MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Anti-Arrhythmic drugs

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

By the end of this lecture, students should be able to:

✓ Understand definition of arrhythmias & their different types

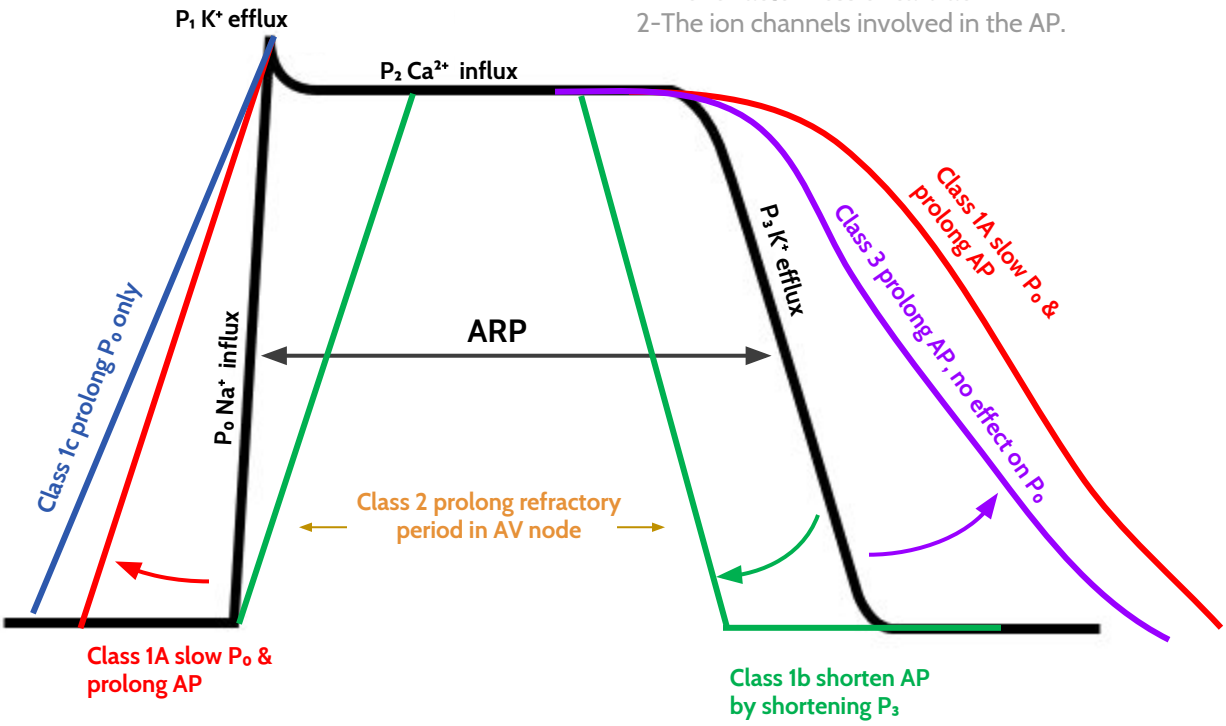
✓ describe different classes of Antiarrhythmic drugs & their mechanism of action.

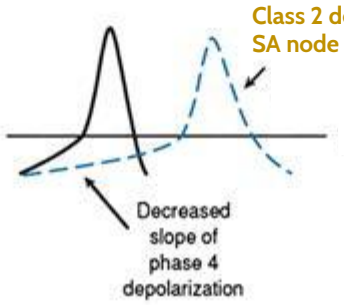
✓ understand their pharmacological actions, clinical uses, adverse effects & their interactions with other drugs.

