Antiarrhythmic Agents – Class I Drugs

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Adapted from: Antiarrhythmic Drugs (Classes I and III)

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Learning Objectives (3) Versions

After completing this brick, you will be able to:

1. Explain the mechanism of action of Class I antiarrhythmic agents.
2. Explain the changes in action potential and the associated ECG changes with Class I antiarrhythmic agents.
3. Recognize the adverse effects of Class I antiarrhythmic agents.

CASE CONNECTION

"She's in v-tach!" the telemetry nurse yells. "Call a code!" The nurse is referring to PT, a 56-year-old female admitted with syncope. PT is successfully cardioverted to normal rhythm. "She's going to need a stress test and a coronary artery

catheterization," the intern on the team says, but you're not so sure. In reviewing PT's chart, you saw her longstanding history of ventricular arrhythmias and QTc prolongation on ECG and that she was given procainamide earlier in the emergency department visit after an initial episode of ventricular tachycardia. You wonder whether changing PT's antiarrhythmic medication and reassessing the ECG changes could avoid unnecessary cardiac testing.

What caused PT's second episode of ventricular tachycardia? How would you approach her care differently? Consider your answers as you read, and we'll revisit PT at the end of the brick.

GO TO CONCLUSION ↓

What Are Antiarrhythmic Drugs? (LO#1)

Antiarrhythmic drugs work on the electrical conduction system of the heart to treat arrhythmias (abnormal cardiac rhythms). This makes them vital in treating and preventing potentially lethal complications of many cardiac disorders, including myocardial infarction (MI), as well as in the resuscitation of patients with sudden cardiac arrest.

Learning these drugs can be daunting, but if we focus on the nodal and cardiac myocyte action potentials, this task is much more manageable.

Classifying Arrhythmias

Although an oversimplification, the Vaughan-Williams classification is a useful tool to classify the different types of antiarrhythmic agents by their mechanism into four classes:

- **Class I, sodium (Na^+)-channel blockers:** these agents are further divided into subclasses A, B, and C. They block fast Na^+ channels within

cardiac myocytes to slow conduction velocity.

- **Class II, β-blockers:** these agents primarily affect slow-channel tissues in nodal cells by blocking sympathetic input.
- **Class III, potassium (K^+)-channel blockers:** these agents act on the K^+ channels in cardiac myocytes to prolong the length of cell repolarization.
- **Class IV, calcium (Ca^{2+})-channel blockers:** these agents work on nodal cells to prolong the action potential.

Here, we'll focus on class I antiarrhythmic drugs that affect the action potential of nonpacemaker cardiac myocytes. Note that classes II and IV antiarrhythmics block the action potential of cardiac pacemaker cells.

repolarization.

because they act on the K_+ channels that regulate cellular

Class III antiarrhythmics prolong the length of cell repolarization

Normal Cardiac Myocyte/Fast-Type Action Potential

Classes I and III antiarrhythmic drugs act mainly by affecting the nonpacemaker cardiac myocyte action potentials. Before describing these effects in more detail, let's first review the cardiac action potential (Figure 1).

