PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Antiarrhythmic drugs

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.

Important
In male and female slides
Only in male slides
Only in female slides
Extra information

helpful video

Editing file

Extra Information

Types of Arrhythmia

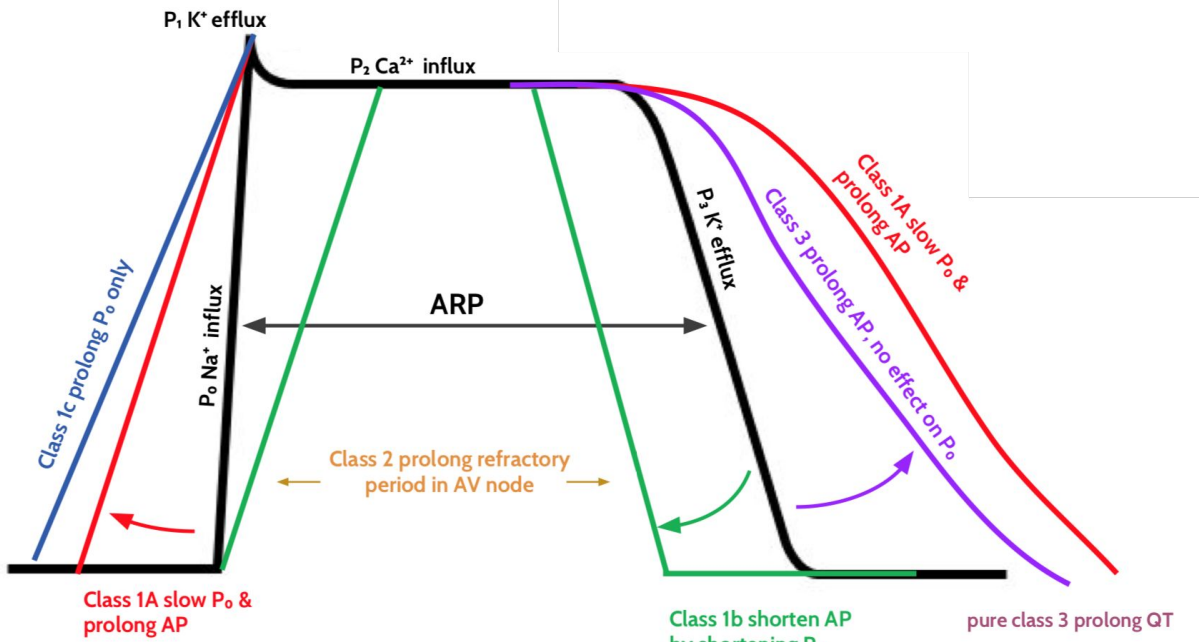
A) Ventricular:
occurs in the ventricles

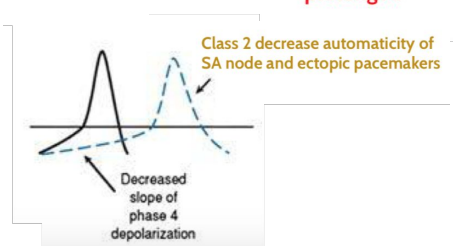
Ventricular Tachycardia: SA node no longer controls the beating of the ventricles "ectopic pacemaker" , this will result in increase heart beats.	**Premature Ventricular Contractions (PVC):** the condition happens when the ventricles contract too soon, out of sequence with the normal heart beat.
Ventricular Fibrillation: The most serious arrhythmia, it has several impulses begin at the same time from different locations with an extremely irregular rhythm	

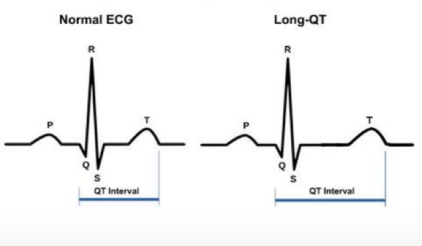
B) Supraventricular:
occurs in the atria

Paroxysmal Supraventricular Tachycardia: Rapid, regular heart beats.	**Wolff-Parkinson-White Syndrome:** Extra electrical pathways between the atria and the ventricles ,the result is a very fast heart rate.
Atrial Fibrillation: Rapid, irregular heart beats	**Atrial Flutter:** Regular ,atrial beats faster than ventricular.

