Anti-arrhythmic Drugs

DEPT. OF PHARMACOLOGY

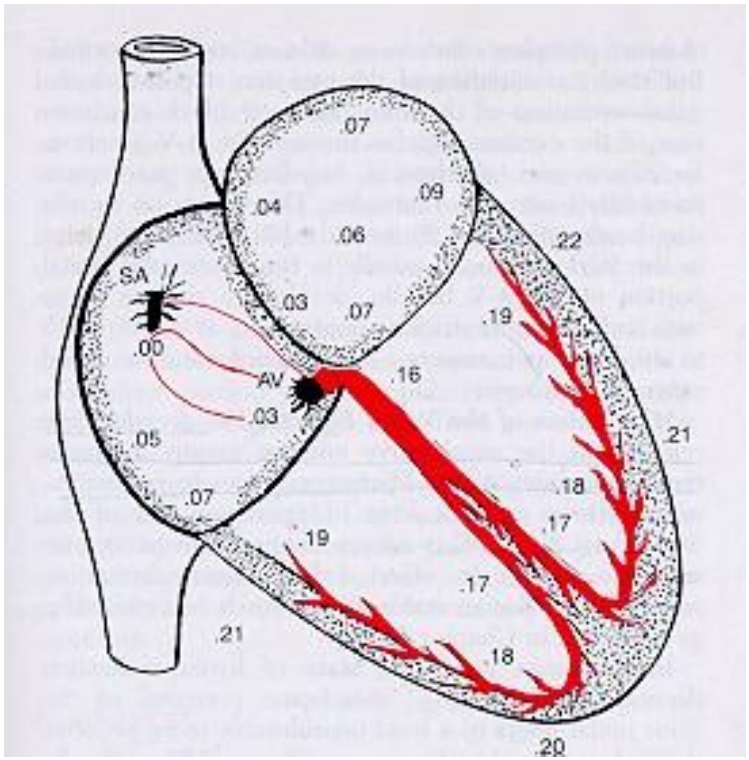
1. Classification of anti-dysrhythmic agents

2. Mechanism of action: effect on action potential

3. Clinical use: By class
   On site of action

4. Individual drug characteristics

Cardiac rhythum control



Rhythum control by – SA node, 72 / min

Arrhythmias;

