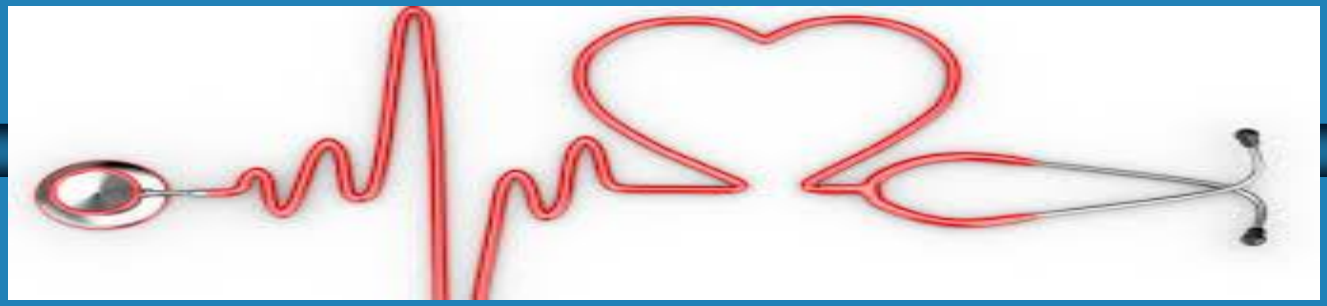
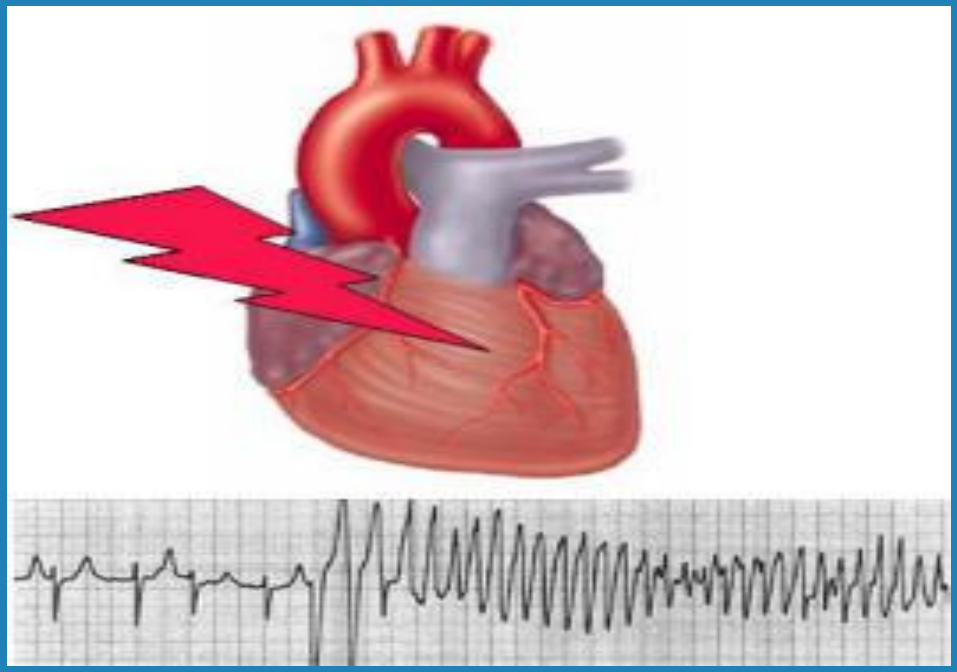
Antiarrhythmic Drugs



Assoc. Prof. Bilgen Başgut- 2014



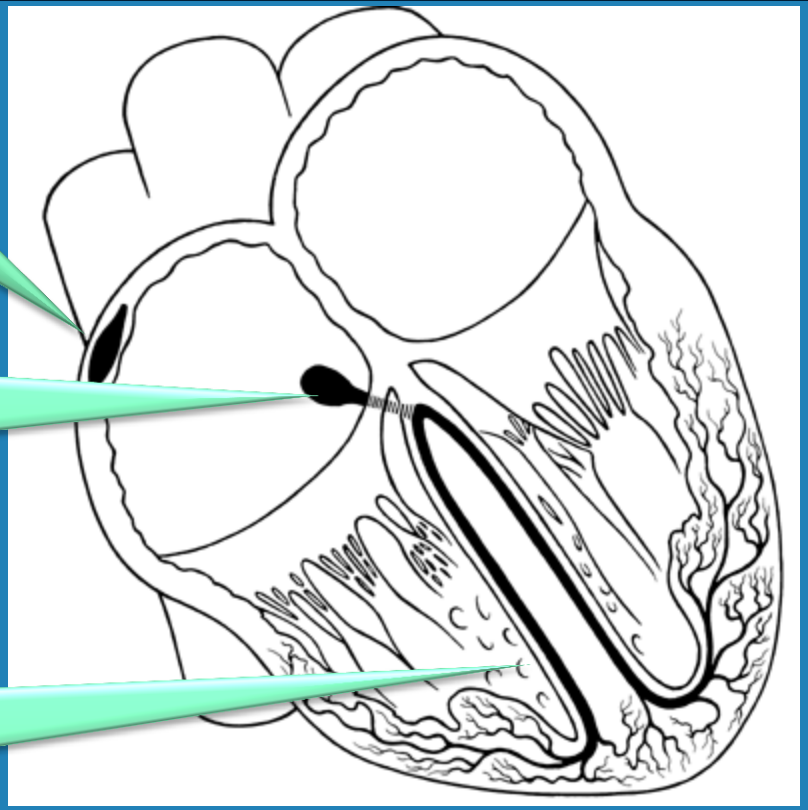
Physiology of the normal heart

Normal conduction pathway:

1- SA node generates action potential and delivers it to the atria and the AV node

2- The AV node delivers the impulse to purkinje fibers

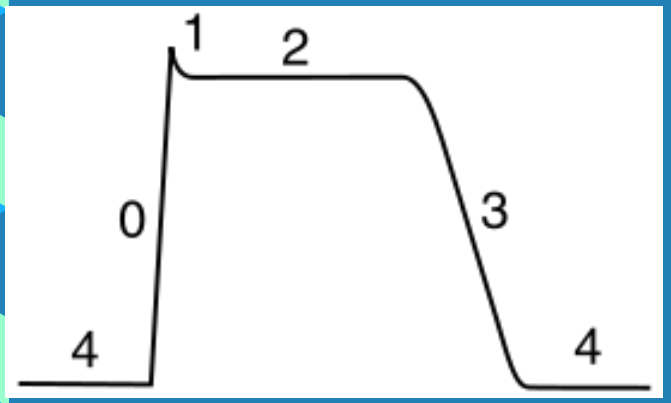
3- purkinje fibers conduct the impulse to the ventricles



