MED441
KING SAUD UNIVERSITY

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3&4. Antiarrhythmic Drugs

Pharmacology
TEAM 441

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.

HELPFUL VIDEOS:

- **Pathophysiology of arrhythmia**
- **Anti-arrhythmic drugs**

Editing file

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

Extra information

Thanks to team 439

Ventricular Muscle Cell Action Potential Phases:

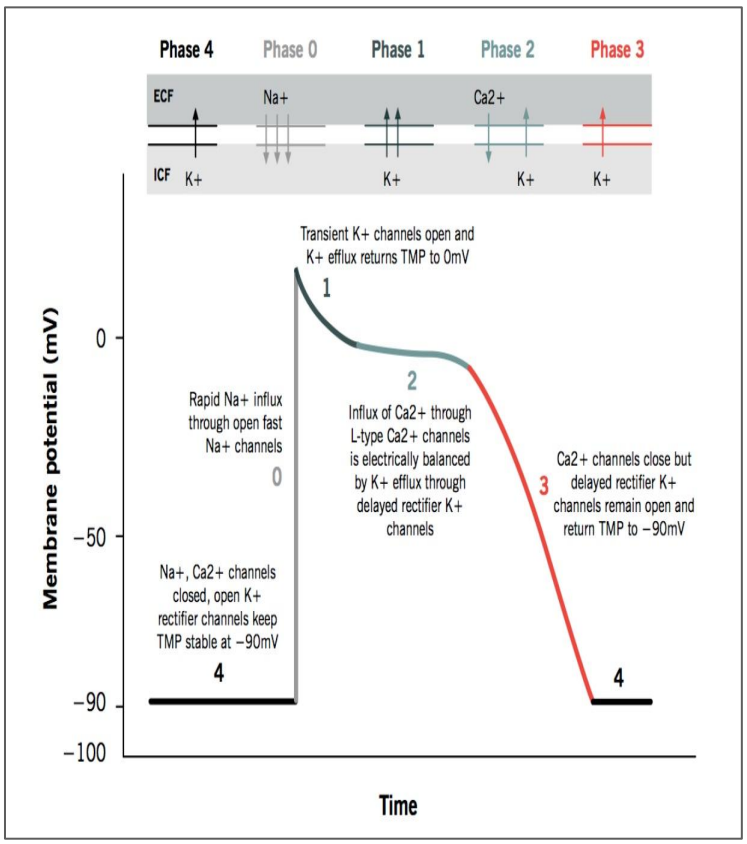
1. **Phase 4** (Resting membrane potential) (polarized)

2. **Phase 0** (Rapid Depolarization Phase): 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.

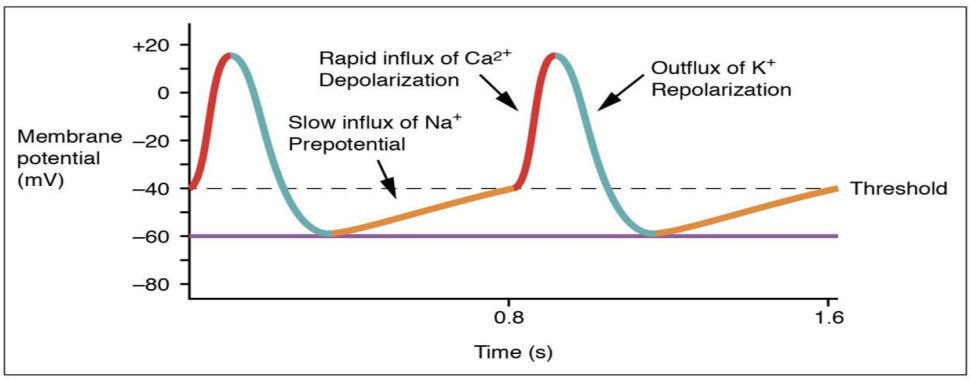
3. **Phase 1** (Initial Repolarization): At peak positivity of the cell, short-term voltage-gated K+ channels open and Na+ channels close. This allows the membrane potential to be slightly decreased to create a potential difference for voltage gated Ca++ channels to open.

4. **Phase 2** (Plateau) (refractory period): 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 afterdepolarization (torsades de pointes). "more on this later in the lecture"

5. **Phase 3** (Repolarization): Extra specialized K+ channels are opened to bring about repolarization and a return to the resting membrane potential.



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.

❖ Pacemaker potential (slow depolarization): Slow Na+ influx and a decreased K+ efflux, making the cells more positive gradually.