- Tachy-arrhythmias

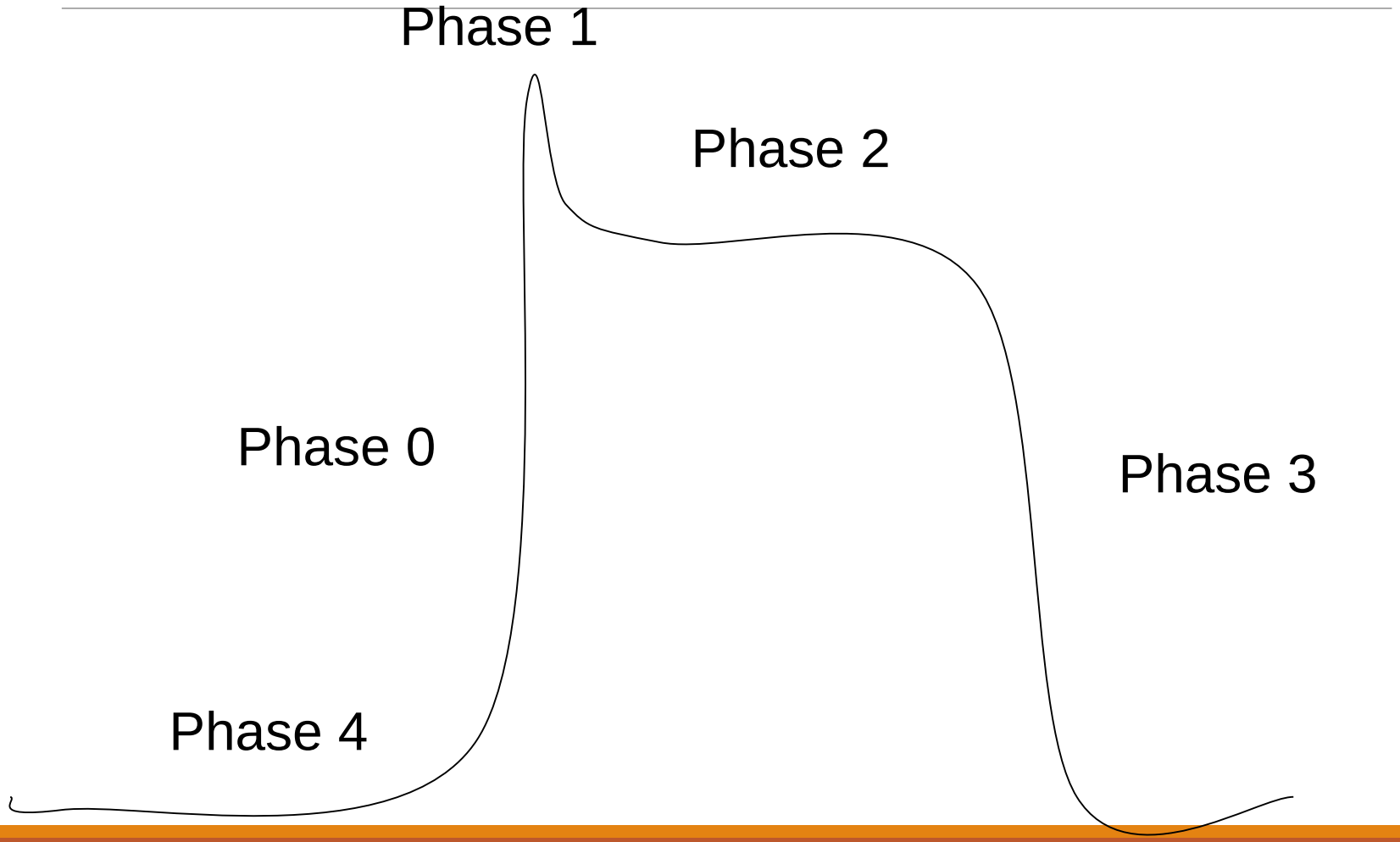
  – pulse > 100

- Bradyarrhythmias

  - pulse < 60

- Tacy-brady syndromes

Cardiac muscle Action potential



Vaughan-Williams classification of anti-dysrhythmic drugs

Class 1 - sodium channel blockers

- slows phase 0

Class 2 - beta adrenoceptor antagonists

- slows phase 4

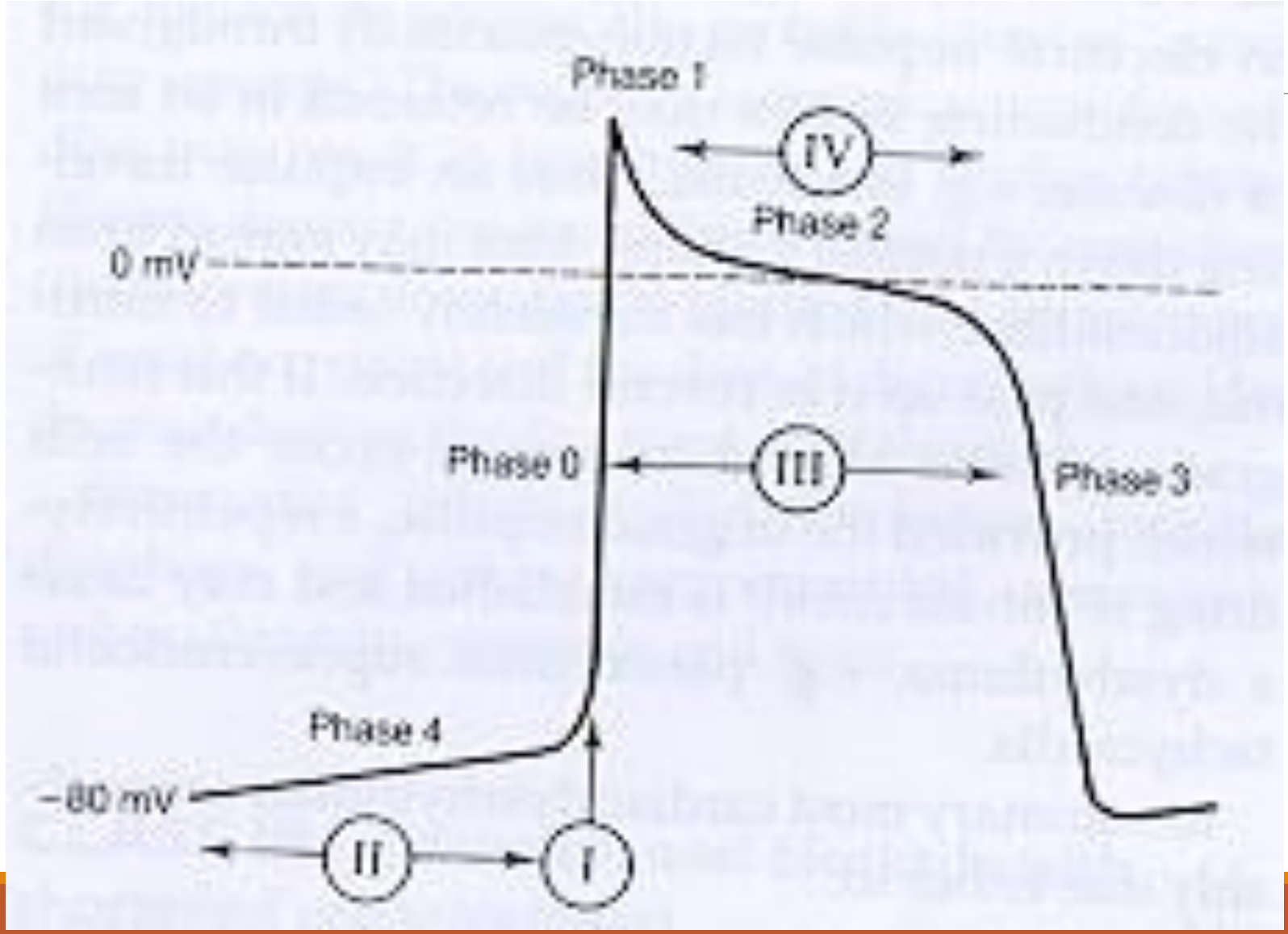
Class 3 - Pottasium channel blockers

- slows phases 1,2 & 3

Class 4 - Calcium channel blockers

- slows phase 2

Classification



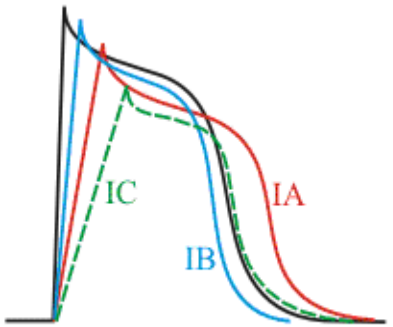
Anti-dysrhythmic drugs classified by mode of action

Class 1 –
- 1a – quinidine, disopyramide, procainamide
- 1b – lignocaine, mexiletene, phenytoin
- 1c – flecainide, propafenone