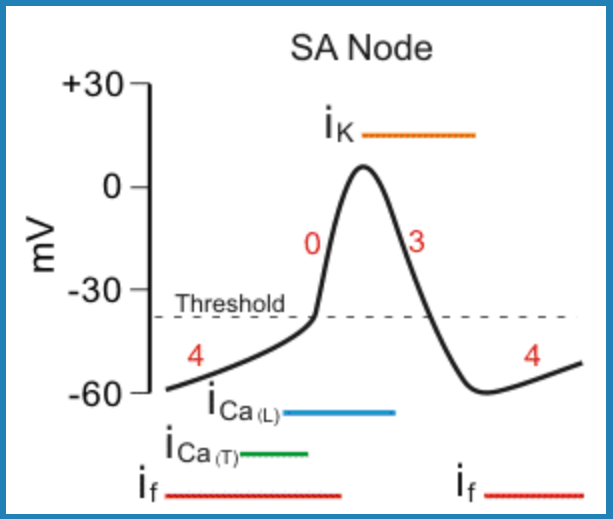
Other types of conduction that occurs <u>between myocardial cells</u>: When a cell is depolarized → adjacent cell depolarizes along

Action potential of the heart:

In the atria, purkinje, and ventricles the AP curve consists of 5 phases



In the SA node and AV node, AP curve consists of 3 phases

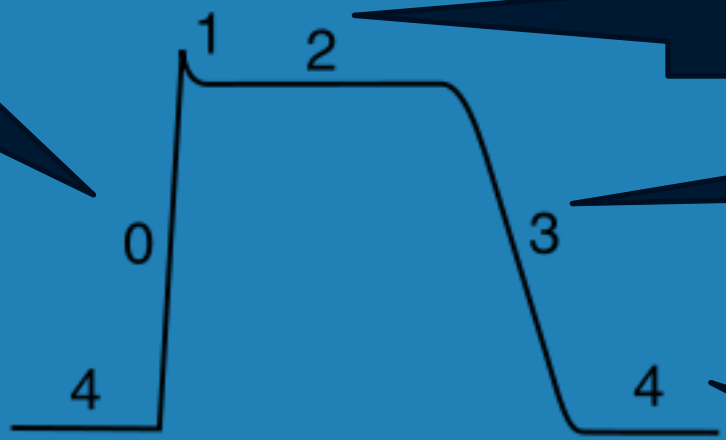


Non-pacemaker action potential

Phase 1: partial repolarization
Due to rapid efflux of K^+

Phase 2: plateu
Due to Ca^{++} influx

Phase 0: fast upstroke
Due to Na^+ influx



Phase 3: repolarization
Due to K^+ efflux

Phase 4: resting membrane potential

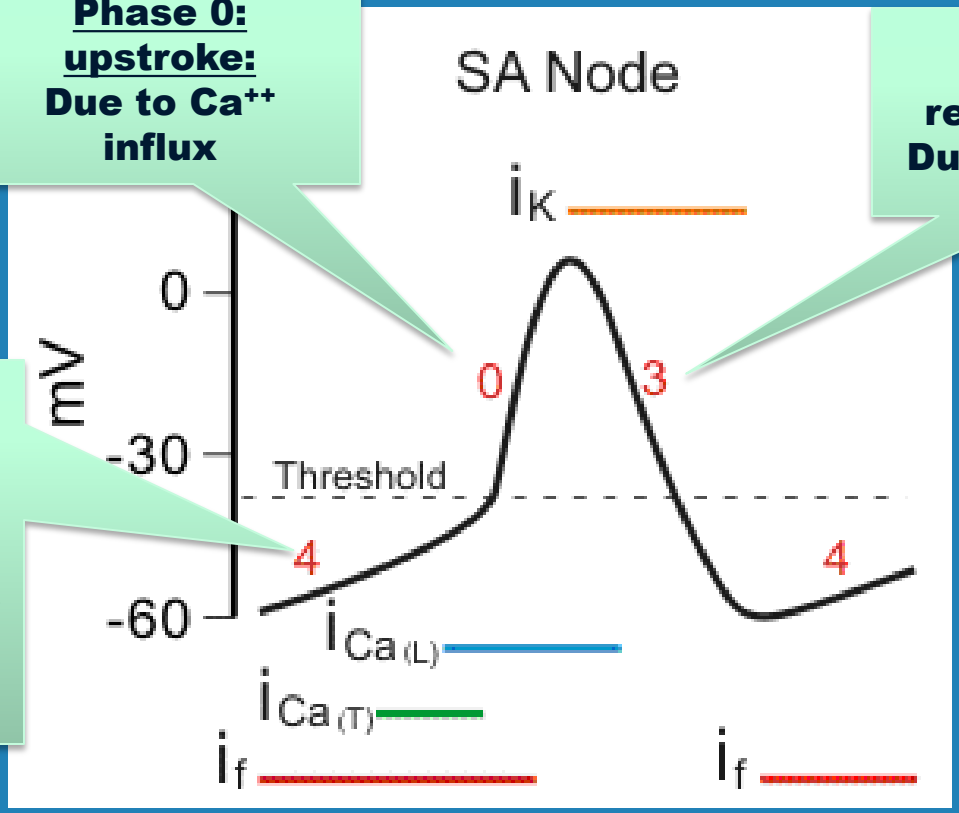
NThe slope of phase 0 = conduction velocity
Also the peak of phase 0 = V_{max}

Pacemaker AP

Phase 0: upstroke: Due to Ca^{++} influx

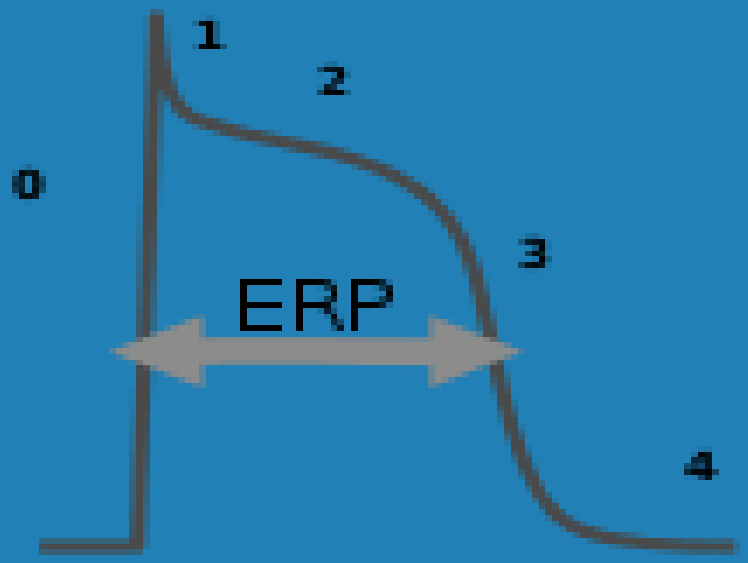
Phase 3: repolarization: Due to K^{+} efflux

Phase 4: pacemaker potential
Na influx and K efflux and Ca influx until the cell reaches threshold and then turns into phase 0



Pacemaker cells (automatic cells) have unstable membrane potential so they can generate AP spontaneously

Effective refractory period (ERP)