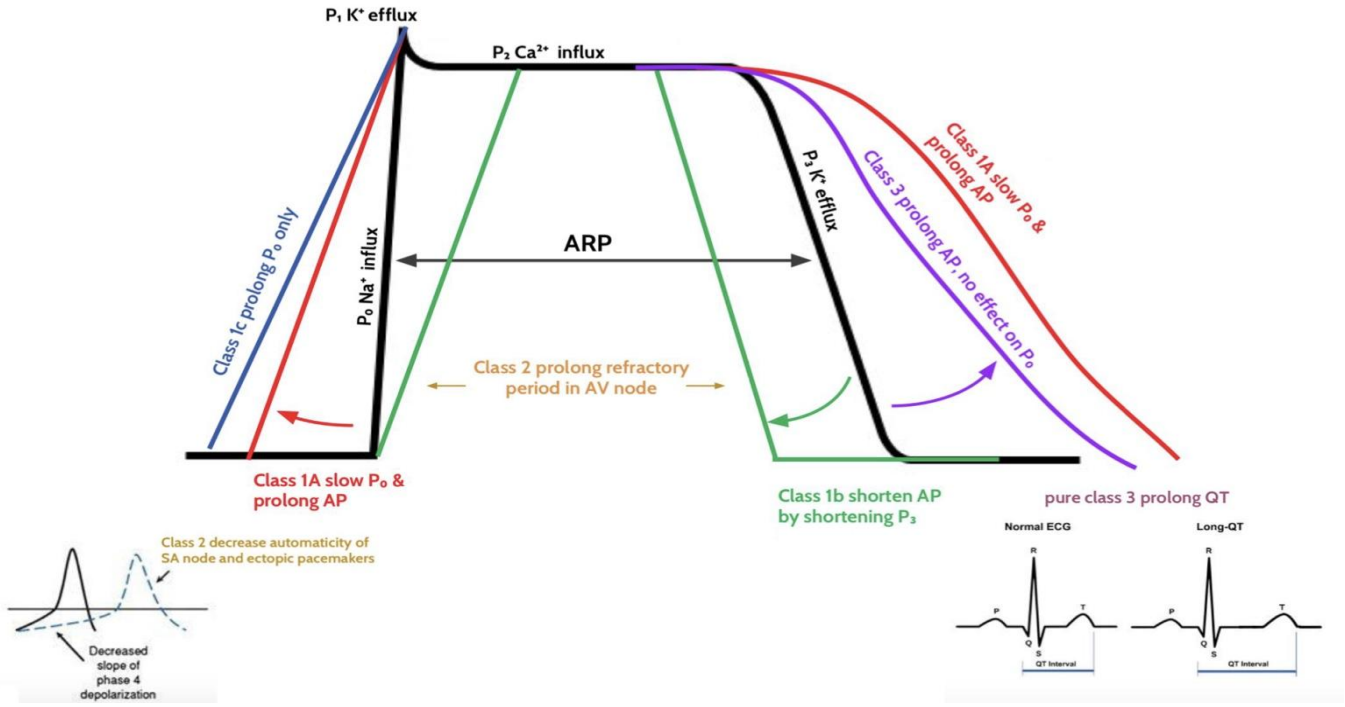
❖ Rapid Depolarization: Ca++ channels open, allowing the cells to be depolarized and action potential is reached.

❖ Repolarization: Inactivation of Ca++ channels and K+ channels are open, the cell repolarizes and Na+ channels begin to open allowing the cycle to restart.

Extra information
(Recommended)

❖ Ventricular (occurs in the ventricles)	Types of arrhythmia	❖ 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 heart beat.		**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.

❖ **Effect of Antiarrhythmic Drugs (Summary):**



Antiarrhythmic Drugs

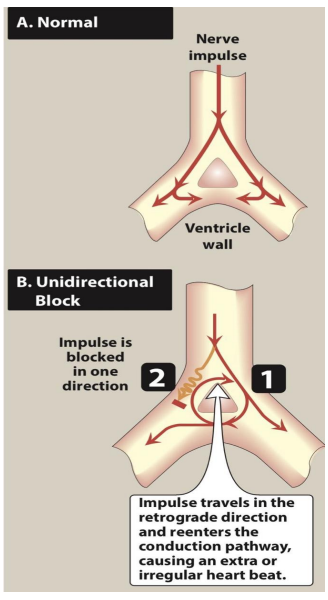
- The conduction system within the heart is responsible for generating and conducting impulses to all part of the heart:

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)
  - **PAC**: Premature Atrial Contraction
  - **PVC**: Premature Ventricular Contraction
- **Site of Origin** e.g. ectopic pacemaker
- **Disturbance in conduction**
  - AV Block > Bradycardia
    AV block has 3 type: 1st,2nd,3rd degree
  - Reentrant circuit > Cause Tachycardia



Antiarrhythmic Drugs, cont..

