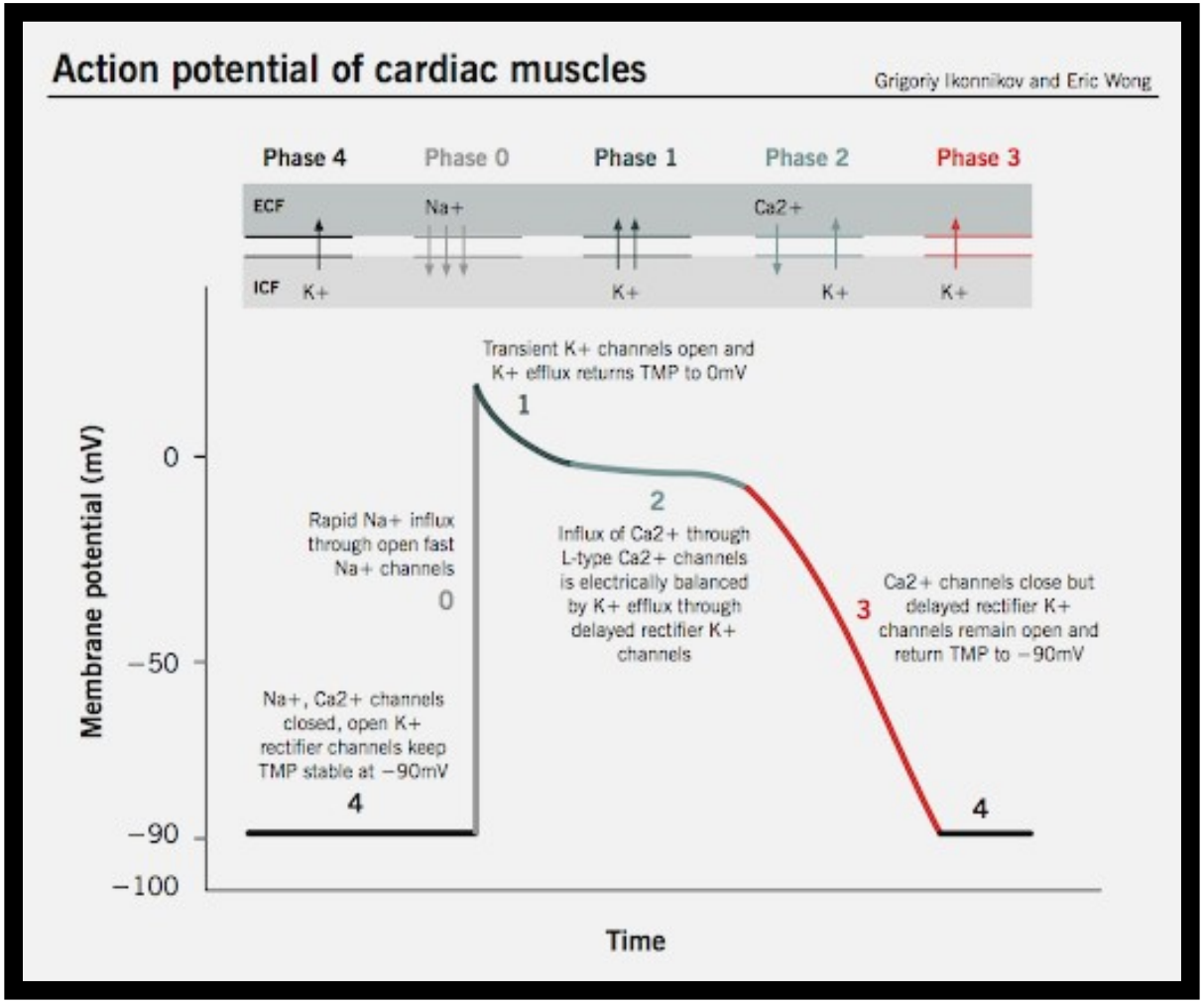
Antiarrhythmic Drugs



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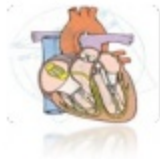


- Definition and mechanisms of arrhythmias
- Physiology of normal cardiac rhythm
- Electrophysiology-Rhythmicity
- Types of arrhythmias
- Causes of arrhythmias
- Mechanism of arrhythmias

1 Definition of arrhythmia

- Cardiac arrhythmia is an abnormality of the heart rhythm
- *Bradycardia* – heart rate slow (<60 beats/min)
- *Tachycardia* – heart rate fast (>100 beats/min)