Effect of Antiarrhythmic Drugs (Summary):

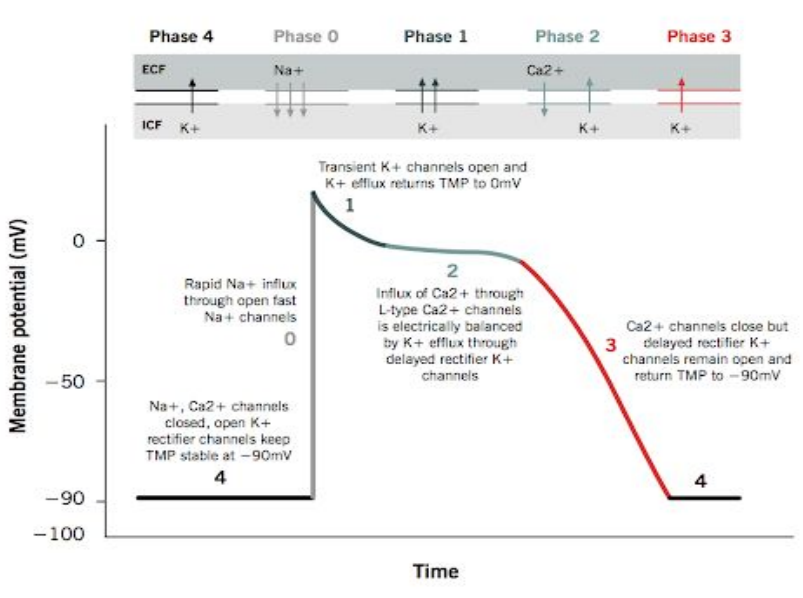






Extra Information

Ventricular Muscle Cell Action Potential Phases:



4- Resting membrane potential (polarized)

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.

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.

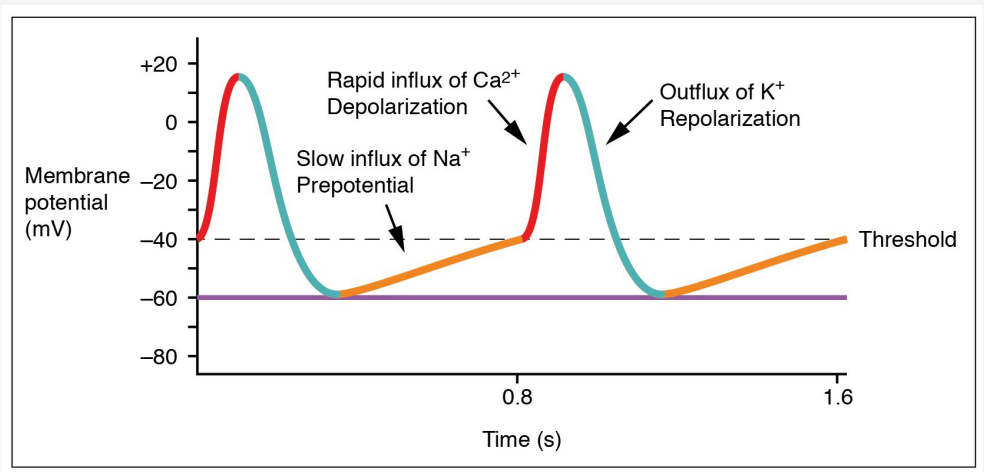
2-Plateau (refractory period):

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"

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.

