Anti-arrhythmic Drugs

Disclaimer

All the content material provided here is only made for teaching purpose.

Arrhythmia

- Definition:

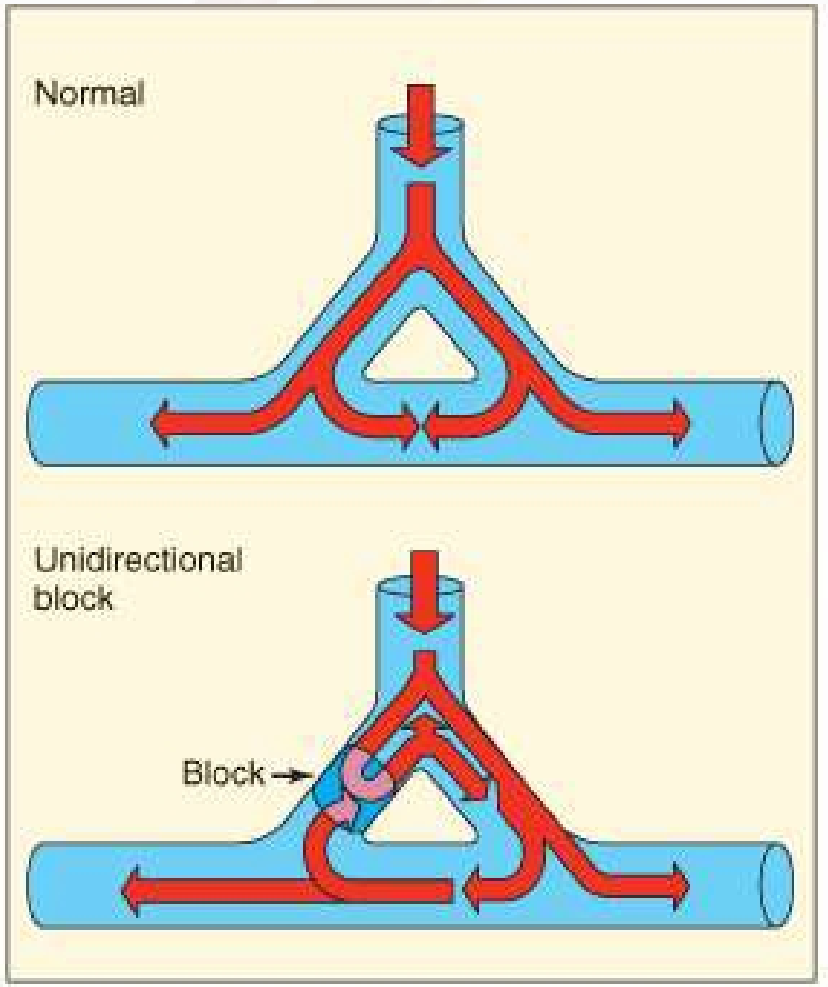
– Disturbances in the heart rate, rhythm, impulse generation or conduction of electrical impulses responsible for membrane depolarization.

– These disturbances can lead to alterations in overall cardiac function that can be life threatening.

Mechanism of arrhythmias

- Disturbances in impulse generation may be due to
  - Abnormal automaticity
  - Delayed after depolarizations
- Disturbances of impulse conduction
  - The impulse may recirculate in heart causing repeated activation (re-entry)
  - Conduction blocks

Re-entry phenomenon



Phases of action potential of cardiac cells

- ***Phase 0 rapid depolarisation*** (inflow of Na+)
- ***Phase 1 partial repolarisation*** (inward Na+ current deactivated, outflow of K+)
- ***Phase 2 plateau (slow inward*** calcium current)
- ***Phase 3 repolarisation (calcium*** current inactivates, K+ outflow)
- ***Phase 4 pacemaker potential*** (Slow Na+ inflow, slowing of K+ outflow) 'autorhythmicity'
- ***Refractory period (phases 1-3)***