Class 2 – atenolol,metoprolol,propranolol

Class 3 – amiodarone, bretylium, sotalol

Class 4 – verapamil, diltiazem



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 1 anti-dysrhythmic drugs

1a

quinidine

procainamide

disopyramide

1b

lignocaine

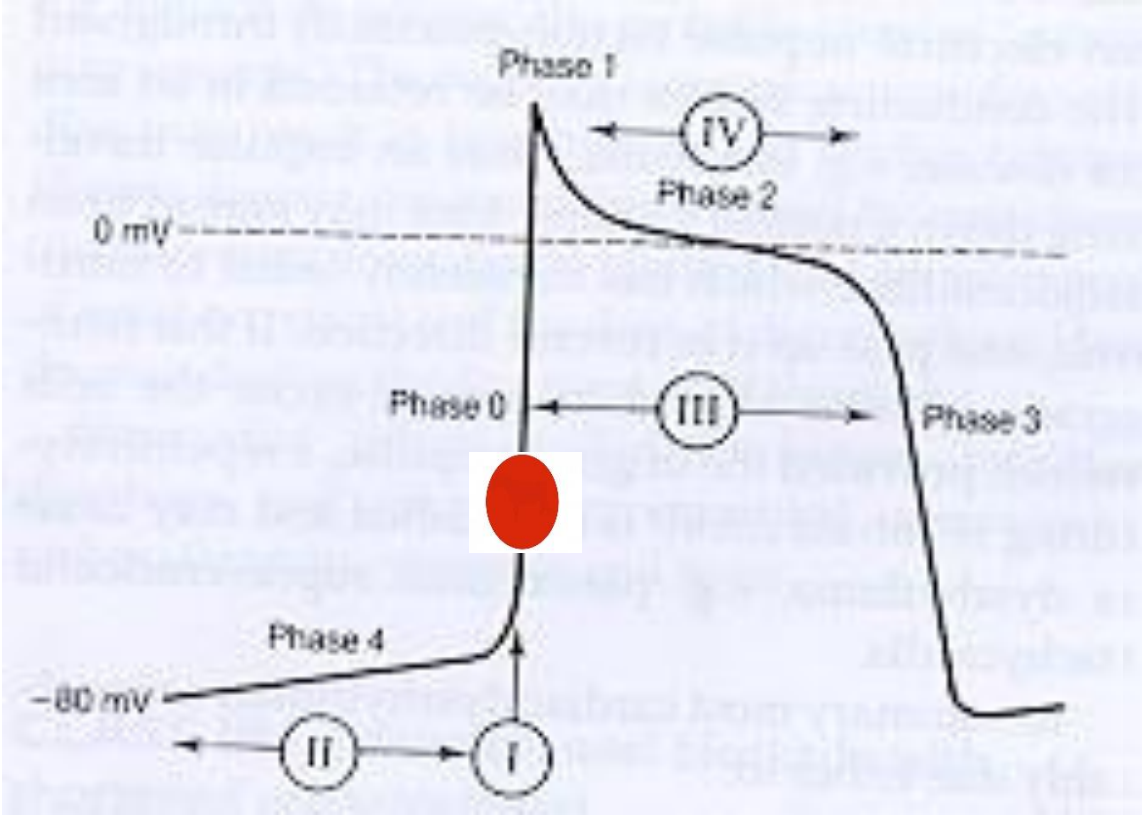
mexiletene

phenytoin

1c

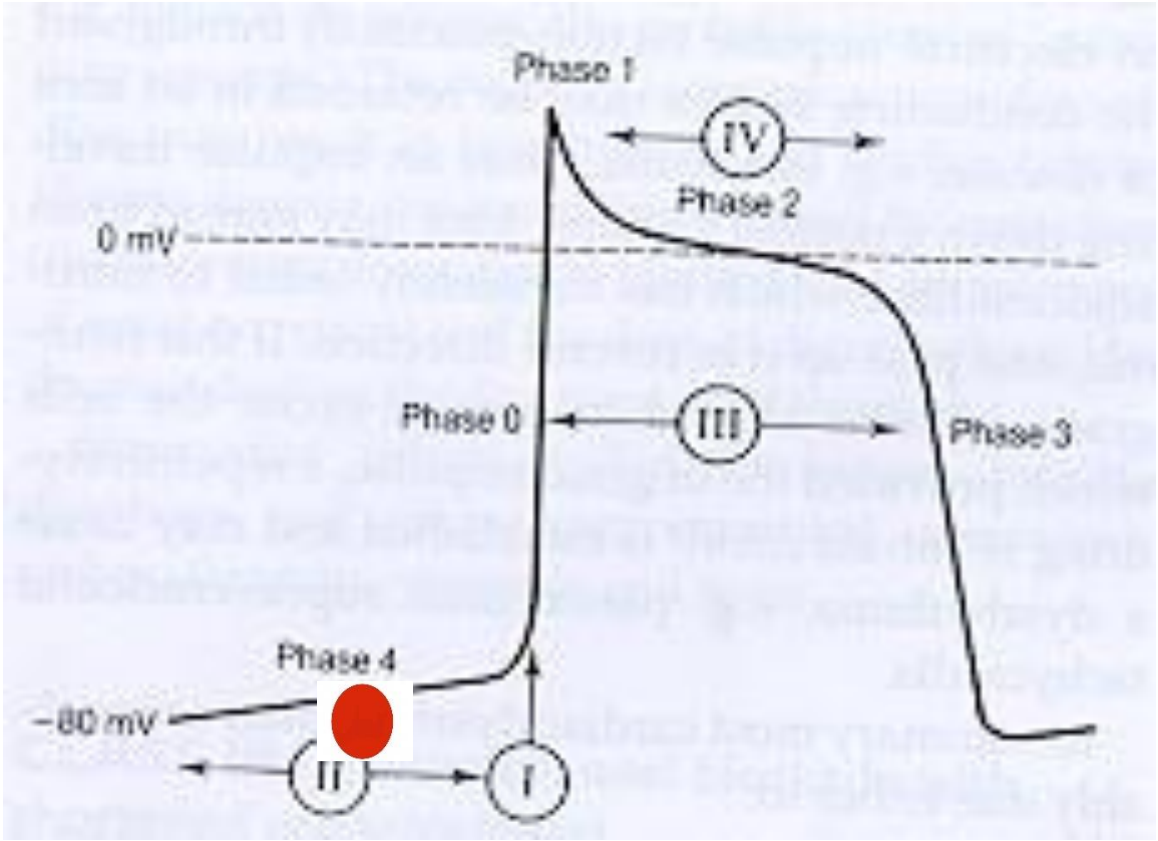
flecainide

propafenone



Class 2 anti-dysrhythmic drugs

