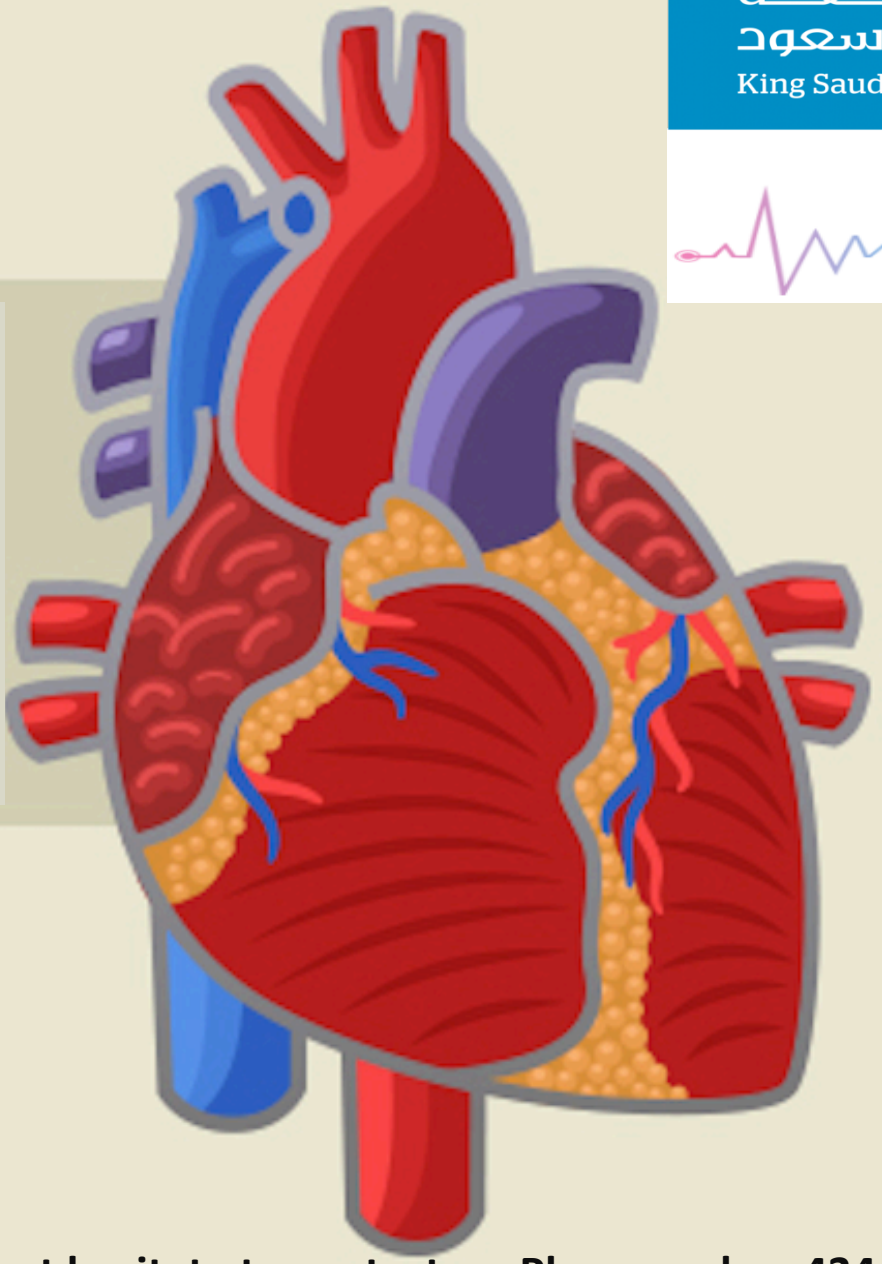
3&4

Antiarrhythmic Drugs.



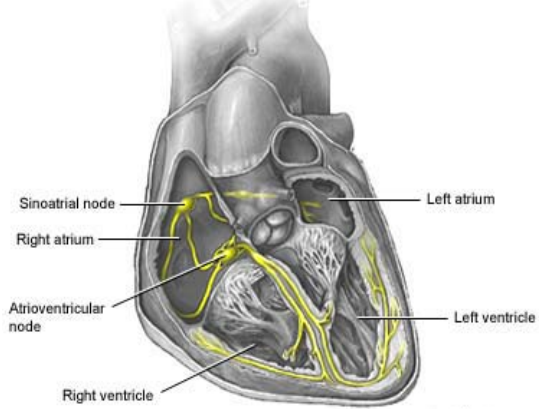
Cardiovascular Block.