Editing File

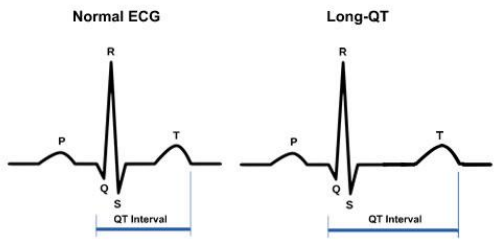
Extra information(recommended)

Main differences between skeletal and cardiac action potential are :
1-The refractoriness of cardiac AP.
2-The ion channels involved in the AP.





pure class 3 prolong QT



EXTRA for better understanding

Types of Arrhythmia

Ventricular : occurs in the Ventricles

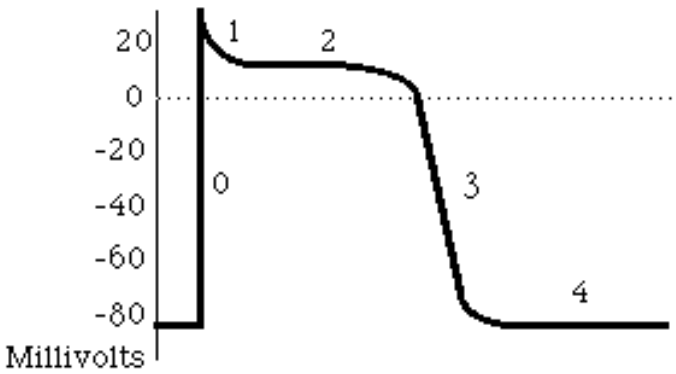
Supraventricular: occurs in the Atria

Ventricular Tachycardia: SA node no longer controls the beating of the ventricles "ectopic pacemaker" , this will result in increase heart beats	**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.	

Paroxysmal Supraventricular Tachycardia: Rapid, regular heart beats.	**Wolff-Parkinson-White Syndrome:** Extra muscle 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.

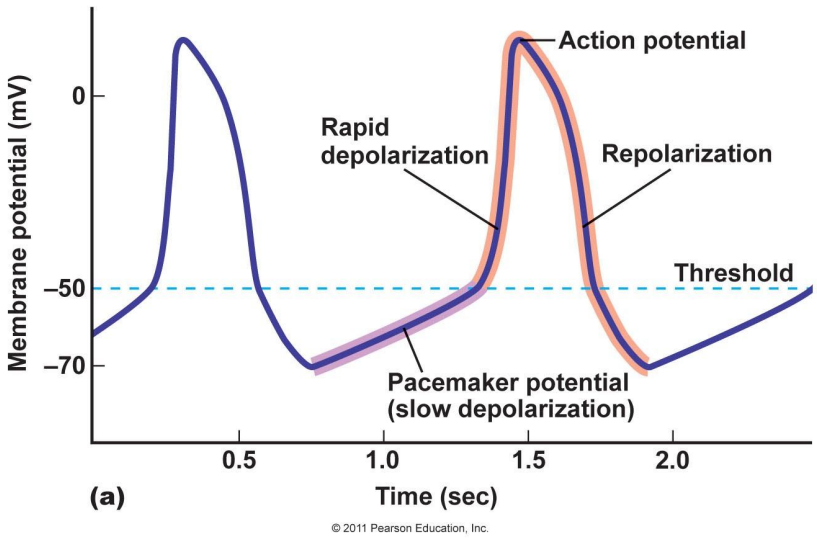
Extra information(recommended)

Ventricular Muscle Cells Action Potential



4- Resting membrane potential (polarized)
0- Rapid Depolarization Phase: Passage of cations (Sodium and Calcium) 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: Short-term Voltage-gated K channels open and Na channels close at peak positivity of the cell and allow 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 calcium channels are open for about most of the period, but the channels are inactivated around the end of this phase and 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