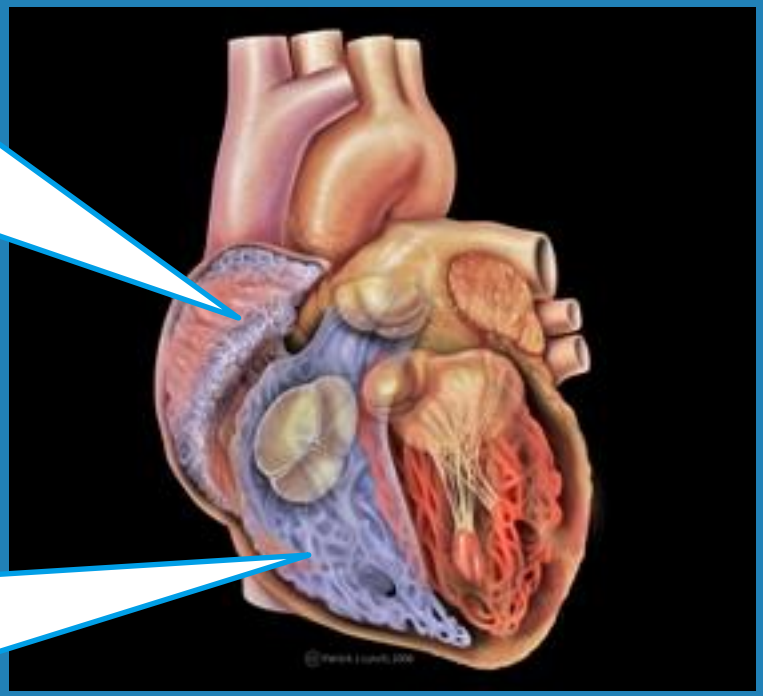
It is also called absolute refractory period (ARP) :

- **In this period the cell <u>can't be excited</u>**
- **Takes place between phase 0 and 3**

Arrhythmia

Arrhythmia /dysrhythmia: abnormality in the site of origin of impulse, rate, or conduction

If the arrhythmia arises from atria, SA node, or AV node it is called supraventricular arrhythmia



If the arrhythmia arises from the ventricles it is called ventricular arrhythmia

Factors precipitate arrhythmias

- May includes :
- Ischemia, hypoxia, electrolytes disturbance, excessive catecholamines exposure , drug toxicity.

Mechanisms of arrhythmias

1- Disturbances in impulse formation.

- **Vagal stimulation or β- receptor blocking drugs slow normal pacemaker .**
- **Acceleration of pacemaker by hypokalemia or β- adrenoceptor stimulants.**
- **Development of ectopic pacemakers.-**

2- Disturbances in impulse conduction

- May result from block (nodal block or bundle branch block .
- Reentry :
- circus movement

  In which one impulse reenters and excites areas of the heart more than ones.
- Some forms of reentry are anatomical in shape as in Wolff- Parkinson –White syndrome.

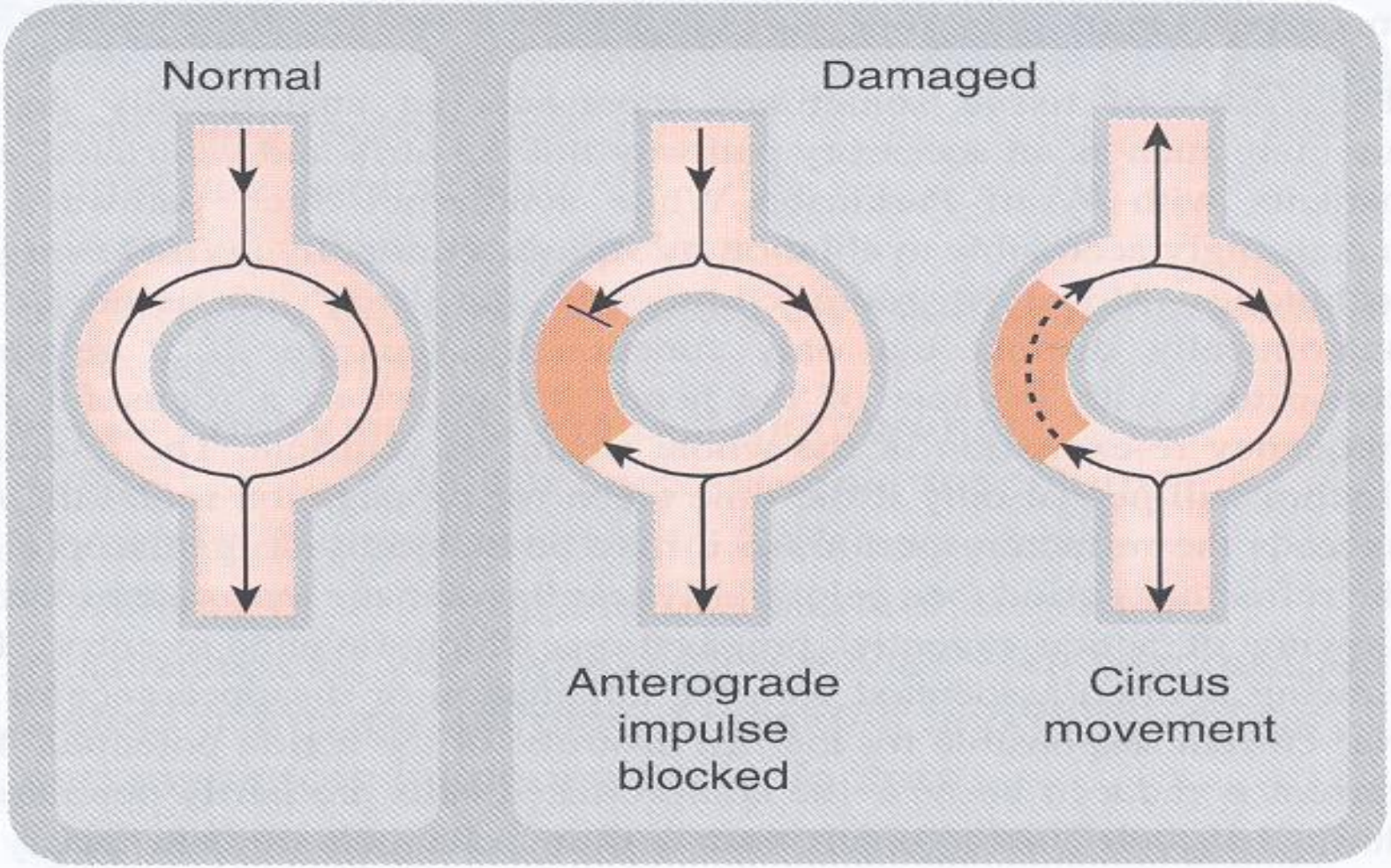


Fig. 17.3 Generation of a re-entrant rhythm by a damaged area of myocardium. The damaged area (brown) conducts in one direction only. This disturbs the normal pattern of conduction and permits continuous circulation of the impulse to occur.

Types of Arrhythmia

Supraventricular Arrhythmias

- ✓ **Sinus Tachycardia: high sinus rate of 100-180 beats/min, occurs during exercise or other conditions that lead to increased SA nodal firing rate**
- ✓ **Atrial Tachycardia: a series of 3 or more consecutive atrial premature beats occurring at a frequency >100/min**
- ✓ **Paroxysmal Atrial Tachycardia (PAT): tachycardia which begins and ends in acute manner**
- ✓ **Atrial Flutter: sinus rate of 250-350 beats/min.**
- ✓ **Atrial Fibrillation: uncoordinated atrial depolarizations.**

AV blocks

A conduction block within the AV node , occasionally in the bundle of His, that impairs impulse conduction from the atria to the ventricles.

