Pharmacology Team

429 Medicine

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Anti-arrhythmic drugs

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ملاحظة :

المذكرة عبارة عن سلايدات د.عزة بالإضافة إلى نوتات التيم.

الدكتورة قالت مهم نعرف :

- استخدام الدواء -
- و أعراضه الجانبية
- لازم نعرف - A.p , refractory period , potency
- الجداول مهمة كتجميع للمعلومات و ما دخلنا في تفاصيل اكثر.

حتى ما دققت في كم مدة الهاف لايف حقت الأدوية ما عدا دوائين :

1- Esmlol→short half life

و يستخدم عند الطوارئ

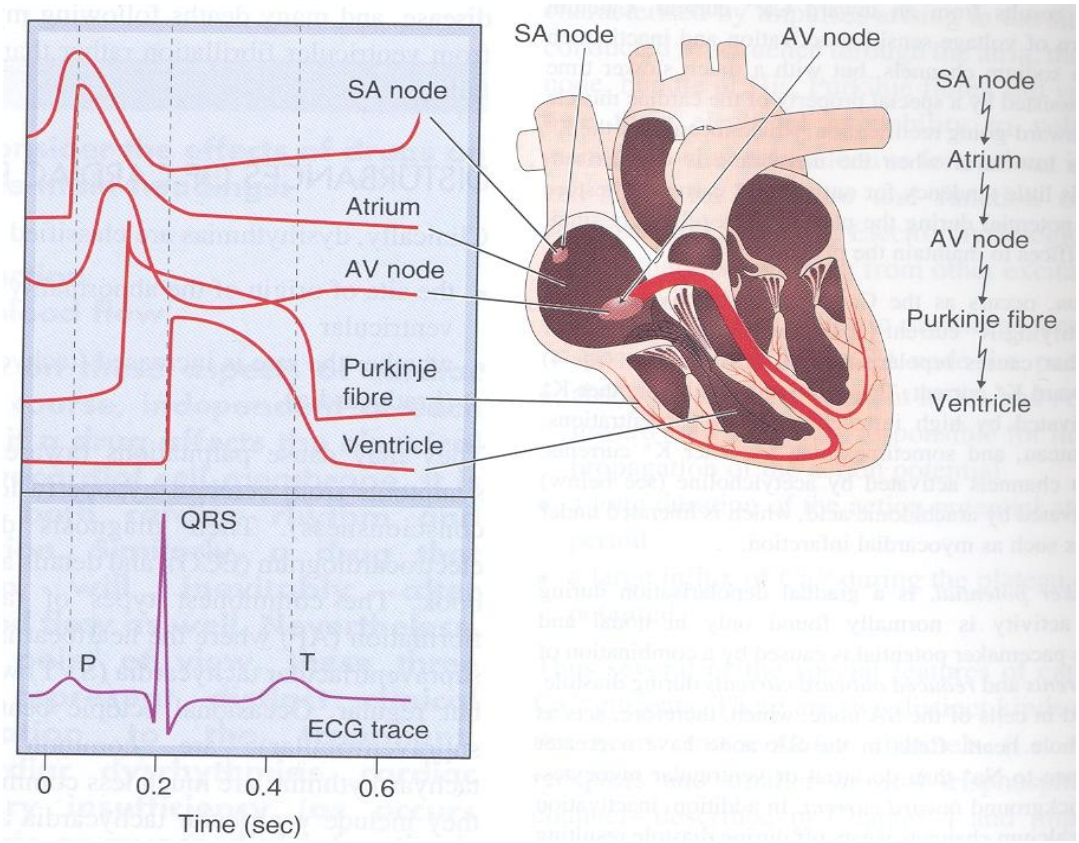
2- Amiodarone → long half life

وكثيرة استخداماته لذلك أعراضه كثيرة

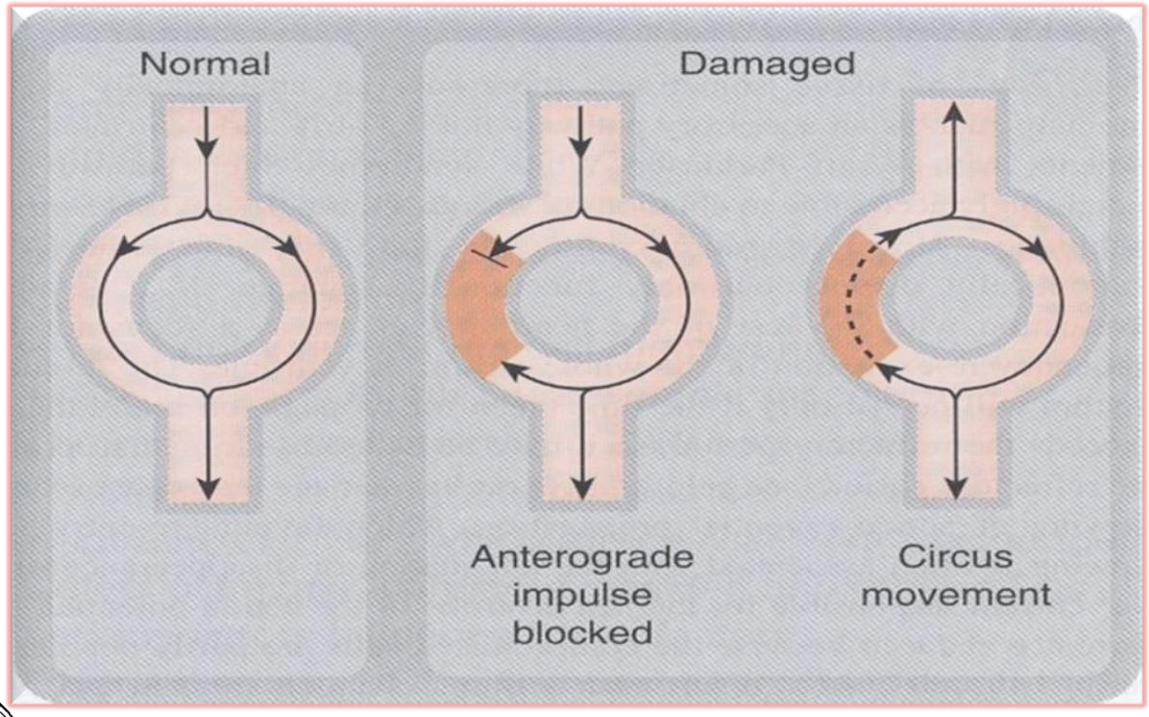
و الدرس مهم نظريا و أهم شي نعرف فيه كلاس 1 و تقسيماته ، و كلاس 3 .
و أهم شي فوق هذا كله .. الـ DRUGS.