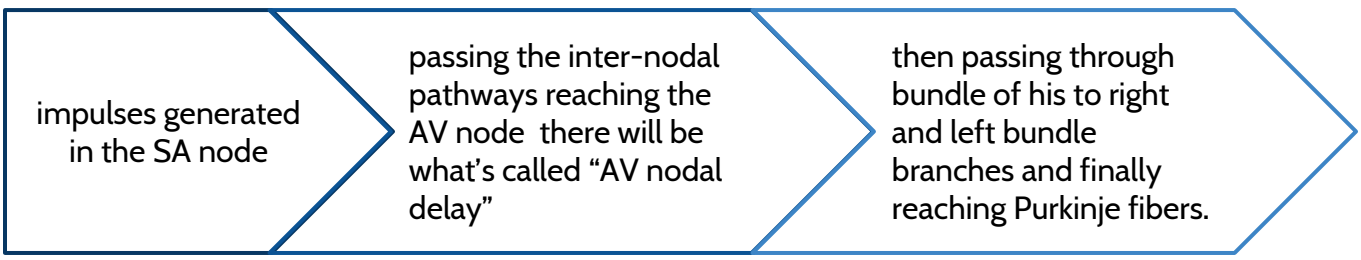


SA Node is made of specialized cardiac cells, (Modified Cardiomyocytes), the cells have high permeability to Na and K, allowing constant, spontaneous action potentials to be generated and a unique way of generating an action potential.
Pacemaker potential (slow depolarization): Slow Na influx and a decreased K efflux, makes the cells more positive gradually.
Rapid Depolarization: Calcium channels open, allowing the cells to be depolarized and action potential is reached.
Repolarization: Inactivation of calcium channels and K channels are open, the cell repolarizes and Na channels begin to open allowing the cycle to restart.

Antiarrhythmic Drugs

Introduction

Within the heart there is a conduction system which is responsible for generating and conducting the impulses to all parts of the heart.



The arrhythmias are conceptually simple, dysfunctions cause abnormalities in impulses formation and conduction in the myocardium.

So arrhythmia is an <u>abnormality</u> in the:

- Rate (>100=tachycardia) (<60=bradycardia)
- Regularity e.g Extrasystole (PAC, PVC)*
- Site of origin e.g Ectopic pacemaker
- Disturbance in conduction

* PAC: Premature Atrial Contraction.
PVC: Premature Ventricular Contraction.

The ultimate goal of antiarrhythmic drugs is

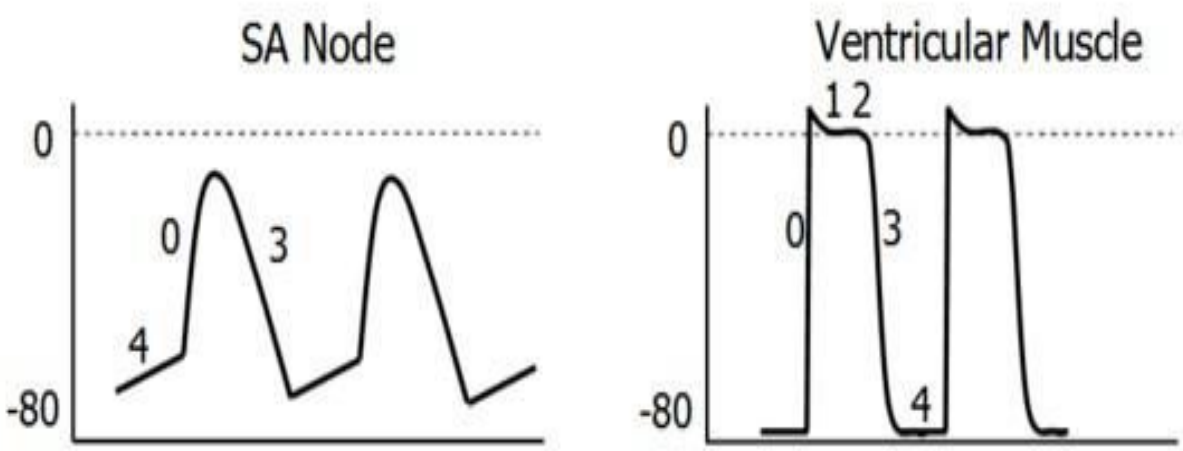
Restoring normal rhythm & conduction by

- Maintenance of normal rhythm
- Prevention of more serious arrhythmias

How do antiarrhythmic drugs produce these effects?