Red = Important
MCQs Also Important

For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com

Introduction:

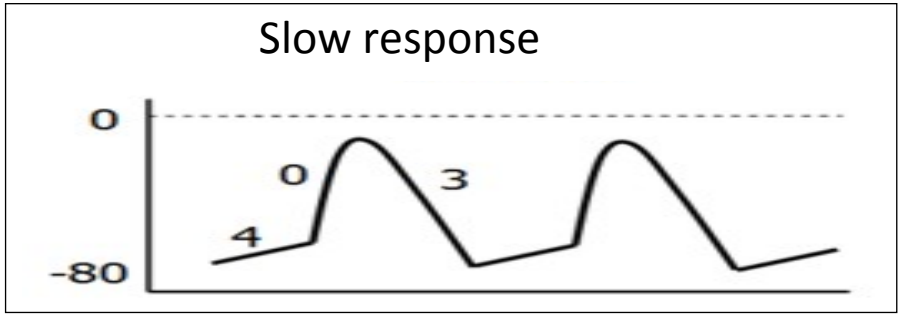
The heart consists of 4 chambers: 2 Atrium and 2 Ventricles. Also has a conduction system, which spontaneously generates rhythm in absence of external stimuli, these impulses originally generate from SA node to AV node by Inter-nodal pathways to Bundle of His and its branches to Purknje fibers.
The heart has 2 types of tissue fast response and slow response, the slow response like in SA and AV node and fast response like in myocardium and purknje fibers.



- **The slow response tissue:** has 3 phases for Action potential. (Phase0,3and4)

The SA and AV nodes have slow upstroke velocity. A smaller magnitude of Action Potential, and brief plateau phase. Also, there are no fast Na Channel, and the action potential is caused by the opening of Ca channel.

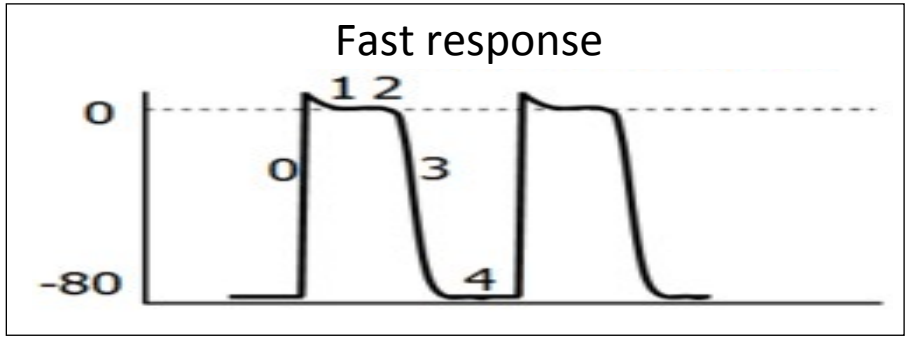
Phase 4: Diastolic Depolarization
Phase 0: Depolarization
Phase 3: Repolarization



- **The fast response tissue:** has 5 phases for Action Potential. (Phase0, 1,2,3 and4)

These table below shows the phases of Action Potential of fast response tissue

Phase	Name	Description
Phase 0	Rapid Depolarization	Open of Na Channel lead to rapid Na influx
Phase 1	Partial Repolarization	Close of Na Channel and Open of K channel lead to K efflux
Phase 2	Plateau	Influx of Ca by open Channel with efflux of K
Phase 3	Rapid Repolarization	Efflux of K continue and Ca channel close
Phase 4	Diastolic Depolarization	Resting membrane potential maintained by K



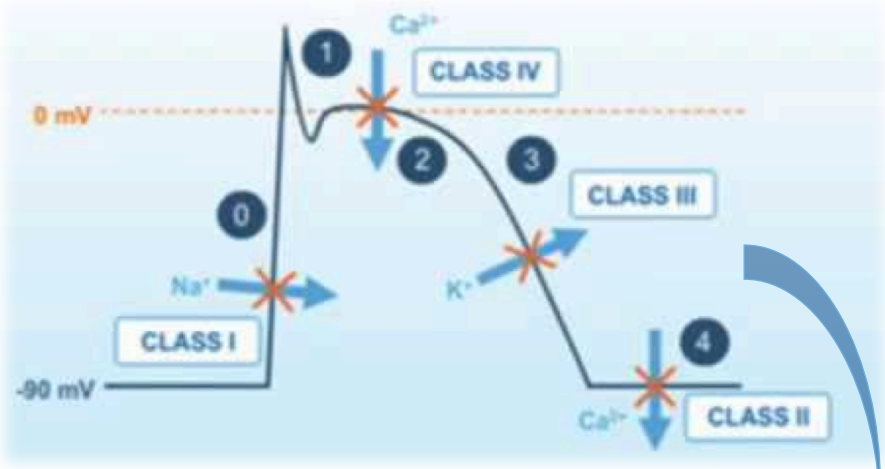
Arrhythmia:

www.youtube.com/watch?v=5xSEZszGDtI

- **Definition:** Dysfunction of impulse Conduction or generation Cause to abnormality in rhythm

- **Arrhythmia is an abnormality in heart:**

1- **Rate**: high: tachycardia, low: bradycardia
2- **Regularity**: like extra systoles
3- **Site of origin**: like ectopic pacemaker
4- **Disturbance in conduction**



- **What is the genesis of arrhythmia?**

1- Altered automaticity: If other area of the heart depolarize more quickly than SA node.
2- Altered conduction: By circus movement or re-entry (Most common).