Ventricular Arrhythmias

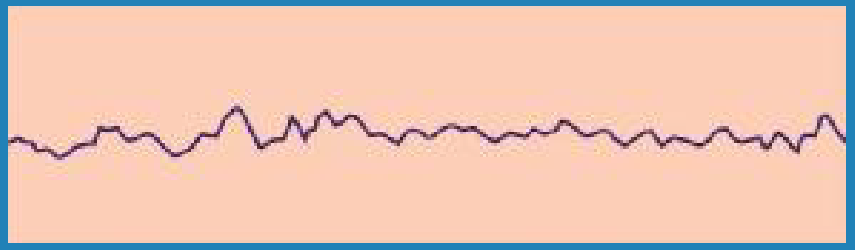
- ✓ **Ventricular Premature Beats (VPBs):** caused by ectopic ventricular foci; characterized by widened QRS.
- ✓ **Ventricular Tachycardia (VT):** high ventricular rate caused by abnormal ventricular automaticity or by intraventricular reentry; can be sustained or non-sustained (paroxysmal); characterized by widened QRS; rates of 100 to 200 beats/min; life-threatening.
- ✓ **Ventricular Flutter** - ventricular depolarizations >200/min.
- ✓ **Ventricular Fibrillation** - uncoordinated ventricular depolarizations

Types of Arrhythmias

Normal Rhythm

Tachycardia

Ventricular Fibrillation



Principles of Human Physiology. Germann and Stanfield. Benjamin Cummings

Pharmacologic Rationale & Goals

- The ultimate goal of antiarrhythmic drug therapy:
  - Restore normal sinus rhythm and conduction
  - Prevent more serious and possibly lethal arrhythmias from occurring.
- Antiarrhythmic drugs are used to:
  - ✓ decrease conduction velocity
  - ✓ change the duration of the effective refractory period (ERP)
  - ✓ suppress abnormal automaticity

Antyarrhythmic drugs

- Most antiarrhythmic drugs are pro-arrhythmic (promote arrhythmia)
- They are classified according to *Vaughan William* into four classes according to their effects on the cardiac action potential

I	Na^+ channel blocker	Change the slope of phase 0	tachyarrhythmia caused by reentry circuit
II	β blocker	↓heart rate and conduction velocity	Can indirectly alter K and Ca conductance
III	K^+ channel blocker	1. ↑action potential duration (APD) or effective refractory period (ERP). 2. Delay repolarization.	Inhibit reentry tachycardia
IV	Ca^{++} channel	Slowing the rate of rise in phase 4 of	↓conduction velocity in SA

Antiarrhythmic Drugs

- **Class 1** : Na+ channel blockers
- Local anaesthetic effect
- -and inotropic action
- **Class 1(A)**: prolongs duration of action potential & refractory period.
- Have K+ channel blocking effect
- Antimuscarinic & hypotensive effects.

. Class1(B):Shorten the duration of action potential & refractory period

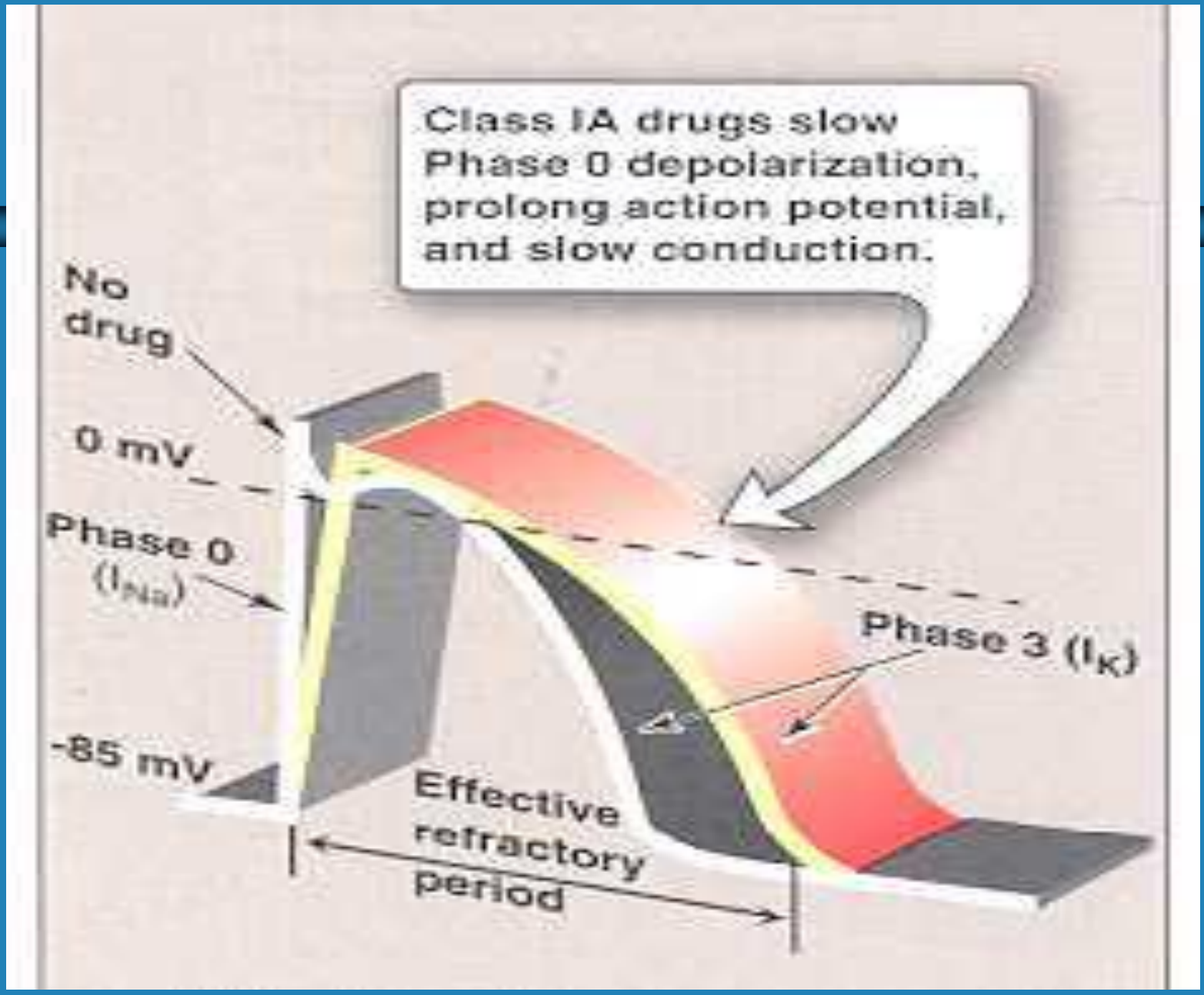
- Class1(C) : No effect on the duration of action or refractory period.

- **Class 2** : β-adrenoceptor blockers.
- **Class 3**: K+ channel blockers,
- Prolong duration of action potential and refractory period.

- **Class 4** : Ca++ channel blockers.
- Miscellaneous drugs.