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

01 Maintenance of normal rhythm

02 Prevention of more serious arrhythmias

❖ **How do antiarrhythmic drugs produce these effects?**

- Slowing the conduction velocity
- Altering the excitability of cardiac cells (by prolonging the effective refractory period "ERP")
- Suppressing ectopic pacemaker activity (by inhibiting phase 4 slow depolarization)

❖ **Classification of Antiarrhythmic Drugs** ***(Helpful video)***

Vaughan-Williams Classification	M.O.A	Effects on Pacemaker Action Potential	Drugs
I	Na+ channel blockers (membrane stabilizing effect)	1- Decrease the rate of rise of rapid depolarization (Phase 0) 2- Decrease Phase 4 slow depolarization (suppress pacemaker activity)	1A.Quinidine & Procainamide 1B.Lidocaine & Mexiletine 1C. Flecainide
II	β-Adrenoreceptor blockers	Slow Phase 4 depolarization	Esmolol,Propranolol, Metoprolol,Atenolol
III	K+ channel blockers	Prolongs action potential duration	Amiodarone, Ibutilide
IV	Ca++ channel blockers	Slow Phase 4 spontaneous depolarization and conduction	Verapamil , Diltiazem
V	*Other M.O.A*	—	Adenosine

Class I drugs

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

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

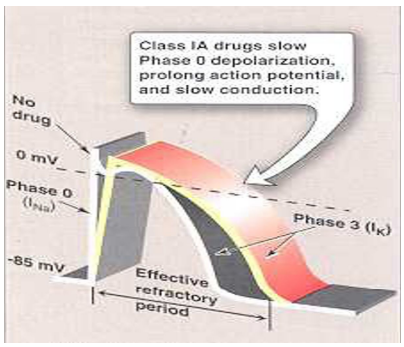
In SA node
Decrease phase 4 slow depolarization (suppress pacemaker activity).

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

I_a

Prolong action potential duration.

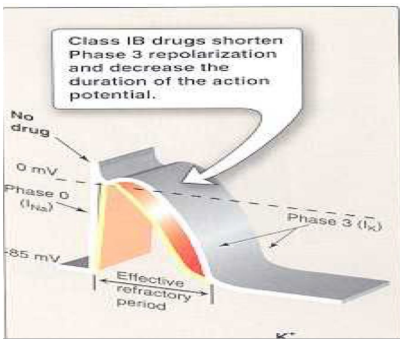
- Blocks Na (I) and K (III) channels
- Slow rate of rise
- Increase ERP
- Increase AP



I_b

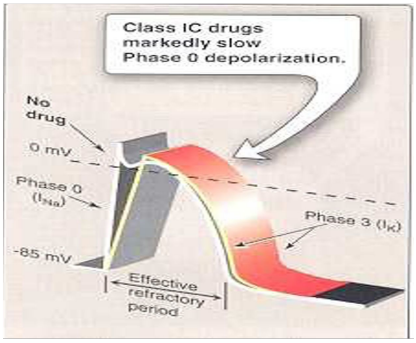
Shorten action potential duration.

- Short Repolarization
- Decrease in AP
- Decrease ERP



I_c

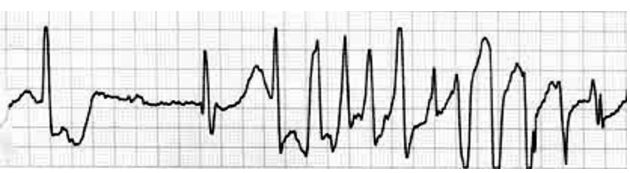
Minimal or no effect on action potential duration.



Class I drugs

"Quarter Pounder with Lettuce Mayo and Fries"