- **What is the ultimate goal of antiarrhythmic drugs?**

1- Restore normal rhythm.
2- Prevent more serious and lethal arrhythmia.

- **How these drugs produce its effect?**

1-Increase or decrease Conduction velocity. 2-Aerting the excitability by changing the refractory period. 3-Suppressing abnormal automaticity.

- **Classification of antiarrhythmic drugs: (in the table below)**

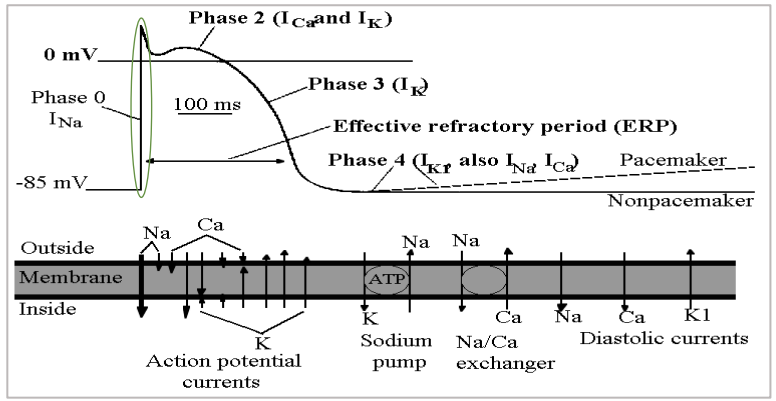
Classification of Drug		Mechanism of Action	Comment	Examples
Class 1	A1	Na Channel Blocker	Slow phase 0 (in ventricular muscle)	Quinidine and Procainamide
	A2	Na Channel Blocker	Shorten Phase 3 (in ventricular muscle)	Lidocaine and Mexiletine
	A3	Na Channel Blocker	Marked slow phase 0 (in ventricular muscle)	Flecainide and Propafenone
Class 2		β- adrenoceptor blockers	Inhibit phase 4 (in SA and AV nodes)	Esmolol, Propranolol, Atenolol, and Metoprolol
Class 3		K Channel Blocker	prolong Phase 3 (in ventricular muscle)	Aminodarone and Ibutilide
Class 4		Ca Channel Blocker	Inhibit action potential (in SA and AV nodes)	Verapamil and Diltiazem
Miscellaneous antiarrhythmic drugs		Does not undergoes specific class. *we can call it Class 5	It is a large group of antiarrhythmic drugs	Adenosine and Digitalis

Class 1 Drugs

This class of drug **block** the rapid inflow of Na+ ions thus:

- Decrease the rate of rise of depolarization (Phase 0).
- Decrease phase 4 diastolic depolarization (suppress Pacemaker activity).
- Has membrane stabilizing effect .
- At high concentration they have local anesthetic effect.
- Negative inotropic effect (cardiac depression).

(depress the contractility)

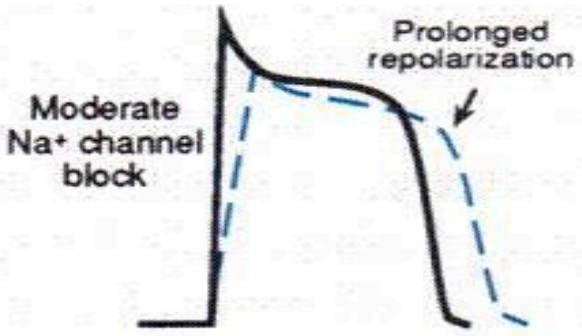


Class 1

1A

Prolong action potential duration

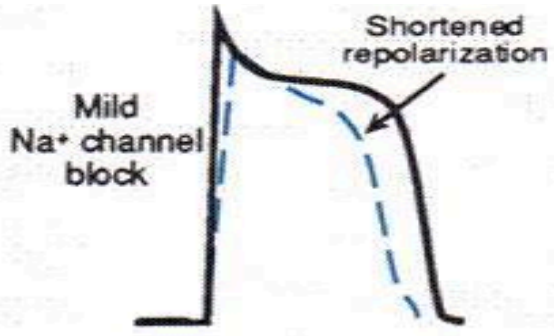
1-Quinidine 2-Procainamide



1B

Shorten action potential duration

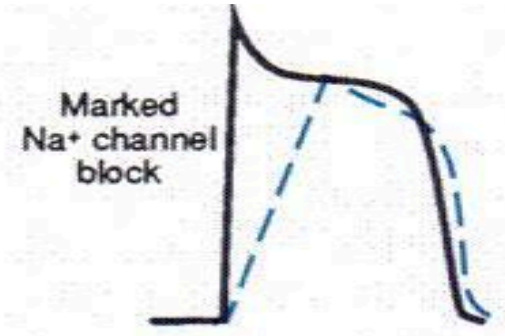
1-Lidocaine 2-Mexiletine

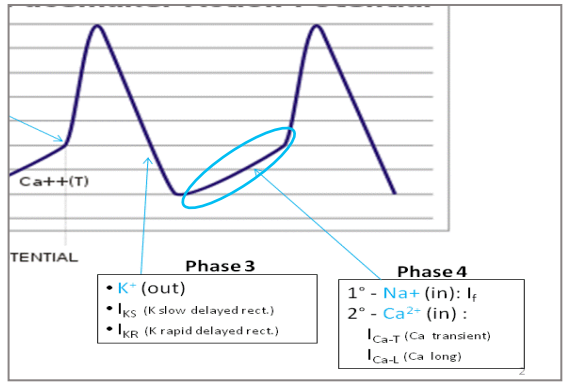


1C

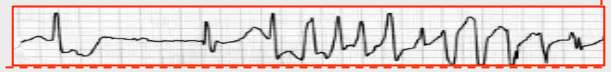
have **NO or little** effect on action potential duration