- Slow conduction velocity
- Altering excitability of cardiac cells by (prolonging the effective refractory period)
  - To allow the heart to rest and restore the SA node function
- Suppressing ectopic pacemaker activity by inhibiting phase 4

Classification of Antiarrhythmic Drugs



Vaughan-Williams Classification	M.O.A	Effects on pacemaker action potential
IA	NA+ channel blocker (Membrane stabilizing drugs) Na initiate the SA node and ventricular action potential	1- Decrease the rate of rise of rapid depolarization (Phase O) 2-Decrease phase 4 slow depolarization (suppress pacemaker activity)
IB		
IC		
II	β-Adrenoceptor blocker	Slow phase 4 depolarization
III	K^+ channel blocker	Prolongs action potential duration
IV	Ca^{2+} 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:

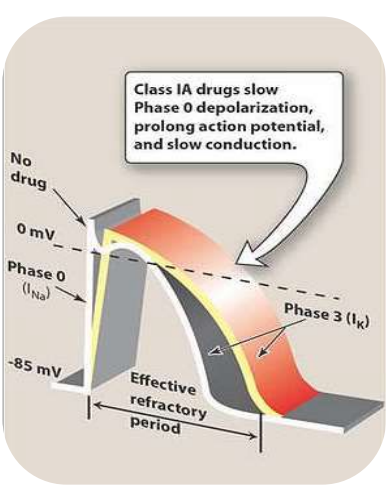
- Decrease the rate of rise of rapid depolarization (Phase O).
- -Decrease phase 4 slow diastolic depolarization (suppress pacemaker activity)

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

Ia

Prolong action potential duration

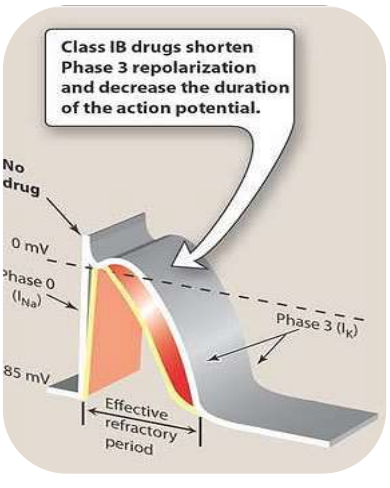
Cause closing of potassium channels, slowing repolarization and increase duration of action potential.



Ib

Shorten action potential duration

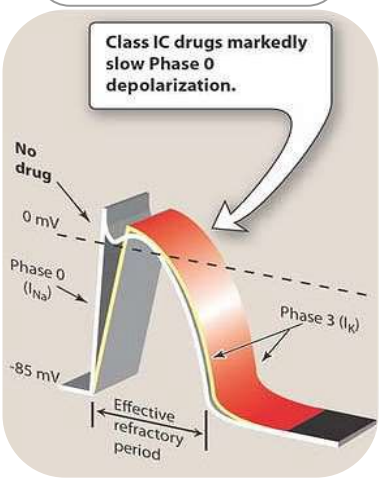
Cause opening of potassium channels, more rapid repolarization and less duration of action potential.



Ic

No effect on action potential duration

No effect on potassium channels, repolarization is unaffected.



The reason for the difference in duration is mainly due to the effect the drugs have on potassium channels.