Classification of antiarrhythmics

- **Class I: Sodium channel blockers**
- **Class II: β-Adrenergic blockers**

– Propranolol, acebutolol, esmolol

- **Class III: Potassium channel blockers**

– Amiodarone, bretylium, sotalol

- **Class IV: calcium channel blockers**

– Verapamil, diltiazem

- **Miscellaneous**

– PSVT: Adenosine, Digoxin

– AV block: Atropine

Class I: Sodium channel blockers

- IA: Prolong repolarization

– Quinidine, procainamide, disopyramide, morcizine

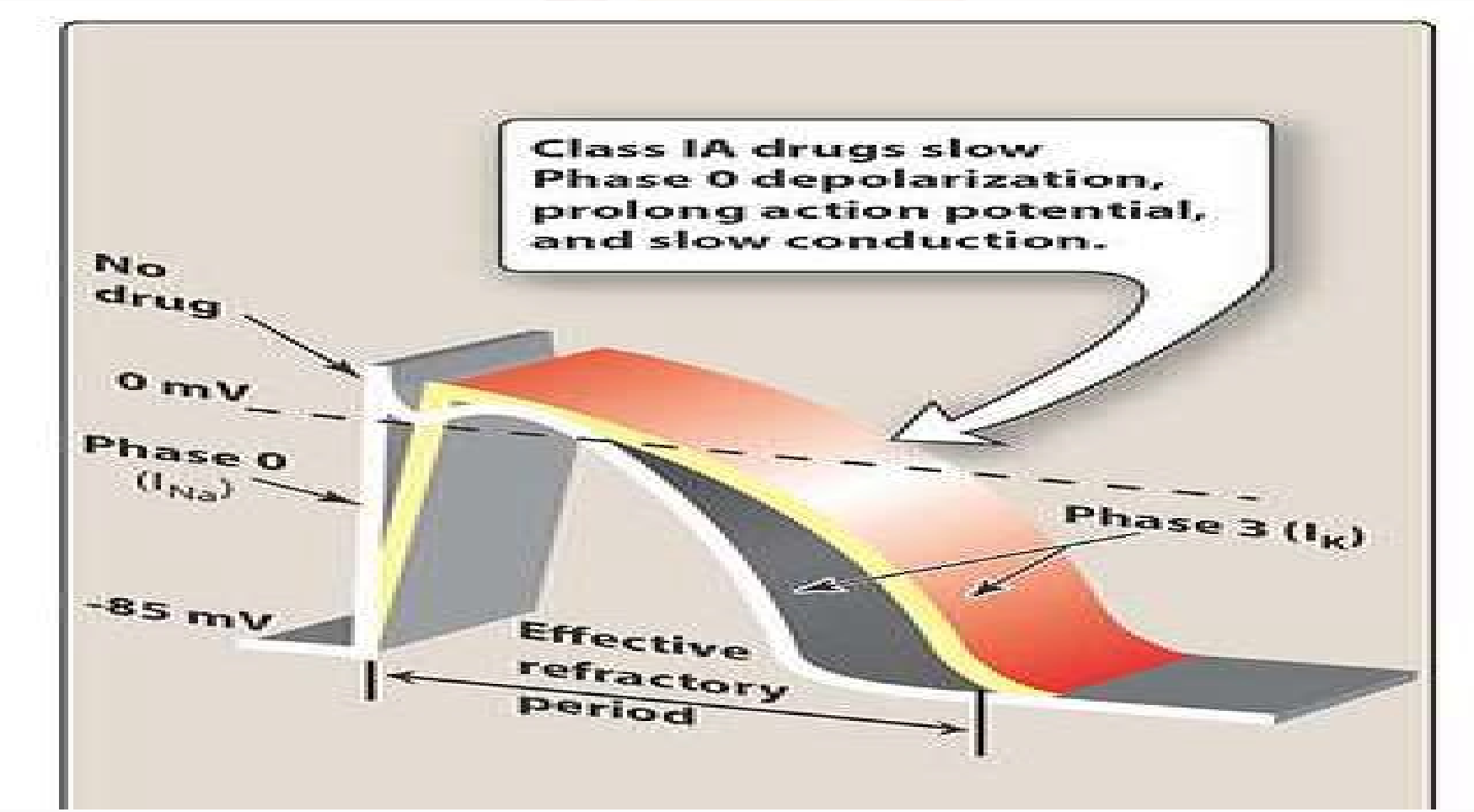
- IB: Shorten repolarization

– Lignocaine, mexiletine, phenytoin

- 1C: Little effect on repolarization

– Encainide, flecainide, propafenone

Class IA


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

Quinidine

- D- isomer of quinine obtained from cinchona bark
- MOA: blocks sodium channels

– ↓ automaticity , conduction velocity and prolongS repolarization

– ↓phase 0 depolarization , ↑ APD & ↑ERP

- Other actions:

