

Class I antiarrhythmics

Sodium channel blockers that depress phase 0 of the cardiac action potential, subdivided into Ia, Ib and Ic by how strongly and how quickly they bind the channel - a difference that changes the QT interval, the arrhythmia they suit and the proarrhythmia they carry.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/class-i-antiarrhythmics>

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Quick revision

One Liner: Class I agents block the fast sodium channels that drive phase 0 of the cardiac action potential, and the whole class is learnt through one question: how tightly and how fast does this particular drug bind, because that determines what happens to action potential duration, to the QT interval and to the risk of causing an arrhythmia rather than treating one.

1. Class I agents block the fast sodium channels responsible for phase 0 of the cardiac action potential, and the three subclasses differ in their effect on the phase 0 slope and on action potential duration. [1]
2. Class Ia produces moderate sodium channel blockade with intermediate kinetics, prolongs action potential duration and lengthens the QTc interval. [1]
3. Class Ib produces mild blockade with rapid kinetics, shortens action potential duration and shortens the QTc interval. [1]
4. Class Ic produces marked blockade with slow dissociation kinetics and does not alter action potential duration, so the QTc interval is left unchanged. [1]
5. The named agents are quinidine, procainamide and disopyramide in Ia; lidocaine and mexiletine in Ib; flecainide and propafenone in Ic. [1]
6. Class Ib agents act on ventricular arrhythmias, especially after myocardial infarction, and are not helpful for atrial arrhythmias. [1]
7. Class Ia agents are the most proarrhythmic of the sodium channel blockers because the QTc prolongation they cause brings torsades de pointes into the risk profile. [1]
8. The Cardiac Arrhythmia Suppression Trials showed increased mortality with class Ic agents in patients with a previous myocardial infarction compared with placebo. [1]
9. Class Ic agents are therefore contraindicated in structural heart disease and are not routinely prescribed where left ventricular dysfunction is present. [1]
10. Flecainide can convert atrial fibrillation into atrial flutter conducting one-to-one, so an atrioventricular nodal blocking agent is used alongside it. [2]
11. Quinidine causes cinchonism - tinnitus, hearing loss, visual disturbance and confusion - and can cause thrombocytopenia. [3]
12. Procainamide can induce a lupus-like syndrome and is also capable of bone marrow toxicity. [1][4]
13. Disopyramide carries anticholinergic effects such as dry skin, urinary retention and confusion, which is what usually limits its use. [1]
14. Every antiarrhythmic drug is potentially proarrhythmic, and intravenous administration is undertaken only with cardiac monitoring in place. [1]
15. In sodium channel blocker toxicity, sodium bicarbonate is described as the cornerstone of treatment. [7]

Overview

1. Class I antiarrhythmics are the sodium channel blockers of the Vaughan Williams system. They act on the fast sodium channels responsible for phase 0 of the cardiac action potential, and blocking those channels slows the rate at

which a myocardial cell depolarises. That single shared action is where the resemblance inside the class ends, because the three subclasses differ in the degree of blockade they produce, in the speed with which they associate with and dissociate from the channel, and consequently in what they do to action potential duration. [1]

2. Those kinetic differences translate directly into the surface electrocardiogram, which is why the subdivision is worth learning properly. Moderate blockade with intermediate kinetics in class Ia lengthens the action potential and the QTc interval. Mild blockade with rapid kinetics in class Ib shortens both. Marked blockade with slow dissociation in class Ic leaves action potential duration and the QTc interval unaltered, while the depressed upstroke shows itself as a broader QRS complex instead. [1][2]

3. The clinical indications follow the same logic. Class Ia agents are used across supraventricular and ventricular tachyarrhythmias and hold specific places in Brugada syndrome, short QT syndrome, hypertrophic obstructive cardiomyopathy and Wolff-Parkinson-White syndrome. Class Ib agents are reserved for ventricular arrhythmias, particularly after myocardial infarction. Class Ic agents are used for symptomatic supraventricular tachycardia, pharmacological cardioversion of atrial fibrillation and the pill-in-the-pocket strategy for paroxysmal atrial fibrillation - but only where the heart is structurally normal. [1]

4. Proarrhythmia is the theme that runs through the whole class, and it is not an incidental adverse effect but a property of the mechanism. Class Ia agents are described as the most proarrhythmic of the sodium channel blockers because of the QTc prolongation they produce. Class Ic agents carry the mortality signal from the Cardiac Arrhythmia Suppression Trials in patients with previous myocardial infarction. Every antiarrhythmic drug in this family is potentially proarrhythmic, and intravenous use is undertaken with cardiac monitoring for exactly that reason. [1]

Classification and drug examples

Intro: The Vaughan Williams system subdivides class I by sodium channel binding kinetics. Reading the subclass letter tells you the degree of blockade, the dissociation speed, the direction of change in action potential duration and therefore the expected movement in the QTc interval - four properties from one label.