Team Note

Cardiac Arrhythmia : Abnormal or irregular heart rate



Circus Movement:



Classification of antiarrhythmic drugs:

According to Vaughn-Williams Classification:

- **Class I:** Sodium channel blockers
- **Class II:** β- adrenoceptor blockers
- **Class III:** Potassium channel blockers
- **Class IV :** Calcium channel blockers

❖ Miscellaneous antiarrhythmic agents

Team Note

في هذا الجدول لازم نعرف كلا من ..

Action potential(A.P) ,, Refractory period and potency

و الـ potency حيكون في class 1 (IA,IB,IC)

Classification of drug	Mechanism of action	comment
IA	Na+ channel blocker/ Having K+ channel blocking effect	Slow phase 0 and Prolong phase 3
IB	Na+ channel blocker	Shortens phase 3 &duration of action potential
IC	Na+ channel blocker	Markedly slow phase 0 No effect on the duration of action potential& refractory period.
II	β-adrenoceptor blocker	Suppresses phase 4
III	K+ channel blocker	Prolonged phase 3
IV	Ca+2 channel blocker	Shortens action potential

I

Antiarrhythmic Drugs:

- Act on open or inactivated channels

  (Use -dependence or State –dependence)

- Have better effect in tissues that are depolarized

Team Note

After depolarization there will be disturbance in rhythm which originate in

- Atria - SA node - Ventricles

Sodium channel blocking drugs:

- **Classified into 3 classes according to interaction with sodium channels :**
- **Class 1A :** intermediate interaction
- **Class1B** : rapid interaction
- **Class1C**: slow interaction

Drugs of Class 1 A:

- **Quinidine** is the prototype of this class
- **Procainamide**
- They possess intermediate rate of association and dissociation with sodium channels
- Having K+ channel blocking effect.
- Are used in treatment of atrial & ventricular arrhythmias

Effect on action potential:

- Slow phase 0
- Prolong phase 3
-
-
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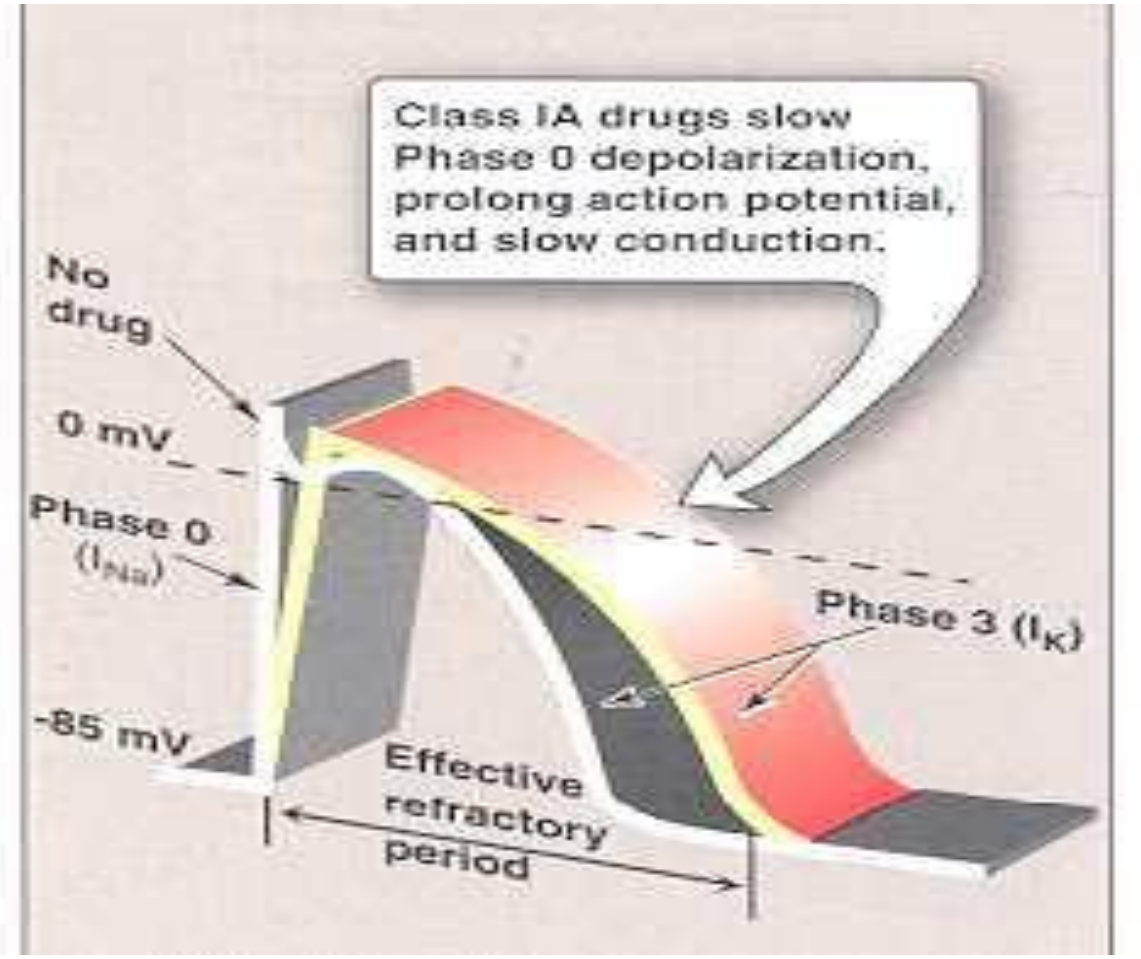
- **Result in :**
- Prolong the duration of action potential & effective refractory period for both atria & ventricles
- Decrease the slope of phase 4