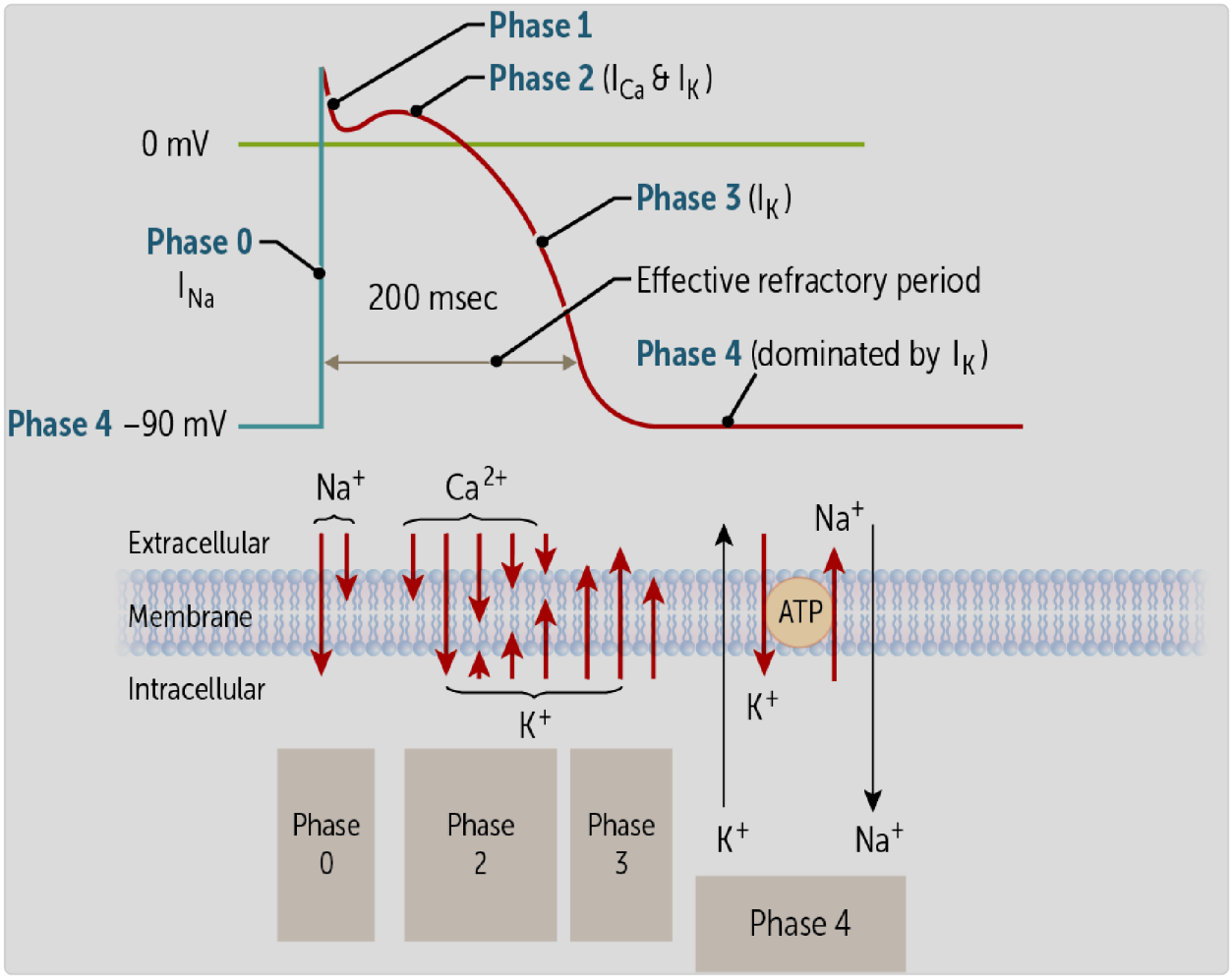


Figure 1 Action potential of cardiac myocytes

The five phases of the nonpacemaker myocyte action potential include:

- Phase 0: Rapid depolarization begins within the cell, triggered by an adjacent myocyte. The cell interior becomes less negatively charged, primarily because of the sodium (Na^+) influx (I_{Na}) via the fast voltage-gated Na^+ channels. This is the steep upstroke in Figure 1.
- Phase 1: Early repolarization is caused primarily by a rapid but short-lived potassium (K^+) efflux (I_K) through outward K^+ channels. The cell voltage becomes more negative.
- Phase 2: A plateau is primarily caused by calcium (Ca^{2+}) influx via L-type Ca^{2+} channels with a minor K^+ efflux (I_K) that balances the Ca^{2+} influx and helps maintain the depolarized state.
- Phase 3: Repolarization is caused by closure of the L-type Ca^{2+} channels and opening of the delayed rectifier K^+ channels (I_K). K^+ flows out of the cell. The cell becomes more negative and the potential falls back to its baseline value of –90 mV.
- Phase 4: This is the resting phase. Channels are mainly closed. Despite leak of Na^+ into the cell and K^+ out of the cell, the Na^+ and K^+ are maintained in equilibrium using the Na^+/K^+-ATPase, as they would be in any cell.

What Are Sodium-Channel Blockers (Class I Antiarrhythmics)? (LO#1–3)

Class I antiarrhythmic drugs block the Na^+ channels that are responsible for the phase 0 spike of the myocyte action potential (both atrial and ventricular),

so they are also called sodium-channel blockers.

Nomenclature

Class I antiarrhythmic drugs are further categorized into classes IA, IB, and IC, based on the drug's binding and dissociation kinetics from the Na^+ channel.

Recall from cardiac action potential (1of 3) brick that Na^+ channels exist in three conformational states: Resting (closed channel), Activated (open channel), and Inactivated (channel inactivated). (Figure 2)