Class 1(A) Quinidine:

- Cinchona plant
- Block open & inactivated sodium channel
- Block potassium channel
- -ve inotropic effect
- Antimuscarinic effect
- ↑duration of action potential & refractory periods of atrium & ventricles.
- Hypotensive


Class IA drugs slow Phase 0 depolarization, prolong action potential, and slow conduction.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period

ECG changes

- Prolong Q-T interval
- Widening QRS complex

Phrmacokinetics

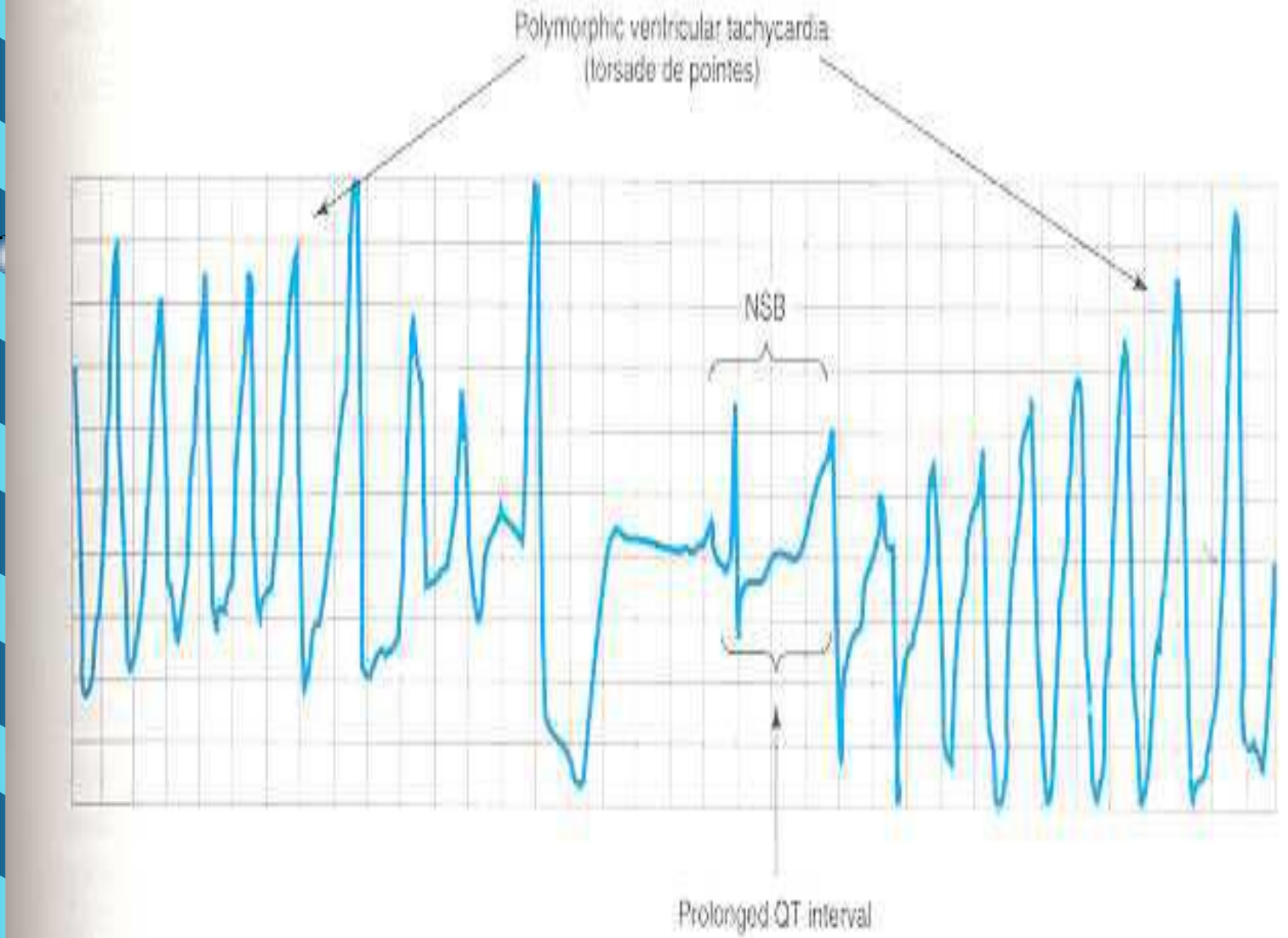
- Well absorbed orally
- Highly bound to plasma proteins
- Metabolized in liver (active metabolite)
- 20% excreted unchanged in urine
- Usually given as slow release formulation
- I.M. painful, I.V(marked hypotension)

Clinical uses

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

Adverse effects

- 1- Cardiac effects
- A) Due to antimuscarinic effect ,in A.F.or A.F. may precipitate ventricular tachycardia
- B) Syncope
- C)Torsade de pointes
- D) Cardiac stand still (asystole) in patients with sick sinus syndrome .


Polymorphic ventricular tachycardia
(torsade de pointes)
NSB
Prolonged QT interval

Extracardiac adverse effects

- Hypotension
- Cinchonism (headache, dizziness,tinnitus,deafness)
- Hypersensitivity reactions (hepatitis,thrombocytopenia)
- GIT, diarrhea,nausea,vomiting

Drug interactions

- Quinidine increases the plasma level of digoxin by :

  a) displacement from tissue binding sites

  b) decreasing digoxin renal clearance

Procainamide

- As quinidine but :
- Less hypotensive
- Less antimuscarinic
- Less cardiotoxic
- Can be given safely by I.M. or I.V.
- Metabolized in liver and give active metabolite which has a class 111 activity .

Continue

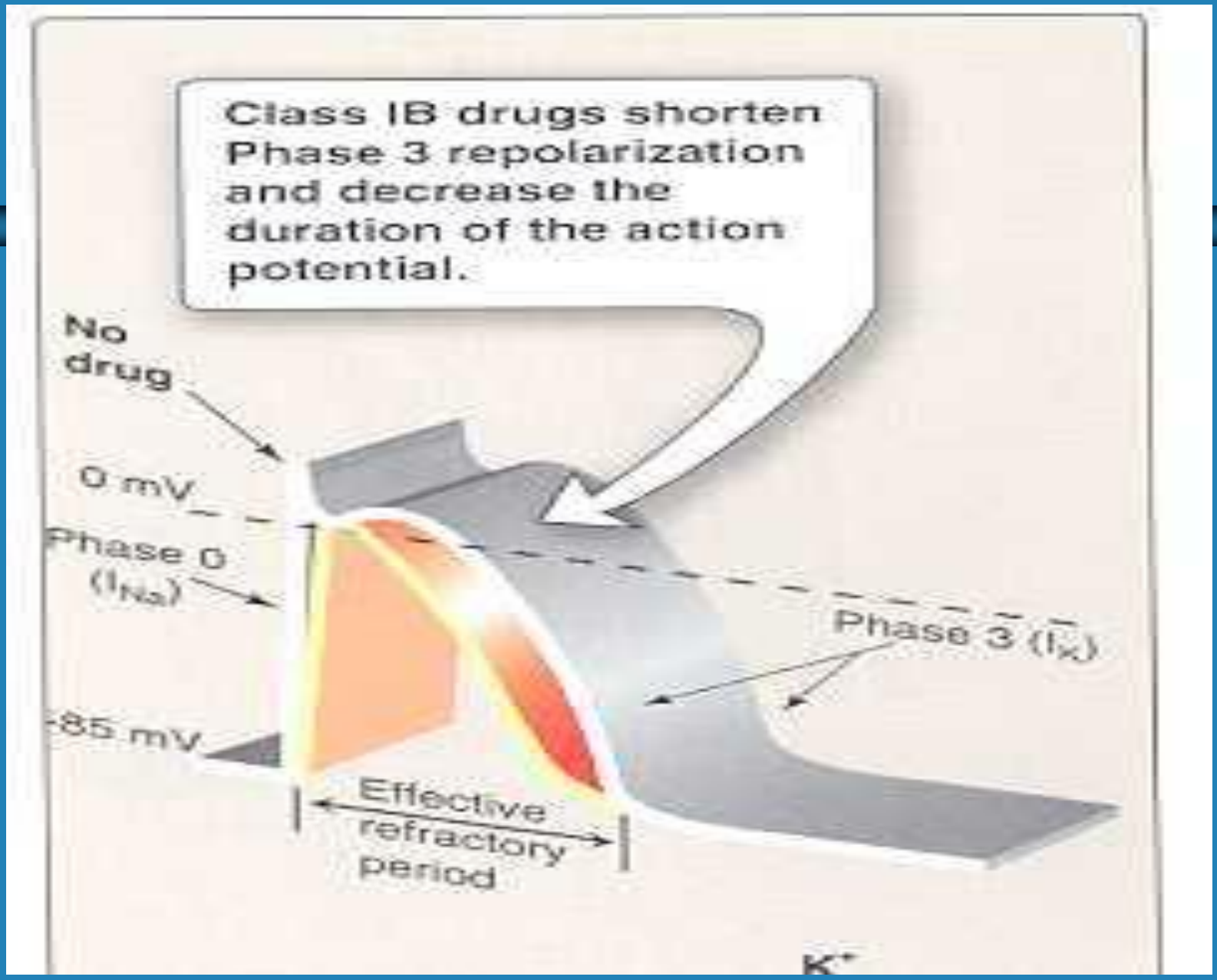
- Eliminated through kidney .
- More effective in ventricular arrhythmias , it is the second drug of choice after lidocaine in treament of ventricular arrhythmia follow acute M.I.
- Effective in A.F. or A.F. due to Wolff Parkinson White syndrome