1. Name: Class Ia - moderate blockade, intermediate kinetics

1. Note: Moderate blockade of the fast sodium channels with intermediate kinetics. These agents prolong action potential duration and lengthen the QTc interval, which is why they are described as the most proarrhythmic of the sodium channel blockers and why torsades de pointes belongs in their risk profile.

1. Name: Quinidine

1. Quinidine sulfate

2. Quinidine gluconate

1. Route: Oral/IV

1. Note: Inhibits the fast inward sodium current and depresses phase 0, prolonging both the QRS and the QTc interval, with a parasympatholytic effect that raises the sinus rate. Holds specific roles in Brugada syndrome and short QT syndrome. [3][1]

2. Name: Procainamide

2. Route: IV

2. Note: Binds fast sodium channels and inhibits their recovery after repolarisation, prolonging the action potential and slowing conduction while decreasing myocardial excitability and contractility. Used in Wolff-Parkinson-White syndrome with atrial fibrillation and to terminate ventricular tachycardia. [4][1]

3. Name: Disopyramide

3. Route: Oral

3. Note: The class Ia agent with prominent anticholinergic effects. Its distinctive place is in hypertrophic obstructive cardiomyopathy alongside a beta blocker or verapamil. [1] [1]

2. Name: Class Ib - mild blockade, rapid kinetics

2. Note: Mild blockade with the fastest dissociation of the three subclasses. These agents shorten action potential duration and shorten the QTc interval, and their usefulness is confined to ventricular arrhythmias; they are explicitly

described as unhelpful in atrial arrhythmias.

1. Name: Lidocaine

Lignocaine

1. Route: IV

1. Note: Slows the rise of the cardiac action potential during phase 0 and raises the effective threshold potential, stabilising sodium channels in their open and inactivated states. Given intravenously for acute ventricular tachyarrhythmias. [6]

2. Name: Mexiletine

2. Route: Oral

2. Note: The orally available class Ib agent. It shortens the QTc interval, which is the basis of its use in long QT syndrome as well as in ventricular arrhythmias. [1] [1]

3. Name: Class Ic - marked blockade, slow dissociation

3. Note: Marked blockade with slow dissociation kinetics. Action potential duration is unchanged and the QTc interval is untouched, but conduction is depressed enough to broaden the QRS complex. This is the subclass whose use is restricted to structurally normal hearts.

1. Name: Flecainide

1. Route: Oral/IV

1. Note: Preferentially binds the open and inactivated states of the sodium channel, producing state-dependent blockade with slow dissociation. Approved for paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, atrioventricular nodal reentrant tachycardia and for atrial fibrillation or flutter in patients without structural heart disease. [2]

2. Name: Propafenone

2. Route: Oral

2. Note: The second class Ic agent, carrying a boxed warning for proarrhythmia in structural heart disease and contraindicated in cardiogenic shock, sick sinus syndrome, atrioventricular block without a pacemaker and Brugada syndrome. [1] [1][2]

Mechanism of action

Summary: Class I agents block the fast sodium channels that generate phase 0 of the cardiac action potential, depressing the upstroke and slowing conduction; the subclass is determined by how strongly the drug binds and how quickly it lets go, which decides whether action potential duration lengthens, shortens or stays the same.

Target: Fast voltage-gated sodium channels of cardiac myocytes and conducting tissue

1. Step: 1

1. Title: Sodium influx normally generates phase 0

1. Detail: Rapid inward movement of sodium through fast voltage-gated channels produces the steep upstroke of the cardiac action potential, and the slope and amplitude of that upstroke set the conduction velocity of the tissue. [1][7]

2. Step: 2

2. Title: The drug occupies the channel and depresses the upstroke

2. Detail: Blockade decreases the slope and amplitude of phase 0, so cells depolarise more slowly and conduction velocity is reduced. Excitability falls with it. [7][4]

3. Step: 3

3. Title: Binding is state-dependent, which is why the effect is rate-dependent

3. Detail: Class I agents preferentially bind the open and inactivated conformations of the channel rather than the resting one, producing use-dependent blockade that bites hardest in tissue that is depolarising rapidly. [2][6]

4. Step: 4

4. Title: Dissociation speed sorts the drugs into subclasses

4. Detail: Rapid dissociation defines class Ib, intermediate kinetics define class Ia and slow dissociation defines class