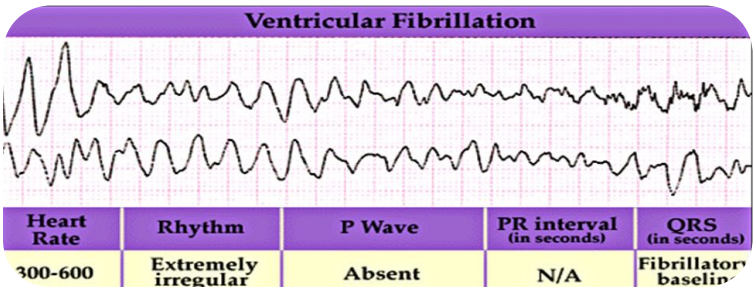
Class I Drugs

Class	Class IA	
Drug	Quinidine	Procainamide
Pharmacological Action	-Has other pharmacological actions include: 1- Anticholinergic effect: • Increase conduction through the A.V node (risk of ventricular tachycardia) 2- α-adrenergic blocking effect: • 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) • 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- No anticholinergic or α-blocking actions
Clinical Uses	- Atrial flutter & fibrillation. - 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.
Administration	GIVEN ORALLY (Rarely given I.V.)	I.V
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: Dry mouth, Blurred vision, Urinary retention, & constipation. 3-Hypotension: Due to depressing contractility & vasodilatation.	1- In long term therapy it causes reversible lupus erythematosus like syndrome. 2- Hypotension. 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.

Torsade de pointes can be treated by Mg injection, because it decreases the influx of Ca



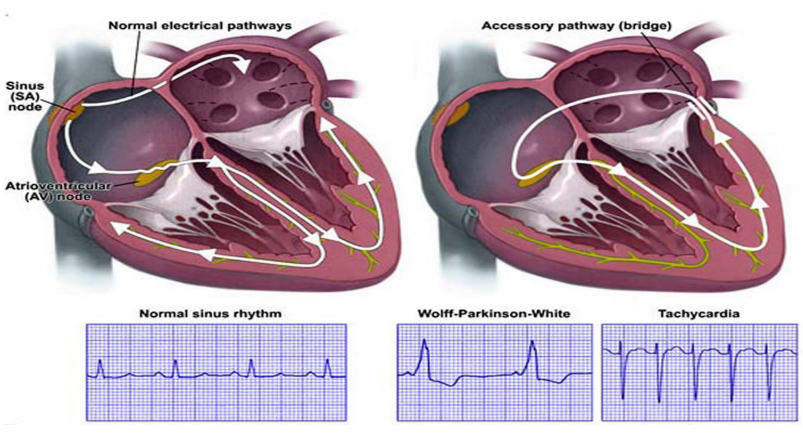
QT Interval: period between ventricular depolarization and repolarization.

In Torsades de pointes:
QRT complex become downward

Class	Class IB		Class IC
Drug	Lidocaine	Mexiletine	Flecainide
Pharmacological Action	Shorten action potential duration		Has no effect on action potential duration (Markedly slow phase 0 depolarization) (very potent)
Clinical Uses	1- Treatment of emergency ventricular arrhythmias. e.g: -During surgery -Following acute myocardial infarction. (NOT effective in atrial arrhythmias)	1- Ventricular arrhythmia 2-Digitalis-induced arrhythmias. (digitalis are pump inhibitors like digoxin, used to treat heart disorders)	1- Supraventricular arrhythmias 2- Wolff-Parkinson-White syndrome (WPW) 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	
ADRs	1- Hypotension 2- CNS ADRs (similar to other local anesthetics): - Paresthesia - Tremor - Dysarthria (slurred speech) - Tinnitus - Confusion - Convulsions: Last stage of ADRs	1- Nausea , Vomiting. 2- Tremor, drowsiness, diplopia. 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.

❖ Wolff-Parkinson-White syndrome (WPW):

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



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.