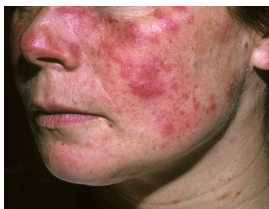
Class	Class I_a drugs	
Drugs	Quinidine "Quarter"	Procainamide "Pounder"
Action potential	Both prolong the action potential duration.	
Pharmacological action	Has other pharmacological actions include: **1-** Anticholinergic effects (Atropine like effect) : Increase conduction through the A.V node (risk of ventricular tachycardia) **2-** α-adrenergic blocking effect (side effects): May cause vasodilation & reflex tachycardia (seen more after I.V dose). **3-** ECG changes: ● Prolongs P-R & Q-T interval. ● Widens QRS complex.	Similar to Quinidine **except**: **1-** Less toxic on the heart (can be given I.V). **2-** More effective in ventricular than in atrial arrhythmias. **3-** Less anticholinergic or α-blocking actions.
Administration	Orally (Rarely I.V)	I.V
Clinical use	❖ Atrial flutter & fibrillation ❖ Maintaining sinus rhythm after cardioversion.	More effective in ventricular than atrial arrhythmias.
ADRs	1- **Quinidine syncope:** episodes of fainting due to **torsades de pointes** (twisting of the spikes) developing at therapeutic plasma levels. 2- **Anticholinergic adverse effects:** "atropine ADRS" Dry mouth, Blurred vision, Urinary retention, constipation. **3- Hypotension**: Due to depressing contractility & vasodilatation. 4- Cinchonism.	**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.

Lupus erythematosus →

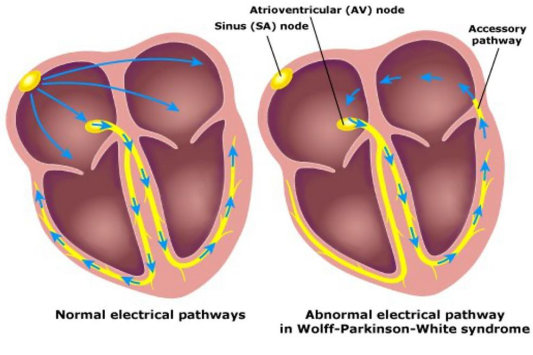


Class I drugs

Class	Class I_b drugs		Class I_c drug
Drug	Lidocaine "Lettuce"	Mexiletine "Mayo"	Flecainide "Fries"
Action potential	Shorten Action potential duration.		No effect on action potential duration. (Markedly slow phase 0 depolarization) "very potent Na channel blockers"
Clinical use	Treatment of emergency ventricular arrhythmias: 1- during surgery. 2- following acute myocardial infarction. **Not** effective in atrial arrhythmias. T ½ : 2 hours	1- Ventricular arrhythmias. 2- Digitalis induced arrhythmias (digoxin induced arrhythmias) T ½ : 10 hours	**1-** Supraventricular arrhythmias **2-**Wolff Parkinson White syndrome. **3-**Very effective in ventricular arrhythmias, but very high risk of proarrhythmia. **4-**Should be reserved for resistant arrhythmias.
Administration	Given I.V. bolus or slow infusion. -**Not** effective orally (3% bioavailability) "due to first pass metabolism"	Effective orally	-----
ADRs "most class 1 drugs have CNS ADRs because of membrane stabilizing effect"	1- Hypotension 2- CNS ADRs (similar to other local anesthetics): -Paresthesia -Tremor -Dysarthria (slurred speech) -Tinnitus -Confusion -**Convulsion**.	1- Nausea, vomiting 2- tremor, drowsiness, diplopia(double vision). 3- arrhythmias & hypotension.	1- Proarrhythmia. (Cause new arrhythmia) 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations, paraesthesia. 3- Heart failure due to -ve inotropic effect.

Wolff-Parkinson-White syndrome:

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



Class II drugs

Class	Class II drugs	
Drug	Esmolol	Propranolol,atenolol & metoprolol
Mechanism of action	block β1 receptors in the heart → Reduce sympathetic effect on the heart which leads to: 1- ↓ Automaticity of S.A. node & ectopic pacemakers. 2-Prolong refractory period (slow conduction) of the A.V node.	
Clinical uses	1- Atrial arrhythmias associated with emotions e.g: (after exercise ,thyrotoxicosis). 2- Wolff Parkinson White syndrome. 3- Digitalis induced arrhythmias."digoxin induced arrhythmias" As in mexiletine	
Specific clinical uses	❖ Given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation ❖ Very short acting (T ½ =10 min)	Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias. (Prophylaxis) Propranolol is contraindicated in asthma patients, I'm sure you remember :)