– ↓ BP (α block), skeletal muscle relaxation

- Uses: Atrial and ventricular arrhythmias
- Adverse effects:

– Arrhythmias and heart block , hypotension, QT prolongation

– GIT , thrombocytopenia, hepatitis , idiosyncratic reactions

– High doses – cinchonism like quinine

Procainamide

– Derivative of procaine
– No vagolytic or α-blocking action unlike quinidine
– Better tolerated

Adverse effects:

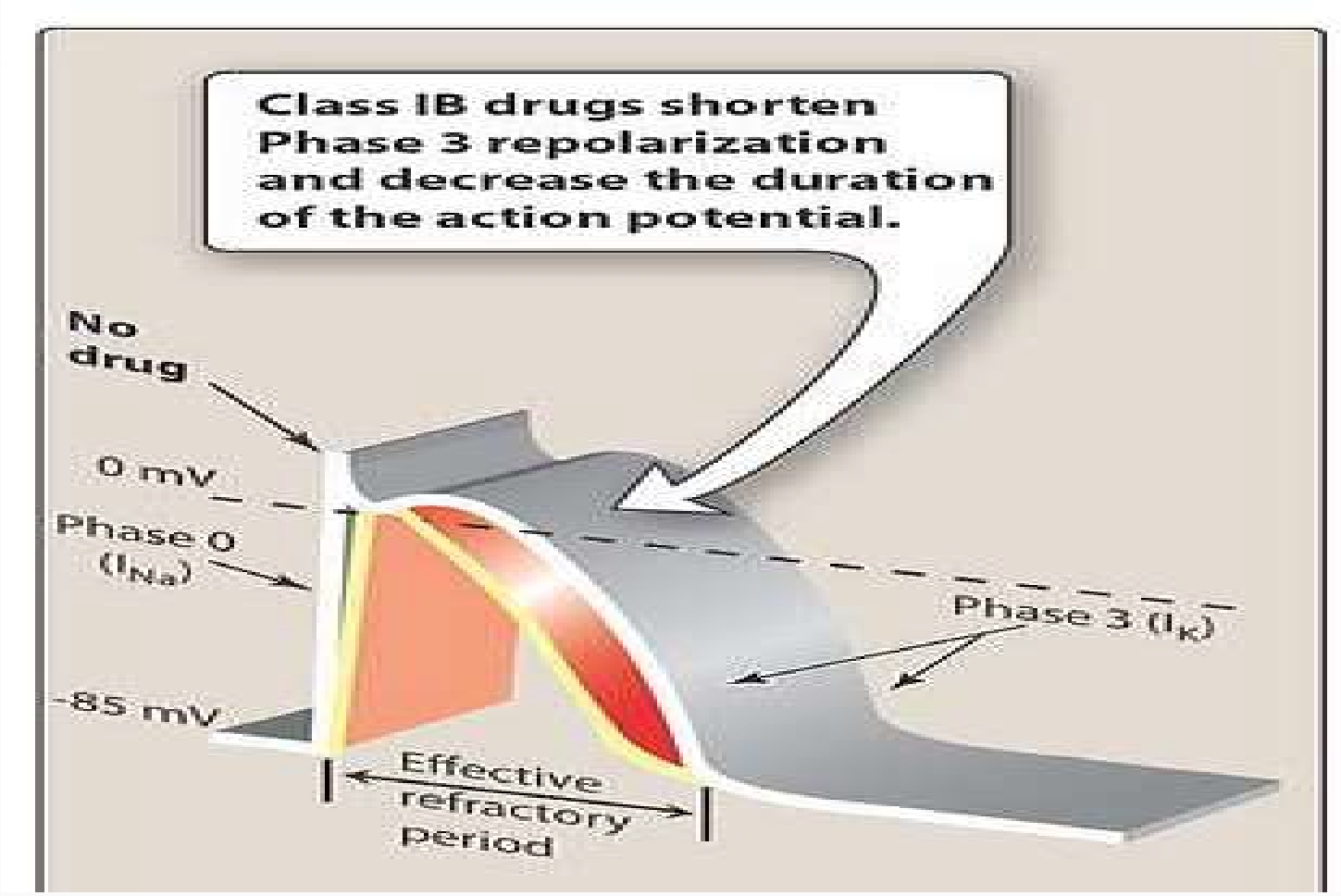
- Nausea, vomiting and hypersensitivity reactions
- Higher doses can cause hypotension, heart block and QT prolongation