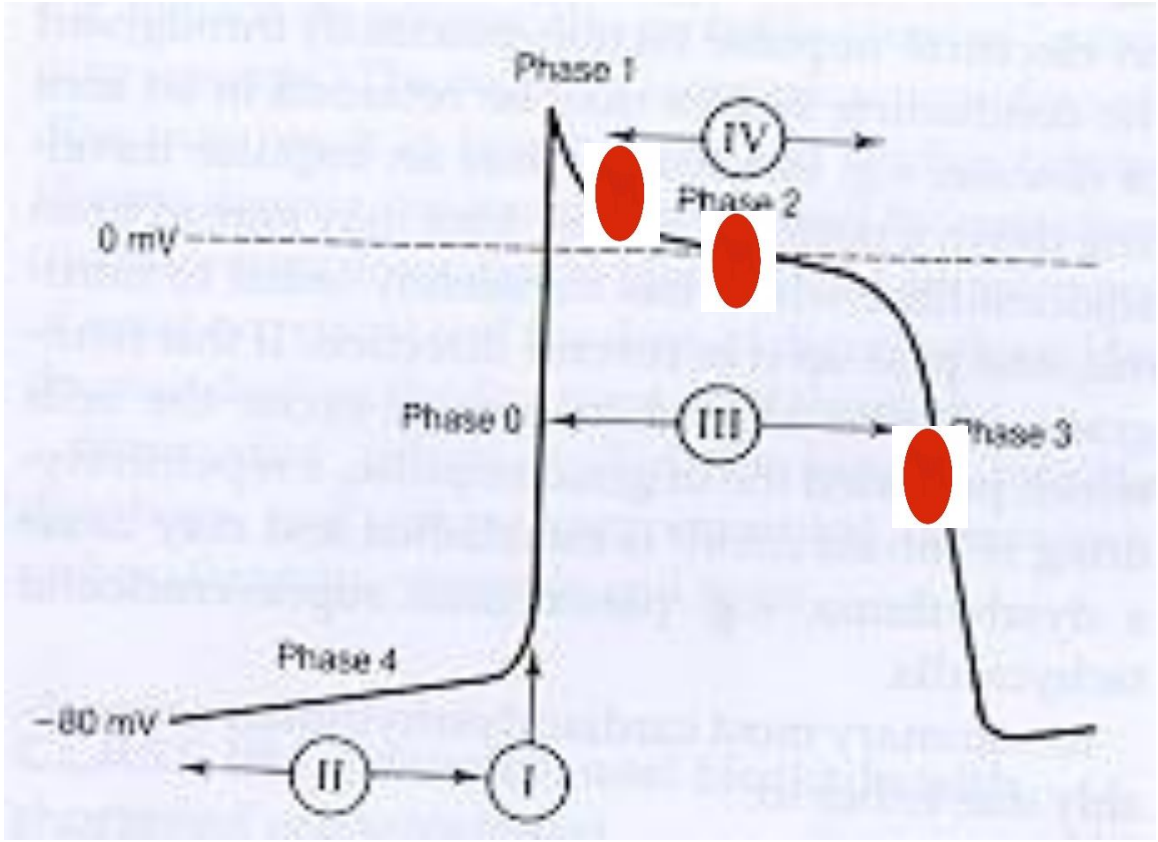
atenolol
metoprolol
propranolol



Class 3 anti-dysrhythmic drugs

amiodarone

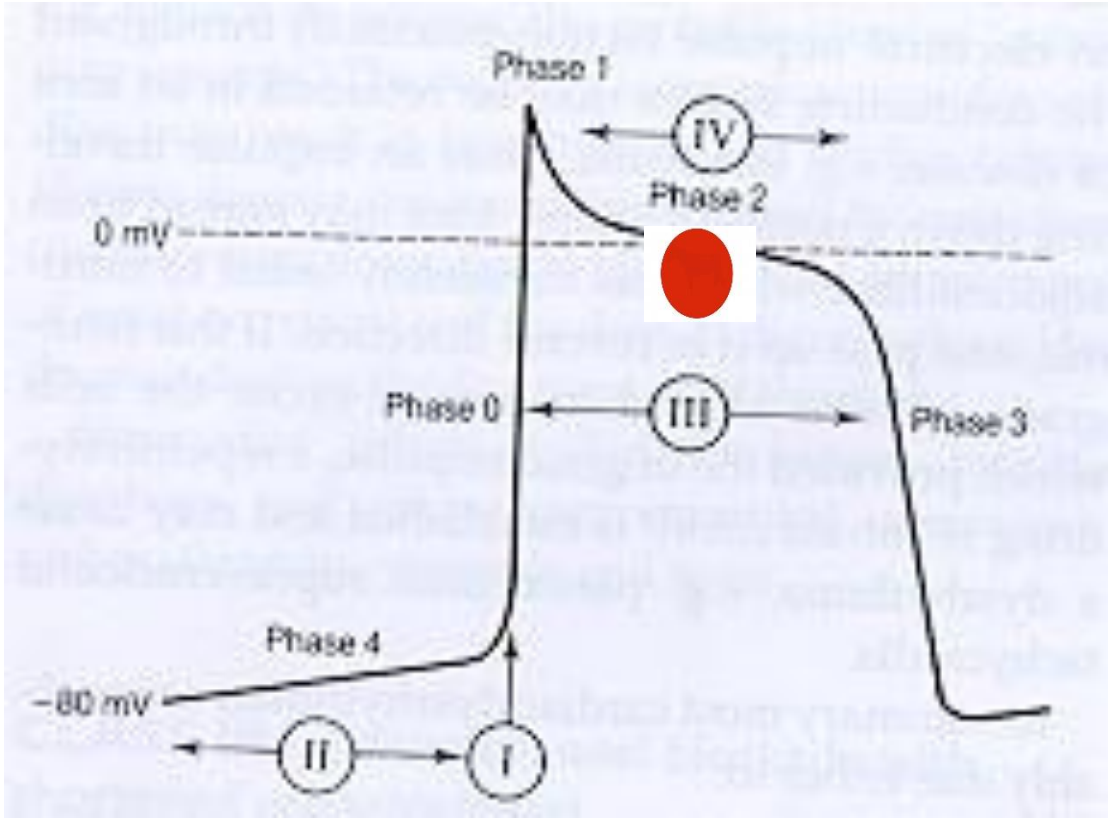
sotalol



Class 4 anti-dysrhythmic drugs

verapamil

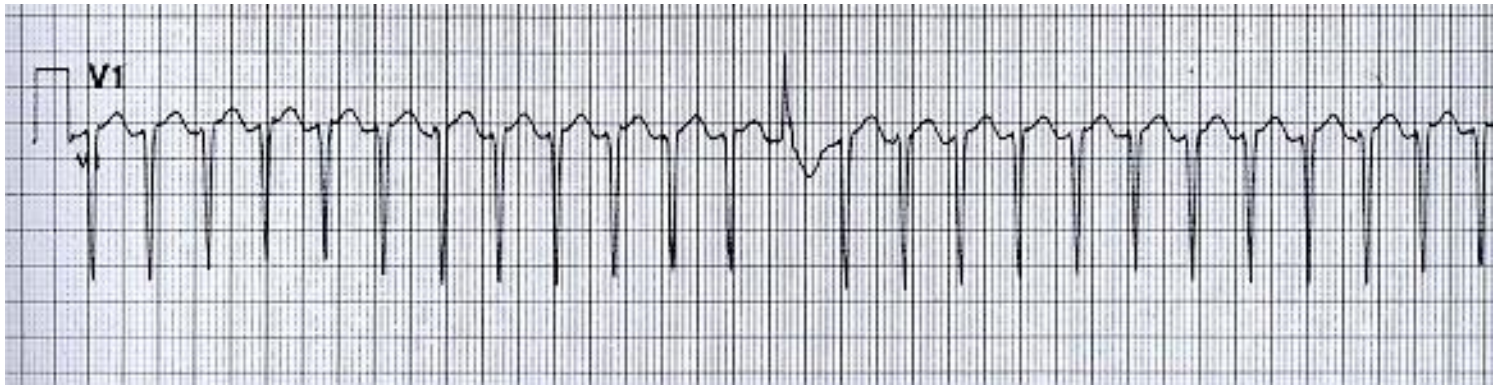
diltiazem



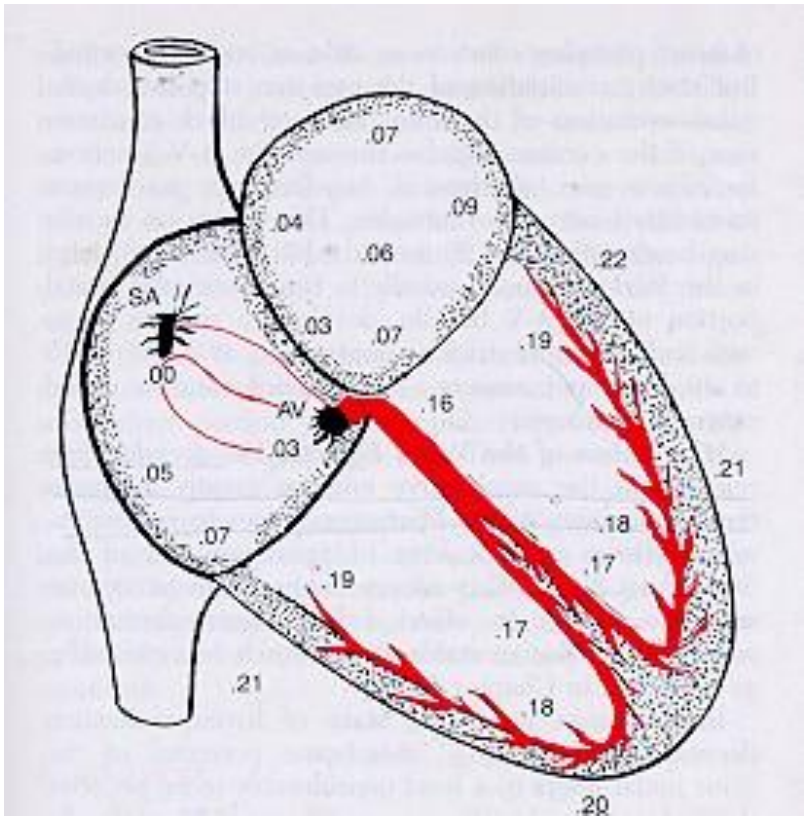
Choice of anti-dysrhythmic drug

How does electrophysiological mechanism relate to choice at the bedside?

A doctor is a pattern recogniser



Choice of anti-dysrhythmic drug by site of action



AV node:

class 2 & 4

digoxin, adenosine

Ventricles:

class 1b

Atria, ventricles, accessory pathways class 1a, 1c & 3

Quinidine

Mechanism

Class 1a

Kinetics

- Well absorbed
- 75% metabolised,
  rest excreted unchanged in the urine: reduce dose in renal impairment
- Displaces warfarin from tissue binding

Quinidine cont.