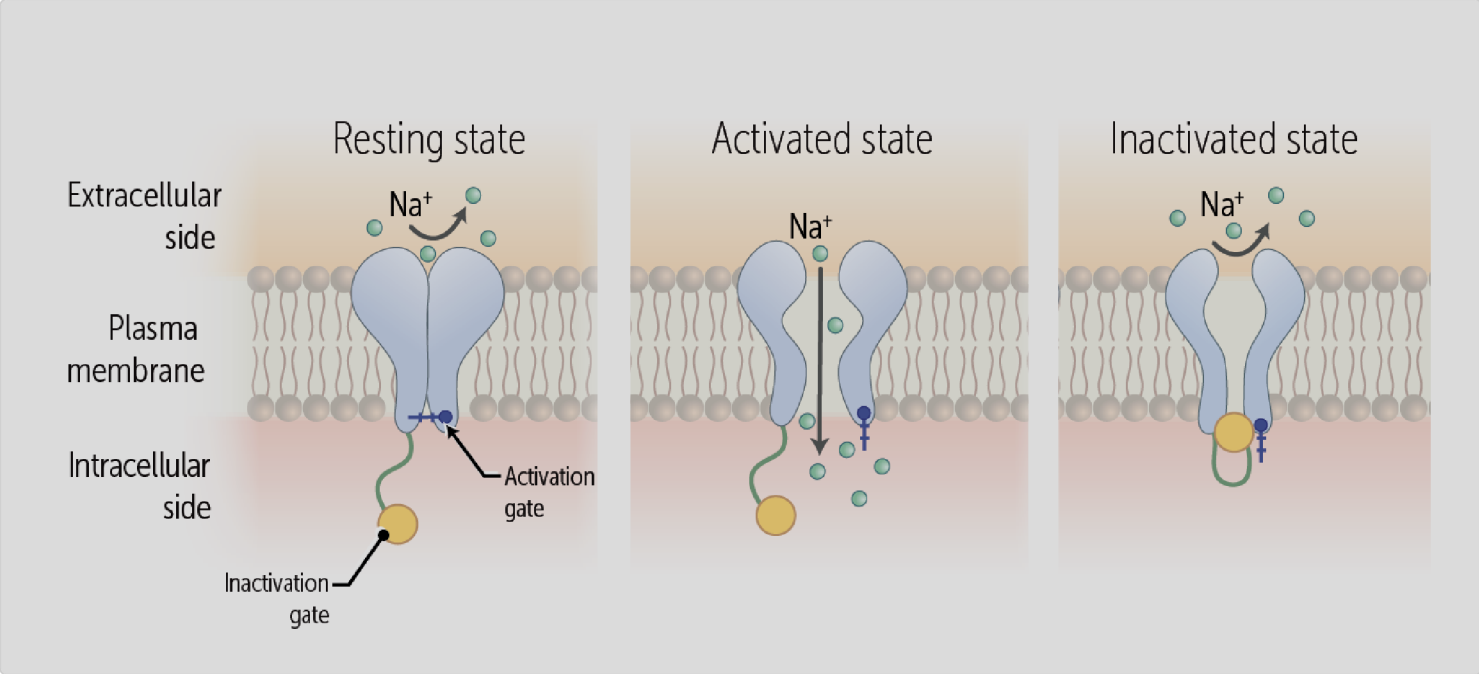


Figure 2 : Conformational States of Na channels

Use Dependence

The dissociation kinetics of these drugs are affected by the heart rate. During fast heart rates, the drugs have less time to dissociate from the Na^+ channels. Less dissociation leads to increased channel blockade and heightened drug effect as well as a greater potential for drug toxicity. This phenomenon is

called **use dependence**. The increased risk of toxicity is why these drugs are commonly co-prescribed with rate-lowering medications to prevent tachycardia and use dependence.

Class IC drugs have the most use dependence, followed by class IA, then class IB.

Class IA Drugs

Class IA antiarrhythmics are used to treat ventricular arrhythmias such as ventricular tachycardia (VT) and supraventricular tachycardias like atrioventricular nodal reentry tachycardia, atrial fibrillation (AF), and Wolff-Parkinson-White syndrome.

Drug Names. Drugs include quinidine, procainamide, and disopyramide.

Mechanism of Action. Class IA drugs attenuate the vertical spike (phase 0) of the action potential, prolonging depolarization. They do this by blocking open

Na^+ channels, reducing the total flow of Na^+ ions into the myocyte during phase 0. They also have some K^+ channel–blocking effect, reducing the overall flow of K^+ ions out of the cell during phase 3. These combined effects alter the myocyte action potential. The slope of the phase 0 upstroke is reduced, and the phase 3 downstroke is delayed. This leads to the prolonged action potential seen in Figure 3.