Quinidine:

- Given only orally
- **Has :**
  - ❖ Atropine like action
  - ❖ a- adrenergic blocking effect

Team Note

I.M. → intra muscular route " painful "

I.V. → intra vascular route "causes hypotension ,tachycardia"

Team Note

It used in CRONIC condition cause it's given Orally

Clinical uses:

- Atrial flutter & Atrial fibrillation it returns the rhythm back to normal sinus rhythm.
- Used in treatment of ventricular arrhythmias.

A) Cardiac adverse effects:
Paradoxical ventricular tachycardia

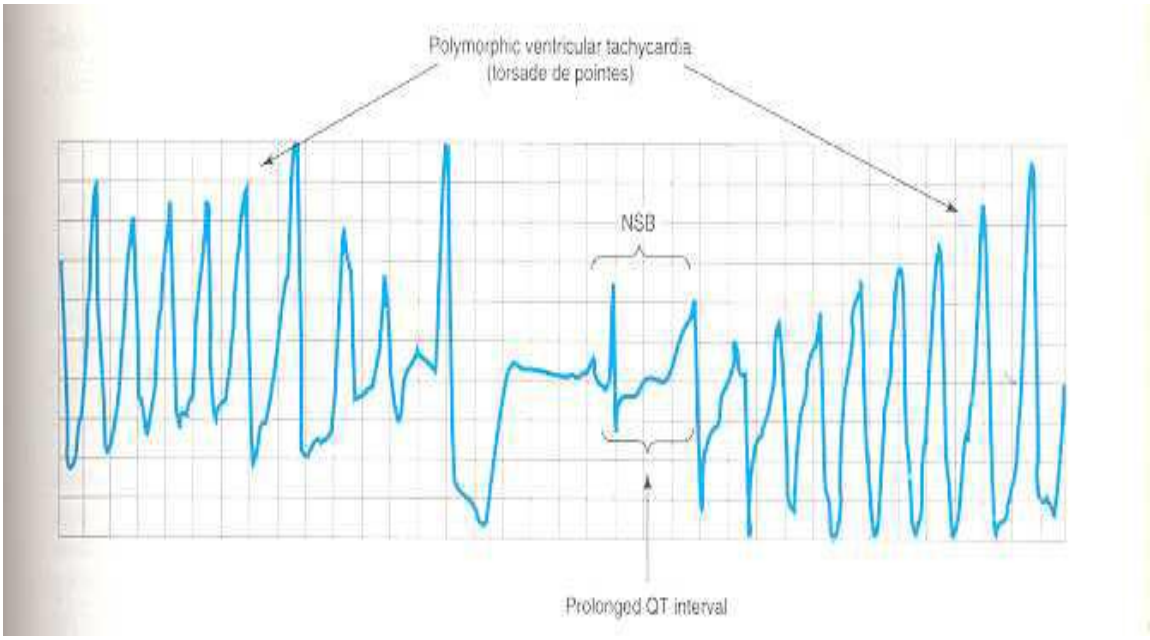
in atrial flutter or fibrillation

* Quinidine shorten A-V refractory period by its atropine- like effect

(So, Digoxin is given before quinidine)

B) A-V block at high plasma level

C) Torsade de pointes



Team Note

<u>Important</u> in general , any drug prolong the A.P → cause Torsade de pointes

Extracardiac adverse effects:

- Hypotension
- Cinchonism (headache, tinnitus, blurred vision
- GIT(diarrhea, nausea,vomiting)

Drug interactions:

Quinidine increase the plasma level of digoxin by displacing digoxin from plasma protein binding sites and decreased digoxin renal clearance.

Procainamide:

- Given safely by I.M. or I.V. routes .
- Metabolized in liver , giving an active metabolite (NAPA) has potassium channel blocking effect.
- More effective in ventricular arrhythmias .
- It is the second drug of choice after lidocaine in the treatment of acute ventricular tachycardia associated with an acute myocardial infarction

Team Note

usually ventricular arrhythmia followed by acute MI → ischemia in the cardiac tissue → increase automaticity→ re-entry or excitation → arrhythmia

Adverse effects:

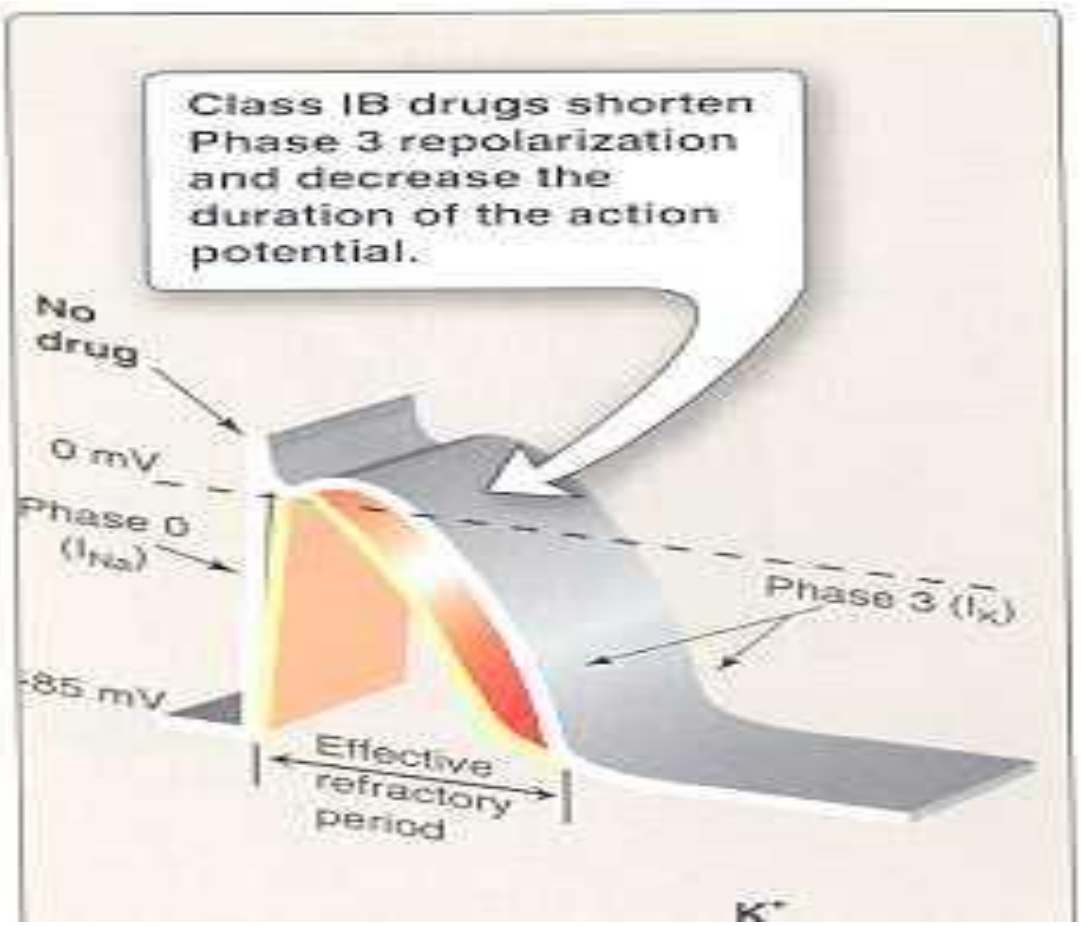
- Systemic lupus erythematosus like syndrome.
- Torsade de pointes

Team Note

Systemic lupus erythematsus like syndrome. caused by a problem in the metabolism of the drug in the liver --> the drug will accumulate in the tissue

Class 1B:

- Shorten phase 3 repolarization &duration of action potential
- Suppress arrhythmias mainly due to ectopic focus
- Show rapid association & dissociation with Na^+ channels.



Drugs of Class 1B:

- **Lidocaine**
- Given only by intravenous route

Team Note

لانها ماتوصل للـ **systemic circulation** بسبب مرورها بما يسمى **first pass metabolism** وهناك يتم امتصاص كميه كبيره من العلاج وبالتالي كمية العلاج الذاهبه للـ **systemic circulation** تصبح اقل .

Therapeutic uses:

First drug of choice in the treatment of **acute** ventricular tachycardia associated with acute myocardial infarction

Team Note

The second choice is Procainamide

Adverse effects:

- **Neurological effects :**

Tremors , nausea of central origin, convulsions.

Mexiletine:

- Effective orally
- Long half-life
- Mexiletine is used in chronic treatment of ventricular arrhythmias.

Adverse effects: Neurologic effects as lidocaine

Team Note

1B

Acute ventricular arrhythmias >> lidocaine

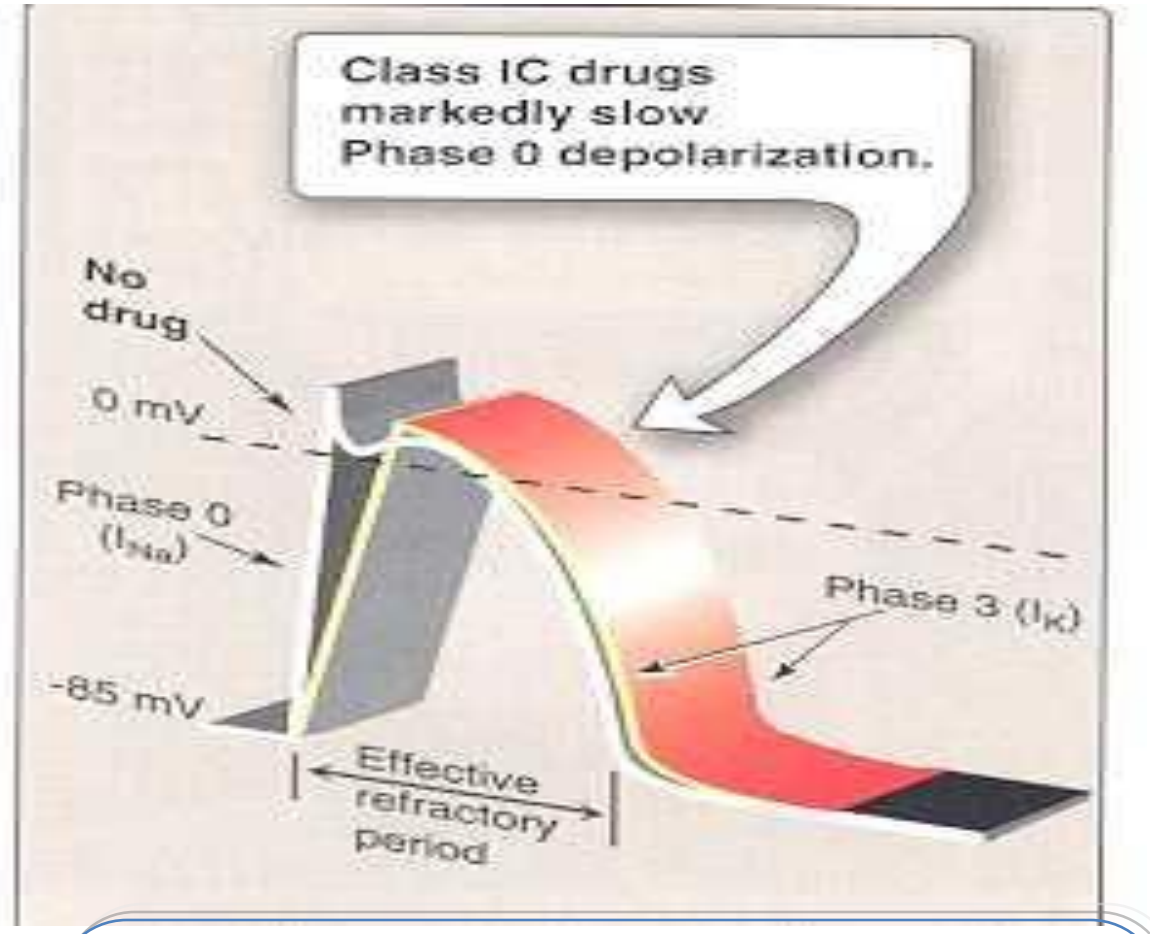
Chronic ventricular arrhythmias >> Mexiletine