Ic. The same channel is blocked in each case; the time course of that blockade is what differs. [1][2]

5. Step: 5

5. Title: Action potential duration moves in three different directions

5. Detail: Class Ia prolongs action potential duration and so lengthens the QTc interval, class Ib shortens it and so shortens the QTc, and class Ic leaves it unaltered so the QTc interval does not change. [1]

6. Step: 6

6. Title: The electrocardiogram shows which mechanism is dominant

6. Detail: Depressed conduction broadens the QRS complex, most conspicuously with class Ic, while prolonged repolarisation lengthens the QT interval, which is the class Ia signature. [2][1]

7. Step: 7

7. Title: The same mechanism generates arrhythmia as well as suppressing it

7. Detail: Slowed conduction and altered repolarisation can create the conditions for reentry or for triggered activity, so proarrhythmia is intrinsic to the class rather than incidental to it, and excessive blockade in overdose produces QRS widening, bradycardias, ventricular tachycardia, ventricular fibrillation or torsades de pointes. [1][7]

Major clinical uses

1. Drug: Quinidine

1. Indication: Brugada syndrome as an alternative to an implantable defibrillator, and short QT syndrome with recurrent ventricular arrhythmias

1. Line: targeted

1. Note: Also used for conversion of atrial fibrillation or flutter and for prevention of relapse, and for suppression of ventricular arrhythmias. Electrocardiographic and haematological monitoring accompany its use. [1][3]

2. Drug: Procainamide

2. Indication: Wolff-Parkinson-White syndrome with atrial fibrillation in the absence of haemodynamic instability, and termination of ventricular tachycardia

2. Line: targeted

2. Note: Given intravenously because its principal role is acute treatment. Widening of the QRS complex during the infusion is the signal to stop. [1][4]

3. Drug: Disopyramide

3. Indication: Hypertrophic obstructive cardiomyopathy, combined with a beta blocker or with verapamil

3. Line: targeted

3. Note: Anticholinergic burden - dry skin, urinary retention and confusion - is what usually restricts its use, and matters most in older patients. [1]

4. Drug: Lidocaine

4. Indication: Acute ventricular tachyarrhythmias, including haemodynamically stable sustained monomorphic ventricular tachycardia

4. Line: targeted

4. Note: Also considered for ventricular fibrillation or pulseless ventricular tachycardia that has not responded to defibrillation. It has no useful role in atrial arrhythmias. [6][1]

5. Drug: Mexiletine

5. Indication: Ventricular arrhythmias, and long QT syndrome where shortening of the QTc interval is wanted

5. Line: targeted

5. Note: The orally available member of class Ib, sharing the ventricular-only profile of the subclass. [1]

6. Drug: Flecainide

6. Indication: Paroxysmal supraventricular tachycardia, atrioventricular nodal reentrant tachycardia, Wolff-Parkinson-White syndrome, and atrial fibrillation or flutter in patients without structural heart disease

6. Line: targeted

- 6. Note: Off-label roles include long QT syndrome type 3, catecholaminergic polymorphic ventricular tachycardia and Andersen-Tawil syndrome. An atrioventricular nodal blocking agent accompanies it in atrial arrhythmias. [2]
- 7. Drug: Propafenone
- 7. Indication: Symptomatic supraventricular tachycardia and pharmacological cardioversion of atrial fibrillation in a structurally normal heart
- 7. Line: targeted
- 7. Note: Carries a boxed warning for proarrhythmia where structural heart disease is present. [1]
- 8. Drug: Class Ic agents as a group
- 8. Indication: Pill-in-the-pocket strategy for paroxysmal atrial fibrillation, selected premature ventricular contractions and catecholaminergic polymorphic ventricular tachycardia
- 8. Line: targeted
- 8. Note: Every one of these uses assumes an absence of structural heart disease; the subclass is not routinely prescribed where left ventricular dysfunction exists. [1]