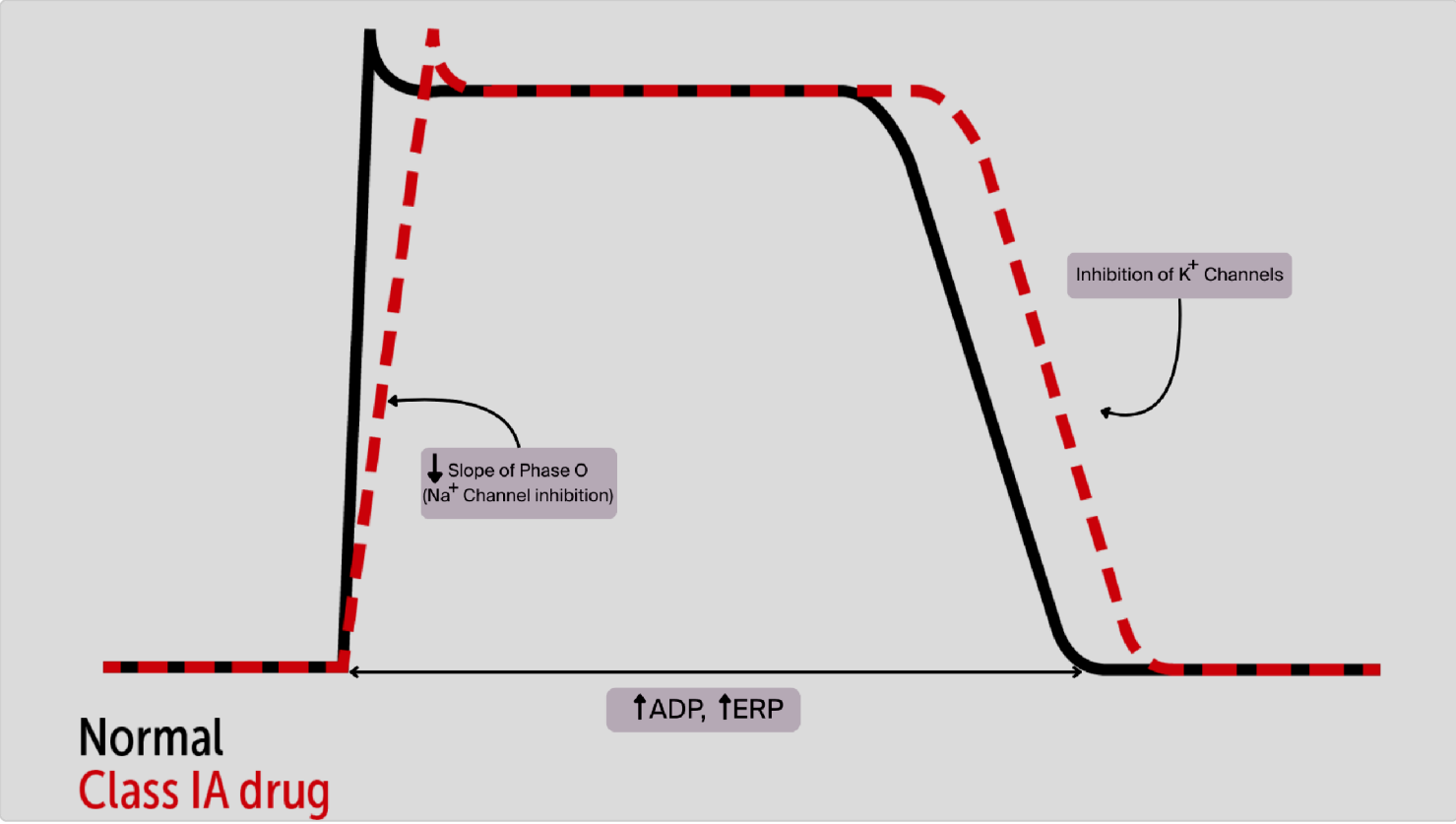


Figure 3; Class IA Drugs

Effect on the Electrocardiogram. The prolonged action potential increases the effective refractory period. The prolonged ventricular depolarization (phase 0) leads to **a widened QRS interval**. Block potassium channels, particularly the rapid component prolongs repolarization. This K channel block can lead to **extending the action potential duration (ADP)**. The prolonged repolarization **increases the Effective Refractory Period (ERP)**, which can be beneficial in preventing premature excitation and interrupting

reentrant circuits. However, this APD prolongation also creates vulnerability to early afterdepolarizations (EADs) and torsades de pointes (Tdp), especially at slow heart rates.

Adverse Reactions. Proarrhythmia—the paradoxical induction or worsening of arrhythmias—represents the most serious cardiac adverse effect of Class I agents. Class IA drugs, particularly quinidine, can cause torsades de pointes (Figure 3) due to their QT-prolonging effects.

CLINICAL CORRELATION

The QT prolongation (with Tdp) typically occurs early in therapy (often within the first few days) and is more common in patients with risk factors such as hypokalemia, hypomagnesemia, bradycardia, or congenital long QT syndrome.

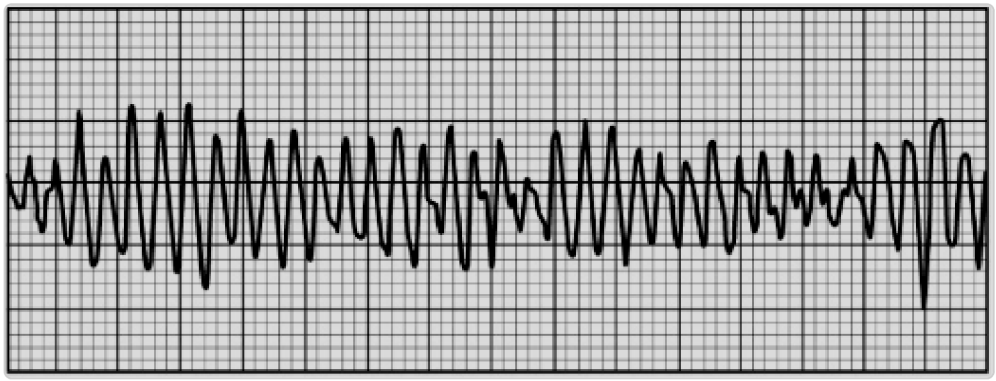


Figure 3 Torsades de pointes

All class IA medications can cause **thrombocytopenia**.

Here are some **specific adverse effects** of the individual drugs:

- **Disopyramide** can cause anticholinergic effects and heart failure. The significant **anticholinergic activity** causes dry mouth (xerostomia), urinary retention, and constipation. The HF occurs because disopyramide decreases cardiac contractility and, therefore, cardiac output. Fortunately, this decline is reversed after drug discontinuation.
- **Procainamide** is known for causing drug-induced lupus, ventricular arrhythmias, and hypotension. The lupus is characterized by rash, joint pain, and pleuritis and is associated with antihistone antibodies in the serum. The syndrome is reversible with drug discontinuation. The ventricular arrhythmias are due to excessive QRS prolongation.
- **Quinidine** is no longer widely used because of the serious adverse effect of quinidine syncope. This is a momentary, self-terminating torsades de pointes that causes diminished cerebral perfusion, causing syncope. The drug can also cause a group of symptoms called cinchonism, consisting of facial flushing, rashes, headaches, blurry vision, tinnitus, dizziness, abdominal pain, nausea, vomiting, diarrhea, and prolonged QT interval on ECG.

Procainamide causes antihistone antibodies due to drug-induced lupus.

Contraindications. These drugs should not be used in patients with second- or third-degree heart block. In addition, contraindications for specific drugs include:

- Disopyramide: shock and long QT interval
- Procainamide: systemic lupus erythematosus
- Quinidine: thrombocytopenia, myasthenia gravis, and concurrent use of quinolone antibiotics

Class IB Drugs

Class IB antiarrhythmics are used primarily for VT. These drugs are most selective for inactive Na^+ channels, such as cells that have experienced prolonged ischemia. So class IB agents are the drugs of choice for **ventricular arrhythmias occurring after MI**.

Drug Names. Class IB drugs include lidocaine and mexiletine.

Mechanism of Action. Class IB agents bind to fast sodium channels in their inactivated state, reducing the slope of the phase 0 upstroke of the myocyte action potential. More sodium channels in inactivated states are found in ischemic myocardium than normal tissue. Compared to classes IA and IC, class IB agents have the lowest affinity for these channels. The quick dissociation of Class IB drugs from the Na channels in the ischemic myocardium, causes the smallest deviation of the phase 0 curve. In addition, these agents **decrease or shorten action potential duration** (Figure 4). The shortened APD can be advantageous in ischemic conditions where APD is already prolonged.