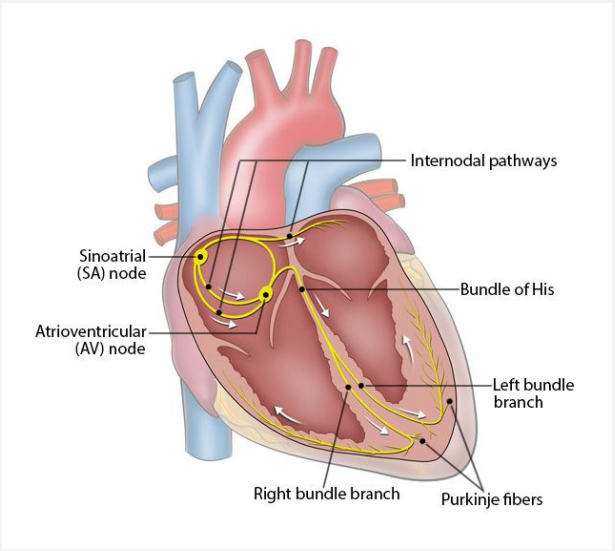
Repolarization: Inactivation of Ca++ channels and K+ channels are open, the cell repolarizes and Na+ channels begin to open allowing the cycle to restart.

Antiarrhythmic Drugs

EXtra information

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

1. SA node generates impulses.
2. **AV Nodal Delay:** these impulses pass the internodal pathways to reach the AV node.
3. Then, these impulses pass through the Bundle of His to the right and left bundle branches to finally reach the purkinje fibers

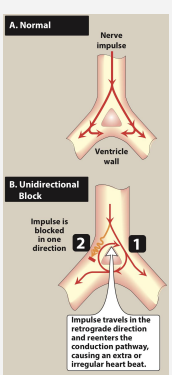


Arrhythmias are conceptually simple, dysfunctions cause abnormalities in the formation and conduction of impulses in the myocardium.

Arrhythmia is an abnormality in the:

- **Rate** (>100=tachycardia, <60=bradycardia)
- **Regularity** e.g. extrasystole (PAC, PVC)*
- **Site of Origin** e.g. ectopic pacemaker
- **Disturbance in conduction**
  - AV Block > Bradycardia
    AV block has 3 type 1st,2ed,3rd degree
  - Reentrant circuit > Cause Tachycardia

* PAC: Premature Atrial Contraction
PVC: Premature Ventricular Contraction



Ultimate goal of antiarrhythmic drugs: **Restore normal rhythm & conduction by**

- Maintenance of normal rhythm
- Prevention of more serious arrhythmias

How do antiarrhythmic drugs work?

- Slow the conduction velocity
- Alter the excitability of cardiac cells (prolong the effective refractory period)
  To allow the heart to rest and restore SA node function.
- Suppress ectopic pacemaker activity (by inhibiting phase 4 slow depolarization)

Classification of Antiarrhythmic Drugs

MBA College

M=class I= **M**embrane stabilization
B= class II= **β** blockade
A=class III= **A**ction potential widening
C=class IV=**C**alcium channel blockers

SoBePoCa (Say: South Beatch Polka)

So=**So**dium channel blockade
Be=**β**-blockers
Po=**Po**tassium channel blockers
Ca=**Ca**lcium channel blockers

No BadBoy Keeps Clean

No=**Na+** channel blockade
Bad=**β**-blockers
Keeps=**K+** channel blockers
Clean=**C**alcium channel blockers

Vaughan-Williams Classification	M.O.A	Effects on Pacemaker Action Potential
IA	Na+ channel blocker (membrane stabilizing drugs) Na+ initaites the both SA node and Ventricular action potential	1-Decrease the rate of rise of rapid depolarization (Phase 0) 2- Decrease Phase 4 slow depolarization (suppress pacemaker activity)
IB		
IC		
II	β-Adrenoreceptor blocker	Slow Phase 4 depolarization
III	K+ channel blocker	Prolongs action potential duration
IV	Ca++ channel blocker	Slow Phase 4 spontaneous depolarization and conduction
V	Miscellaneous antiarrhythmics	---

