Pharmacology

Team 444

MED444
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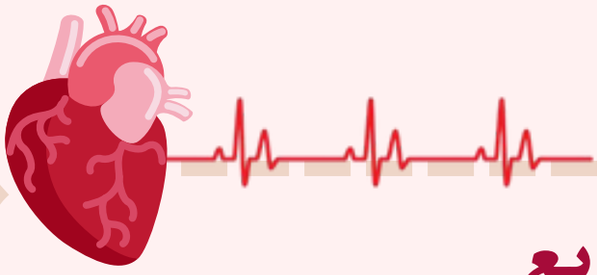
L4.
Antiarrhythmic drugs [1]&[2]

EDITING FILE

COLOR INDEX :
- MAIN TEXT
- IMPORTANT
- GIRL'S SLIDES
- BOY'S SLIDES
- NOTES
- EXTRA

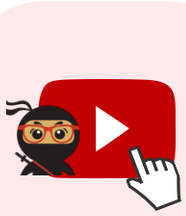


إذا اختلّ الرذم لا تنسى أربع
تسكّرها وتعالج فيها بايدك
غير الصوديوم بيتا وترى اسمع
كالسيوم، بوتاسيوم تفيدك

✍️ علي العبدالعظيم

Objectives:

- Understand definition of arrhythmias & their different types.
- Describe different classes of Antiarrhythmic drugs & their mechanism of action.
- Understand their pharmacological actions, clinical uses, adverse effects & their interactions with other drugs.



Part 1:
1-intro first 16 min
- -Heart block min 9:30
- - atrial fibrillation min 11:00
- - wolf white syndrome min 13:00

2- Action potential min 16:00
3- absolute refractory period min 35:00
4- Torsades de pointes min 40:00

Part 2:
1- class Ia min 00:00
2- class Ib min 21:10
3- class Ic min 33:25
4- class II min 39:04
5- class III min 44:30
6- class IV min 55:18
7- non pharmacological method 1:03:49

Ventricular Muscle Cell Action Potential Phases:

Phase 4

(Resting membrane potential):
Polarized

Phase 0

Influx of Na+ and Ca++ from neighboring cardiac cells causes the resting membrane potential to slightly increase, allowing voltage gated Na channels to open, and the cell is said to be depolarized.

Phase 1

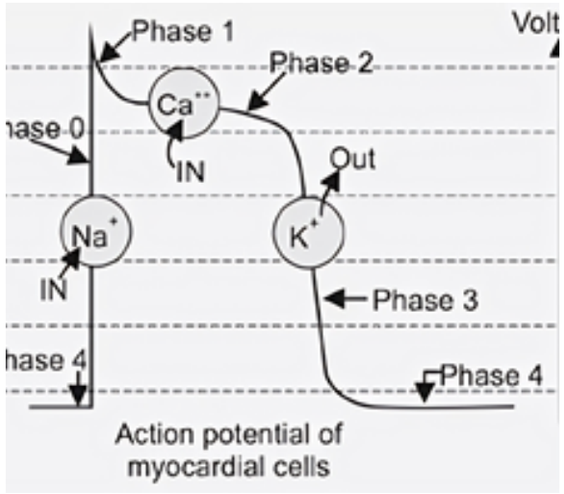
At peak positivity of the cell, short-term voltage-gated K+ channels open and Na+ channels close. This allows the membrane potential to be slightly decreased to create a potential difference for voltage gated Ca++ channels to open.

Phase 2

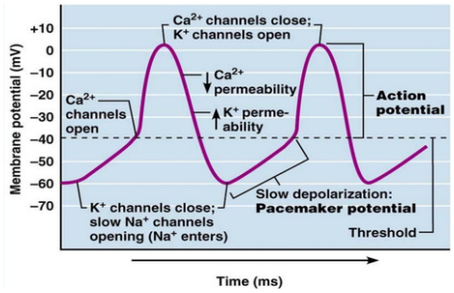
Voltage gated Ca++channels are open for about most of the period, but the channels are inactivated around the end of this phase and phase 3 (K+ efflux starts). If this phase is prolonged, inactivated Ca++ channels can reopen, creating an after depolarization (torsades de pointes).