Arrhythmia

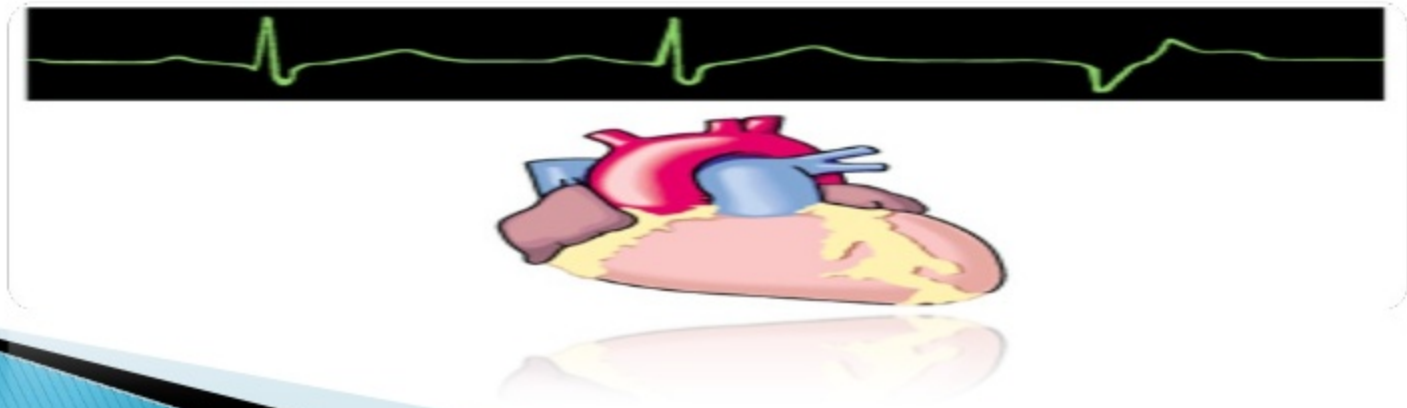
Heart condition where disturbances in-

- Pacemaker impulse formation
- Contraction impulse conduction
- Combination of the two

Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO)

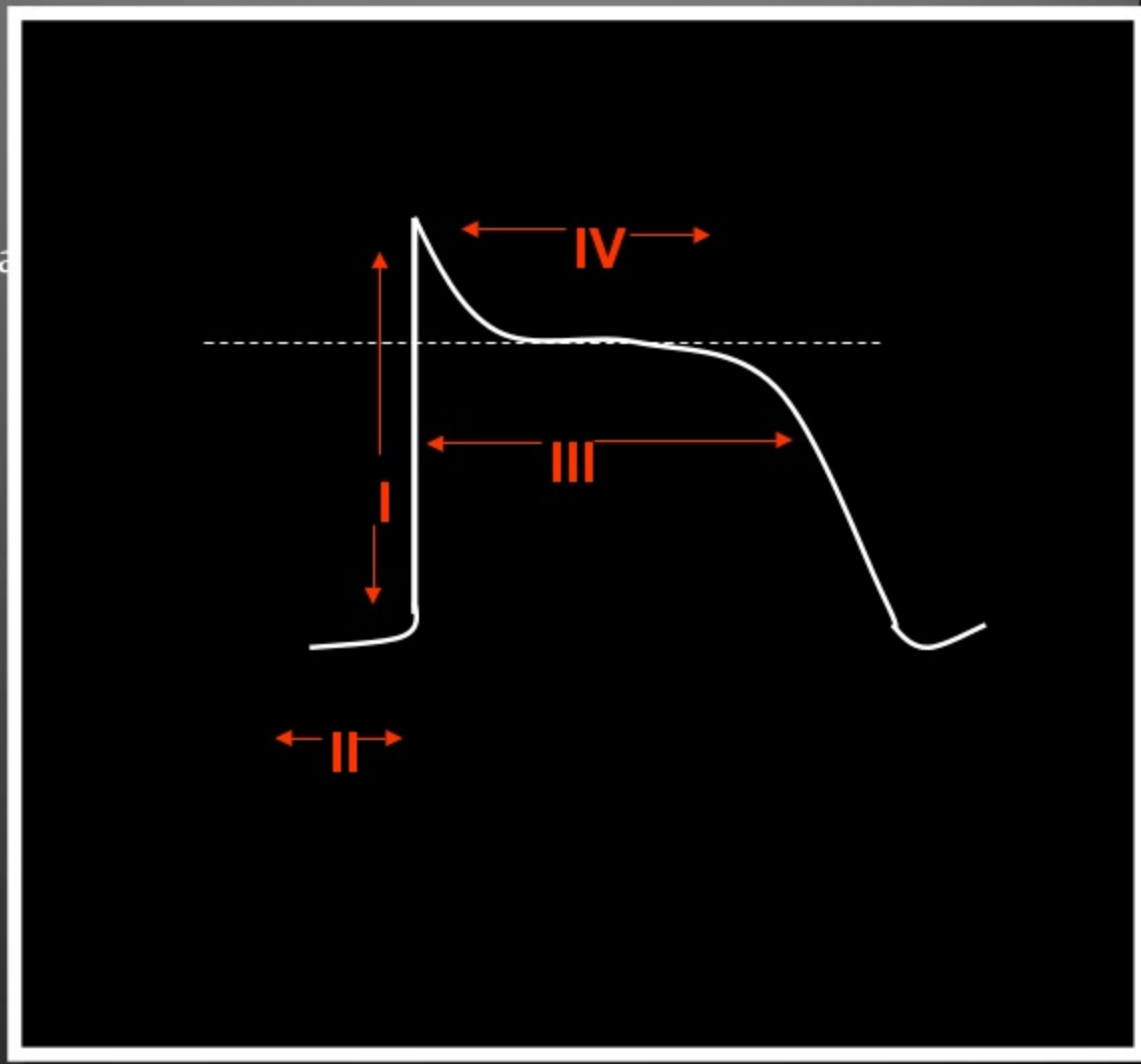
2 Physiology of cardiac rate and rhythm

- Cardiac myocytes are **electrically excitable**
- Resting intracellular voltage of myocardial cells is negative -90mV (SA node is -40mV)
- Resting state - K^+ inside and Na^+ outside cell (Na^+/K^+ pump)
- **Action potential** occurs when Na^+ enters the cell and sets up a depolarising current
- Stimulation of a single muscle fibre causes electrical activity to spread across the myocardium