1-Flecainide 2-Propafenone





Class 1A Drugs

Drug	Quinidine (Isomer of quinine)	Procainamide
Clinical use	- In almost all types of arrhythmias - Common uses: atrial flutter& fibrillation. - Can be used for ventricular tachycardia - Maintaining sinus rhythm after D.C (Direct current[1]) cardioversion	- Effective against most atrial and ventricular arrhythmias - Second choice (after lidocaine) in ventricular arrhythmias after acute myocardial infarction - More effective in ventricular than Quinidine in atrial arrhythmias
Mechanism of Action	- Effects : 1. Membrane stabilizing effect: Block potassium channels leading to prolongation of action potential duration → Prolongation of atrial and ventricular refractory period. 2. Anticholinergic effect : Increase conduction through the A.V. node (May lead to high ventricular rate in atrial flutter. Can be prevented by prior administration of a drug that slow A.V. conduction such as digoxin, β-blockers calcium channel blockers) - Depress cardiac contractility . - ECG changes: Prolongation of P-R .. Prolong Q-T Cause Torsades de pointes interval widens QRS complex - Cause α-adrenergic blocking effect: which cause vasodilatation and reflex sinus Tachycardia , This effect is seen more after i.v. dose - **Important:** For Procainamide No anticholinergic or α-blocking actions & Less depression of contractility **Torsades de pointes:** (in drugs prolong QT interval) (twisting of the spikes) developing at therapeutic plasma levels (may terminate spontaneously or lead to fatal ventricular fibrillation). 	
Route of Administration	GIVEN ORALLY , rarely given I.V. because of toxicity and hypotension due to α-blocking effect.	less toxic on the heart, can be given I.V.
Adverse Effect	• GIT: Anorexia(فقدان الشهية), nausea, vomiting and diarrhea • CARDIAC: - Quinidine syncope: episodes of fainting due to torsades de pointes , Hypotension • may terminate spontaneously or lead to fatal ventricular fibrillation • CNS: tinnitus , headache & dizziness • Anticholinergic adverse effects • Cinchonism: (poisoning caused by an overdose of cinchona or the alkaloids quinidine) • At toxic concentrations: can precipitate arrhythmia and produce asystole (cardiac arrest) if serum concentrations exceed 5 µg/ml or in high potassium levels (> 5mmol/L).	- In long term therapy it cause reversible lupus erythematosus-like syndrome in 5-15% of patients - Hypotension - Torsades de pointes - Hallucination & psychosis
Drug Interaction	• Increase concentration of digoxin: - Displacement from plasma proteins - Inhibition of digoxin renal clearance	

Class 1B		
Drugs	Lidocaine	Mexiletine
Route of Administration	Given I.V. bolus or slow infusion	Effective orally.
Clinical Uses	Ventricular arrhythmias in emergency e.g. cardiac surgery, acute myocardial infarction. •Not effective in atrial arrhythmias.	•Ventricular arrhythmia. •Digitalis-induced arrhythmias. •Chronic pain e.g. diabetic neuropathy and nerve injury.
Pharmacokinetics	Not effective orally (3% bioavailability). Half-life: 2 Hours	Half-life: 10 Hours
Adverse effects	•Cardiac: Hypotension. •CNS: paresthesia, tremor, dysarthria (slurred speech), hearing disturbances, confusion and convulsions.	•GIT: Nausea, vomiting. •CNS: Tremor, drowsiness, diplopia. •Cardiac: Arrhythmias & hypotension.

CLASS 1C

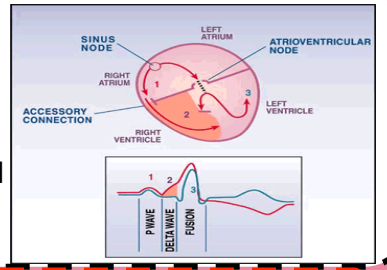
Drugs	Uses	Adverse effects
Flecainide	1. Used in supraventricular arrhythmias in patients with normal hearts. 2. Wollf-parkinson-white syndrome[1]. 3. Very effective in ventricular arrhythmias, but very high risk of proarrhythmia[2]. 4. Should be reserved for resistant arrhythmias.	1. CNS: dizziness, tremor, blurred,vision, abnormal taste sensations, paraesthesia. 2. Proarrhythmia[2] Especially with ventricular arrhythmias 3. Heart failure due to –ve inotropic effect.