Uses

Atrial, ventricular, accessory pathway dysrhythmias esp. atrial

Problems

- Reduces cardiac contractility (negatively inotropic): heart failure and hypotension
- Reduces vagus nerve activity on the heart (anti-muscarinic): tachyarrhythmias
- Cinchonism - non cardiac effects

Lignocaine

Mechanism

Class 1b

Kinetics

- >90% first pass metabolism: inactive orally
- half life 90 mins: given by continuous iv infusion
- hepatic metabolites (longer T1/2) less anti-dysrhythmic and more toxic:
  - limit use for 24-48 hrs
  - reduce doses in liver failure

Lignocaine cont.

Uses

- Ventricular dysrhythmias (treatment and prevention)
  esp. post MI or cardiac surgery
- Local anaesthesia

Problems

- CNS toxicity: confusion and convulsions
- Hypokalaemia reduces effect

Flecainide

Cardiac arrhythmia suppression trial (CAST) NEJM 1989

Uses

Difficult-to-treat dysrhythmias outside the post MI situation

Beta receptor antagonists

Mechanism

- Reduces rate of firing of SA node
- Prolongs refractory period of AV node
- Some have Class 2 action (propranolol) and others have Class 3 action (sotalol)

Kinetics

- Orally available
- Propranolol and esmolol (T1/2 9mins) also iv. titrate dose

Beta receptor antagonists cont.

Uses

- Supraventricular dysrhythmias, esp in exercise, emotion and hyperthyroidism
- Accessory pathway and digoxin-induced dysrhythmias

Problems

- Negatively inotropic and chronotropic;
  heart failure & heart block
- IV Ca channel blockers with beta blockers cause conduction defects

Amiodarone

Mechanism

Class 3 (sotalol also has class 3 action)

Kinetics

- Huge volume of distribution (widely tissue bound) and T1/2 54 days; slow release from these sites.
- Needs a loading regimen.

Amiodarone cont.

Uses

- Very powerful drug
- Useful in atrial and ventricular dysrhythmias

Problems:

- CVS: heart block & vent. dysrhythmias
- Iodine: biochemical and clinical hypo/ hyper thyriodism
- Photosensitive rash, pulmonary fibrosis, hepatitis
- Tissue binding displaces warfarin and digoxin

Verapamil

Mechanism

Class 4

Slow AV conduction and SA automaticity

Kinetics

- well absorbed
- 85% first pass metabolism
- given orally or by slow iv infusion

Verapamil cont.