Pharmacokinetics

- 1. Drug: Flecainide
- 1. Route: Oral/IV
- 1. Absorption: Well absorbed orally, supporting the pill-in-the-pocket strategy
- 1. Metabolism: Hepatic via the cytochrome P450 system; a CYP2D6 substrate, so metabolism varies with genetic polymorphism
- 1. Elimination: Partly urinary as unchanged drug, with caution required in renal impairment
- 1. Half Life: Long enough in adults for regular oral administration, and age-dependent - shortest in young children
- 1. Dose Adjust: Renal or hepatic impairment; CYP2D6 metaboliser status alters exposure [2]
- 2. Drug: Lidocaine
- 2. Route: IV
- 2. Absorption: Given intravenously for its antiarrhythmic indication, so oral absorption does not apply
- 2. Metabolism: Hepatic, by CYP1A2 and CYP3A4, producing the metabolites monoethylglycinexylidide and glycinexylidide
- 2. Elimination: Renal excretion of metabolites
- 2. Half Life: Short, which is why it is given as an infusion rather than intermittently
- 2. Dose Adjust: Hepatic impairment and reduced hepatic blood flow reduce clearance [6]
- 3. Drug: Procainamide
- 3. Route: IV
- 3. Absorption: Administered intravenously because its use is acute
- 3. Metabolism: Hepatic, by acetylation to N-acetylprocainamide
- 3. Elimination: Renal excretion of the drug and its principal metabolite
- 3. Half Life: See a current prescribing reference
- 3. Dose Adjust: Hepatic impairment; caution in heart failure, electrolyte disturbance, myasthenia gravis and renal impairment [4]
- 4. Drug: Quinidine
- 4. Route: Oral/IV
- 4. Absorption: Available in oral salts as well as parenterally
- 4. Metabolism: Hepatic, and susceptible to enzyme induction - phenobarbital and phenytoin halve its half-life
- 4. Elimination: See a current prescribing reference
- 4. Half Life: Shortened markedly by enzyme-inducing drugs
- 4. Dose Adjust: Interacting drugs, particularly enzyme inducers, erythromycin and other QT-prolonging agents [3]
- 1. Route follows acuity within this class: procainamide and lidocaine are given intravenously because their primary use

- is acute treatment, while flecainide, propafenone, mexiletine, quinidine and disopyramide have oral roles. [1]
- 2. Intravenous administration of any antiarrhythmic in this family is undertaken only under cardiac monitoring, because all of them are potentially proarrhythmic. [1]
- 3. The Bazett formula overestimates the corrected QT interval during atrial fibrillation, which can lead to unnecessary reduction of antiarrhythmic exposure and loss of efficacy. [1]
- 4. This page gives no dose regimens by design. Doses depend on indication, formulation, comorbidity, renal and hepatic function and metaboliser status, and belong in a prescribing reference used by the treating clinician.

Adverse effects

- 1. Effect: Dizziness and visual disturbance
 - 1. Detail: Reported with flecainide alongside dyspnoea, palpitations, chest pain, tremor, asthenia, abdominal pain and constipation. [2]
- 2. Effect: Gastrointestinal upset
 - 2. Detail: Diarrhoea and nausea are described with quinidine, and gastrointestinal symptoms are a common reason the class is poorly tolerated. [3]
- 3. Effect: Central nervous system effects
 - 3. Detail: Dizziness, fatigue and ataxia occur with quinidine. [3]
- 4. Effect: Anticholinergic effects
 - 4. Detail: Dry skin, urinary retention and confusion characterise disopyramide. [1]
- 5. Effect: Negative inotropy
 - 5. Detail: A feature of the class Ia and class Ic agents rather than of class I as a whole. Procainamide decreases both excitability and contractility and flecainide is described as having negative inotropic effects, whereas lidocaine, a class Ib agent, produces no change in myocardial contractility at usual therapeutic doses. [4][2][5]
- 1. Effect: Proarrhythmia
 - 1. Detail: Every antiarrhythmic drug is potentially proarrhythmic, and the class Ia agents are described as the most proarrhythmic of the sodium channel blockers because they prolong the QTc interval.
 - 1. Action: Intravenous administration takes place under cardiac monitoring, and the QT interval is checked before and after starting a class Ia agent. [1]
- 2. Effect: Torsades de pointes
 - 2. Detail: Quinidine, procainamide and disopyramide prolong the QTc interval and thereby raise the risk of this polymorphic ventricular tachycardia.
 - 2. Action: Electrocardiographic surveillance with correction of potassium and magnesium; concurrent QT-prolonging drugs are avoided. [1][3]
- 3. Effect: Excess mortality with class Ic agents after myocardial infarction
 - 3. Detail: The Cardiac Arrhythmia Suppression Trials found higher mortality in post-infarct patients treated with flecainide, encainide or moricizine than with placebo.
 - 3. Action: Class Ic agents are not used where structural heart disease, ischaemic heart disease or heart failure is present. [1][2]
- 4. Effect: Drug-induced lupus erythematosus
 - 4. Detail: Procainamide can produce positive antinuclear antibody titres with chronic use, presenting with arthritis, arthralgias and pleuritis.
 - 4. Action: The reaction prompts reassessment of the drug by the treating clinician. [1][4]
- 5. Effect: Bone marrow toxicity
 - 5. Detail: Agranulocytosis and pancytopenia are described with procainamide, and quinidine can cause thrombocytopenia.
 - 5. Action: Full blood count monitoring accompanies chronic therapy. [4][3]
- 6. Effect: Sodium channel blocker toxicity in overdose

6. Detail: Presents with a widened QRS complex, lengthened QT interval, new right axis deviation, bradydysrhythmias, ventricular tachycardia, ventricular fibrillation or torsades de pointes.