Adverse effects

- Systemic lupus erythematosus like syndrome.
- GIT : Nausea , diarrhea
- Torsade de pointes
- Hypotension

Class 1(B)

- Lidocaine
- Shorten the duration of A.P.& R.P.
- Effective in ventricular arrhythmias.


Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period
K^+

Pharmacokinetics

- Well absorbed after oral administration . Only 3% reach general circulation.
- Given only by I.V. route
- Excreted via kidney .
- Half-life 2hrs.

Therapeutic uses

- First drug of choice in treatment of ventricular arrhythmias due to
- Acute myocardial infarction
- Digitalis toxicity
- Anaesthesia
- Open heart surgery

Adverse effects

- **Neurological effects :**

(contraindicated in epileptic patients).

- **Arrhythmias uncommon**
- **Hypotension**

Mexiletine

- Effective orally
- Half-life (8-20hrs).
- Used in chronic treatment of ventricular arrhythmias.
- Effective in relieving chronic pain due to diabetic neuropathy& nerve injury.

Adverse effects

- Neurologic side effects

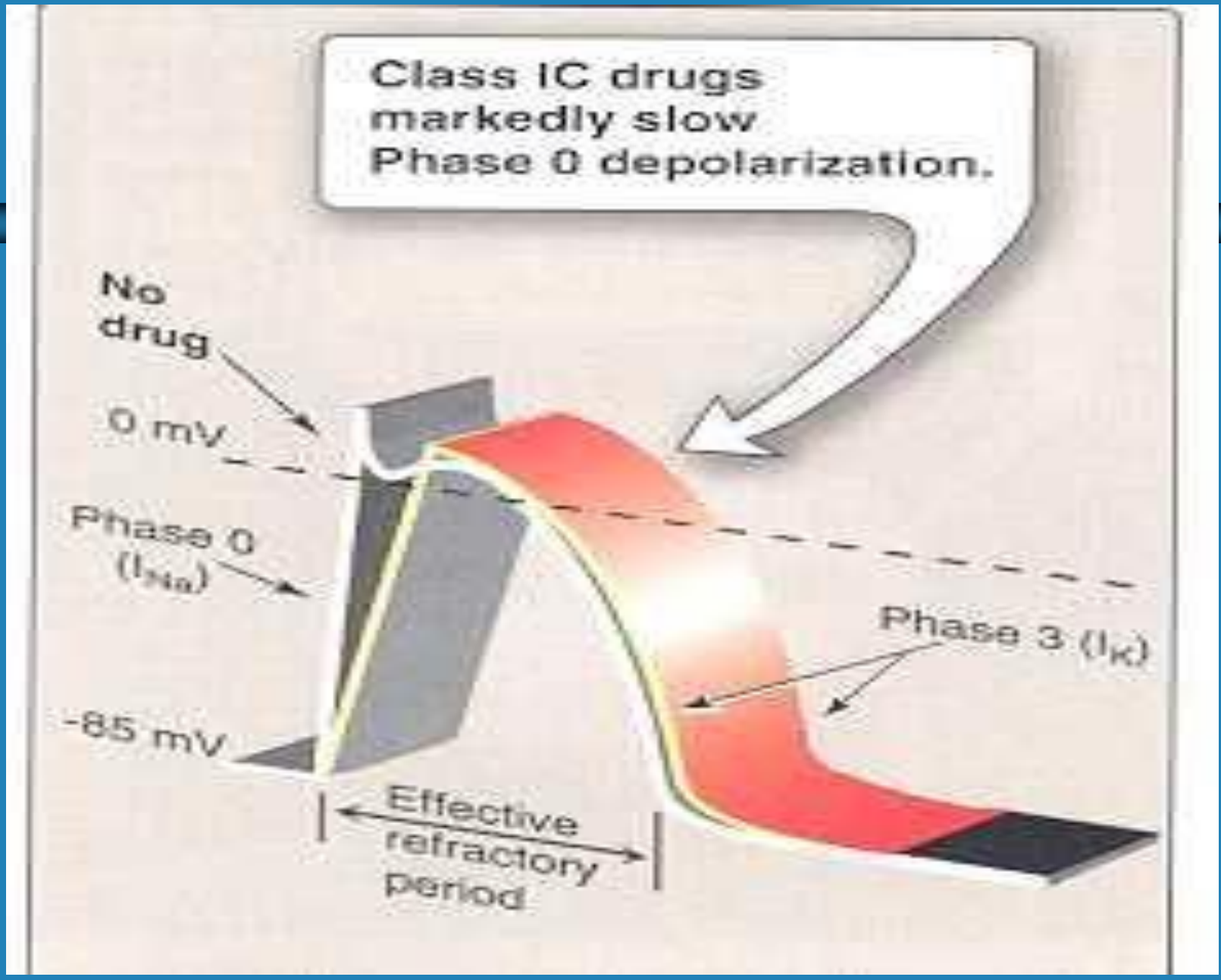
Class1(c)

- **Flecainide**

  No effect on the duration of A.P.& R.P.

- **Proarrhythmic**

- **Approved for refractory ventricular arrhythmias.**


Class IC drugs markedly slow Phase 0 depolarization.
No drug
0 mV
Phase 0 (I_{Na})
-85 mV
Phase 3 (I_K)
Effective refractory period

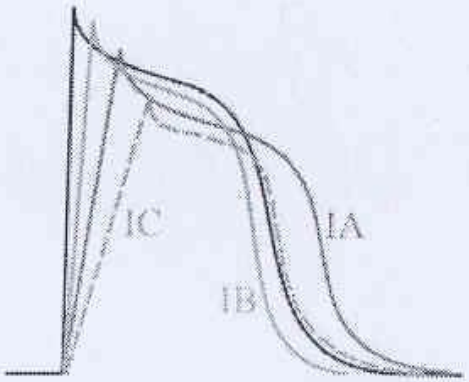
Propafenone

- Has a weak β-blocking effect.
- Used to maintain sinus rhythm in patients with supraventricular arrhythmias including AF.
- **Adverse effects :**

  Metallic taste, constipation .