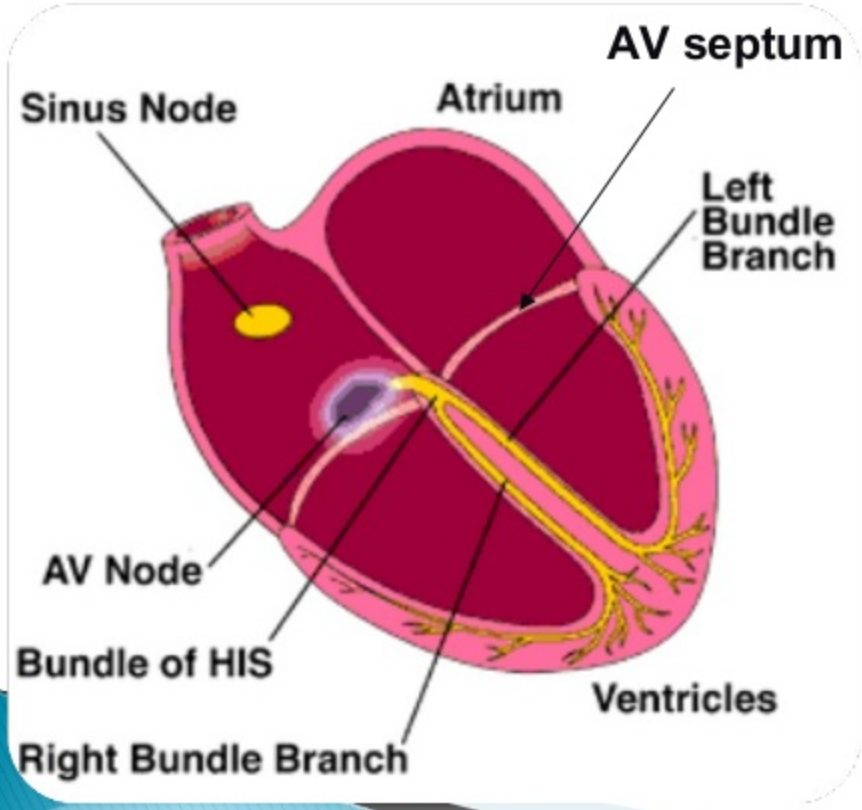
Phases of action potential of cardiac cells

- ***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)