Phase 3

Extra specialized K+ channels are opened to bring about repolarization and a return to the resting membrane potential



Non-pacemaker AP



pacemaker AP

Pacemaker Action Potential Phases:

SA Node is made of specialized cardiac cells (Modified Cardiomyocytes) that exhibit a unique way of generating an action potential (automaticity; do not require CNS stimulation). These cells have high permeability to Na+ and K+, allowing constant, spontaneous action potentials to be generated

-What is the difference between the pacemaker and non- pacemaker AP ?

the plateau phase in the non-pacemaker AP , The pacemaker (SA node) initiates electrical impulses in the heart, regulating the rhythm and heart rate. Non-pacemaker action potentials transmit these signals throughout the heart, coordinating the contraction and relaxation of the atria and ventricles.

Types of arrhythmia

Ventricular (occurs in the ventricles)	Supraventricular (occurs in the atria)
Ventricular Tachycardia: SA node no longer controls the beating of the ventricles "ectopic pacemaker", this will result in increase heart beats	**Paroxysmal Supraventricular Tachycardia:** Rapid, regular heart beats
Premature Ventricular Contractions (PVC): the condition happens when the ventricles contract too soon, out of sequence with the normal	**Wolff-Parkinson-White Syndrome:** Extra electrical pathways between the atria and the ventricles,the result is a very fast heart rate
Ventricular Fibrillation: The most serious arrhythmia, impulses stimulate one part of the ventricles, then another, then itself. Many parts contract at the same time while other parts relax (Circus movement)	**Atrial Fibrillation:** Rapid, irregular heart beats. **Atrial flutter:** Regular, atrium beats faster than ventricle.

Cardiac conduction system

The conduction system within the heart is responsible for generating and conducting impulses to all part of the heart:

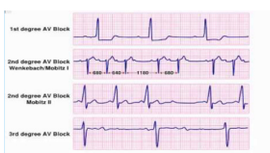
RATE

SA node generates impulses → these impulses pass the internodal pathways to reach the **AV node**, there will be what's called "AV nodal delay" → Then, these impulses pass through the **Bundle of His** to the **right and left bundle branches** to finally reach the **purkinje fibers**

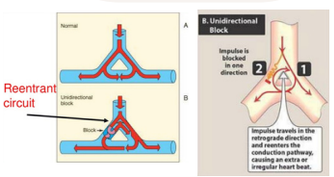
Arrhythmias are conceptually simple, dysfunctions cause abnormalities in the formation and conduction of impulses in the myocardium.

Arrhythmia is an abnormality in the:

- **RATE**
  - **>100=tachycardia**
  - **<60=bradycardia**
- **REGULARITY**
  - **e.g. extrasystoles (PAC, PVC)**
- **SITE OF ORIGIN**
  - **e.g. ectopic pacemaker**
    An ectopic pacemaker refers to an abnormal site in the heart that generates electrical impulses and takes over the role of the natural pacemaker (SA node) in initiating the heart's rhythm. This can result in irregular heartbea
- **DISTURBANCE IN CONDUCTION**
  - **AV Block -> Bradycardia**



  - **Reentrant circuit -> Cause Tachycardia**



Antiarrhythmic Drugs

Antiarrhythmic drugs are often used to treat abnormal heart rhythms caused by ectopic pacemakers, then the SA node conditions.

The ultimate goal of antiarrhythmic drugs is to restore normal rhythm & conduction by:

1- Maintenance of normal rhythm

2- Prevention of more serious arrhythmias

How do antiarrhythmic drugs produce these effects

Slowing the conduction velocity. it gives the heart time to recharge and normalize itself

Altering the excitability of cardiac cells (by prolonging the effective refractory period "ERP".

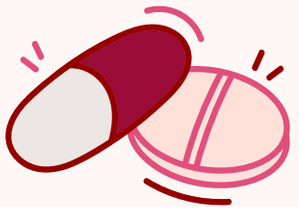
Suppressing **ectopic pacemaker** activity (by inhibiting phase 4 slow depolarization)

The effective refractory period refers to a period of time in which cardiac cells are unable to be stimulated again, even by a strong electrical impulse(from phase 0 to phase 3). During this period, the cardiac cells are in a state of repolarization and are not yet fully ready to generate another action potential. This helps ensure that the heart has enough time to complete one contraction before being stimulated again, allowing for proper coordination and rhythm of cardiac contractions.