Class1C:

Team Note

work in atrial and ventricular

- Interact slowly with sodium channels
- Markedly slow phase 0
- No effect on the duration of action potential& refractory period.



أعلى potency هو C1 ثم A1 ثم B1

potency: force of blocking

اما من ناحية A.P فأطولهم هو A1 ثم C1 ثم B1 --> هنا ليش ذكرنا C مع انه ليس له تأثير ؟لأن بعض الكتب قالت أن له تأثير بسيط فحطوه قبل B1

Team Note

ب واللي لازم نعرفه كما ذكر في المحاضرة أنه A.p لكل من :

A1 طويل

B1 قصير

C1 لا تأثير ... حتى انه هذا الكلاس لا يستخدم

لأنه في therapeutic dose يعمل arrhythmia.

Uses of Class 1C Drugs:

- **Flecainide**

❖ Only approved for refractory ventricular arrhythmias

- **Propafenone**

❖ Has weak β-blocking activity

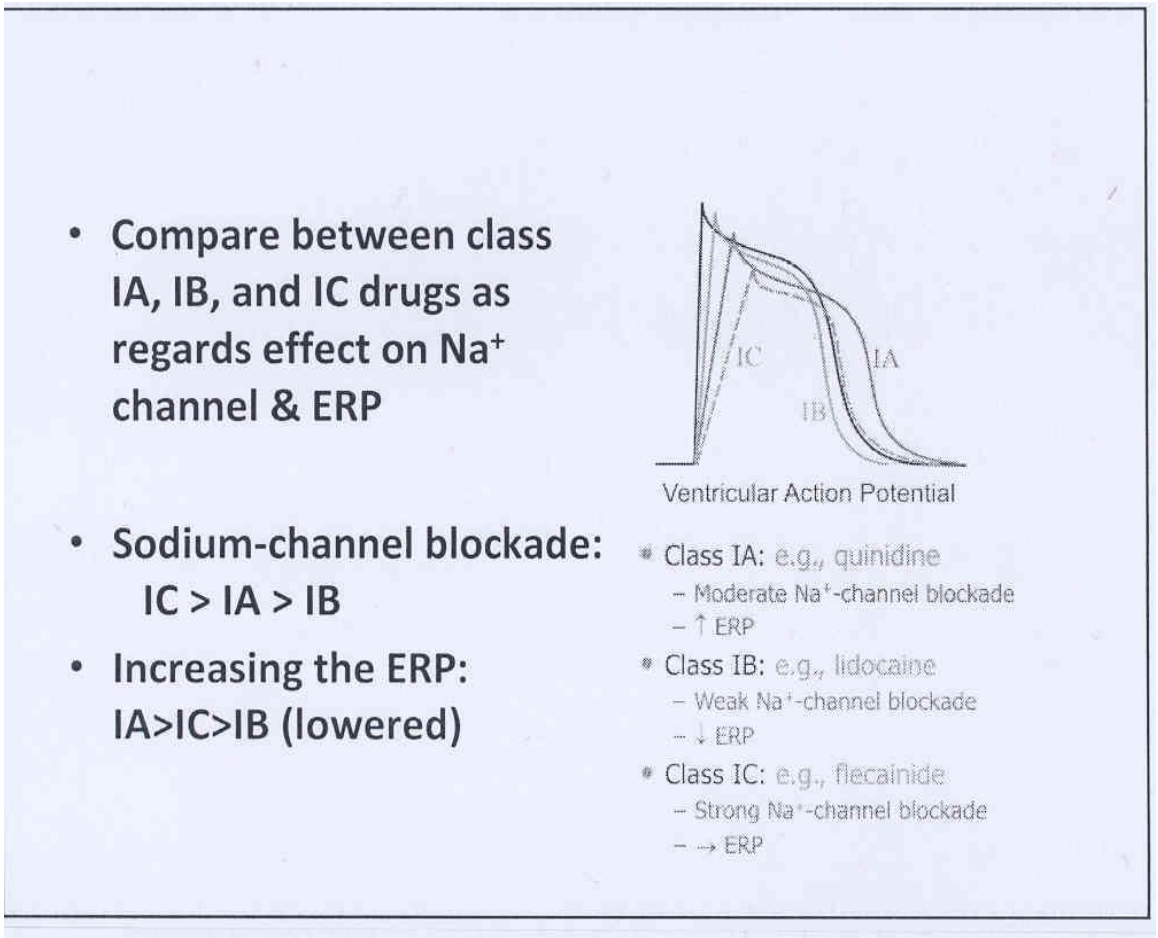
❖ Used in atrial flutter or fibrillation return rhythm to normal sinus rhythm

Team Note

Refractory: not responding to any other drug ,, which makes FLECAINIDE my last choice

Toxicity of Class 1 C:

- Severe proarrhythmic drugs
- Life- threatening ventricular tachycardia
- **Flecainide** increase the mortality rate in patients with premature ventricular contractions following myocardial infarction.