6. Action: Sodium bicarbonate is the cornerstone of treatment, working by raising serum pH and increasing extracellular sodium. [7]

7. Effect: Local anaesthetic systemic toxicity

7. Detail: Lidocaine toxicity begins neurologically with slurred speech, tinnitus and circumoral paraesthesia and can progress to seizures or loss of consciousness, with cardiovascular effects at higher concentrations.

7. Action: Recognition of the early neurological features is what allows the infusion to be stopped before cardiovascular collapse. [6]

1. Drug: Quinidine

1. Effect: Cinchonism - tinnitus, hearing loss, visual disturbance and confusion - together with thrombocytopenia and hypersensitivity-mediated hepatotoxicity. [3]

2. Drug: Procainamide

2. Effect: A lupus-like syndrome and bone marrow toxicity, the two reactions that define its long-term tolerability problem. [4][1]

3. Drug: Disopyramide

3. Effect: Anticholinergic toxicity, and depressed contractility that is exploited therapeutically in hypertrophic obstructive cardiomyopathy but is a liability elsewhere. [1]

4. Drug: Flecainide

4. Effect: Conversion of atrial fibrillation to atrial flutter with one-to-one atrioventricular conduction, and arrhythmias as a listed adverse reaction in their own right. [2]

5. Drug: Propafenone

5. Effect: Boxed warning for proarrhythmia in patients with structural heart disease. [1]

Contraindications, precautions and interactions

1. Class Ic agents in structural heart disease, ischaemic heart disease or heart failure. [2][1]

2. Flecainide after a recent myocardial infarction, and in chronic atrial fibrillation. [2]

3. Class Ic agents in cardiogenic shock, sick sinus syndrome, atrioventricular block without a pacemaker, and Brugada syndrome. [1]

4. Procainamide in complete heart block. [1]

5. Quinidine in heart block beyond first degree, in congenital long QT interval, in thrombocytopenic purpura and where there is hypersensitivity to quinine or mefloquine. [3]

6. Lidocaine where there is hypersensitivity to amide-type anaesthetics. [1]

7. Pre-existing conduction abnormalities, for flecainide. [2]

1. Heart failure, electrolyte disturbance, myasthenia gravis and hepatic or renal impairment, for procainamide. [4]

2. Reduced renal function for flecainide, where clearance of the unchanged drug falls. [2]

3. Hypokalaemia and hypomagnesaemia, which lower the threshold for QT-related arrhythmia across the class Ia agents. [3]

4. Older patients taking disopyramide, in whom urinary retention and confusion carry more consequence. [1]

5. Atrial fibrillation itself distorts QT assessment, because the Bazett formula overestimates the corrected interval in that rhythm. [1]

1. With: Digoxin

1. Effect: Quinidine reduces the total clearance of digoxin, raising digoxin exposure and the risk of toxicity. [3]

2. With: Other QT-prolonging drugs such as clarithromycin or amiodarone

2. Effect: Additive prolongation of the QT interval with a correspondingly higher risk of torsades de pointes when combined with a class Ia agent. [3]

3. With: Enzyme inducers such as phenobarbital or phenytoin

3. Effect: Halve the half-life of quinidine, reducing exposure and therapeutic effect. [3]
4. With: Erythromycin
4. Effect: Decreases quinidine clearance and so increases the risk of quinidine toxicity. [3]
5. With: CYP2D6 inhibitors
5. Effect: Flecainide is a CYP2D6 substrate, so inhibition of that enzyme raises its plasma concentration and with it the proarrhythmic risk. [2]
6. With: Atrioventricular nodal blocking agents
6. Effect: A beta blocker or a calcium channel blocker is used deliberately with flecainide in atrial arrhythmias to prevent one-to-one conduction of a flutter the drug itself may generate. [2]
7. With: Other sodium channel blocking drugs such as tricyclic antidepressants, carbamazepine or cocaine
7. Effect: Additive sodium channel blockade, with a widened QRS complex and the associated dysrhythmia risk. [7]