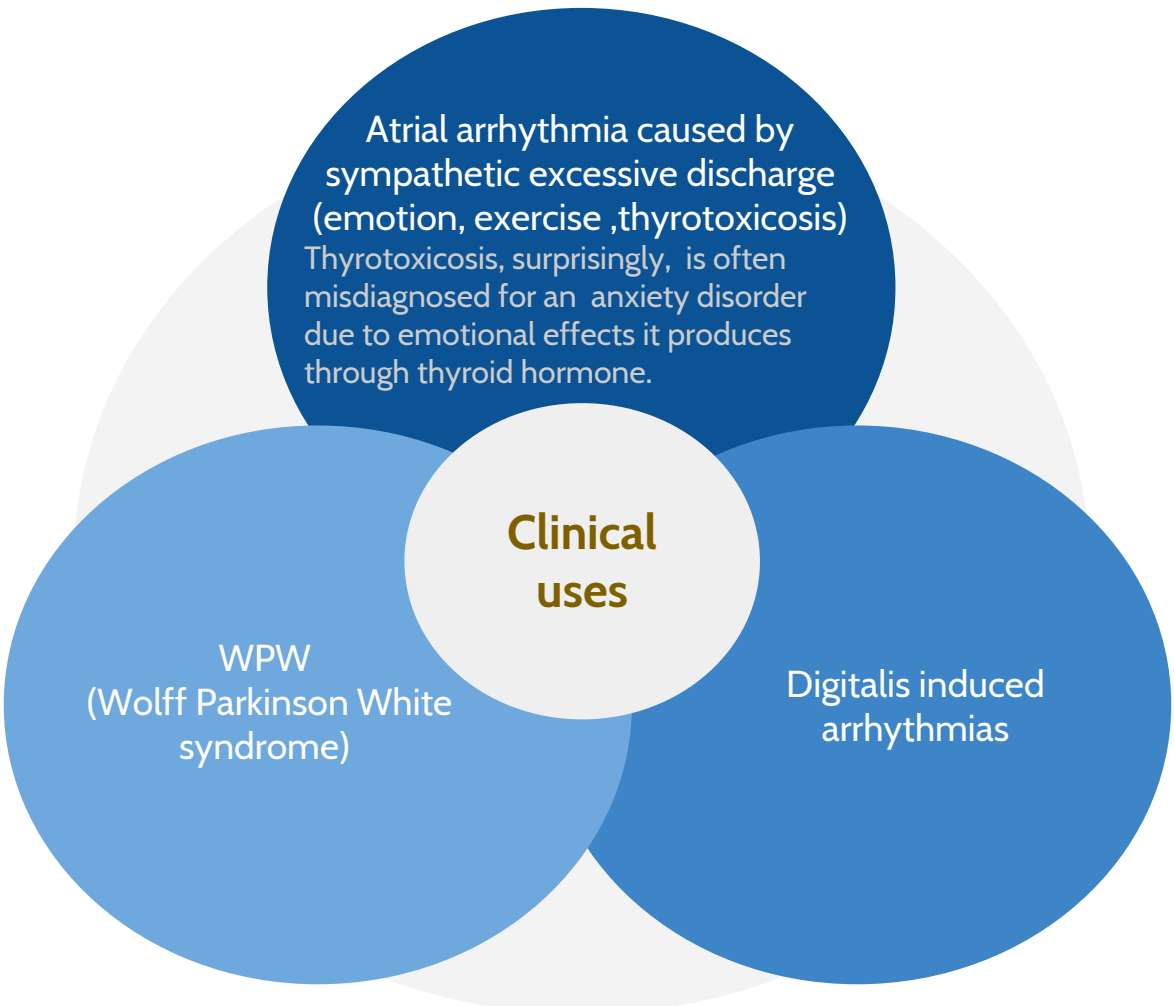
Class II Drugs

Mechanism Of Action

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



Drug	Clinical use
Esmolol	- Rapid control of ventricular rate in patients with atrial fibrillation or flutter (Tachycardia) -Very short acting (t1/2 = 10min) Can be used in emergency due to its short half life. Given I.V.
Propranolol Atenolol metoprolol	-Used in patients who had myocardial infarction to reduce incidence of sudden death due to ventricular arrhythmias -(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 III Drugs