Classification of Antiarrhythmic Drugs

Vaughan-Williams Classification	I	II	III	IV	V
M.O.A	**Na+ channel blockers (membrane stabilizing drugs).** The Na+ channel is the starting of AP in both atria and ventricles	**β-Adrenorecept Blockers**	**K+ Channel blockers**	**Ca++ Channel blockers**	**Other M.O.A**
Effects on Pacemaker Action Potential	**1- Decrease the rate of rise of rapid depolarization (phase 0). 2- Decrease phase 4 slow depolarization (suppress pacemaker activity).**	**Slow Phase 4 depolarization.**	**Prolongs Action Potential Repolarization .**	**Slow phase 4 → spontaneous depolarization and conduction.**	**-**
Drugs	**Ia-Quinidine & Procainamide. Ib-Lidocaine & Mexiletine. Ic-Flecainide.**	**1-Esmolol. 2-Propranolol. 3-Metoprolol. 4-Atenolol.**	**1-amiodarone 2-Ibutilide.**	**1-Verapamil 2-Diltiazem**	Adennosine

Class I Drugs



◆Drugs that block the influx of Na+ ions through Na channels (Membrane stabilizing effect)

1

In contractile cells
Decrease the rise rapid depolarization (phase 0).

2

In SA node
Decrease phase 4 slow depolarization (suppress pacemaker activity).

Class I drugs are sub classified according to their **effect** on **action potential duration** into:

Ia **Prolonged** action potential duration

- ❖Blocks Na (I) & K (III) channels.
- ❖Slow rate of rise.
- ❖increase ERP.
- ❖Increase AP.

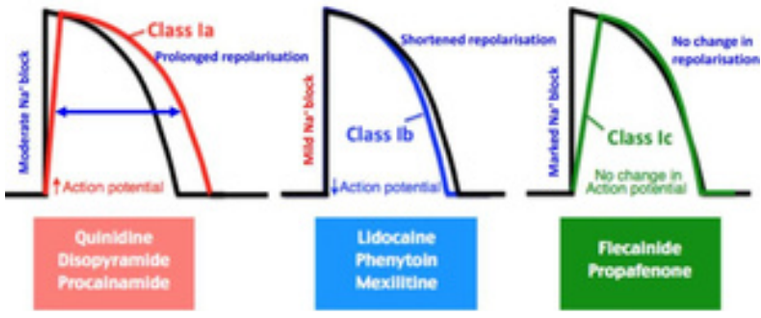
Ib **Shorten** action potential duration

- ❖shorten repolarization.
- ❖Decrease in AP.
- ❖Decrease ERP.

ERP= effective refractory period

Ic **Minimal or no** effect on action potential duration

Pure Na channel blockers
Depress rate of rise
Slows conduction velocity
Minimal/No change in AP



MNEMONIC

ملكة دين <-- QUINDINE --> QUIN DINE
MEXILETINE --> مكس لاتيه

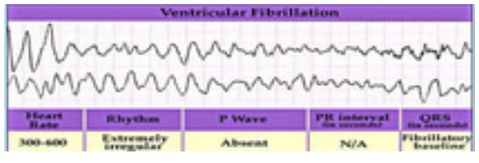
PRO"CAIN"AMIDE, LIDO"CAINE", FLE"CAIN"IDE

اخر ثلاثه فيها cain

Class Ia

Drug	AP	Pharmacological action	Clinical use	ADRs
Quinidine Orally (Rarely I.V)	***Important*** **Prolong the action potential duration**	1. Anticholinergic effects (Atropine like effect): increase conduction through AV node (risk of ventricular tachycardia). (disadvantage) 2. α- adrenergic blocking effect (side effect): May cause vasodilation & reflex sinus tachycardia (seen more after I.V dose). 3. ECG changes: ● Prolong P-R & Q-T interval. ● Widens QRS complex.	1- Atrial flutter & fibrillation. (both are tachycardia, but the difference is : the flutter is regular rapid heart rate, while the fibrillation is irregular rapid heart rate) 2- Maintaining sinus rhythm after cardioversion (electrical supply of the heart) 3-we can use it in malaria	1. Quinidine syncope: episodes of fainting due to **torsades de pointes** (twisting of the spikes) developing at therapeutic plasma levels. -due to partial potassium channel blocking properties ***Important*** 2. Anticholinergic adverse effects: Dry mouth, blurred vision, urinary retention constipation. 3. Hypotension: Due to depressing contractility & vasodilation.
Procainamide I.V		Similar to Quinidine except: 1. Less toxic on the heart (can be given I.V). 2. More effective in ventricular than in atrial arrhythmia. 3. Less anticholinergic or α- blocking actions.	More effective in Ventricular than atrial arrhythmia.	1. **Torsades de pointes** (at toxic dose). 2. In long term therapy, it causes reversible **lupus erythematosus like syndrome.** 3. Hypotension —> Because it reduces peripheral resistance. 4. Hallucination & psychosis.