Comparison tables

1. Title: Class Ia, Ib and Ic side by side
1. Caption: Binding kinetics decide everything downstream - action potential duration, the QTc interval and the arrhythmia the subclass suits. Actual therapy is governed by a current prescribing reference.
1. Key: subclass
1. Label: Subclass
1. Is Row Header: true
2. Key: binding
2. Label: Sodium channel blockade and kinetics
3. Key: apd
3. Label: Action potential duration and QTc
4. Key: drugs
4. Label: Named drugs
5. Key: use
5. Label: Characteristic use
1. Subclass: Class Ia
1. Binding: Moderate blockade, intermediate kinetics
1. Apd: Prolonged; QTc lengthens
1. Drugs: Quinidine, procainamide, disopyramide
1. Use: Supraventricular and ventricular tachyarrhythmias, Brugada syndrome, short QT syndrome, hypertrophic obstructive cardiomyopathy [1]
2. Subclass: Class Ib
2. Binding: Mild blockade, rapid kinetics with the fastest dissociation
2. Apd: Shortened; QTc shortens
2. Drugs: Lidocaine, mexiletine
2. Use: Ventricular arrhythmias, especially after myocardial infarction; no role in atrial arrhythmias [1]
3. Subclass: Class Ic
3. Binding: Marked blockade, slow dissociation
3. Apd: Unchanged; QTc unchanged, QRS broadens
3. Drugs: Flecainide, propafenone
3. Use: Supraventricular tachycardia and atrial fibrillation in a structurally normal heart only [1][2]
2. Title: The signature toxicity of each agent
2. Caption: Examiners test the drug-specific reaction rather than the shared ones. Recognition prompts review by the treating clinician, not self-directed change.
1. Key: drug

1. Label: Drug
1. Is Row Header: true
2. Key: subclass
2. Label: Subclass
3. Key: toxicity
3. Label: Signature toxicity
1. Drug: Quinidine
1. Subclass: Ia
1. Toxicity: Cinchonism, thrombocytopenia and torsades de pointes [3]
2. Drug: Procainamide
2. Subclass: Ia
2. Toxicity: Drug-induced lupus erythematosus and bone marrow toxicity [4]
3. Drug: Disopyramide
3. Subclass: Ia
3. Toxicity: Anticholinergic effects and depressed contractility [1]
4. Drug: Lidocaine
4. Subclass: Ib
4. Toxicity: Neurological toxicity progressing to seizures at higher concentrations [6]
5. Drug: Flecainide
5. Subclass: Ic
5. Toxicity: Proarrhythmia in structural heart disease, and atrial flutter with one-to-one conduction [2]
6. Drug: Propafenone
6. Subclass: Ic
6. Toxicity: Boxed warning for proarrhythmia in structural heart disease [1]

High-yield exam pearls

1. Pearl: The subclass letter predicts what the QT interval does.
1. Why: Class Ia lengthens the QTc because it prolongs action potential duration, class Ib shortens the QTc because it shortens action potential duration, and class Ic leaves the QTc alone because it does not change action potential duration at all. [1]
2. Pearl: Binding kinetics, not binding site, separate the subclasses.
2. Why: All three subclasses act on the same fast sodium channel; Ia binds moderately with intermediate kinetics, Ib binds mildly and dissociates fastest, and Ic binds markedly and dissociates slowly. [1]
3. Pearl: Class Ic widens the QRS complex without touching the QT interval.
3. Why: Slow dissociation from open and inactivated sodium channels markedly reduces the maximal upstroke velocity, which broadens the QRS while leaving repolarisation essentially untouched. [2]
4. Pearl: A structurally normal heart is the precondition for class Ic use.
4. Why: The Cardiac Arrhythmia Suppression Trials found excess mortality in post-infarct patients given class Ic agents, which is why structural heart disease, ischaemic heart disease and heart failure now sit on the contraindication list. [1][2]
5. Pearl: Quinidine is used in Brugada syndrome; class Ic is contraindicated in it.
5. Why: Quinidine is described as an alternative to an implantable defibrillator in Brugada syndrome and is also used in short QT syndrome with recurrent ventricular arrhythmias, whereas Brugada syndrome appears on the contraindication list for class Ic agents. [1]
6. Pearl: Disopyramide has a niche that comes from its negative inotropy.
6. Why: It is used in hypertrophic obstructive cardiomyopathy in combination with a beta blocker or with verapamil, a use that follows from depressed contractility rather than from rhythm control alone. [1]

7. Pearl: Class Ib is a ventricular story only.

7. Why: Lidocaine and mexiletine are directed at ventricular arrhythmias, particularly after myocardial infarction, and are explicitly described as unhelpful in atrial arrhythmias; mexiletine additionally shortens the QTc in long QT syndrome. [1]