Drug	Amiodarone (prototype)		
Pharmacological Action	Main effect: prolong action potential duration and prolong refractory period by prolonging 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) -Metabolized to its major active metabolite N-desethylamiodarone(even stronger) by cytochrome P450 (CYP3A4 and CYP2C8) -Eliminated primarily by hepatic metabolism -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 re-entry arrhythmias) reserved in severe ad resistant cases only, due to its side effects.		
ADR's	Many side effects: -Exacerbation of ventricular arrhythmias (with 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	**(pharmacodynamics)** Co-administration of amiodarone with drugs that prolong the QT interval increases the risk of Torsades de Pointes e.g. 1-Macrolides like Clarithromycin & Erythromycin 2- Azole antifungals like Ketoconazole	**(pharmacokinetic)** Enzyme inhibitors increase serum concentration of Amiodarone e.g. Loratadine, Ritonavir (AIDS/HIV drug), Trazodone(anti-depressant), Cimetidine, Grapefruit juice	**(pharmacokinetic)** Enzyme inducers decrease serum concentration of Amiodarone e.g. Rifampin

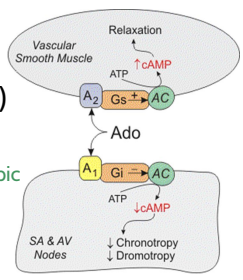
Class III Drugs cont.

Drug	Ibutilide (Pure Class III)
Pharmacological Action	QT interval prolongation (phase 3)
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

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
Clinical use	-Atrial arrhythmias -Re-entry supraventricular arrhythmias (e.g. WPW) (NOT effective in ventricular arrhythmia)

Class V Drugs
(Miscellaneous Antiarrhythmic Drug)

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) 3- Inhibiting phase 4 pacemaker action potential at SA node (-ve chronotropic effect) c.AMP increases the ionotropic and chronotropic effect 
Pharmacokinetics	Half-life is less than 10 sec
Clinical Use	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 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
Clinical Use	Used for maintenance of sinus rhythm following cardioversion in patients with atrial 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)

*Congener: a chemical substance related to another by origin or structure.

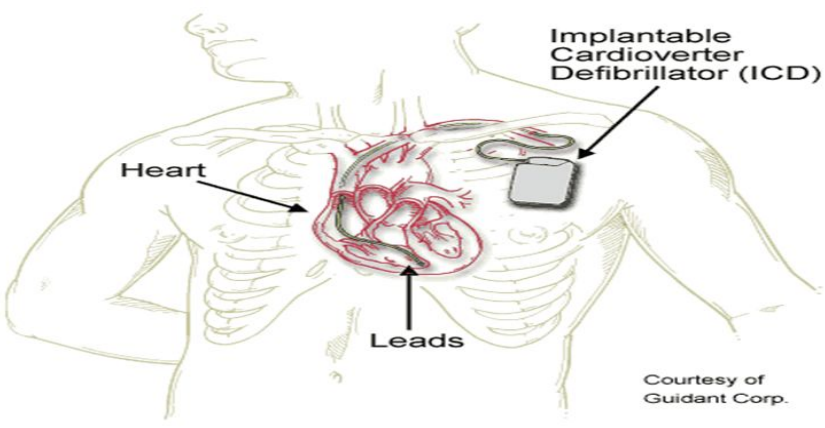
Bradyarrhythmias

Drug	Atropine
Clinical Use	-Used in sinus bradycardia after myocardial infarction and in heart block -In emergency heart block isoprenaline may be combined with atropine (caution) because combination of these 2 drugs can cause sinus tachycardia

Nonpharmacologic Therapy of Arrhythmias

Implantable Cardiac Defibrillator (ICD):

- Can automatically detect and treat fatal arrhythmias such as ventricular fibrillation (are able to perform cardioversion,defibrillation, and pacing of the heart .)