Other class 1C drugs:

Propafenone:

- Chemical structure similar to propranolol.
- Has weak beta-blocking action.
- Cause metallic taste and constipation.

[1]: **Wolff-parkinson-white sydrome**
- Pre-excitation of the ventricles due to an accessory pathway known as the Bundle of Kent.
- This accessory pathway is an abnormal electrical communication from the atria to the ventricles.



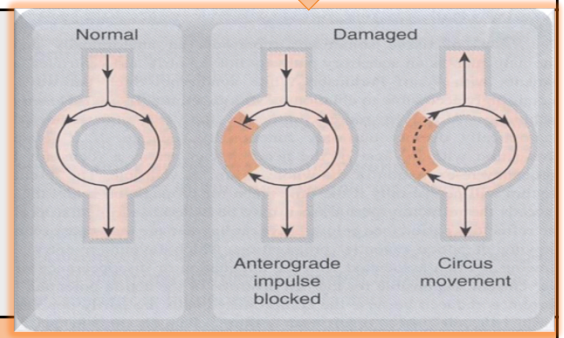
[2]: means can cause new or reactivate arrhythmia

*N.B. :These drugs are not used anymore because they may increase mortality when administered to patients surviving myocardial infarction, So these drugs the last choice when all antiarrhythmic drugs not effective.

Class II (2)

β- adrenorecptor blockers

Pharmacological Action	block β1 receptor in the heart → reduce sympathetic Effect on the heart lead to : 1-decrease automaticity of S.A. node and ectopic pacemakers 2- prolong refractory period (slow conduction) of the A.V node this help prevent re-entry arrhythmias
Clinical Uses	1- (SA node / AV node) atrial arrhythmia 2- Arrhythmia because sympathetic over activity (emotion – exercise – thyrotoxicosis) causes tachycardia. 3- Wolff-Parkinson-White syndrome (WPW) 4- digitalis-induced arrhythmias



Examples

Drugs	Clinical uses
Esmolol	Acute emergency atrial arrhythmia or tachycardia . Very Short duration of action. IV injection.
Propranolol Atenolol Metoprolol	- Normal cases of arrhythmia (emotion of exam) . - Used as prophylactic in post myocardial infraction to reduce the incidence of sudden death due to ventricular arrhythmia .

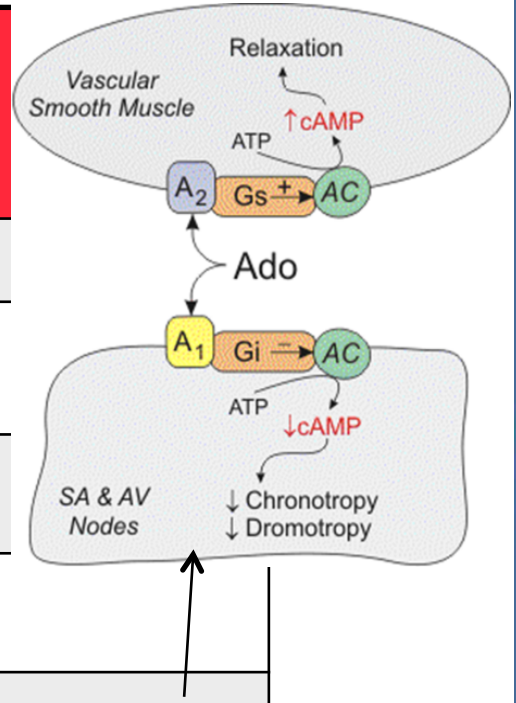
Class III (3) Drugs

Drug	Aminodarone Many side effects	Ibutilide (Pure class 3)
Characteristic	- Prolong action potential duration and refractory period (Potassium blocking) - Prolong phase 3 repolarazation . - Additional actions of classes 1A, 2 & 4 - vasodilating effects (*because of α- and β-adrenoceptor blocking effects and calcium channel blocking effects)	- In ECG: Causes QT interval prolongation - Just Prolong Refractory Period - Prolong phase 3 .
Clinical Uses	1-Main Use: serious resistant ventricular arrhythmias 2- Maintenance of sinus rhythm after D.C. cardioversion of atrial flutter and fibrillation 3- Wolff-parkinson-white sydrome: resistant supraventricular arrhythmias(useful in re-entry arrhythmias)	1- Atrial Flutter & Fibrillation
Route of administration	Not absorbed after oral administration, mainly IV	Given by a rapid I.V. infusion (in Emergency or acute status)
Half Life	Extremely long Half-life (t1/2) = 13-103 days	
Adverse effects	1- Pulmonary fibrosis 2- Hyper or hypothyroidism 3- Photodermatitis 4- Bluish Discoloration of skin 5- corneal microdeposits 6- hepatocellular necrosis 7- peripheral neuropathy 8- constipation 8- Cardiac: Bradycardia, heart block, heart failure, hypotension 9-CNS: tremor, headache, ataxia, paresthesia	Induce Torsade de pointes
Drugs Interaction	Reduce Renal Clearance of Quinidine, Warfarin, Procainamide ,and Flecainide	