Class 1 : Na Channel Blocker

Classes	Drugs	How it's given	uses	Adverse effects
IA	-Quinidine →	Orally	→ 1- Atrial flutter & Atrial fibrillation it returns the rhythm back to normal sinus rhythm. 2- in treatment of ventricular arrhythmias.	→ - Hypotension -Cinchonism (headache, tinnitus, blurred vision - GIT(diarrhea, nausea,vomiting)
	-Procainamide →	IV	→ 1- ventricular arrhythmias . 2- second drug of choice after lidocaine in the treatment of acute ventricular tachycardia associated with an acute myocardial infarction	→ - Systemic lupus erythematosus like syndrome. - Torsade de pointes
IB	Lidocaine →	IV	→ First drug of choice in the treatment of acute ventricular tachycardia associated with acute myocardial infarction → in chronic treatment of ventricular arrhythmias.	→ Neurological effects:Tremors,nausea of central origin, convulsions.
	Mexiletine→	orally		→Neurologic effects as lidocaine
IC	Flecainide →	Orally and IV	→Only approved for refractory ventricular arrhythmias → Used in atrial flutter or fibrillation	Severe proarrhythmic drugs Life- threatening ventricular tachycardia Flecainide increase the mortality rate in patients with premature ventricular contractions following myocardial infarction.
	Propafenone →	Orally and IV		

Class 11: β-drenoceptor blocking drugs:

- Decrease heart rate & cardiac contractility
- Suppress abnormal automaticity & prolong A-V conduction

Team Note

β-drenoceptor blocking drugs decreases all cardiac progresses such as, excitability , conductibility , contractility , automaticity)

- the drugs will block β1 receptor that innervate all the heart

Uses of Class 11 Drugs:

1- Effective in atrial & ventricular arrhythmias that associated with Increased sympathetic activity

(**High catecholamine states**)

Team Note

(used with any drug that prolonged A.P)

2-With quinidine in A.F.& A.F.

3- Effective in preventing post infarct arrhythmias as premature ventricular contraction ,they increase survival rate

Class 11 Drugs:

- **Propranolol**

– Is used to reduce the sudden arrhythmic death following myocardial infarction

Team Note

Non selective β blocker (both β1 and β2 blockers) which mean we can't prescribe it for asthmatic patients because it will increase the bronchospasm

- **Metoprolol**
- Selective β_1 blocker , used in asthmatic patients . Reduce the rate of mortality due to post infarct arrhythmias.
- **Esmolol**

- Is a short acting β1 blocking drug.
- Used mainly for intraoperative acute arrhythmias

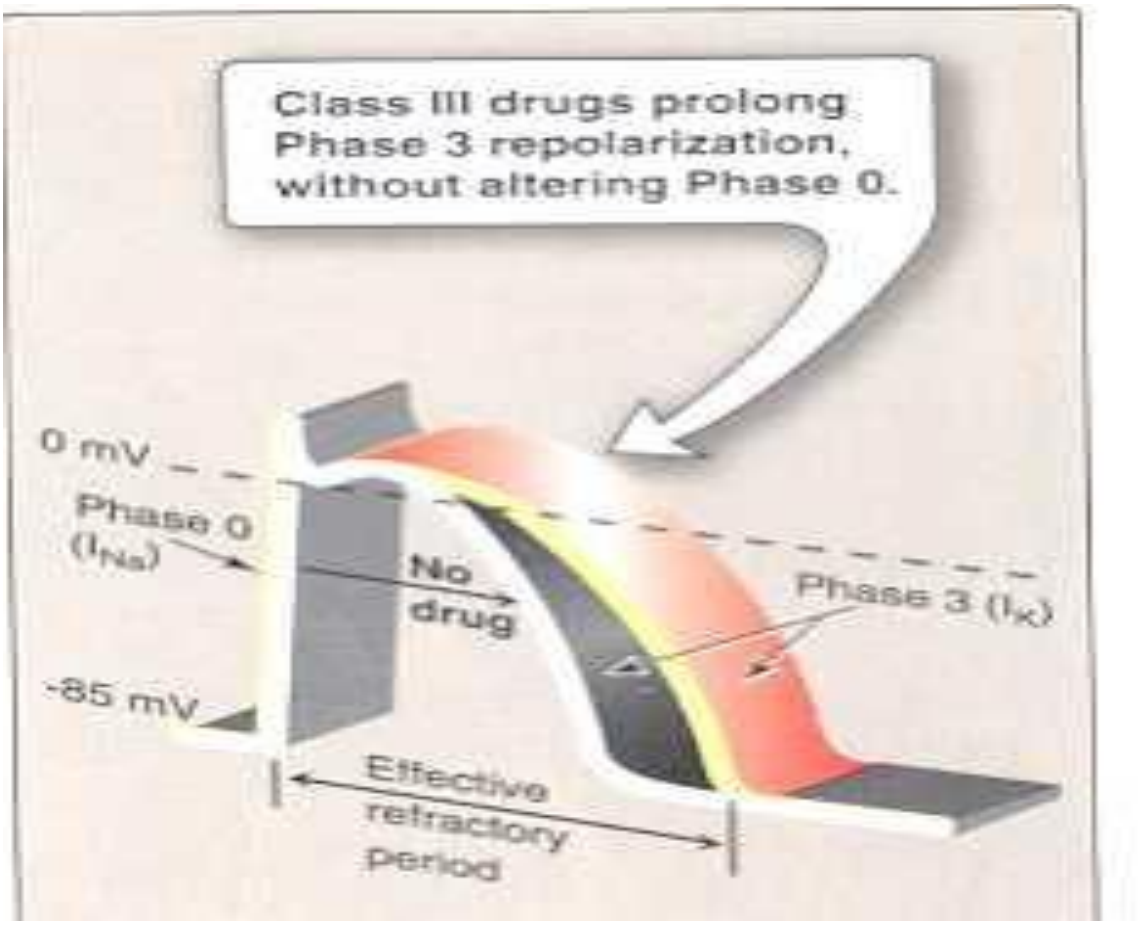
- **Class 11 Drugs [Team Note]**

drug	Use	Adverse effect
Propranolol	Non-selective ,, Is used to reduce the sudden arrhythmic death following myocardial infarction	**All of the three drugs dpress the aympathatic activity ..** - **Hypotension** - **hypoglycemia** - **branchspasm**
Metoprolol	Selective β_1 blocker , used in asthmatic patients . Reduce the rate of mortality due to post infarct arrhythmias.	
Esmolol (have shor half life)	Is a short acting β1 blocking drug. So it's given by IV " in emergency " Used mainly for intraoperative acute arrhythmias	