Class I Drugs

Mechanism of action

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

They have the following effects on the cardiac action potential:

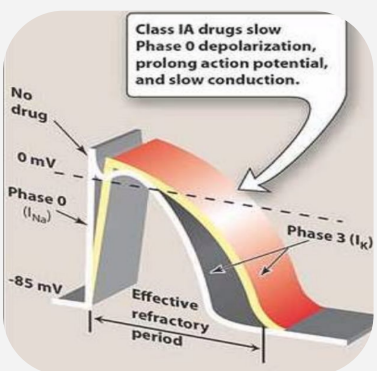
- Decrease the rate of rise of rapid depolarization (Phase 0).
- Decrease phase 4 slow diastolic depolarization (suppress pacemaker activity).

Sub classified according to their effect on Action potential duration into:

Ia

Prolong action potential duration

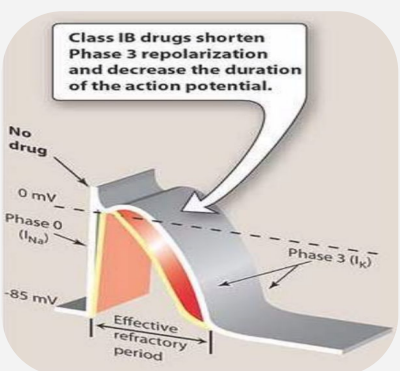
Cause closing of potassium channels, slowing repolarization and increase duration of action potential.



Ib

Shorten action potential duration

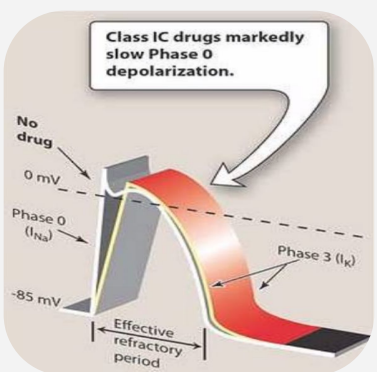
Cause opening of potassium channels, more rapid repolarization and less duration of action potential.



Ic

No effect (Minimal effect) on action potential duration

No effect on potassium channels, repolarization is unaffected.



Mnemonic :
Double Quarter Pounder (IA), with Lettuce and Mayo(IB) and Fries Please (IC)

Class I Drugs

Class	Class IA (Double Quarter Pounder)	
Drug	**Quinidine**	**Procainamide**
AP	Prolong action potential duration A for Active people who have potential for more duration	
Pharmacological Action	-Has other pharmacological actions include: **1/** Anticholinergic effects (Atropine like action) : • Increase conduction through the A.V node (risk of ventricular tachycardia) **2/** α-adrenergic blocking effect (side effects): • May cause vasodilation & reflex tachycardia (due to sympathetic baroreceptor reflex)(seen more after I.V dose) (So avoid I.V administration) **3/** ECG changes: • Prolongs P-R & Q-T interval (reason for torsades de pointes) يطول البركات • Widens QRS complex Ventricular contraction	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. Pro =Professional ; cause its less toxic, No anticholinergic or α-blocking actions.
Administration	Given ORALLY (Rarely given I.V)	I.V
Clinical Use	-Atrial flutter* & fibrillation**. Atrial=عطر|So the queen likeالعطر -Maintaining sinus rhythm after cardioversion. (cardioversion is a medical procedure that restores normal heart rhythm by sending electric shocks to your heart)	More effective in ventricular than in atrial arrhythmias.
ADR's N/V/D : Nausea /vomiting /diarrhoea	1- Quinidine syncope: -Episodes of fainting due to torsades de pointes (twisting of the spikes) developing at therapeutic plasma levels 2- Anticholinergic adverse effects: Dry mouth, Blurred vision, Urinary retention, N/V/D & constipation 3-Hypotension: Due to depressing contractility(-ve inotropic effect)& vasodilatation.	1- In long term therapy it causes reversible **lupus erythematosus like syndrome.** سلي نفسك بالروك = SLE Prokainamide ميوزك 2- **Hypotension**. Because it reduces peripheral resistance 3- **Torsades de pointes** (At toxic dose) 4- Hallucination & psychosis