Class IV (4)		
Examples	Verapamil	Diltiazem
Mechanism of action	This group of antiarrhythmic drugs works by blocking the Ca++ channels which are preset only in the SA node and AV node leads to slow the conduction & prolong refractory period.	
Clinical uses	1- Effective only in atrial arrhythmia 2- re-entry supraventricular(nodal & atrial) Note : it is not effective in ventricular arrhythmia (because the ventricle contraction activated by influx of Na+)	

Class V (5)

(Miscelleneous antiarrhythmic drugs : It is a large group of antiarrhythmic drugs)
(E.g. Adenosine and DIGITALIS)



Drug	Adenosine (Naturally occurring nucleosides)
Clinical use	- drug of choice for acute management of paroxysmal supraventricular tachycardia . - preferred over verapamil (because it safer and does not depress contractility)
Route of Administration	given 6 mg I.V. bolus(Rapid) followed by 12 mg if necessary
pharmacokinetics	Naturally occurring nucleoside Half life = less than 10 seconds
Mechanism of action	Binds to type 1(A1) receptors which are coupled to Gi- proteins , activation of this pathway cause : 1 - Opening of potassium channels (hyperpolarization) 2 - Decrease cAMP which inhibits L-type calcium channels (⬇ calcium influx) causing decrease in conduction velocity (negative dromotropic effect) mainly at AVN. 3- In cardiac pacemaker cells (SAN) , inhibits pacemaker current, which ⬇ the slope of phase 4 of pacemaker action potential (⬇ spontaneous firing rate {negative chronotropic effect})
Adverse effects	1- flushing in about 20% of patients 2- shortness of breath and chest burning in 10% of patients (bronchospasm) (contraindicated in asthmatic patient) 3- brief AV block (contraindicated in heart block) 4- Rarely: hypotesion, nausea, paresthesias,headache