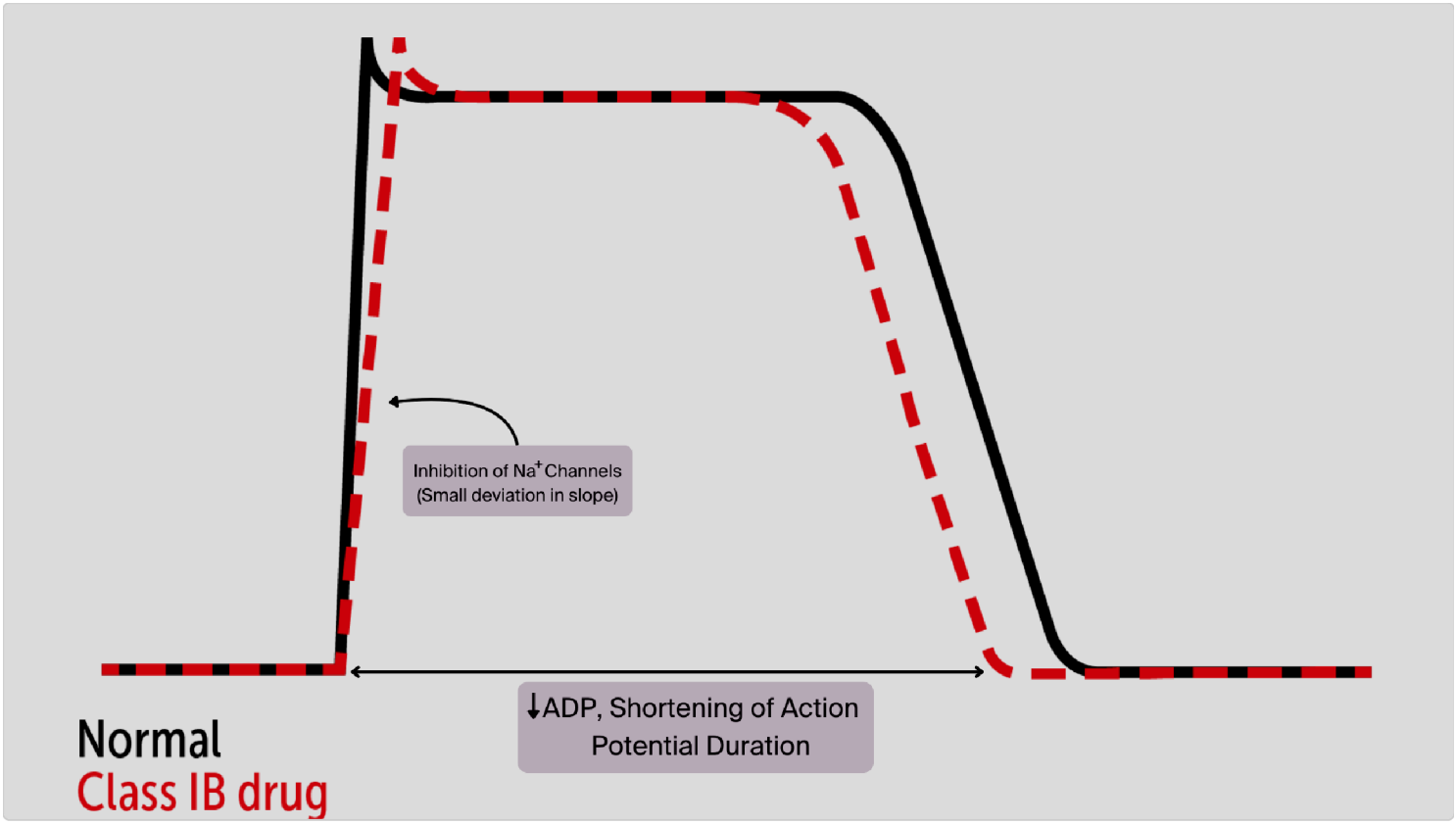
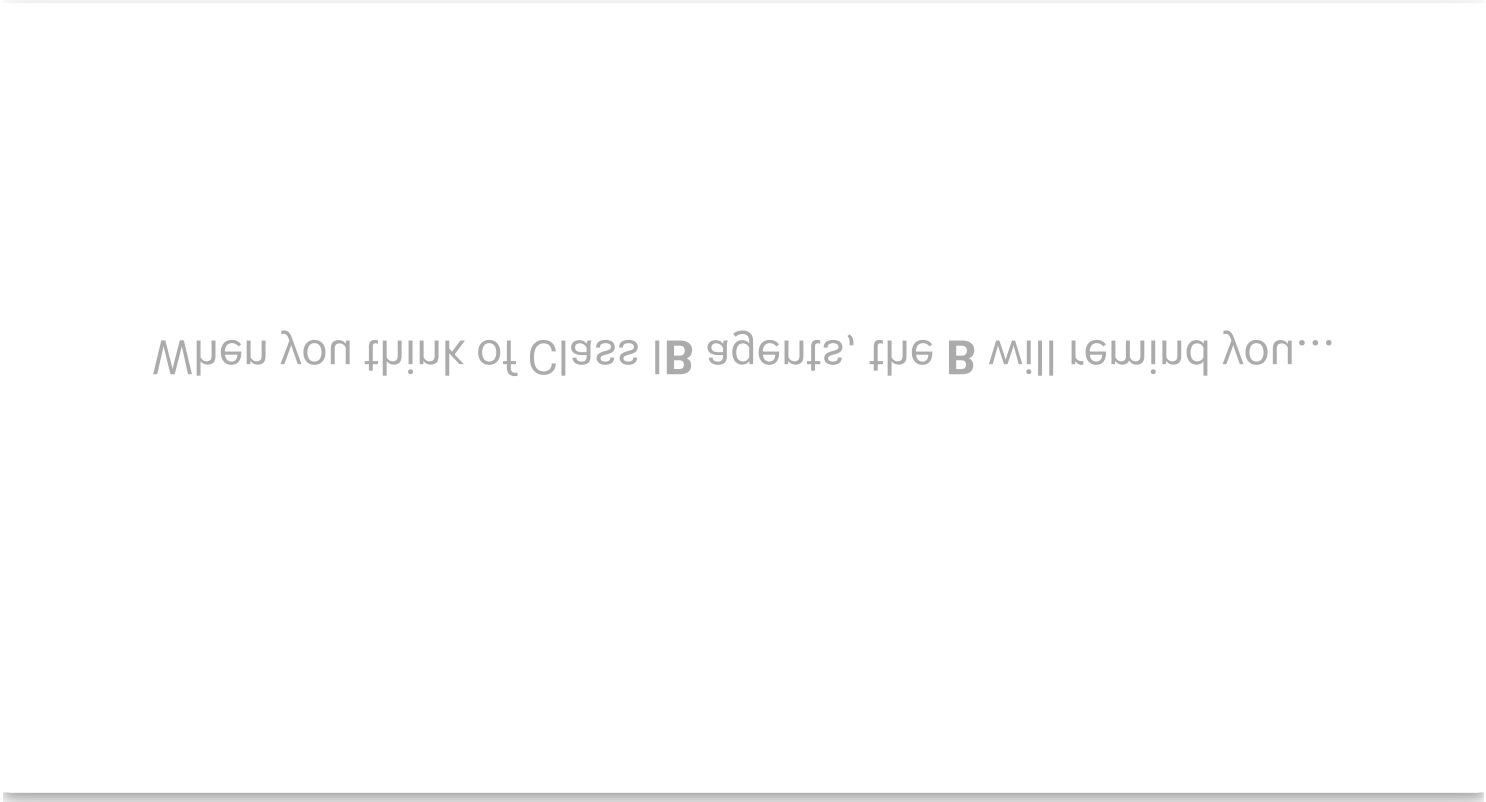