8. Pearl: The overdose picture is a wide QRS complex, and the answer is alkalinisation.

8. Why: Sodium channel blocker toxicity produces QRS widening, QT lengthening, a new right axis deviation and ventricular dysrhythmias, and sodium bicarbonate works by raising serum pH and increasing extracellular sodium so that the electrochemical gradient offloads the blocked channels. [7]

Common exam traps

1. Trap: "All class I agents prolong the QT interval."

1. Correction: Only class Ia does. Class Ib shortens the QTc interval and class Ic does not affect it, because the three subclasses act differently on action potential duration. [1]

2. Trap: "Flecainide is a reasonable choice after a myocardial infarction."

2. Correction: It is the opposite. Flecainide was associated with increased mortality from fatal arrhythmias in post-infarct patients in the Cardiac Arrhythmia Suppression Trial, and it should not be used after a recent myocardial infarction. [2]

3. Trap: "Flecainide alone is enough to control atrial fibrillation."

3. Correction: Given alone it can convert atrial fibrillation into atrial flutter conducted one-to-one, so a beta blocker or a calcium channel blocker is used concurrently to block the atrioventricular node. [2]

4. Trap: "Lidocaine is a general-purpose antiarrhythmic."

4. Correction: Its antiarrhythmic role is in acute ventricular tachyarrhythmias, including haemodynamically stable sustained monomorphic ventricular tachycardia, and class Ib agents are not helpful in atrial arrhythmias. [6][1]

5. Trap: "Cinchonism is a malaria phenomenon that has nothing to do with cardiology."

5. Correction: Quinidine, a class Ia antiarrhythmic, produces cinchonism with tinnitus, hearing loss, visual disturbance and confusion, so the syndrome belongs in the antiarrhythmic adverse effect list too. [3]

6. Trap: "Drug-induced lupus from procainamide means the drug is simply stopped and forgotten."

6. Correction: Procainamide can also cause bone marrow toxicity including agranulocytosis and pancytopenia, so haematological surveillance matters alongside the antinuclear antibody story. [4]

Self-test questions

1. Question: Which statement correctly matches a class I subclass to its effect on the QTc interval?

1. Class Ia shortens the QTc, class Ib prolongs it, class Ic prolongs it
2. Class Ia prolongs the QTc, class Ib shortens it, class Ic does not affect it
3. All three subclasses prolong the QTc to the same degree
4. None of the class I subclasses has any effect on repolarisation

1. Explanation: Class Ia prolongs action potential duration and therefore increases the QTc interval. Class Ib decreases action potential duration and shortens the QTc. Class Ic does not affect action potential duration, so it leaves the QTc interval unchanged. [1]

2. Question: What did the Cardiac Arrhythmia Suppression Trials demonstrate about class Ic agents?

1. They abolished all ventricular ectopy without any change in outcome
2. They reduced mortality in patients with a previous myocardial infarction
3. They increased mortality in patients with a previous myocardial infarction compared with placebo
4. They were shown to be superior to implantable defibrillators

2. Explanation: The Cardiac Arrhythmia Suppression Trials showed increased mortality in patients who had a previous myocardial infarction and were treated with class Ic agents rather than placebo. That result is the reason class Ic agents are contraindicated in structural heart disease and are avoided where left ventricular dysfunction is present. [1]

3. Question: Why is an atrioventricular nodal blocking agent used alongside flecainide in atrial fibrillation or flutter?