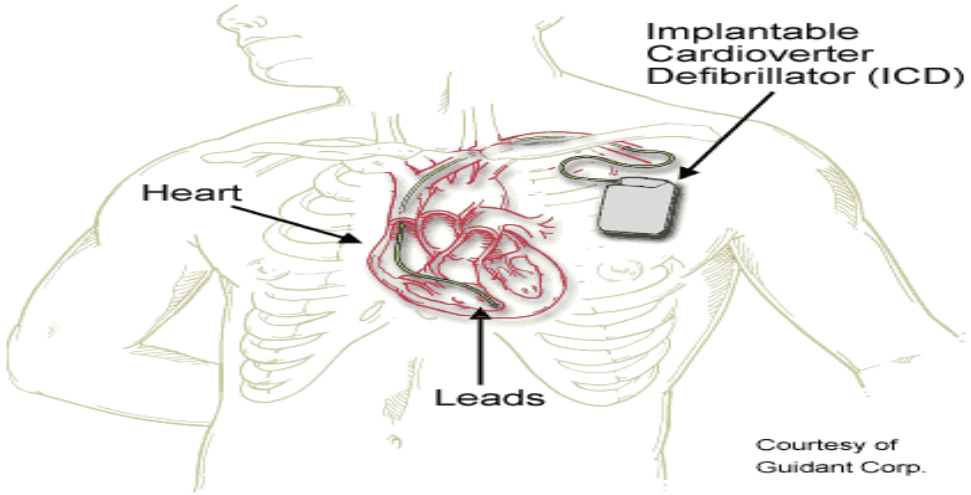
BRADYARRHYTHMIAS

ATROPINE

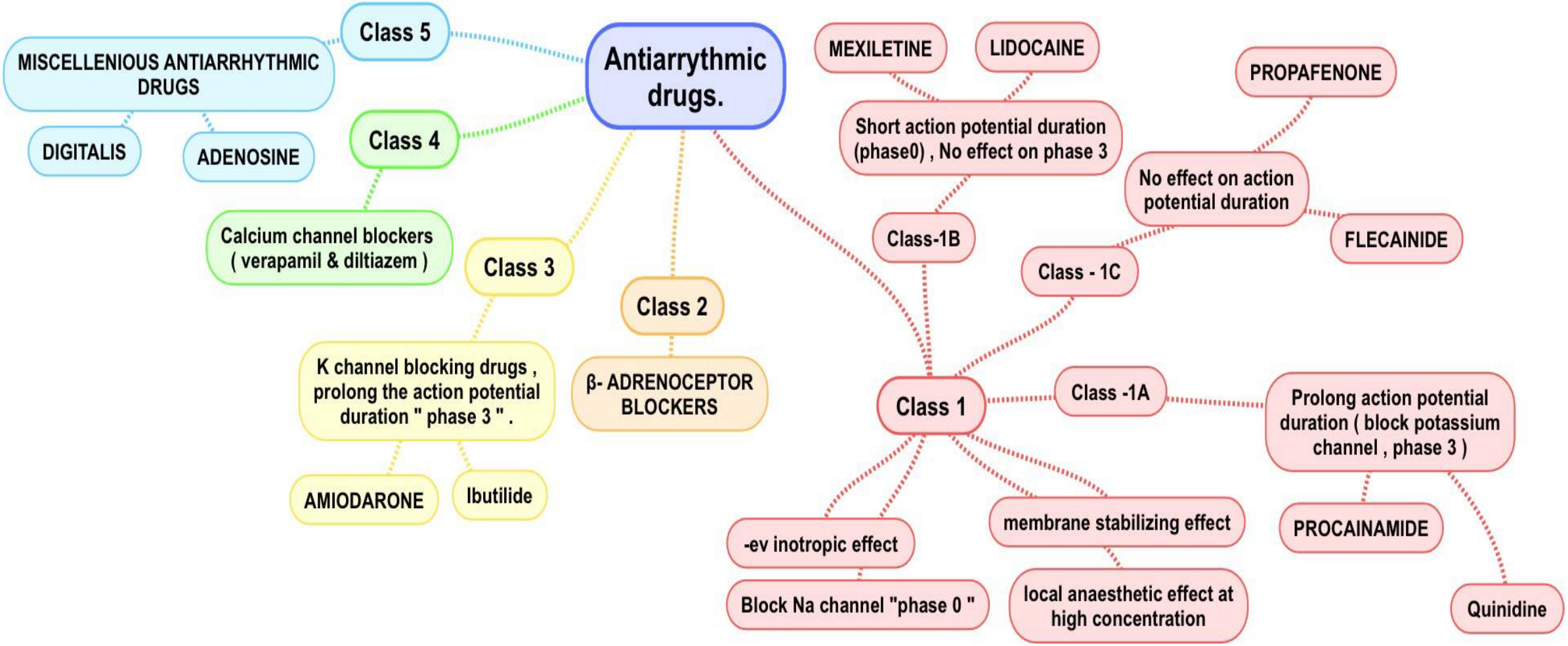
- can be used in sinus bradycardia after myocardial infarction and in heart block.
- in emergency heart block **isoprenaline** may be combined with atropine (Caution)

NON-PHARMACOLOGIC THERAPY OF ARRHYTHMIAS

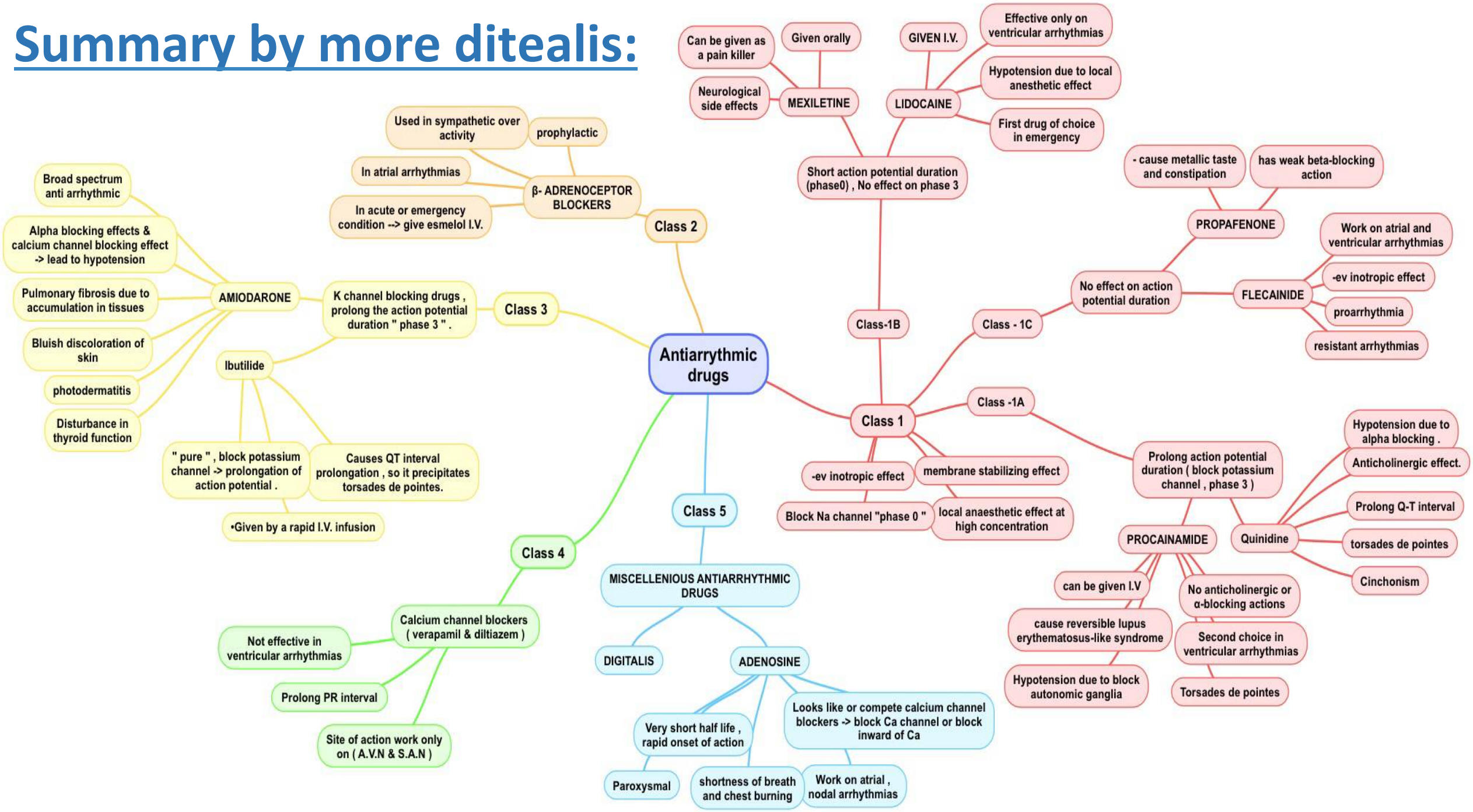
Implantable Cardiac Defibrillator **(ICD)** can automatically detect and treat fatal arrhythmias such as ventricular fibrillation