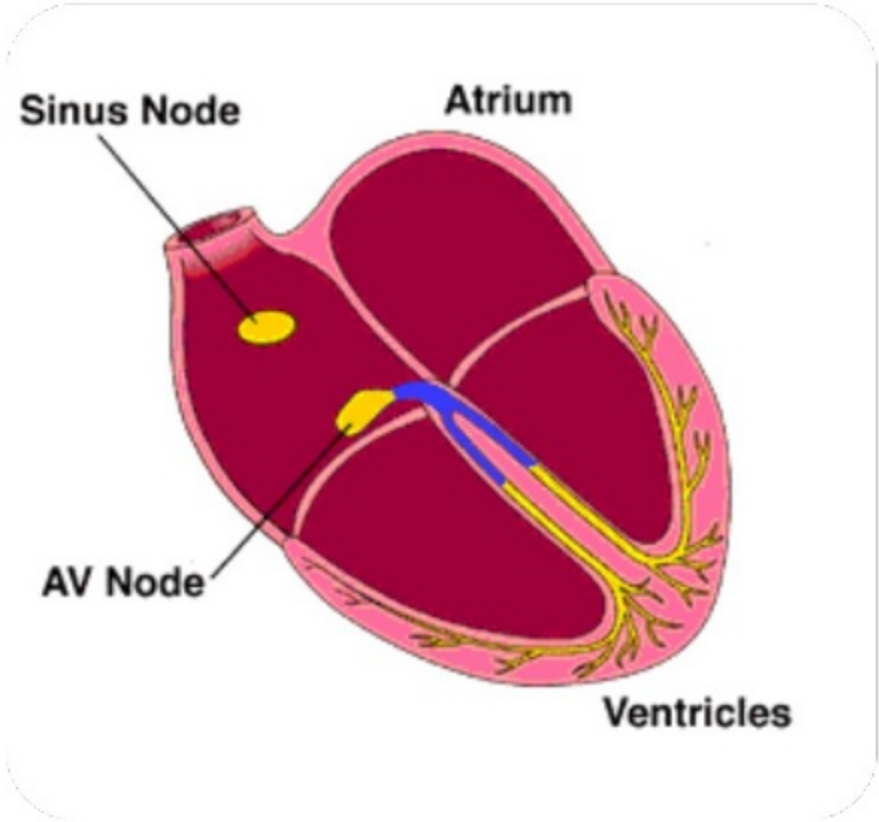


Normal heartbeat and atrial arrhythmia

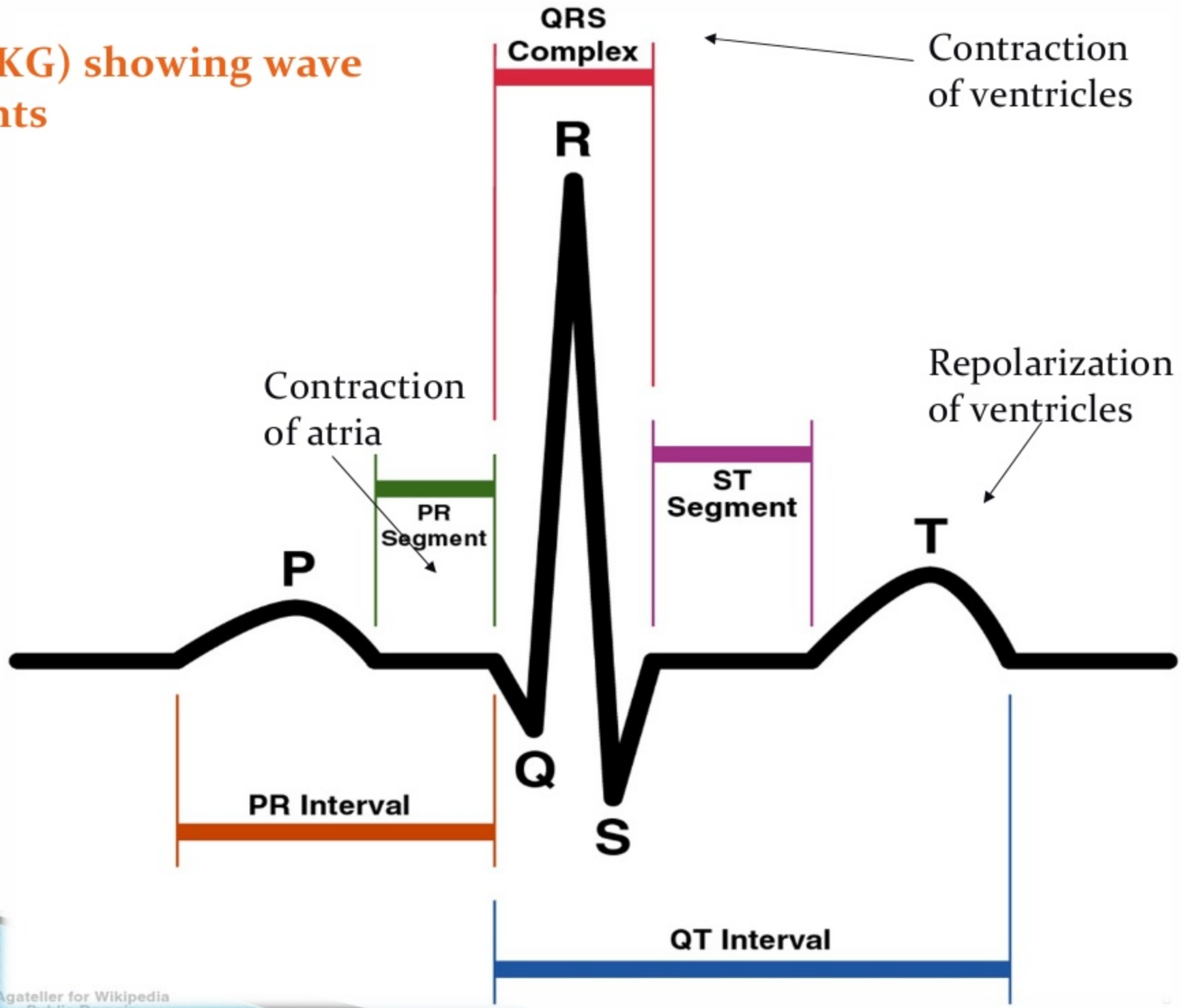
Normal rhythm



Atrial arrhythmia



ECG (EKG) showing wave segments

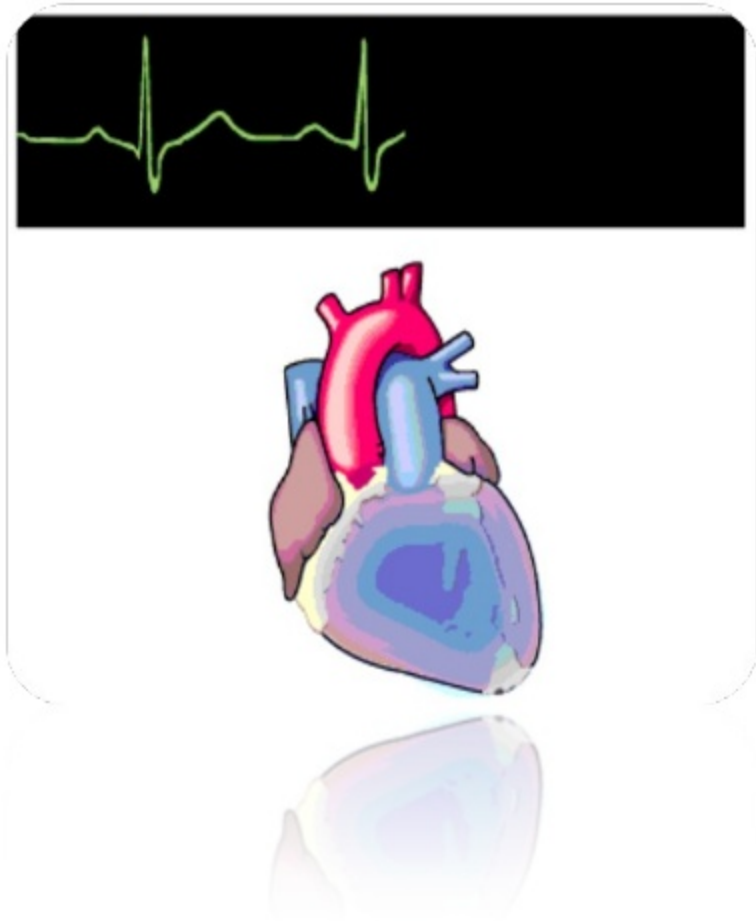


Electrocardiogram(ECG)

- Recording of electrical activity of the heart
- Net sum of depolarisation and repolarisation potentials of all myocardial cells
- P-QRS-T pattern
- P - atrial depolarisation
- QRS -ventricular depolarisation
- T - ventricular repolarisation

Ventricular Arrhythmia

- Ventricular arrhythmias are common in most people and are usually not a problem but…
- VA's are most common cause of sudden death
- Majority of sudden death occurs in people with neither a previously known heart disease nor history of VA's