Class III:K+ channel blockers:

- Prolong the action potential duration & refractory period .
- **Prolong phase 3** .

A.P بالتالي يطول الـ



Drugs of class 111:

- Sotalol
- Amiodarone
- Ibutilide

Sotalol:

- Nonselective **β**- adrenergic receptor blocker .
- Is used for the treatment of :

  1- Life- threatening ventricular arrhythmias.

  2-To maintain sinus rhythm in patients with atrial fibrillation.

  3- For treatment of supra & ventricular arrhythmias in pediatric age group.

- May induce torsade de pointes

Ibutilide:

- Given by a rapid I.V. infusion
- Used for the acute conversion of atrial flutter or atrial fibrillation to normal sinus rhythm.
- QT interval prolongation , so it precipitates torsade de pointes.

Amiodarone:

- **A) cardiac effects**
- Has a broad actions :
- Sodium channel blocking
- Potassium channel blocking
- Calcium channel blocking
- β- adrenoceptor blocking
- **B) Extracardiac effect:**

Peripheral vasodilataion

Team Note

كلما زاد الـ pharmacological زاد عندي الـ side effectو بالتالي اصبح استخدامه محصور

Team Note

Peripheral vasodilataion= Hypotension

((because it has a- adrenergic blocking effect))

Pharmacokinetics:

- Given orally
- Slow onset of action
- Long half-life(60 days).

Team Note

لا يعطى بكثرة لأنه حيزيد (side effect)

لان إخراجه من الجسم بطئ و بسبب ترسبه

- Concentrated in many tissues.
- Eliminated by liver mostly as active metabolites.

Clinical uses:

- Recurrent ventricular arrhythmias resistant to other drugs.

With patient who didn`t response for another drug

Team Note

- In maintaining sinus rhythm in patients with atrial fibrillation.

Adverse effects:

Because of deposition

- Gray- blue skin discoloration " لو ترسب تحت الجلد"
- Corneal microdeposits " لو ترسب في الـ قولون " →corneal opacity ,optic neuritis, blindness " لو ترسب بالعين"
- pulmonary fibrosis
- Hypo or hyperthyroidism
- Gastrointestinal upset
- Hepatic toxicity
- Arrhythmias
- Hypotension

Drugs of class 111

drug	comment	use	Adverse effect
Sotalol	Nonselective **β**- adrenergic receptor blocker .	**1-** life threatening vernacular arrhythmia **2-**To maintain sinus rhythm in patients with atrial fibrillation. **3-**For treatment of supra & ventricular arrhythmias in pediatric age group.	May induce torsade de pointes
Ibutilide	Given by a rapid I.V. infusion	Used for the acute conversion of atrial flutter or atrial fibrillation to normal sinus rhythm.	QT interval prolongation , so it precipitates torsade de pointes.
Amiodarone	Given orally Have a long half life And have a broad actions	Recurrent ventricular arrhythmias resistant to other drugs. In maintaining sinus rhythm in patients with atrial fibrillation.	***important*** Gray- blue skin discoloration Corneal microdeposits →corneal opacity ,optic neuritis, blindness pulmonary fibrosis - Hypo or hyperthyroidism Gastrointestinal upset Hepatic toxicity Arrhythmias Hypotension

Class 1V: Calcium channel blockers

Verapamil, Diltiazem

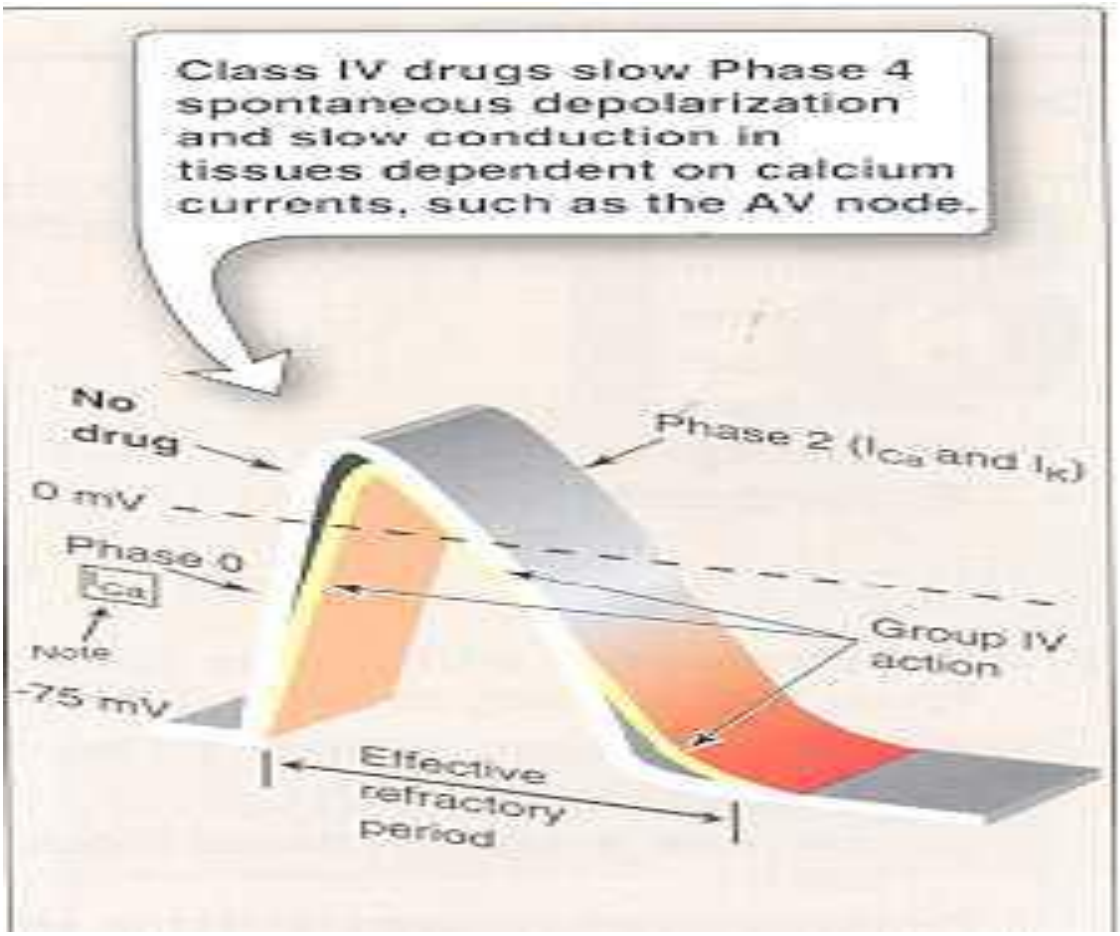
- Their main site of action is A.V.N & S.A.N(slow conduction & prolong effective refractory period).