Torsades de pointes: may terminate spontaneously or lead to **fatal ventricular fibrillation**



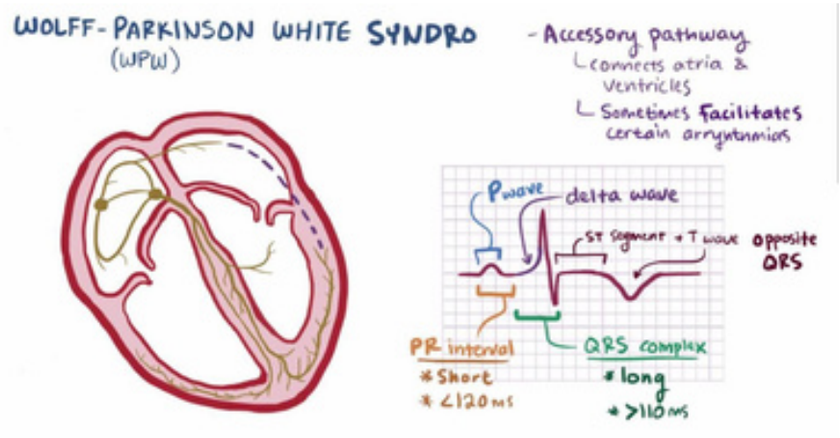
class Ib

Drug	AP	Administration	Clinical use	ARDs
Lidocaine (T ½ : 2H) is a widely used local anesthetic that is commonly used in dentistry.	**Shorten the Action potential duration**	Given I.V. bolus or slow infusion. -**Not effective orally** (low bioavailability [3%] due to first pass metabolism) t1/2 = 2 h	Treatment of emergency ventricular arrhythmias: 1- during surgery. 2-following acute myocardial infarction. Not effective in atrial arrhythmias...	1- Hypotension 2- CNS ADRs (similar to other local anesthetics), in order : -Paresthesia(numbness) -Tremor -Dysarthria (slurred speech) -Tinnitus -Confusion -Convulsion
Mexiletine (T ½ : 10H)		**Effective orally** t1/2 = 10 h	1- Ventricular arrhythmias. 2- Digitalis induced arrhythmias (digoxin induced arrhythmias)	1- Nausea, vomiting 2- tremor, drowsiness, diplopia(double vision). 3- arrhythmias & hypotension.

class Ic

Drug	AP	Clinical use	ARDs
Flecainide	**No effect on action potential duration. (Markedly slow phase 0 depolarization) "very potent and pure Na channel blockers"**	1- Supraventricular arrhythmias 2- Should be reserved for resistant arrhythmias. 3- Very effective in ventricular arrhythmias, but very high risk of **proarrhythmia**. 4- Wolff Parkinson White syndrome.	1- Proarrhythmia. (Cause new arrhythmia) 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations, paraesthesia. 3- Heart failure due to (-ve) inotropic effect.

Is Pre-excitation of the ventricles due to an **accessory pathway** known as the Bundle of Kent.



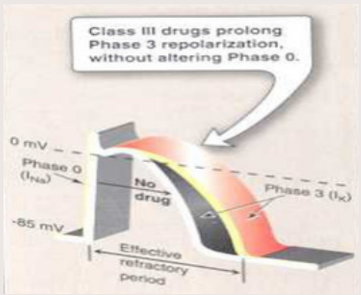
Class II drugs

39:00

drug	**Esmolol** (T 1/2 : 9min)	**Propranolol, Atenolol & Metoprolol**
Important **M.O.A / Pharmacological action**	**β-AdrenoreceptBlockers** Block B1 receptors in the heart reducing sympathetic effect on the heart which leads to: 1- Decrease automaticity of S.A node & ectopic pacemakers. 2- Prolong refractory period (slow conduction) of the A.V node.	
Clinical uses / therapeutic uses	1- Atrial arrhythmias associated with emotions (e.g: after exercise, thyrotoxicosis). We can use it as protective . 2- Wolff Parkinson White syndrome. (WPW) 3- Digitalis induced arrhythmias (digoxin induced arrhythmias).	
Specific uses	• Very short acting (half-life =9min) • Given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation.	• Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias. (prophylaxis)