Figure 4 Action of class IB antiarrhythmics (change figure to atrial depolarization)

Class IB antiarrhythmic agents act on inactive Na_+ channels, present in myocytes that have undergone prolonged ischemia, which is why they are the drug of choice in these patients to prevent arrhythmias.

Effect on the Electrocardiogram. Class IB agents (lidocaine, mexiletine) produce minimal QRS widening in normal cardiac tissue, typically less than 10% at therapeutic doses.



Adverse Reactions. Class IB agents have the lowest proarrhythmic potential among Class I drugs, partly because they do not prolong (and may even shorten) the APD. Neurological adverse effects are common with Class I agents due to their ability to cross the blood-brain barrier and block sodium channels in the central and peripheral nervous systems. For the individual drugs:

- **Lidocaine:** CNS effects ranging from mild symptoms (perioral numbness, paresthesias, dizziness) to severe manifestations (confusion, seizures, respiratory depression) at higher levels.
- **Mexiletine:** Ataxia, tremors, and confusion.

Class IC Drugs

Drug Names. Class IC drugs include propafenone and flecainide.

Mechanism of Action. Class IC drugs bind very strongly to open Na^+ channels and have slow dissociation kinetics. By binding to and blocking open Na^+ channels, class IC drugs cause each myocyte to take longer to depolarize. The delayed depolarization (phase 0) translates to a significant blunting of the upstroke (or decrease in the slope of phase 0) of the myocardial action potential (Figure 5). They markedly decrease conduction velocity through the His-Purkinje system and ventricles with minimal effects on repolarization.