- Medications which decrease incidence of VA's do not decrease (and may increase) the risk of sudden death → treatment may be worse then the disease!

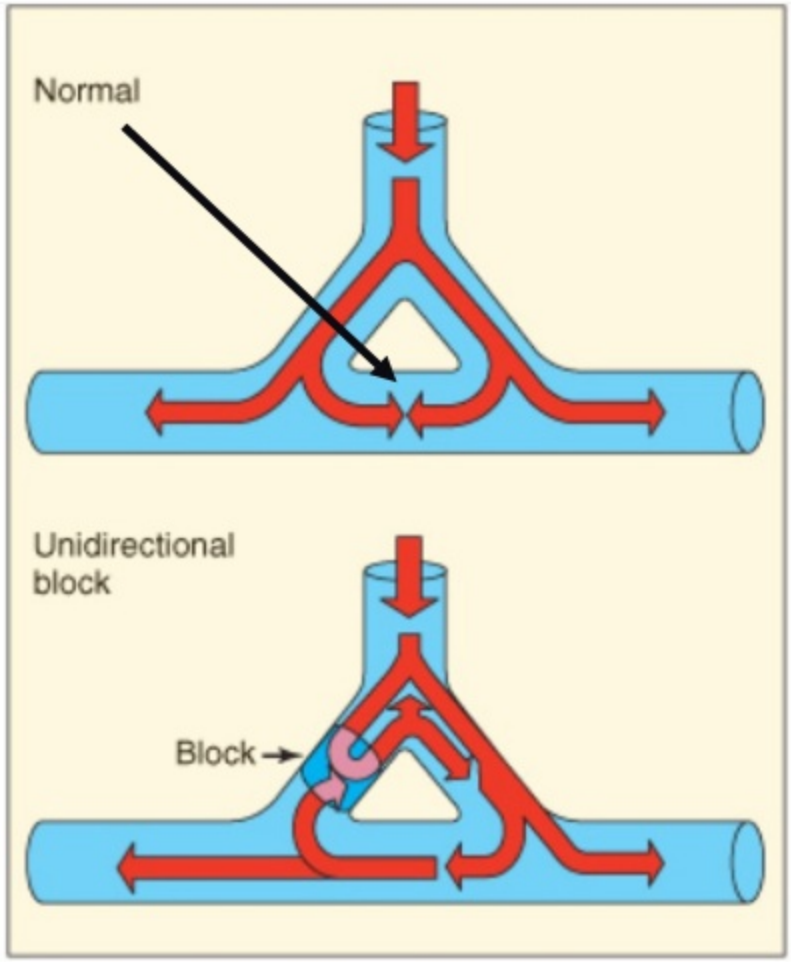


Disorders of impulse formation

- No signal from the pacemaker site
- Development of an ectopic pacemaker
  - May arise from conduction cells (most are capable of spontaneous activity)
  - Usually under control of SA node → if it slows down too much conduction cells could become dominant
  - Often a result of other injury (ischemia, hypoxia)
- Development of oscillatory afterdepolarizations
  - Can initiate spontaneous activity in non-pacemaker tissue
  - May be result of drugs (digitalis, nor-epinephrine) used to treat other cardiopathalogies.