Team Note

Because **A.V.N & S.A.N** depend on

Ca influx to do their work

Main use → atrial or supra ventricular arrhythmia



- They are used in treatment of atrial flutter & fibrillation.
- They are the second drugs of choice for the treatment of **paroxysmal supra-ventricular tachycardia**

Team Note

-sudden onset and termination → Attack

-Mainly S.A node A.V node arrhythmia

Class 1V :

Drug	Comment
Diltiazem	Their main site of action is A.V.N & S.A.N(slow conduction & prolong effective refractory period). ---------- They are used in treatment of atrial flutter & fibrillation. They are the second drugs of choice for the treatment of paroxysmal supra-ventricular tachycardia
Verapamil,	

Miscellaneous Drugs:

- **Adenosine** naturally found in the body
- Binds to specific adenosine receptors (A1- purinergic receptors)
- ((**these Rs specially for SA & AV tissues**))
- decreasing SA & AV nodal automaticity , conduction velocity & prolong effective refractory period

Pharmacokinetics & Uses:

- Very **rapid** onset of action .
- Short half- life (seconds)

Team Note

differ from Ca channels that it's very rapid onset action and short duration takes second to end its effect and that's why it's preferred over Ca-channels blocking drugs.

- Given as a rapid I.V. bolus injection
- First choice for the treatment of paroxysmal supraventricular tachycardia

Second choice is classIV

Adverse effects:

- Bronchospasm
- Shortness of breath
- Chest pain or burning
- Flushing → (redness of skin) Hypotension.
- Less effective in the presence of adenosine receptors blockers such as theophylline or caffeine

Team Note

classIV لهذا السبب

أفضل للمرضى اللي معاهم

supraventricular tachycardia

+ asthma

Team Note

asthmatics or patients who take theophylline or take caffeine when given adenosine it wont work affectively cause they will block adenosine receptors another reason to give Ca-blockers

Digoxin:

- Treatment of atrial flutter and fibrillation , but not return the atrial rhythm back to normal sinus rhythm

هنا ننتبه مو زي الـ Quinidine الي يرجع الـ rhythm الى الـ normal

Treatment of Atrial Fibrillation/Flutter

❑ **Goals:**

- 1- Reduce Stroke Risk → anticoagulant warfarin
- **2- Ventricular Rate Control:**

IV β-Adrenergic Blockers	IV Ca^{2+}-antagonists	Digoxin; oral/IV
o 1st choice after MI/surgery, o Caution in acute control of HF patients	o Alternative to **β-ARA**	o ONLY in HF/LV dysfunction

Treatment of Atrial Fibrillation/Flutter

➢ ***3- Conversion to Normal Sinus Rhythm:***

Class III Drugs	Class IA Drugs	Class IC Drugs
•IV ibulitide •IV/oral amiodarone •Oral sotalol	Quinidine (PO), + digoxin/other ventricular rate controller before	•Propaphenone, po •PO/IV flecainide

➢ Quinidine (IA), flecainide (IC), sotalol & dofetilide (III) are FDA approved for maintenance of sinus ryhthm, besides amiodarone & propaphenone

❑ Direct Current (DC, electric) Conversion

- DC conversion is reserved for hemodynamically unstable patients, it needs general anesthesia

Treatment of Ventricular Arrhythmias

❑ *Premature Ventricular Contractions (PVCs)* are index for *Sudden Cardiac Death (SCD)* in patients with low ejection fraction after MI

❑ Treatment Include:

➢ ***β- adrenergic blockers*** (IV followed by oral) early after MI [Metoprolol & Sotalol (class III)], proved to increase survival

➢ Amiodarone especially in HF patients, 2nd choice

➢ Class IC drugs should be avoided as they showed increased mortality in post-MI patients

Treatment of Ventricular Tachycardia

In hemodynamically stable patients, acute treatment include the following:

- ❑ **Lidocaine IV** is the drug of 1st choice
  - ✓ Injection may be repeated after 10 minutes to overcome its short distribution $t_{1/2}$
- ❑ Procainamide IV is 2nd choice
  - ✓ Dose adjusted in renal failure to avoid accumulation of parent & NAPA
- ❑ Class III drugs especially amiodarone & sotalol