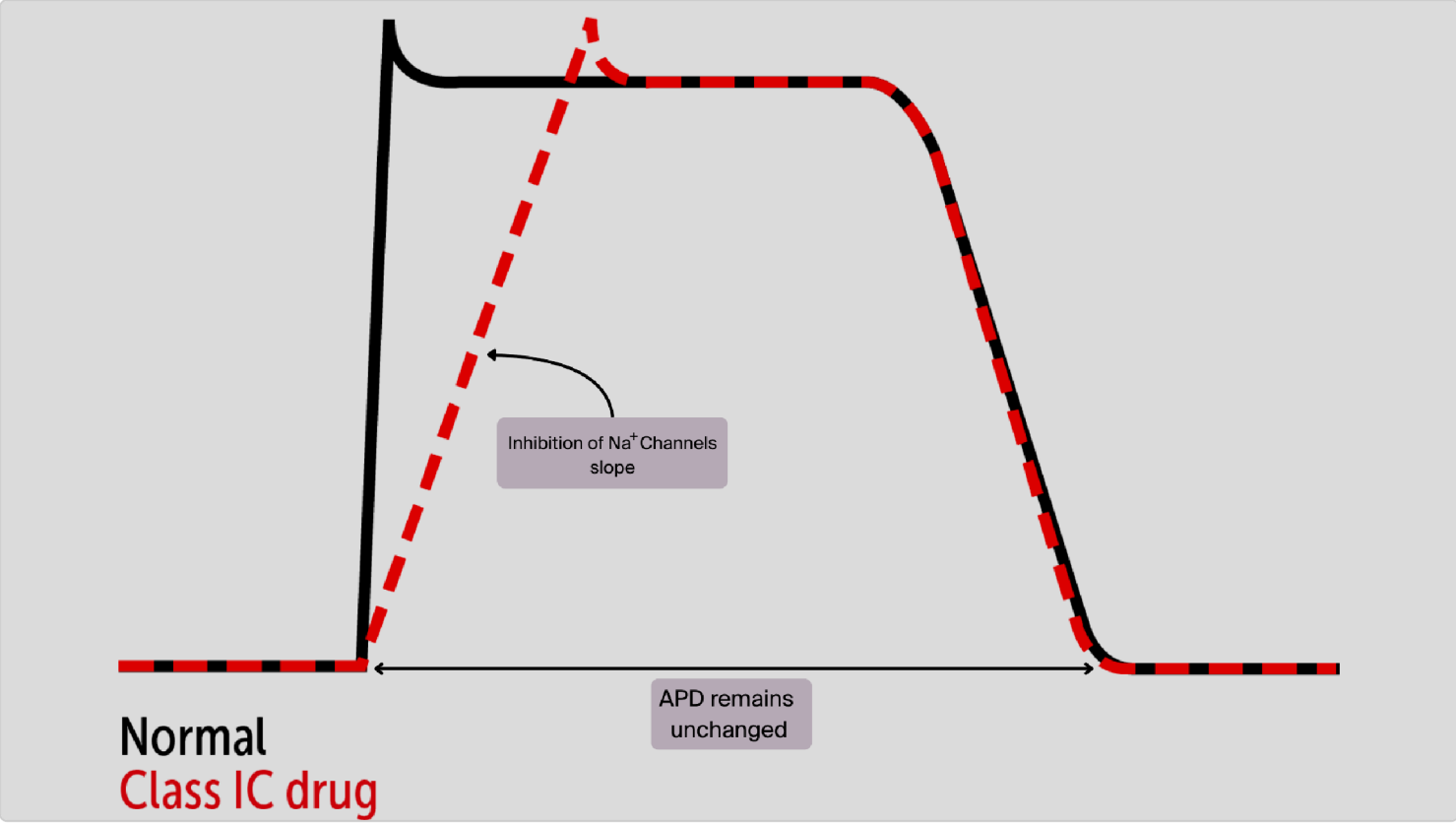


Figure 5: Class IC drugs

In contrast to class IA agents, the **duration of the action potential does not change** because there is no effect on K^+ channels.

Effect on Electrocardiogram. Class IC blockers significantly slow conduction throughout the heart, resulting in pronounced QRS widening. The QT interval is unchanged because the action potential duration is unchanged.

Adverse Reactions. Class IC agents can cause arrhythmias, especially in post-MI patients. For the individual drugs:

- **flecainide** causes visual disturbances and dizziness.
- **propafenone** can cause heart failure, bradycardia.

Class IC agents can provoke ventricular tachycardia or fibrillation, especially in patients with structural heart disease or previous myocardial infarction.

CLINICAL CORRELATION

Structural Heart Disease (SHD): Structural heart disease refers to abnormalities in the heart's valves, chambers, walls, or vessels that alter its normal anatomy and function. Common examples include valvular disorders (e.g., aortic stenosis, mitral regurgitation), septal defects (atrial or ventricular), and cardiomyopathies. These conditions can lead to altered hemodynamics, heart failure, arrhythmias, or thromboembolic events.

Contraindications. Class IC agents are contraindicated in patients with structural heart disease or myocardial ischemia, such as MI, coronary artery disease, and cardiomyopathy because they can cause arrhythmias in these conditions.

How Can Knowledge of Class I Antiarrhythmics Predict Potential Drug Interactions? (LO#2 and 3)

Quinidine is primarily metabolized by CYP3A4, making it susceptible to interactions with potent inhibitors of this enzyme such as ketoconazole, erythromycin, and certain HIV protease inhibitors. Additionally, quinidine itself inhibits CYP2D6, potentially increasing levels of drugs metabolized by this pathway (e.g., metoprolol, some antidepressants). Procainamide undergoes acetylation by N-acetyltransferase to N-acetylprocainamide (NAPA).

CLINICAL REASONING

Procainamide levels are monitored because both the parent drug and its metabolite (NAPA) are active and have arrhythmogenic properties.

Class IB agents like lidocaine undergo extensive first-pass hepatic metabolism, making them sensitive to changes in hepatic blood flow.

Class IC agents have complex metabolic profiles. Flecainide is metabolized primarily by CYP2D6 while Propafenone is metabolized by multiple CYP enzymes (CYP2D6, CYP1A2, CYP3A4), creating numerous potential interaction pathways. Amiodarone, a potent inhibitor of multiple CYP enzymes, can significantly increase levels of both flecainide and propafenone when co-administered.

How can an antiarrhythmic drug cause arrhythmias? The strong use dependence of class IC antiarrhythmic drugs means that they do not bind effectively to ischemic or damaged cardiac myocytes. So, if these drugs are used in a heart with structural disease or ischemia, they would be more active

in normal tissue and less active in the ischemic areas. The discrepancy between active and inactive areas can lead to arrhythmias.

Class IC antiarrhythmics would be more active in normal tissue in these patients, as they are use-dependent and would not bind effectively in ischemic cells, thereby increasing the risk of arrhythmias.

The class I antiarrhythmics are summarized in Table 1.