- Compare between class IA, IB, and IC drugs as regards effect on Na^+ channel & ERP

- Sodium-channel blockade:
  IC > IA > IB
- Increasing the ERP:
  IA>IC>IB (lowered)



Ventricular Action Potential

- Class IA: e.g., quinidine
  - Moderate Na^+-channel blockade
  - ↑ ERP
- Class IB: e.g., lidocaine
  - Weak Na^+-channel blockade
  - ↓ ERP
- Class IC: e.g., flecainide
  - Strong Na^+-channel blockade
  - → ERP

Class 2

Beta-Adrenoceptor-Blocking Drugs.

Effective in atrial & ventricular arrhythmias that associated with

Increase in sympathetic activity .

Reduce the incidence of sudden arrhythmic death after myocardial infarction.

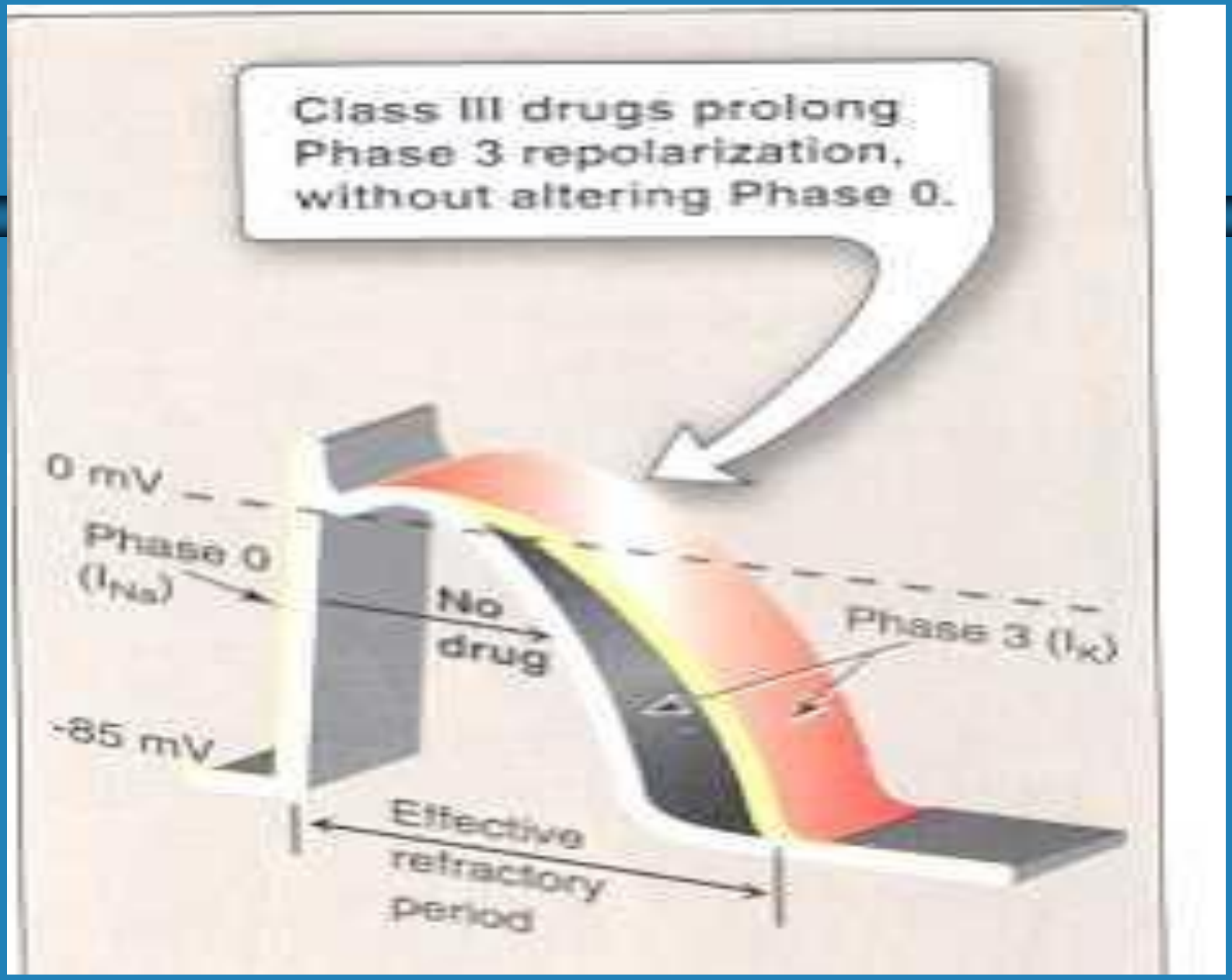
Continue

- Propranolol
- Metoprolol (β_1 selective)
- Esmolol

  Very short acting used for intraoperative & acute arrhythmias

Class 3

- Potassium channel blockers
- (Drugs that Prolong duration of action potential & refractory period).


Class III drugs prolong Phase 3 repolarization, without altering Phase 0.
0 mV
Phase 0 (I_{Na})
No drug
Phase 3 (I_K)
-85 mV
Effective refractory period

Sotalol

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

  Life- threatening ventricular arrhythmias.

  To maintain sinus rhythm in patients with atrial fibrillation.

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

Ibutilide

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

Amiodarone

- **A) cardiac effects**

Sodium channel blocking

Potassium channel blocking

Calcium channel blocking

β- adrenoceptor blocking

Continue

- **B) Extracardiac effect**

  Peripheral vasodilation

Pharmacokinetics

- Given orally
- Slow onset of action
- Long half-life(13-103 hrs).
- Cumulative drug
- Is highly lipophilic , is concentrated in many tissues.
- Eliminated by liver mostly as active metabolites.

Clinical uses

- Recurrent & refractory ventricular & supraventricular arrhythmias .
- Arrhythmias associated with Wolff Parkinson syndrome.
- In maintaining sinus rhythm in patients with AF.