Summary

Drug	Class	Uses
Quinidine	Class IA	-Atrial flutter & fibrillation. - Maintaining sinus rhythm after cardioversion.
Procainamide		More effective in ventricular arrhythmias
Lidocaine	Class IB	Treatment of emergency ventricular arrhythmias. e.g: -During surgery -Following acute myocardial infarction.
Mexiletine		1- Ventricular arrhythmia 2-Digitalis-induced arrhythmias.
Flecainide	Class IC	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 (β_1 Blockers)	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 (prototype)	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
Verapamil, Diltiazem	Class IV	-Atrial arrhythmias -Re-entry supraventricular arrhythmias (e.g. WPW)
Adenosine	Class V	Drug of choice for acute management of paroxysmal supraventricular tachycardia
Dronedarone	New Antiarrhythmic Drugs	maintenance of sinus rhythm following cardioversion in patients with atrial fibrillation or flutter
Atropine	**Bradyarrhythmias** Anticholinergic	-Used in sinus bradycardia after myocardial infarction and in heart block -In emergency heart block isoprenaline may be combined with atropine

QUIZ

MCQs:

1- 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- Quinidine

2- Which arrhythmia can be treated with Lidocaine?

A- Paroxysmal Supraventricular ventricular tachycardia B- Atrial fibrillation C- Atrial Flutter D- Ventricular tachycardia

3- All of the following are adverse effects of amiodarone EXCEPT:

A- Cinchonism B- Hyperthyroidism C- Hypothyroidism D- Photodermatitis

4- A 60-year-old man comes to the emergency department with severe chest pain. ECG reveals ventricular tachycardia with occasional normal sinus beats, and ST-segment changes suggestive of ischemia. A diagnosis of myocardial infarction is made, and the man is admitted to the cardiac intensive care unit. His arrhythmia should be treated immediately with....

A- Adenosine B- Verapamil C- Lidocaine D- Quinidine

5- When working in outlying areas, this 62-year-old rancher is away from his house for 12–14 h at a time. He has an arrhythmia that requires chronic therapy. Which of the following has the longest half-life of all antiarrhythmic drugs?

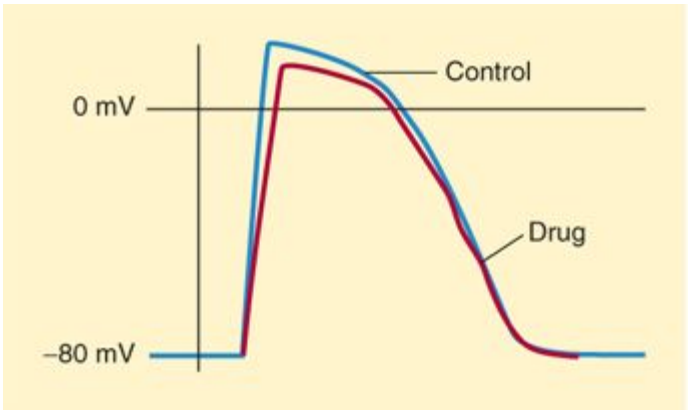
A- Amiodarone B- Lidocaine C- Flecainide D- Mexiletine

Answers:
1-C, 2-D, 3-A, 4-C, 5-A

QUIZ

SAQ:

1- A drug was tested in the electrophysiology laboratory to determine its effects on the cardiac action potential in normal ventricular cells. The results are shown in this diagram.



What drug can cause this result? Mention 2 of it's ADR's.

2- Which drug blocks K+ channels in the heart responsible for cardiac repolarization, and also blocks calcium channels in the AV node? Mention 2 of it's ADR's.

Answers:

1- Flecainide (markedly slow phase 0 (depolarization)), proarrhythmia and dizziness.

2- Amiodarone, pulmonary fibrosis and hyper or hypothyroidism

pharmacology

Team 438

GOOD LUCK

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Share with us your ideas !