Class III drugs

44:00

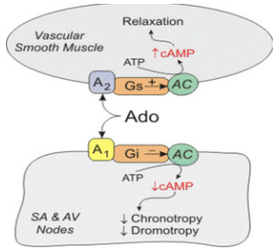
Drug	1- Amiodarone أم يدرون
Pharmacological action 	Mainly cause: 1- Prolong AP duration and prolong refractory period. (Main effect) 2- Prolong phase 3 repolarization. And additional effects: يسوي Block للكل • Class IA (Membrane stability + a-adrenergic blocking effect). • Class II (B1 Blocker). • Class IV (Ca Block). • Vasodilating effects (due to its alpha & 3-adrenoceptor blocking effects and its calcium channel blocking effects).
Important **Pharmacokinetic**	• Extremely long half-life (13 - 103 Days). • Metabolized by (CYP3A4 and CYP2C8) to its major active metabolite: N-desethylamiodarone. • Eliminated primarily by hepatic metabolism (so it's contraindicated in patients with liver problems). • Can cross placenta, and appear in breast milk (so it's contraindicated in pregnant woman and breastfeeding).
Clinical uses / therapeutic uses	1- Main use: serious resistant ventricular arrhythmias. 2- Maintenance of sinus rhythm after D.C. cardioversion. 3- Resistant supraventricular arrhythmias e.g. WPW.
Important **ADRs**	• Exacerbation of ventricular arrhythmias (high dose). • Bradycardia and heart failure. • Pulmonary fibrosis & necrosis. • Hyper or hypothyroidism (because it contain iodine). *contraindicated in thyrotoxicosis • Photodermatitis & skin deposits (patients should avoid exposure to the sun). • Neurological (e.g. tremors and peripheral neuropathy). • Nausea, vomiting and constipation. • Corneal micro deposits. • Hepatocellular necrosis.

Drug interactions	1-Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes. (e.g. -› Macrolides antibodies: Clarithromycin & Erythromycin. -> Azole antifungals : Ketoconazole). 2- Drugs (or substances) that inhibit CYP3A4 & CYP2C8 enzymes cause increase in serum concentration of amiodarone. (e.g. Loratadine, Ritonavir (AIDS/HIV drug), Trazodone (antidepressant), Cimetidine, Grapefruit juice). 3- Drugs that induce these enzymes cause decrease in serum concentration of amiodarone. (e.g. Rifampin).
Drug	**2- Ibutilide** Beauty lied -> كذب الجمال 😔 (Pure class III)
Important **M.O.A / Pharmacological action**	1-Prolong the Action potential duration & RP 2-Prolong phase 3 repolarization -Causes QT interval prolongation (phase3)
Clinical use	Used for acute conversion of atrial flutter or fibrillation to normal sinus rhythm
Administration	Given by rapid I.V infusion
Important **ADRs**	May cause Torsades De pointes

Class IV Drugs

Drug	1- Verapamil 2- Diltiazem
M.O.A/ pharamcological action	• Calcium channel blockers (heart selective) • Main site of action is S.A & A.V nodes causes: 1-Slowing of conduction 2-Prolongation of effective refractory period (ERP)
Clinical use	1. Atrial arrhythmias 2. Re-entry supraventricular arrhythmias (e.g. WPW) 3. NOT effective in ventricular arrhythmia (because they have action more on SA & AV nodes)

Class V Drugs

Drug	Adenosine (Miscellaneous Antiarrhythmic Drugs)
M.O.A	**Inhibit cAMP by binding to adenosine A1 receptors causing the following actions:** 1- Opening of potassium channels (Hyperpolarization) 2-Decreasing conduction velocity ,mainly at AV node (Negative dromotropic effect) and chronotropic effect 3- Inhibiting phase 4 pacemaker action potential at SA node (Negative chronotropic effect) 
Pharmacokinetics	Half life = less than 10 sec
Therapeutic uses	• Drug of choice for acute management of paroxysmal supraventricular tachycardia • preferred over verapamil (because it's safer and does not depress contractility)
ADRs	1. Flushing (in about 20% of patients) vasodilation of superficial vessels 2. Shortness of breath & chest burning (in 10% of patients) due bronchospasm 3. Brief A.V block (Contraindicated in heart block)

New Antiarrhythmic Drugs

Drug	Dronedarone
Overview	A non-iodinated congener of Amiodarone
Pharmacological action	It has antiarrhythmic properties belonging to all four classes
Uses	Used for maintenance of sinus rhythm following cardioversion in patients with atrial flutter or fibrillation
Contraindications -warning-	• Should NOT be used in patients with severe (class IV) heart failure. (Risk of death may be increased in these patients) • Should NOT be used in patients with permanent atrial fibrillation. (Risk of death and stroke may be increased in these patients)