Torsades de pointes:

- Torsades de pointes is a specific form of polymorphic ventricular tachycardia in patients with a long QT.
- It may terminate spontaneously or lead to fatal ventricular fibrillation.
- Torsades de pointes can treated by Mg injection, because it decreases the influx of Ca

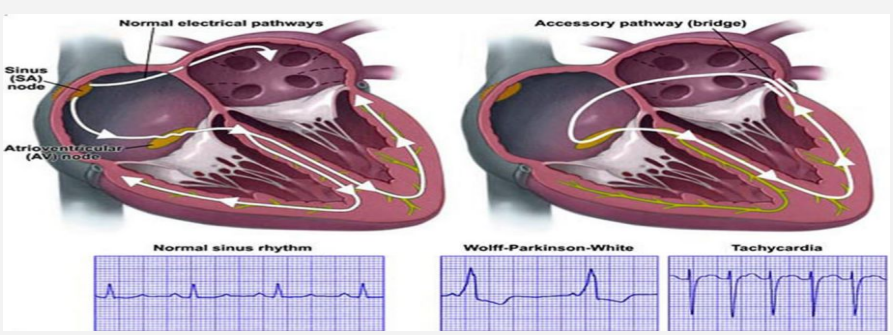
*Atrial flutter: heart is beating rapidly
**Atrial fibrillation: irregular tachycardia

QT interval: period between ventricular depolarization and repolarization.
In Torsades de pointes:QRS complex become downward.

	Class IB with Lettuce and Mayo		Class IC and Eries Please
Drug	Lidocaine	Mexiletine	Flecainide
P.A	Shorten action potential duration. B for Bored, not active people; have less or shortened potential.		Has no effect on action potential duration (Markedly slow phase 0 depolarization) (very potent)
Clinical uses	1/Treatment of emergency ventricular*Lidocaine = (Lee do what u can) (to save people in ER) arrhythmias e.g: 1-During surgery 2-Following acute myocardial infarction. (NOT effective in **atrial** arrhythmias) *Dr's note : you have to know which drugs are used in ventricular/atrial arrhythmia	1/ventricular arrhythmias 2/Digitalis-induced-arrhythmias.(digitalis are pump inhibitors like digoxin, used to treat heart disorder) ابطال الديجيتال was excellent (Mexiletine) (Digitalis)	1/Supraventricular arrhythmias 2/Wolff-Parkinson-White syndrome (WPW) WPW = iNi Flecainide 3/Very effective in ventricular arrhythmias, **but very high risk of proarrhythmia** 4/Should be reserved for resistant arrhythmias. (It's not the first choice, used if the arrhythmia resistant to other drugs)
$T_{1/2}$	2 hours	10 hours	.....
Administration	Given I.V. bolus or slow infusion. (NOT effective orally due to only 3% bioavailability)	Effective Orally Effective orally, Mexiletine = tongue	
ADRs	1/Hypotension 2/CNS ADRs (similar to other local anesthetics): -Paresthesia -Tremor -Dysarthria (slurred speech) -Tinnitus -Confusion -Convulsion: Last stage of ADRs	1- nausea, vomiting 2- tremor, drowsiness,diplopia (double vision) 3- arrhythmias & hypotension	1/Proarrhythmia proarrhythmia means it cause new arrhythmia due to interference with electrolytes. 2- CNS : dizziness , tremor, blurred vision, abnormal taste sensations, paraesthesia. 3- Heart failure due to -ve inotropic effect. It decreases heart force of contraction

Wolff-Parkinson-White syndrome (WPW):

- It is the Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent. It represents an abnormality in the conduction system



The use of class 1b is reserved for special conditions, people following a myocardial infarction have a decreased amount of ATP leading to a dysfunctional Na-K pump, Na builds up inside the cells and depolarization persists for a long time, therefore a shortened action potential duration is the target.