SUMMARY:


Antiarrythmic drugs.
Class 1
Class -1A
Prolong action potential duration (block potassium channel , phase 3)
PROCAINAMIDE
Quinidine
membrane stabilizing effect
local anaesthetic effect at high concentration
-ev inotropic effect
Block Na channel "phase 0 "
Class-1B
Short action potential duration (phase0) , No effect on phase 3
MEXILETINE
LIDOCAINE
Class - 1C
No effect on action potential duration
PROPAFENONE
FLECAINIDE
Class 2
β- ADRENOCEPTOR BLOCKERS
Class 3
K channel blocking drugs , prolong the action potential duration " phase 3 " .
AMIODARONE
Ibutilide
Class 4
Calcium channel blockers (verapamil & diltiazem)
Class 5
MISCELLENIOUS ANTIARRHYTHMIC DRUGS
DIGITALIS
ADENOSINE

Summary by more ditealis:



MCQs

1- A 66-years-old man had myocardial infract. Which one of the following would be appropriate prophylactic anti arrhythmic drugs

A) Lidocaine
B) Metpprolol
C) Procainamide
D) Verapamil

2- Group of drugs has membrane stabilizing effect :

A) Class 1
B) Class 2
C) Class 3
D) Class 4

3- A patient with atrial fibrillation was given an anti arrhythmic drug orally, he developed syncope due to torsades de pointes, what is the drug that was given to this patient?

A) Procainamide
B) Ibutilide
C) Quinidine
D) Mexiletine

4- What is the side effect that you have to aware a patient taking a procainamide as an anti arrhythmic drug

A) Lupus erythematosus-like syndrome
B) Cinchonism
C) Convulsions
D) Hypothyroidism

5- A patient developing an abnormal pre-excitation of the ventricles because of an accessory pathway , taking a drug that affect the repolarization of the cells ?

A) Ibutilide
B) Propafenone
C) Amiodarone
D) Adenosine

6- A Patient developed an arrhythmia due to digoxin toxicity, Which of these drugs is used in such condition and is taken orally

A) Mexiletine
B) Lidocaine
C) Flecainide
D) Propafenone

7- A patient came to your clinic who has an arrhythmia, and you have used all the drugs that could be used and there is no clinically improvement of the patient . Which of these drugs you can use in this situation and what is the adverse effect of the drug ?

A) PROPAFENONE → metallic taste
B) FLECAINIDE → Proarrhythmia
C) Adenosine → bronchospasm
D) Amiodarone →pulmonary fibrosis

8- A person had a final football match and he is under stress, Unfortunately, he developed an arrhythmia , Which of these classes of anti-arrhythmic drugs is more effective in this patient ?

A) Class III
B) Class IA
C) Class II
D) Class IV

9- A doctor prescribed a quinidine with Amiodarone to a patient suffering from arrhythmia , what is the interaction between these drugs ?

A) Amiodarone cause Proarrhythmia
B) Amiodarone Cause liver failure
C) Amiodarone Reduce renal clearance of Quinidine
D) Quinidine syncope

10- A 13 year old patient had several attacks of asthma, and he came to ER by an ambulance because of arrhythmia. Which of the following drugs is contraindicated to be used?

A) Procainamide
B) Quinidine
C) Lidocaine
D) Adenosine

11-A patient came to the ER because of tachycardia arrhythmia , One of the following drugs is contraindicated in this situation?

A) Procainamide
B) Atropine
C) Metpprolol
D) Flecainide

12) Which antiarrhythmic drugs works by blocking the Ca++ channels:

A) Metpprolol & Esmolol
B) Quinidine & Procainamide
C) Verapamil & Diltiazem
D) Flecainide &Propafenone

1- B 2-A 3-C 4-A 5-C 6-A 7- B 8-C 9-C 10-D 11-B 12-C

www.youtube.com/watch?v=AeuX_CR6GXE

Long video but it is helpful

GOOD LUCK!

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