Table 1 Classes I antiarrhythmic drugs

Class	Target	Examples	Used to treat	Adverse effects
IA	Na^+-channel blocker	Quinidine, procainamide, disopyramide	Ventricular tachycardia or supraventricular tachycardia	Thrombocytopenia Quinidine: cinchonism and torsades de pointes Disopyramide: heart failure and anticholinergic effects Procainamide: drug-induced lupus, torsades de pointes, hypotension

Class	Target	Examples	Used to treat	Adverse effects
IB	Na^+-channel blocker	Lidocaine, mexiletine	Ventricular tachycardia	CNS depression or stimulation, cardiovascular depression Lidocaine: hypotension, tremor Mexiletine: bradycardia, tremor, GI symptoms (nausea, vomiting, heartburn)
IC	Na^+-channel blocker	Propafenone, flecainide	Rhythm control (conversion) of atrial fibrillation	Arrhythmias in patients with structural heart disease

CASE CONNECTION BACK TO INTRODUCTION

Thinking back to PT, what caused her second episode of ventricular tachycardia? How do you approach her care now?

Procainamide may have worsened PT's prolonged QTc interval and precipitated ventricular tachycardia. She is given mexiletine, an alternative antiarrhythmic that is associated with a lesser risk of QTc prolongation, but requires careful monitoring for neurologic and gastrointestinal side effects. The attending says, "I agree PT doesn't need further testing. Sometimes, taking the time to review the record and do a good history is the most cost-effective approach to patient care."

Summary

- Antiarrhythmic drugs treat arrhythmias by acting on the heart's electrical conduction system.
- The Vaughan-Williams classification categorizes antiarrhythmic drugs into four classes based on their mechanism: sodium-channel blockers

(Class I), β-blockers (Class II), potassium-channel blockers (Class III), and calcium-channel blockers (Class IV).

- Class I antiarrhythmics block Na+ channels, slowing the action potential in cardiac cells; they are divided into subclasses IA, IB, and IC based on binding kinetics.
- Class IA drugs, such as procainamide, disopyramide, and quinidine, prolong the action potential and ventricular depolarization, potentially causing thrombocytopenia and torsades de pointes.
- Class IB drugs, like lidocaine and mexiletine, are selective for ischemic myocardium, shorten action potential duration, and have minimal ECG effects but can cause CNS depression.
- Class IC drugs, including propafenone and flecainide, significantly slow conduction, resulting in pronounced QRS widening and are contraindicated in patients with structural heart disease or ischemia.

Review Questions

1. **A patient is started on flecainide for an arrhythmia. Which of the following correctly describes this drug's mechanism of action?**

   A. Calcium-channel blocker

   B. Inhibits sympathetic input to cardiac myocytes

   C. Potassium-channel blocker

   D. ◉ Sodium-channel blocker with strong use dependence

   E. Sodium-channel blocker with weak use dependence

Hide Explanation

The correct answer is sodium-channel blocker with strong use dependence (D). Flecainide is a class IC antiarrhythmic that exhibits strong use dependence. A calcium-channel blocker (A) is a class IV drug that works predominantly on nodal cells. A β-blocker inhibits sympathetic input to cardiac myocytes (B) and decreases heart rate. A potassium-channel blocker (C) is a class III antiarrhythmic. Sodium-channel blocker with weak use dependence (E) describes class IB antiarrhythmics.

2. A female starts having joint pain and an erythematous rash on her face after being treated for a supraventricular arrhythmia. Which of the following medications most likely caused her symptoms?

A. Amiodarone

B. Lidocaine

C. ◉ Procainamide

D. Propranolol

E. Sotalol

Hide Explanation

The correct answer is procainamide (C). An important adverse effect of procainamide is drug-induced lupus, which presents with rash and arthralgias due to autoantibodies. None of the other drugs is associated with drug-induced lupus. Amiodarone (A) can cause a rash (photodermatitis and blue-gray skin pigmentation) and other side effects like thyroid, lung, and liver toxicity. Lidocaine (B) would not be used for supraventricular arrhythmias and causes CNS

depression. Propranolol (D) can cause impotence and exacerbation of asthma. Sotalol (E) can induce torsades de pointes.

3. **Which of the following antiarrhythmic agents is matched incorrectly according to the Vaughn-Williams classification?**

A. Class IB: lidocaine

B. ◉ Class IC: disopyramide

C. Class III: dofetilide

D. Class IA: quinidine

Hide Explanation

The correct answer is class IC: disopyramide (B). Class IB: lidocaine (A), Class III: dofetilide (C), and Class IA: quinidine (D) are each correctly matched.

4. **Which agent can decrease the slope of phase 0 of an cardiac action potential without changing the APD?**

A. Procainamide

B. Disopyramide

C. Mexiletine

D. ◉ Propafenone

Hide Explanation

The correct answer is propafenone (D). Propafenone is a Class IC antiarrhythmic medication which inhibits Na channels thus decreasing the slope of phase 0, but does not alter K channel function and hence does not change action potential duration (APD). Choice A (propafenone) and C (Disopyramide) are Class IA antiarrhythmic medications which can decrease the slope of phase 0 and since they inhibit K channels can increase APD. Choice C (Mexiletine) is a Class IC antiarrhythmic which can does not change the slope of phase 0.

How would you rate this Brick?

References

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Review Learning Objectives

Check off the objectives when you feel comfortable with the concept

01 ☑ Explain the mechanism of action of Class I antiarrhythmic agents.

02 ☑ Explain the changes in action potential and the associated ECG changes with Class I antiarrhythmic agents.

03 ☑ Recognize the adverse effects of Class I antiarrhythmic agents.

Objective Confidence: 3/3