Class II Drugs

Class	Class II	
Drug	**Esmolol**	**Propranolol, Atenolol, metoprolol**
Mechanism of action	block β_1 receptors in the heart → Reduce sympathetic effect on the heart <u>which leads to:</u> 1- ↓ automaticity of S.A. node & ectopic pacemakers 2-prolong RP (refractory period) (slow conduction) of the A.V node	
Clinical uses:	1- atrial arrhythmias associated with emotions e.g.: (after exercise ,thyrotoxicosis) 2- WPW (Wolff Parkinson white syndrome) 3- Digitalis induced arrhythmias (بينك)beta blockers(مليان الكترونيات)digitalis	
Clinics Uses	- given I.V. for rapid control of ventricular rate in patients with atrial flutter or fibrillation -Very short acting (t1/2 = 9min) (لما نعطي الانجكشن) IV (نسمي ونقول اسمالله عليك) Esmolol (وكل شيء يتيسر و يصير بسرعة)rapid action 9 min	-Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias (Used as a prophylaxis) -(Propranolol is contraindicated with asthma patients)

The heart generates its own electrical impulses, but is affected by sympathetic impulses in flight or fight responses, hence the need for these drugs.

Class	Class III		
Drug	**Amiodarone (prototype)** أمي تدير كل شي		
Pharmacological Action	أمي حالتها خطيرة **Main effect:** 1- prolong action potential duration and prolong refractory period 2- Prolong phase 3 repolarization (blocking K channels). 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)		
P.K	-Extremely long half-life (13 - 103 DAYS) (longest half life of all antiarrhythmic drugs) آمي الله يطول بعمرها -Metabolized by cytochrome P450 (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) أمي حملت وأرضعت		
Clinical Use	-**Main use**: serious resistant ventricular arrhythmias. -Maintenance of sinus rhythm after D.C. cardioversion -Resistant supraventricular arrhythmias e.g. WPW: (useful in re-entry arrhythmias) reserved in severe and resistant cases only, due to its side effects.		
ADR's	Many side effects: آمي عندها بلاوي كثيرةcause of many ADRs -Exacerbation of ventricular arrhythmias (high dose) -**Bradycardia** and heart failure -**Pulmonary fibrosis** -**Hyper or hypothyroidism** (because it contain iodine) -**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 آمي صاحبة مشاكل cause of many drug interactions	(pharmacodynamics) Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes E.g. 1-Macrolides : Clarithromycin & Erythromycin 2- Azole antifungals Ketoconazole	(pharmacokinetic) 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	(pharmacokinetic) Drugs that **induce** these enzymes Cause decrease in serum concentration of amiodarone **e.g.** Rifampin

Class III Drugs cont.

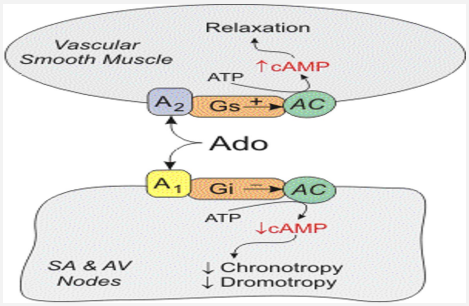
Class	Class III
Drug	Ibutilide (Pure Class III)
Mechanism of action	Prolong the action potential duration & RP Prolong phase 3 repolarization
Pharmacological Action	Causes QT interval prolongation (phase 3)
Administration	Given by rapid I.V. infusion
Clinical Use	Used for acute conversion of atrial flutter اي بطلت احط عطر و عطر=Atrium or fibrillation to normal sinus rhythm
ADR's	May cause Torsades De Pointes