Adverse effects

- Gray- blue skin discoloration & photodermatitis .
- Corneal microdeposits →corneal opacity ,optic neuritis, blindness
- pulmonary fibrosis

Continue

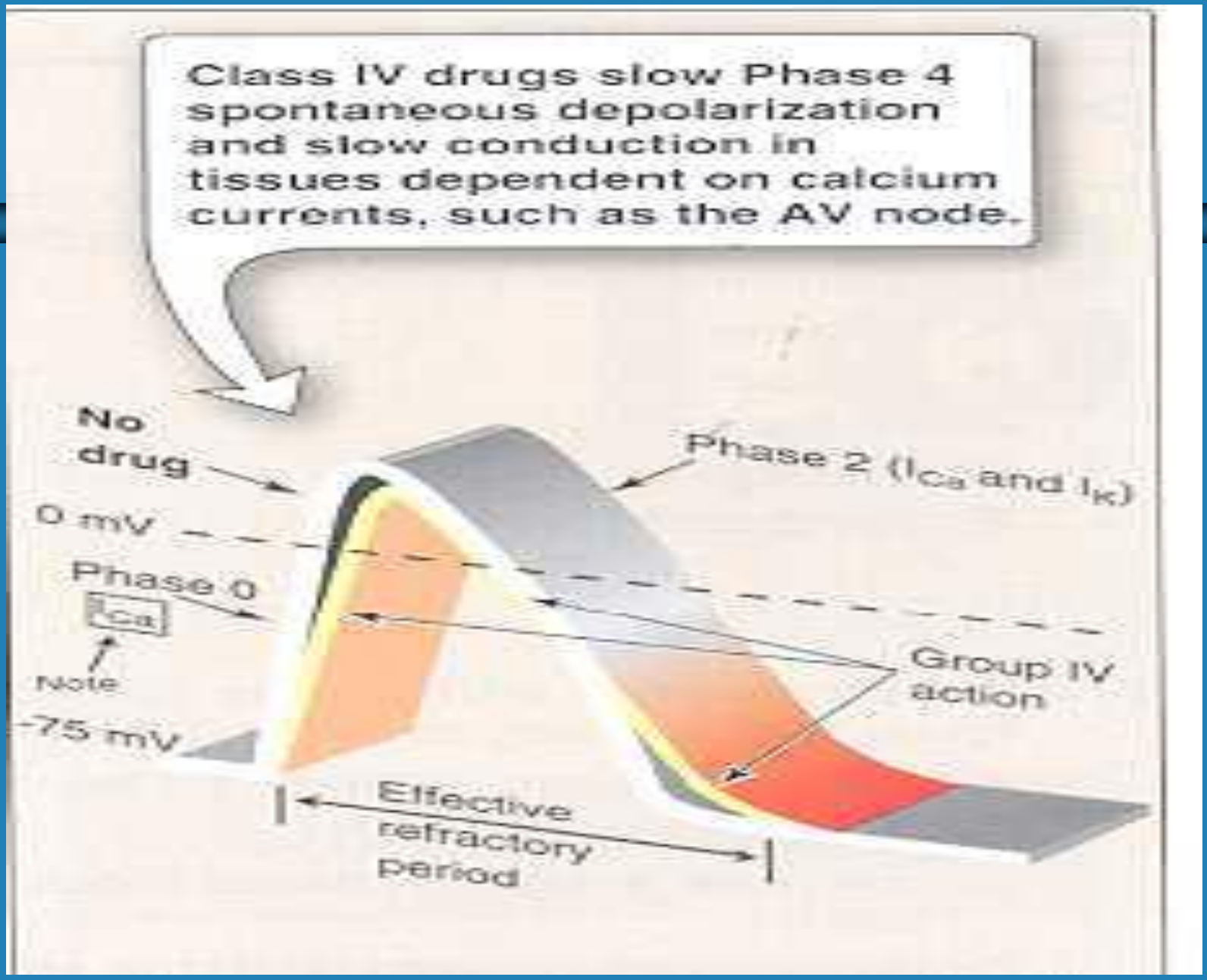
- hypo or hyperthyroidism
- Nausea & constipation
- Hepatic impairment
- neurological effects
- A-V block & bradycardia
- Hypotension

Drug interactions

- Oral anticoagulant →bleeding
- Digoxin→digoxin toxicity
- β- blockers →additive effect

Class 1V

- Calcium channel blockers
- e.g. Verapamil, Diltiazem
- Their main site of action is A.V.N & S.A.N.
- Effective only in atrial arrhythmias


Class IV drugs slow Phase 4 spontaneous depolarization and slow conduction in tissues dependent on calcium currents, such as the AV node.
No drug
Phase 2 (I_{Ca} and I_K)
0 mV
Phase 0
I_{Ca}
Note
Group IV action
-75 mV
Effective refractory period

Continue

- Second drugs of choice for the treatment of paroxysmal supraventricular tachycardia
- Not effective in Wolff Parkinson White syndrome.

Adverse effects

- -inotropic effect causes H.F.
- A-V block
- Constipation , headache , peripheral edema

Miscellenous drugs

- **Adenosine**

  Binds to specific G protein – coupled adenosine receptors

  (A_1&A_2)→opening K+ channel→hyperpolarization.

- **↓ influx of calcium**

Pharmacokinetics & Uses

- Very rapid onset of action .
- Short half- life (seconds)
- Given as a rapid I.V. bolus injection

  For the acute termination of re-entrant supraventricular tachycardia (paroxysmal attack) First choice.

Adverse effects

- Bronchospasm
- Chest pain
- Shortness of breath
- Flushing
- A-V block
- Hypotension

Contraindications

- Bronchial asthma
- A-V block

Drug interactions

- Less effective with adenosine receptor blockers (Caffeine or theophylline
- More effective with uptake inhibitors as dipyridamole

Magnesium

- Used in:
- Digitalis induced arrhythmias
- Torsade de pointes
- Sinus tachycardia

Potassium

- Used in:
- Digitalis induced arrhythmias

Treatment of atrial flutter/fibrillation

1st: Reduce thrombus formation by using anticoagulant warfarin

2nd: Prevent the arrhythmia from converting to ventricular arrhythmia:

First choice: class II drugs:

- **After MI or surgery**
- **Avoid in case of heart failure**

Second choice: class IV

Third choice: digoxin

- **Only in heart failure of left ventricular dysfunction**

3rd: Conversion of the arrhythmia into normal sinus rhythm:

Class III:

IV ibutilide, IV/oral amiodarone, or oral sotalol

Class IA:

Oral quinidine + digoxin (or any drug from the 2nd step)

Class IC:

Oral propaphenone or IV/oral flecainide

Use direct current in case of unstable hemodynamic patient

Treatment of ventricular arrhythmia

Premature ventricular beat (PVB)

First choice: class II

- **IV followed by oral**
- **Early after MI**

Second choice: amiodarone

Avoid using class IC after MI

→ ↑ **mortality**

Treatment of ventricular tachycardia

First choice: Lidocaine IV

- **Repeat injection**

Second choice: procainamide IV

- **Adjust the dose in case of renal failure**

Third choice: class III drugs

- **Especially amiodarone and sotalol**

(IA, IC, class III) → torsades de pointes.

Classes II and IV → bradycardia (don't combine the two)

In atrial flutter use (1st ↓impulses from atria to ventricular to prevent ventricular tachycardia)

1. Class II
2. Class IV
3. Digoxin.

2nd convert atrial flutter to normal sinus rhythm use:

1. Ibutilide
2. Sotalol
3. IA or IC.

If you use quinidine combine it with digoxin or β blocker (because of its anti muscarinic effect)

Avoid IC in myocardial infarction because it ↑ mortality

QUESTIONS

1- In ventricular tachycardia and stable hemodynamic which drug to be used?
A- propranolol
B- procainamide
C- quinidine
D- verapamil

2- Mr.Green devloped an arrhythmia and was treated. A month later, he has arthralgia, fever, pleural inflammation. What was the treatment of arrhythmia?
A- esmolol
B- class III
C- procainamide
D- propafenone

3- Cinchonism occurs with digoxin (F)

A- pulmonary fibrosis → **amiodarone**
B- bradycardia → **diltiazem**

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