Uses

Paroxysmal supraventricular tachycardia

Problems

Vasodilatation: headache, flushing, hypotension, ankle oedema

Caution together with beta blockers iv

Digoxin

Mechanism

Indirect: decrease vagal activity

slows SA and AV nodal conduction

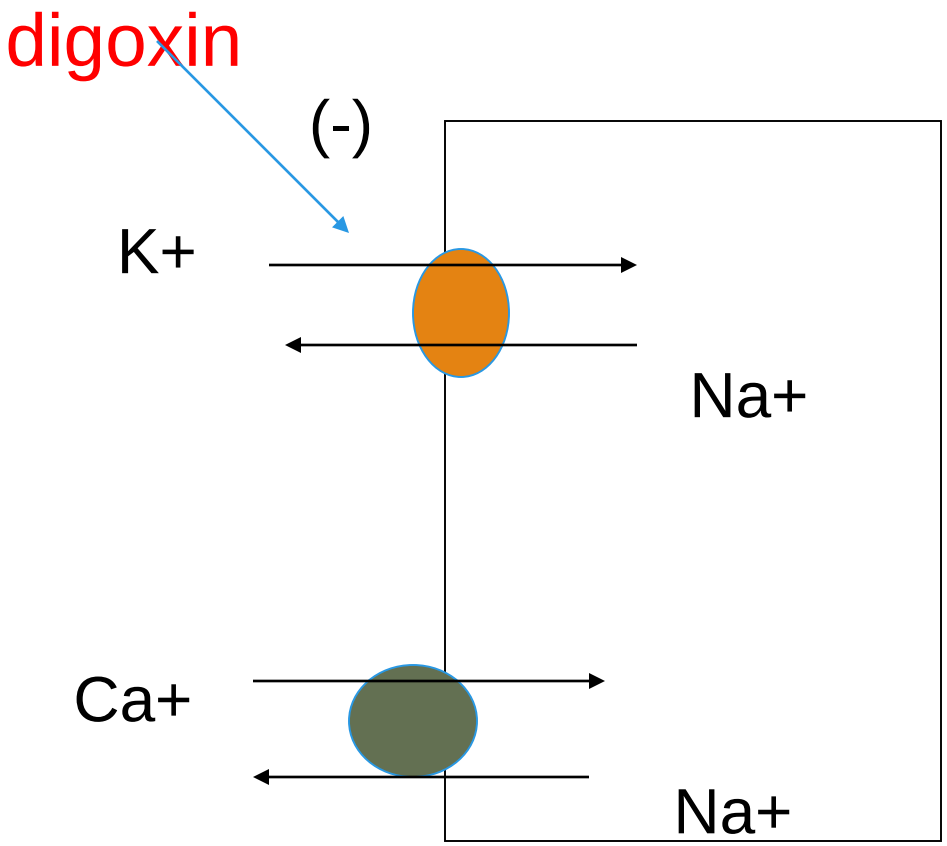
- more important

Direct: inhibits Na/K ATPase

increase intra cellular Ca

increase contractility & excitability

Mode of action of digoxin



Digoxin cont.

Kinetics

- Oral or iv
- t1/2=36hrs,
- highly tissue bound, large VD, needs loading dose
- 85% excreated unchanged in urine, so dose in renal failure

Uses

- controlling ventricular rate in AF and other SVT's
- cardiac failure

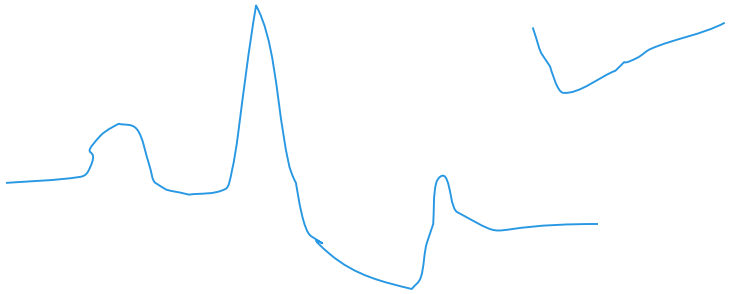
Problems narrow therapeutic index

- GI: anorexia, nausea and vomiting
- Cardiac: ventricular tachydysrhythmias
- Other: gynaecomastia

Digoxin cont.

Toxicity -

- monitor serum levels (target serum level 1ng/ml)
- aggravated by hypokalaemia
- characterized by ST segment depression



Management-

- stop drug
- Correct serum pottasium
- Rx tachydysrhythmias - phenytoin,
  bradydysrhythmias - atropine,
- If life threatening complications - digoxin specific monoclonal antibody; Fab

Adenosine

Mechanism

- endogenous purine nucleotide
- slows AV conduction,
- dilates coronary and peripheral arteries

Kinetics

- Rapidly metabolized by circulating **adenine deaminase**
- T1/2 few seconds
- Given iv by bolus injection

Adenosine cont.

Uses: with ECG monitoring

- **diagnostic:**
  - in broad complex tachycardias - differentiates between ventricular and supraventricular tachyarrhythmias (with aberrant conduction)
- **therapeutic:**
  - terminating re-entrant paroxysmal SVT's

Problems (only short lasting)

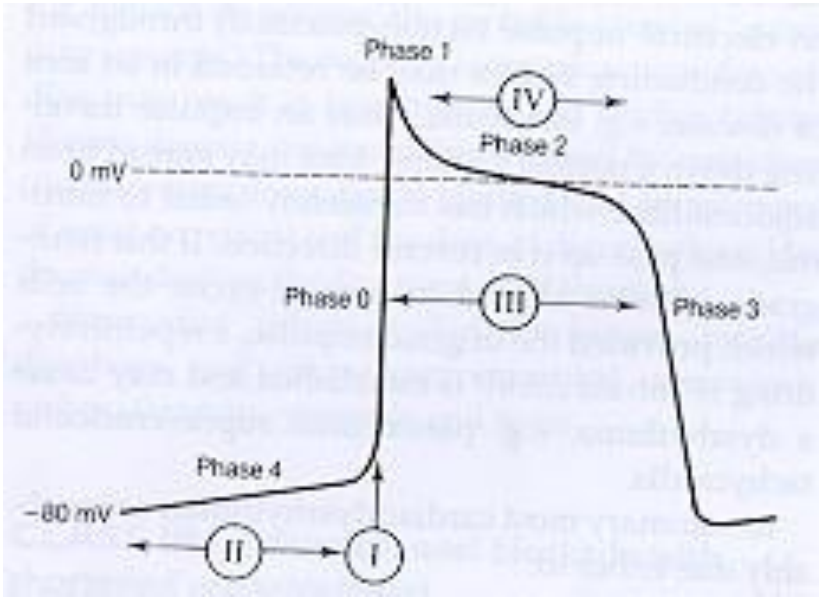
- dyspnoea, flushing, chest pain,
- avoid in asthmatics and heart block

Summary

Classification of anti-arrhythmics

On mode of action

On site of action



- AV node:

  class 2 & 4

  digoxin, adenosine

- Ventricles:

  class 1b

- Atria, ventricles, accessory pathways

  class 1a,1c, 3