Class III Drugs

Class	Class III		
Drug	Amiodarone		
Pharmacological Action	Main effects: 1-prolong AP duration and prolong refractory period 2-Prolong phase 3 repolarization Additional effect: -Class IA (Membrane stability + α-adrenergic blocking effect) -Class II(β1 Blocker) -Class IV (Ca Block) -**Vasodilating effects** (due to its α & β-adrenoceptor blocking effects and its calcium channel blocking effects)		
Pharmacokinetics	-Extremely long half-life (13 - 103 DAYS) longest half life of all antiarrhythmic drugs -Metabolized by (CYP3A4 and CYP2C8) to its major **active** metabolite; N-desethylamiodarone (even stronger) -Eliminated primarily by hepatic metabolism (contraindicated in patients with liver problems) -Can cross placenta, and appear in breast milk (contraindicated in pregnancy and lactating women)		
Clinical use	-Main use: serious resistant ventricular arrhythmias. -Maintenance of sinus rhythm after D.C. cardioversion -Resistant supraventricular arrhythmias e.g. WPW: (useful in reentry arrhythmias) reserved in severe and resistant cases only, due to its side effects.		
ADR's	Many side effects: -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	Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes E.g. 1-Macrolides antibodies : Clarithromycin & Erythromycin 2- Azole antifungals Ketoconazole	Drugs (or substances) that inhibit CYP3A4 & CYP2C8 enzymes cause increase in serum concentration of amiodarone e.g. Loratadine, Ritonavir (AIDS/HIV drug), Trazodone (anti-depressant), Cimetidine, Grapefruit juice	Drugs that induce these enzymes Cause decrease in serum concentration of amiodarone e.g. Rifampin

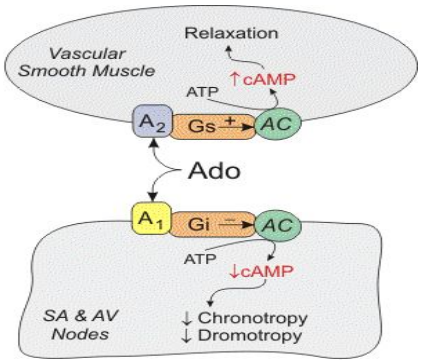
Contd Class III Drugs

Class	Class III
Drug	Ibutilide (pure Class III)
Mechanism of action	1-Prolong the Action potential duration & RP 2-Prolong phase 3 repolarization
Pharmacological action	Causes QT interval prolongation (phase3)
Administration	Given by rapid I.V infusion
Clinical use	Used for acute conversion of atrial flutter or fibrillation to normal sinus rhythm
ADR's	May cause Torsades De pointes

Class IV Drugs

class	Class IV
Drug	Verapamil/Diltiazem
M.O.A & pharmacological action	-Calcium channel blockers. -Main site of action is S.A & A.V nodes, causes: -Slowing of conduction -Prolongation of effective refractory period **(ERP)**
Clinical use	-Atrial arrhythmias -Re-entry supraventricular arrhythmias (e.g. WPW) (NOT effective in ventricular arrhythmia)

Class V Drugs
(Miscellaneous Antiarrhythmic Drugs)

class	Class V
Drug	Adenosine
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 (-ve dromotropic effect) and chronotropic effect 3- Inhibiting phase 4 pacemaker action potential at SA node (-ve chronotropic effect) 
Pharmacokinetics	Half life is 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)
ADR's	-Flushing (in about 20% of patients) (vasodilation of superficial vessels) -Shortness of breath & chest burning (in 10% of patients) due to bronchospasm -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	-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)

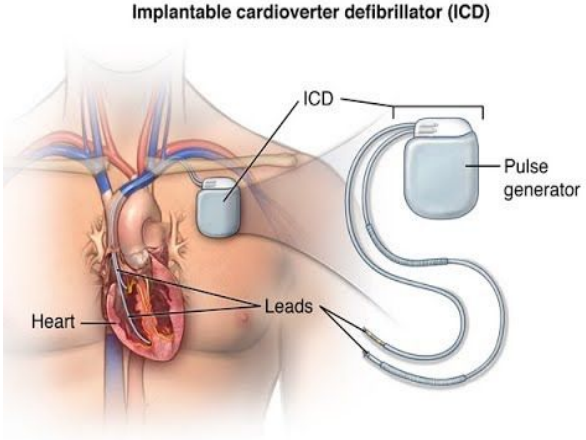
Bradyarrhythmias

Drug	Atropine
Uses	-Used in sinus bradycardia after myocardial infarction and in heart block -In emergency heart block isoprenaline may be combined with atropine (caution) due to its additive effects

Nonpharmacologic 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



SAQs:

Q1: A 57 years old patient has atrial arrhythmia, a certain medication was given to him, after a while he came with some symptoms including (headache, dizziness, tinnitus and Cinchonism). Which medication was the cause?

Q2: What is the mechanism of action of class III antiarrhythmic drugs?

Click here!

Answers:

A1: Quinidine.

A2: Potassium channel blockers.

Test yourself

From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

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