Disorders of impulse conduction

- May result in
  - Bradycardia (if have AV block)
  - Tachycardia (if reentrant circuit occurs)



Reentrant circuit

3 Electrophysiology resting potential

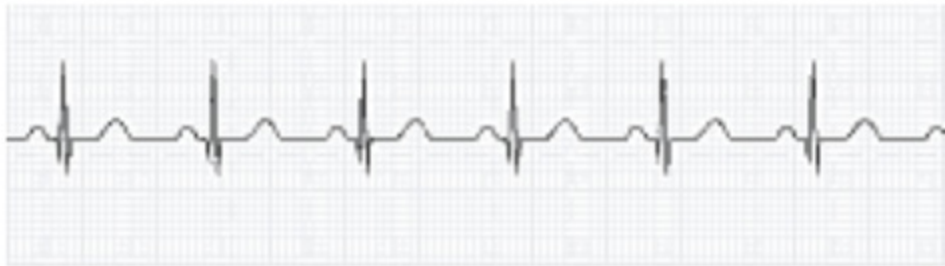
- A transmembrane electrical gradient (potential) is maintained, with the interior of the cell negative with respect to outside the cell

- Caused by unequal distribution of ions inside vs. outside cell
  - Na^+ higher outside than inside cell
  - Ca^+ much higher " " " "
  - K^+ higher inside cell than outside

- Maintenance by ion selective channels, active pumps and exchangers

Sinus rhythm

- Sinoatrial node is cardiac pacemaker
- Normal sinus rhythm 60-100 beats/min
- Depolarisation triggers
- depolarisation of atrial myocardium ('forest fire')
- Conducts more slowly through AV node
- Conducts rapidly through His bundles and Purkinje fibres



Sinus rhythm

- Sinoatrial rate controlled by autonomic nervous system
- Parasympathetic system predominates (M2 muscarinic receptors)
- Sympathetic system (ß1 receptors)
  - Increased heart rate (positive chronotropic effect)
  - Increased automaticity
  - Facilitation of conduction of AV node

5 Causes of Cardiac Arrhythmias

- Cardiac ischemia
- Excessive discharge or sensitivity to autonomic transmitters
- Exposure to toxic substances
- Unknown etiology

6 Mechanisms of arrhythmia production

- Result from disorders of impulse formation, conduction, or both as:

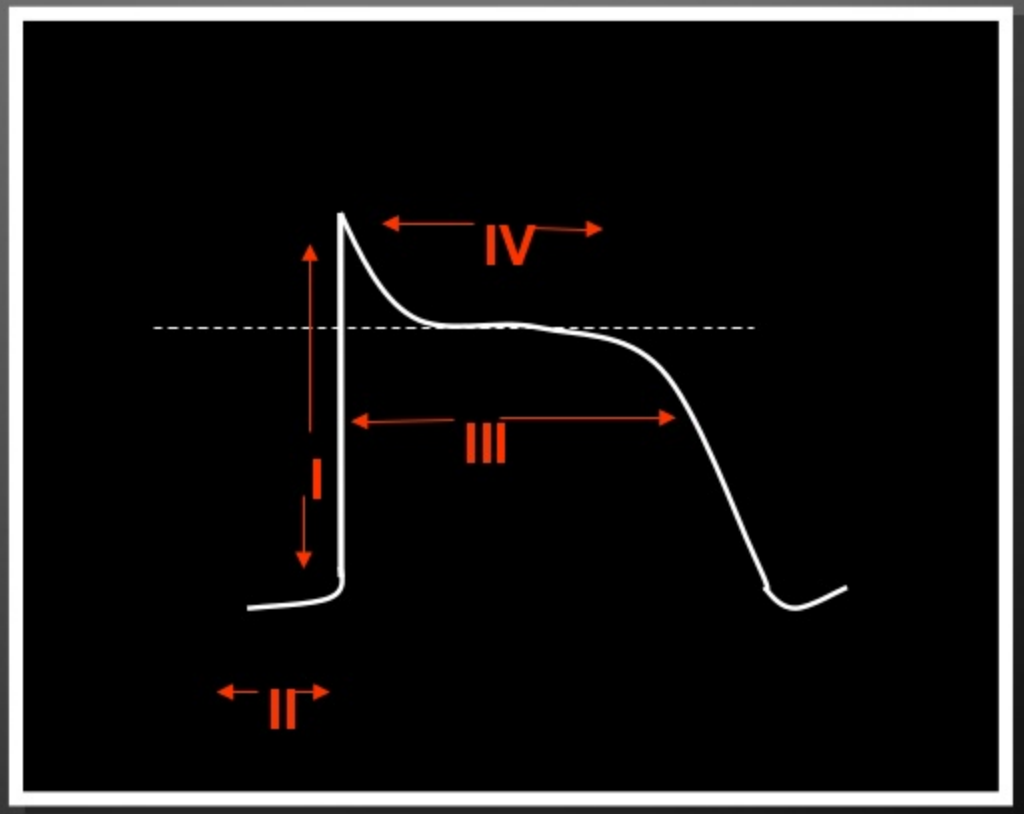
Re-entry (refractory tissue reactivated due to conduction block, causes abnormal continuous circuit. eg accessory pathways linking atria and ventricles in Wolff-Parkinson-White syndrome)