Class IV Drugs

Class	Class IV
Drug	Verapamilفيه raperاسمها أمل, Diltiazem دليتي عازم ؟
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 Used only for atrial = عازم وامل يحبون العطر -Re-entry supraventricular arrhythmias (e.g. WPW) (NOT effective in ventricular arrhythmia)

Class V Drugs

(Miscellaneous Antiarrhythmic Drug)

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)

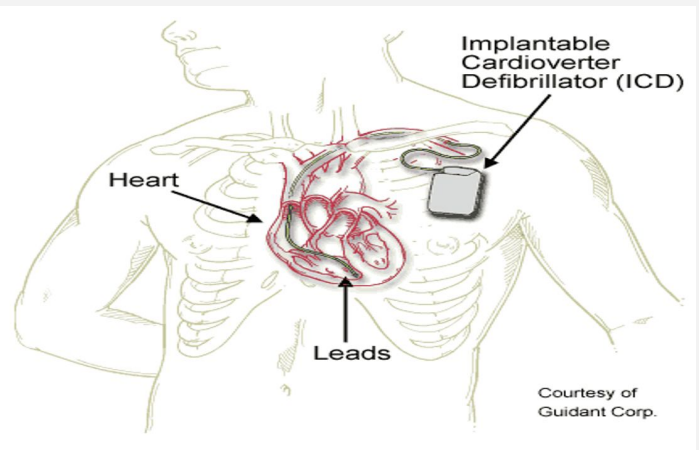
Bradyarrhythmias

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



Summary

Drug	Class	Uses
Quinidine	Class Ia a) Do Pulse Quickly	-**Atrial** flutter & fibrillation. - Maintaining sinus rhythm after cardioversion.
Procainamide		More affective in **ventricular** arrhythmia
Lidocaine	Class Ib b) Low Mute?	Treatment of emergency **ventricular** arrhythmias. e.g: -During surgery -Following acute myocardial infarction.
Mexiletine		1- **ventricular** Arrhythmia 2- digitalis induced arrhythmia
Flecainide	Class Ic c) Find paddles	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.
Esmolol	Class II (**β1 blockers**) Beta blockers? LOI	Rapid control of **ventricular** rate in patients with atrial fibrillation or flutter
Propranolol Atenolol metoprolol		Used in patients who had myocardial infarction to reduce incidence of sudden death due to **ventricular** arrhythmias
Amiodarone	Class III	-Main use: serious resistant **ventricular** arrhythmias.
Ibutilide (Pure Class III)		Used for acute conversion of **atrial** flutter or fibrillation to normal sinus rhythm
Diltiazem,Verapamil	Class IV I and V in **IV**	**Atrial** arrhythmia Re- entry **supraventricular** arrhythmia (e.g.WPW)
Adenosine	Class V	drug of choice for acute management of paroxysmal **supraventricular** tachycardia
Dronedarone	New Antiarrhythmic drug	Maintenance of sinus rhythm following cardioversion in patients with **atrial** fibrillation or flutter
Atropine	Bradyarrhythmias	Used in sinus bradycardia after myocardial infarction and heart block in emergency heart block isoprenaline may be combined with atropine

Summary:

Common uses

- ★ **Wolff-Parkinson-White syndrome**
  Flecainide،β_1 Blockers (class ll), Amiodarone,Verapamil, Diltiazem
- ★ **Digitalis-induced -arrhythmia** Mexiletine, β_1 Blockers,
- ★ **Ventricular arrhythmia** Flecainide, Mexiletine, Lidocaine (emergency), Amiodarone (resistant), Procainamide (more effective)
- ★ **Atrial arrhythmia**
  β_1 Blockers,Verapamil, Diltiazem
- ★ **atrial fibrillation or flutter.**
  Esmolol,Quinidine,Ibutilide,Dronedarone(**Not** for permanent atrial fibrillation)