- Disopyramide:

– Significant anticholinergic properties:

- Dry mouth, blurred vision, constipation, urinary retention

Class IB drugs



Lignocaine

- Local anaesthetic
- Raises threshold for action potential, ↓automaticity
- Suppress electrical activity of arrhythmogenic tissues, normal tissues less effected
- High first pass metabolism so given parenterally
- Use: ventricular arrhythmias
- Adverse effects:

– Drowsiness, hypotension, blurred vision, confusion and convulsions

Phenytoin

– Antiepileptic also useful in ventricular arrhythmias (not preferred) and digitalis induced arrhythmias

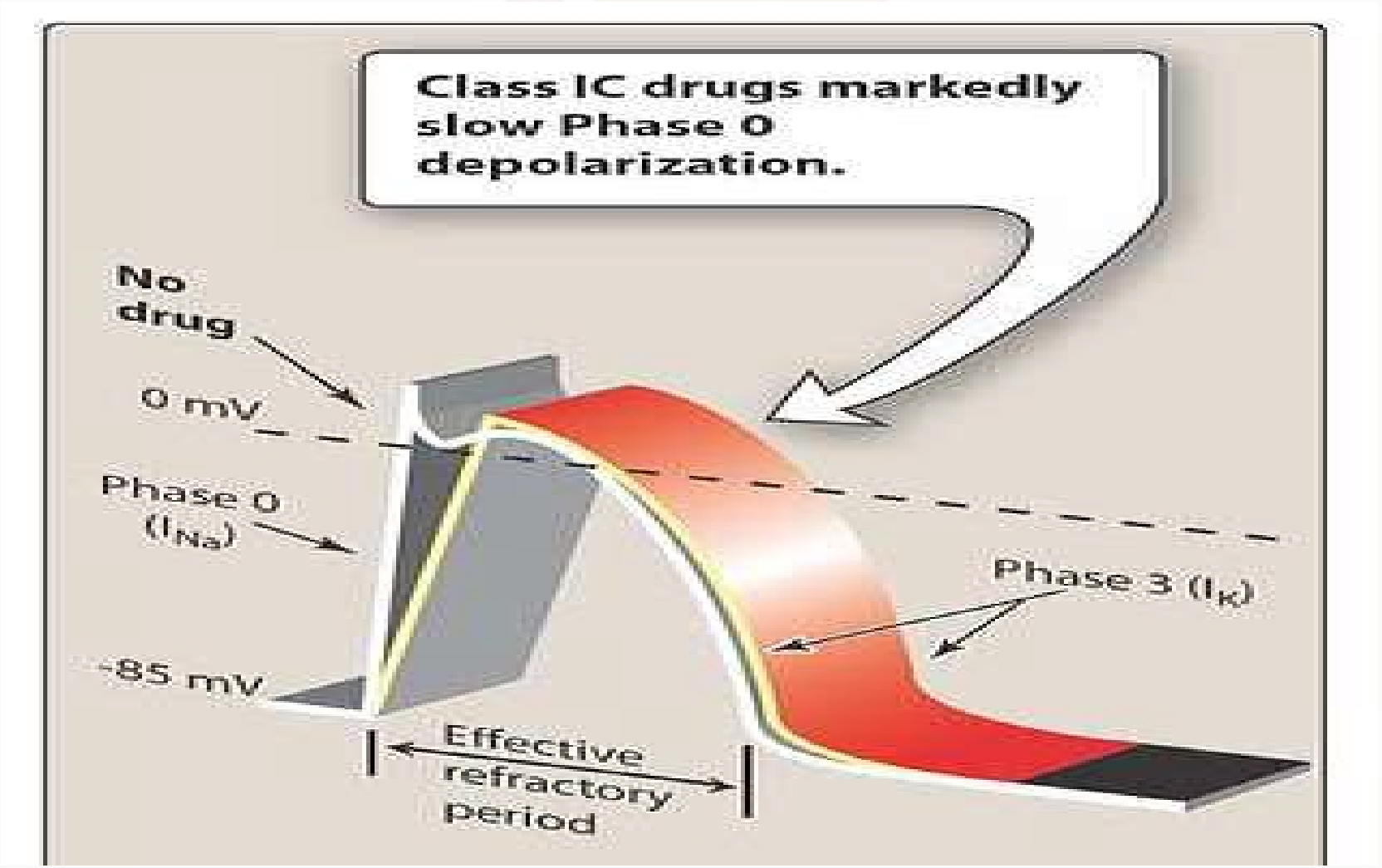
- Mexiletine:

– Can be used orally causes dose related neurological adverse events like tremors and blurred vision

– Nausea is common

– Used as alternative to lignocaine in ventricular arrhythmias

Class I C drugs



Class II drugs

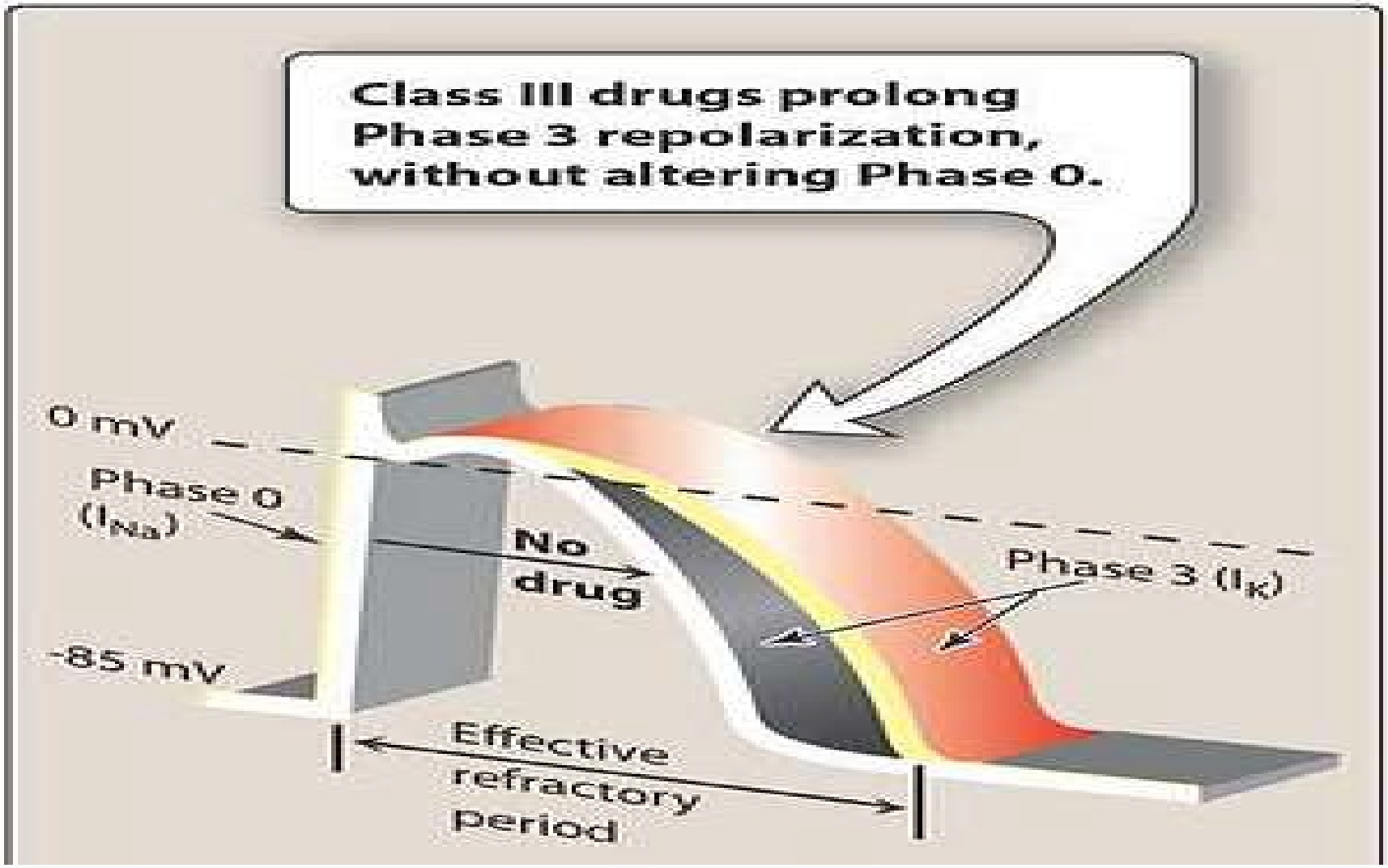
- Supress adrenergically mediated ectopic activity
- Antiarrhythmic action due to of β blockade
- Depress myocardial contractility, automaticity and conduction velocity
- Propranolol:

– Treatment & prevention of supraventricular arrhythmias especially associated with exercise, emotion or hyperthyroidism

- Esmolol:

– IV short acting can be used to treat arrhythmias during surgery , following MI & other emergencies

Class III drugs



Amiodarone

- Iodine containing long acting drug
- Mechanism of action: (Multiple actions)
  - Prolongs APD by blocking K+ channels
  - blocks inactivated sodium channels
  - β blocking action , Blocks Ca2+ channels
  - ↓ Conduction, ↓ectopic automaticity
- Pharmacokinetics:
  - Variable absorption 35-65%
  - Slow onset 2days to several weeks
  - Duration of action : weeks to months
  - Many drug interactions

Amiodarone

- Uses:
  - Can be used for both supraventricular and ventricular tachycardia
- Adverse effects:
  - Cardiac: heart block , QT prolongation, bradycardia, cardiac failure, hypotension
  - Pulmonary: pneumonitis leading to pulmonary fibrosis
  - Bluish discoloration of skin
  - GIT disturbances, hepatotoxicity
  - Blocks peripheral conversion of T4to T3 can cause hypothyroidism or hyperthyroidism

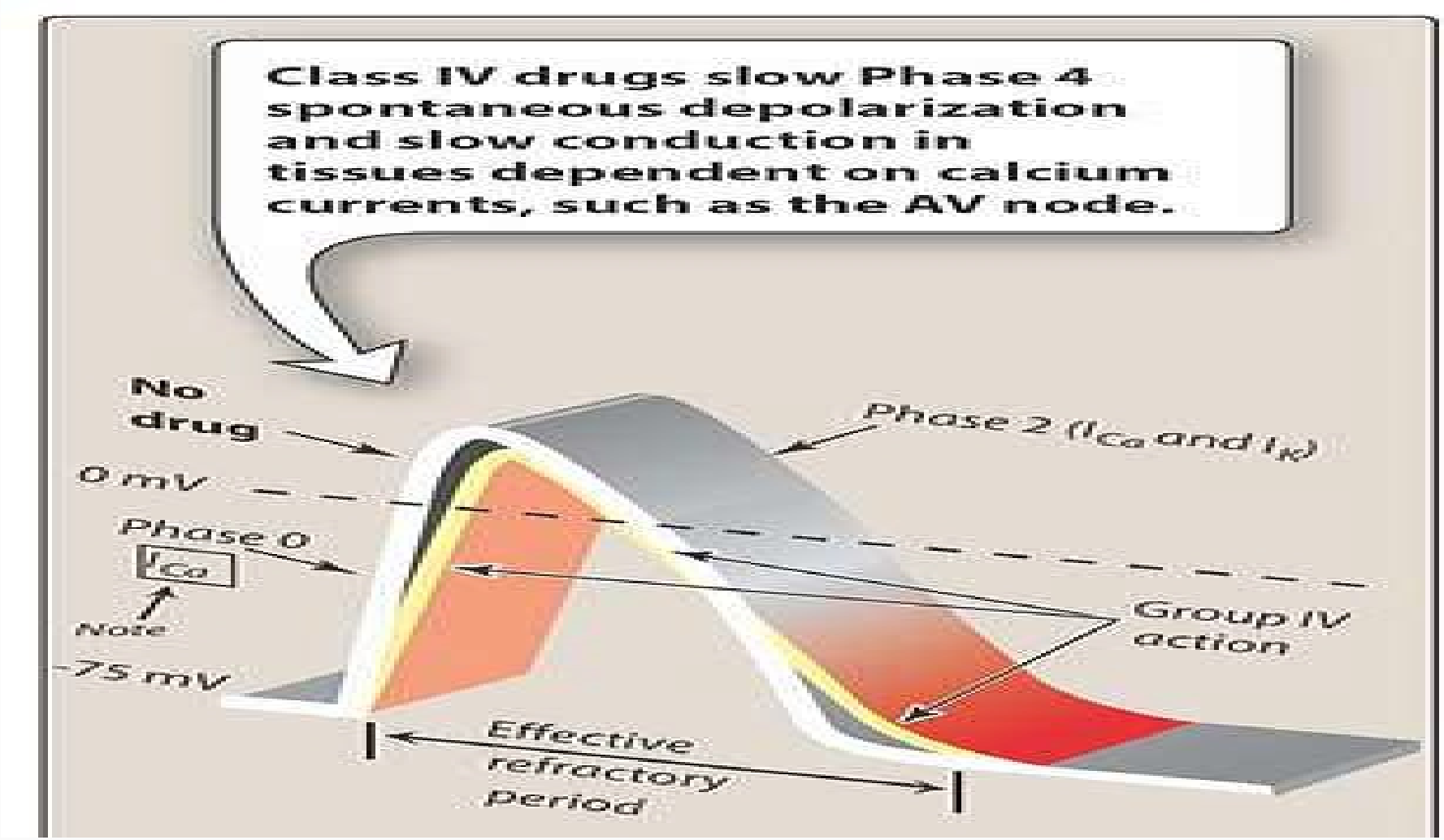
- Bretylium:
  - Adrenergic neuron blocker used in resistant ventricular arrhythmias

- Sotalol:
  - Beta blocker

- Dofetilide:
  - Selective K+ channel blocker, less adverse events
  - Oral use in AF to convert or maintain sinus rhythm

- Ibutilide:
  - K+ channel blocker used as IV infusion in AF or flutter can cause QT prolongation

Calcium channel blockers (Class IV)



Verapamil

- Uses:
  - Terminate PSVT
  - control ventricular rate in atrial flutter or fibrillation

- Drug interactions:
  - Displaces digoxin from binding sites
  - ↓ renal clearance of digoxin

Other antiarrhythmics

- Adenosine :
  - Purine nucleotide having short and rapid action
  - Mechanism of action: Acetylcholine sensitive K+ channels and causes membrane hyperpolarization through interaction with A1 type of adenosine GPCRs on SA node
  - IV suppresses automaticity, AV conduction and dilates coronaries
  - Drug of choice for PSVT

Adverse events:

- Nausea, dyspnoea, flushing, headache
- Atropine: Used in sinus bradycardia
- Digitalis: Atrial fibrillation and atrial flutter
- Magnesium SO4: digitalis induced arrhythmias

References

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3. Satoskar RS, Ainapure SS, Bhandarkar SD, Kale AK, ‘Pharmacology and pharmacotherapeutics’, 14th edition, Popular Prakashan, Mumbai, 1995.