Abnormal pacemaker activity in non-conducting/conducting tissue (eg ischaemia)

Delayed after-depolarisation (automatic depolarisation of cardiac cell triggers ectopic beats, can be caused by drugs eg digoxin)

Vaughan Williams classification of antiarrhythmic drugs

- **Class I**: block sodium channels
  - Ia (quinidine, procainamide, disopyramide)
  - Ib (lignocaine,phenytoin)
  - Ic (flecainide,propaferone)
- **Class II**: ß-adrenoceptor antagonists (propranolol,atenolol, sotalol)
- **Class III**: prolong action potential and prolong refractory period (suppress re-entrant rhythms) (amiodarone, dronedarone)
- **Class IV**: Calcium channel antagonists. Impair impulse propagation in nodal and damaged areas (verapamil,diltiazem)

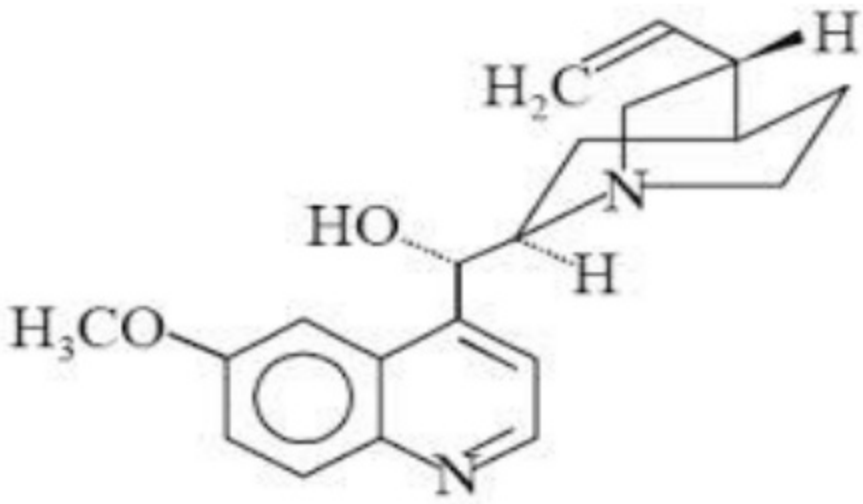


Class I;sodium channel blockers

- Membrane stabilizing agents.
- These classes of drugs are local anasthetics acting on nerve & myocardial membranes to slow conduction by inhibiting phase 0 of action potential.
- They decrease the maximal rate of depolarisation without changing the resting potential.
- Class I is subclassified into three class:-class Ia, class Ib, class Ic.

