxic effects, and it is described as first-line for severe, life-threatening toxicity. [3][2]
7. Question: Why can a person be poisoned by a cardiac glycoside without ever taking digoxin?
7. Answer: Because these compounds are natural. They occur in plants including foxglove and oleander and in some amphibians, so ingestion of plant material or animal-derived preparations can reproduce the whole picture of digoxin overdose. [2]
8. Question: Is digoxin still a first-line drug?
8. Answer: No. The reference literature describes it as reserved as a backup option in current practice when first-line agents are ineffective. Safer alternatives exist for both rate control and heart failure, though digoxin remains relevant for selected patients. [1][2]

References

- [1] Digoxin (StatPearls). StatPearls Publishing / NCBI Bookshelf 2024. <https://www.ncbi.nlm.nih.gov/books/NBK556025/>
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