Bradyarrhythmias

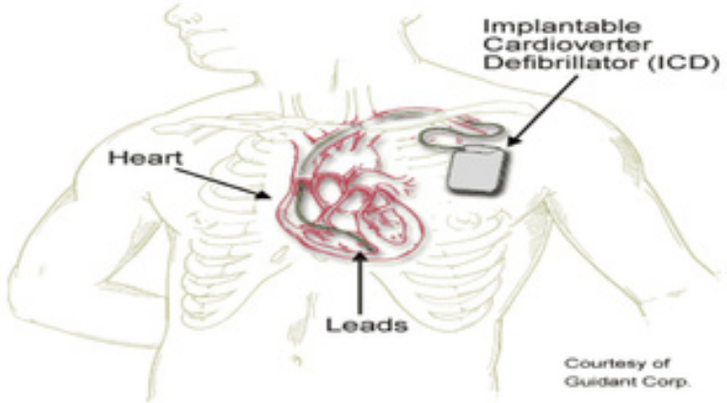
Drug	**Atropine** sympathomimetics
Uses	• Used in sinus bradycardia after myocardial infarction and in heart block • In emergency heart block **isoprenaline** (non-selective beta-adrenegic agonist) may be combined with atropine (caution) due to its additive effects

1:03:00

Nonpharmacological Therapy of Arrhythmias

Implantable Cardiac Defibrillator (ICD):

- Can automatically detect and treat fatal arrhythmias. such as ventricular fibrillation
- used if pharmacological options didn't work



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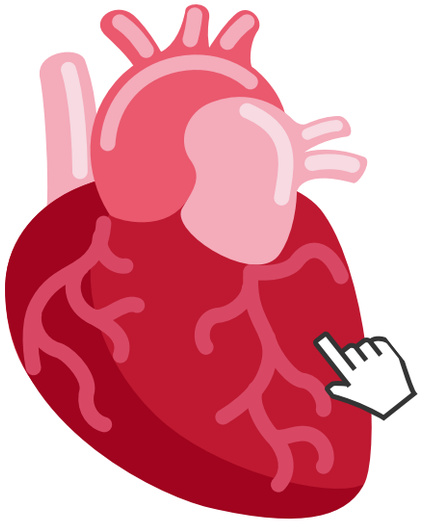

Highly recommended !!

MCQs

1 Which of the following statements about pure class III ibutilide is true?

- A: It is administered orally for the acute conversion of atrial flutter or fibrillation to normal sinus rhythm.
- B: It does not cause QT interval prolongation
- C: It is used for the treatment of ventricular tachycardia
- D: It may cause torsades de pointes

2 Which one of these drugs is used to treat medical emergency ventricular arrhythmia ?

- A: Quinidine
- B: lidocaine
- C: Mexiletine
- D: Procainamide

3 How does class Ic affects AP?

- A: Prolong Ap
- B: Shorten Ap
- C: No effects on Ap
- D: All

4 Which of the following drugs has pulmonary fibrosis as a side effect?

- A: Dronedarone
- B: Amiodarone
- C: Esmolol
- D: Ibutilide

1)D 2)B 3)c 4)B

MCQs

5 Which of the following drugs is used for rapid control of ventricular rate in patients with atrial flutter or fibrillation?

A Amiodarone B Mexiletine C Propanolol D Esmolol

6 Which of the following is used in serious ventricular arrhythmias ?

A Amiodarone B Verampile C Ibutilide D Diltiazem

7 A 37 years old woman came to your clinic complaining of repeated episodes of dizziness, racing heart beats and fatigue. After investigations, you found that she has paroxysmal supraventicular tachycardia. Which one of the following is the drug choice for her case?

A Ibutilide B Propanolol C Adenosine D Quinidine

8 Which one of the following drugs is NOT effective in treatment of venticular arrhythmia?

A Lidocaine B Verapamil C Atropine D Amiodarone

5)D 6) A7) C 8)B

SAQs

1. **how does class Ia cause torsades de pointes?**

Important

- by blocking K channels

2. **What is the mechanism of action of class II drugs?**

- Block B1 receptors in the heart reducing sympathetic effect on the heart

3. **What are the primary enzymes involved in the metabolism of amiodarone and what is active metabolite?**

Important

- -the primary enzymes: CYP3A4 and CYP2C8
  -active metabolite: N-desethylamiodarone

4. **What is the primary mechanism responsible for the elimination of amiodarone from the body?**

Important

- hepatic metabolism

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