Important ADRs

- ★ Quinidine: Quinidine syncope, Anticholinergic ADRs
- ★ Procainamide: SLE
- ★ **Torsades de pointes:**
  Procainamide (toxic dose), Quinidine, Amiodarone(with other drugs), Ibutilide
- ★ Amiodarone : Pulmonary fibrosis, Hyper/hypothyroidism, Photodermatitis, Corneal micro deposits, Hepatocellular necrosis...
- ★ Adenosine:Flushing, bronchospasm, Brief A.V block

MCQ

Check out our Quiz

1. A patient brought to the emergency department unconscious. His relatives said the he have complained recently of hypotension, nausea and vomiting. ECG is immediately performed and it shows torsades de pointes. What is the most likely drug to cause those symptoms?			
A-Flecainide	B-Propafenone	C-Qunidine	D-Lidocaine

2-Antiarrhythmic drugs:			
A-Promote ectopic pacemaker activity	B-Increase the conduction velocity	C- Decrease effective refractory period	D-Prolong effective refractory period

3- Which of the following class of antiarrhythmic drugs is a Ca++ channel blockers			
A- IV	B- III	C- I	D- II

4- Which of the following is NOT effective in atrial arrhythmia			
A-Mexiletine	B-Lidocaine	C-Dronedarone	D-Flecainide

5- Which of the following is describing Class I mechanism of action, act by blocking the			
A-efflux of Na	B-influx of K	C-efflux of K	D-influx of Na

6- Which of the following widens QRS complex			
A-Quinidine	B-Procainamide	C-Mexiletine	D-Dronedarone

7- A 60-year-old woman had a myocardial infarction. Which of the following should be used to prevent life-threatening arrhythmias that can occur post– myocardial infarction in this patient?			
A-Digoxin	B-Flecainide	C-Metoprolol	D-Procainamide

Answers

1	2	3	4	5	6	7
C	D	A	B	D	A	C

MCQ

8-which one of the following have antiarrhythmic properties belonging to all four classes?			
A-Dronedarone	B-Diltiazem	C-Esmolol	D-Mexiletine

9-all the following side effects of adenosine EXCEPT:			
A-flushing	B-shortness of breath	C-hepatocellular necrosis	D-brief AV block

10-in emergency heart block we use atropine in combine with			
A-amiodarone	B-adenosine	C-propafenon	D-isoprenaline

11-MEXILETINE use for treatment of emergency ventricular tachycardia following cardiac surgery or acute myocardial infarction			
A-T	B-F		

12-Arrhythmia is a disturbance in all cardiac signal_____. EXCEPT:			
A- Regularity	B- Site of Origin	C- Pressure	D-Rate

13- Which statement regarding dronedarone is correct?			
A-Dronedarone is more effective than amiodarone.	B-QT interval prolongation is not a risk with dronedarone.	C-Dronedarone increases the risk of death in patients with permanent atrial fibrillation or class IV heart failure.	D-There is no need to monitor liver function with dronedarone. Answer is C

Answers

8	9	10	11	12	13
A	C	D	B	C	C

SAQ

Q1) Flecainide can't be used as first line drug, why ?

Q2) what is the mechanism of action for Class II Drugs ?

Q3) What happen to the QRT complex in torsades de pointes

Q4) what's the contraindications of Dronedarone?

Q5)what's the M.O.A of verapamil?

Q6) a patient with arrhythmia was treated with Amiodarone, he had a fungal infection, a)what is the drug that should be avoided, b) why?

Answers

A1) because it Might lead to proarrhythemia

A2) β_1 Blockers → Reduce sympathetic effect which leads to:

1- ↓ S.A Node automaticity (ability to spontaneously generate electrical impulses)

2-↑ refractory period of A.V Node

A3) it become downward

A4) patients with severe (class IV) heart failure and patients with permanent atrial fibrillation.

A5)Calcium channel blockers. -Main site of action is S.A & A.V nodes, causes:

-Slowing of conduction -Prolongation of effective refractory period

A6) a) ketoconazole, b) it prolong the QT interval which increases the risk of Torsades de Pointes when administered with Amiodarone

GOOD LUCK!

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