1. Because flecainide is inactivated in the stomach unless another drug is present

2. Because flecainide can convert atrial fibrillation to atrial flutter with one-to-one conduction
3. Because flecainide has no effect on the atrium by itself
4. Because the combination is required to prevent cinchonism
3. Explanation: Flecainide can convert atrial fibrillation into atrial flutter that conducts one-to-one through the atrioventricular node, producing a dangerously fast ventricular response. A beta blocker or a calcium channel blocker is therefore used concurrently to slow nodal conduction. [2]
4. Question: Which agents are the class Ib representatives, and what are they used for?
1. Quinidine and disopyramide, used for supraventricular tachyarrhythmias
2. Flecainide and propafenone, used for pharmacological cardioversion of atrial fibrillation
3. Lidocaine and mexiletine, used for ventricular arrhythmias especially after myocardial infarction
4. Amiodarone and sotalolol, used for maintenance of sinus rhythm
4. Explanation: Class Ib comprises lidocaine and mexiletine. These agents cause mild sodium channel blockade with rapid kinetics, shorten the QTc interval and are directed at ventricular arrhythmias, particularly in the post-infarct setting. They are not helpful for atrial arrhythmias. [1]
5. Question: A patient taking a class Ia antiarrhythmic develops tinnitus, hearing loss, visual disturbance and confusion. Which drug and syndrome does this suggest?
1. Procainamide causing drug-induced lupus
2. Quinidine causing cinchonism
3. Disopyramide causing anticholinergic toxicity
4. Lidocaine causing local anaesthetic systemic toxicity
5. Explanation: Cinchonism is the recognised quinidine adverse effect and presents with tinnitus, hearing loss, vision disturbance and confusion. Drug-induced lupus points to procainamide, anticholinergic features such as dry skin and urinary retention point to disopyramide, and the class Ib toxicity picture is different again. [3][1]
6. Question: Which distinctive haematological adverse effect is associated with procainamide?
1. Bone marrow toxicity, including agranulocytosis and pancytopenia
2. Polycythaemia
3. Iron overload
4. Methaemoglobinaemia as the defining reaction
6. Explanation: Procainamide is known to cause bone marrow toxicity, with agranulocytosis and pancytopenia described. It is separately associated with a lupus-like reaction featuring positive antinuclear antibody titres, arthritis, arthralgias and pleuritis on chronic use. [4]
7. Question: What is described as the cornerstone of treatment in sodium channel blocker toxicity?
1. Intravenous calcium gluconate
2. Sodium bicarbonate
3. Naloxone
4. Flumazenil
7. Explanation: Sodium bicarbonate is the cornerstone of treatment for sodium channel blocker toxicity. It raises serum pH and increases extracellular sodium, which widens the electrochemical gradient across the cell membrane and helps to offload the blocked sodium channels. [7]
8. Question: Which class Ia agent is used in hypertrophic obstructive cardiomyopathy in combination with a beta blocker or verapamil?
1. Quinidine
2. Procainamide
3. Disopyramide
4. Mexiletine
8. Explanation: Disopyramide is the class Ia agent described for hypertrophic obstructive cardiomyopathy, used together with a beta blocker or with verapamil. Quinidine's distinctive indications are Brugada syndrome and short QT

syndrome, while procainamide features in Wolff-Parkinson-White syndrome with atrial fibrillation and in terminating ventricular tachycardia. [1]

Frequently asked questions

1. Question: What actually separates class Ia, Ib and Ic?

1. Answer: All three block the fast sodium channel that generates phase 0, but they differ in the degree of blockade and in their binding kinetics. Class Ia is moderate with intermediate kinetics, class Ib is mild with rapid kinetics, and class Ic is marked with slow dissociation. Those kinetics decide whether action potential duration lengthens, shortens or stays the same. [1]

2. Question: Why are class Ic agents avoided in structural heart disease?

2. Answer: Because the Cardiac Arrhythmia Suppression Trials showed increased mortality in patients with a previous myocardial infarction who received class Ic agents rather than placebo. Flecainide specifically was associated with increased mortality from fatal arrhythmias in that population, and the subclass is now restricted to structurally normal hearts. [1][2]

3. Question: Why is a beta blocker or calcium channel blocker given with flecainide?

3. Answer: Flecainide can convert atrial fibrillation into atrial flutter that conducts one-to-one across the atrioventricular node. Blocking that node concurrently prevents the resulting very rapid ventricular rate. [2]

4. Question: Do class I agents work in atrial arrhythmias?

4. Answer: Class Ia and class Ic agents do have atrial roles, including cardioversion and relapse prevention in atrial fibrillation. Class Ib agents do not; lidocaine and mexiletine are described as unhelpful in atrial arrhythmias and are used for ventricular rhythms. [1]

5. Question: What is cinchonism?

5. Answer: It is the toxicity syndrome produced by quinoline derivatives such as quinidine, and it presents with tinnitus, hearing loss, visual disturbance and confusion. Quinidine is a class Ia antiarrhythmic as well as an antimalarial, so the syndrome appears in cardiology teaching too. [3]

6. Question: How is class I overdose recognised and treated?

6. Answer: Sodium channel blocker toxicity shows itself on the electrocardiogram as a widened QRS complex, a lengthened QT interval, a new right axis deviation and ventricular dysrhythmias. Sodium bicarbonate is described as the cornerstone of treatment, raising serum pH and increasing extracellular sodium so that blocked channels are offloaded. [7]

7. Question: Why does quinidine raise digoxin levels?

7. Answer: Quinidine reduces the total clearance of digoxin, so digoxin exposure rises when the two are combined. Given digoxin's narrow therapeutic index, that interaction is one of the classic examinable pairs. [3]

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treatment.