Class Ia

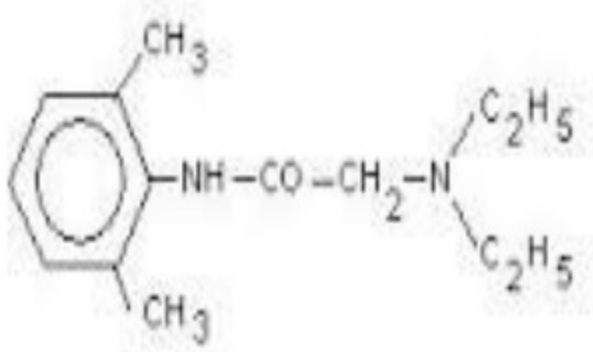
- Quinidine



Quinidine

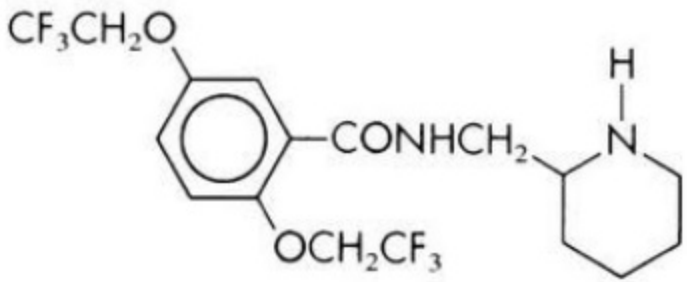
Class Ib

- lignocaine



Class Ic

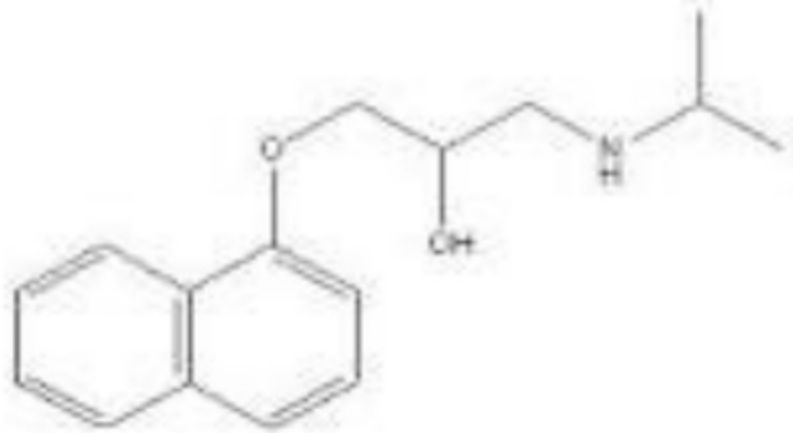
- flecainide



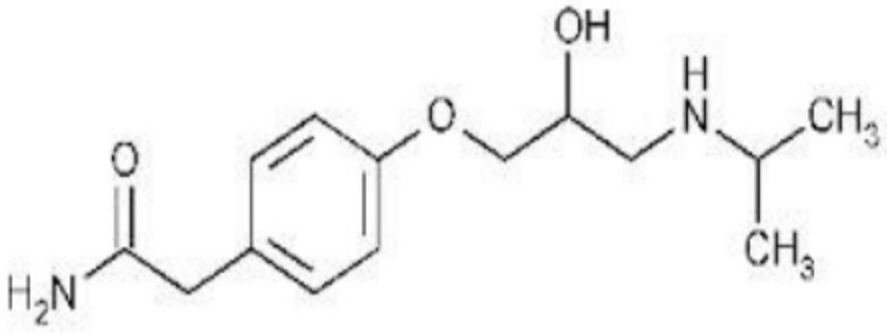
Class-II ;Beta Blockers

- Non-selective(β) :Propranolol,sotalol, atenolol

✓ propranolol structure ;



✓ atenolol

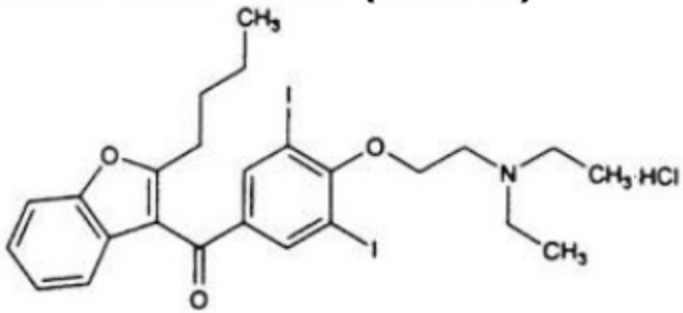


Beta Blockers:

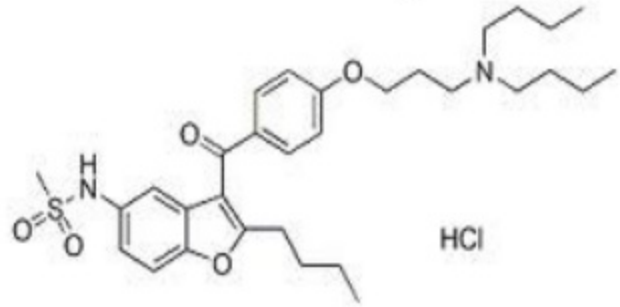
- They depress automaticity,prolong A.V. Conduction ,reduce heart rate,and also decrease contractibility.

Class III drugs

- Amiodarone(HCl)



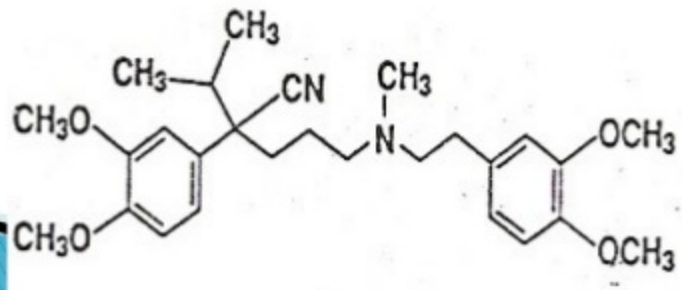
Dronedarone(HCl)



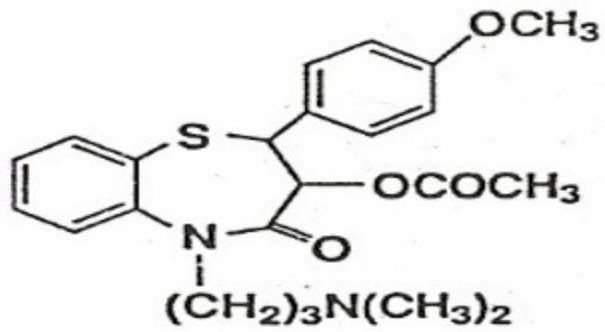
- These drugs cause a homogeneous prolongation of duration of action potential.
- These results in a prolongation of the effective refractory period.
- They act through phase 3 of action potential by blocking potassium channels

Class IV;Calcium channel blockers

- They causes a prolongation of refractory period in the AV node and the atria,a decrease in atrioventricular conduction,&a decrease in spontaneous diastolic depolarisation.
- These effects block conduction of premature impulses at AV node & thus very effective in treating supraventricular arrhythmias.



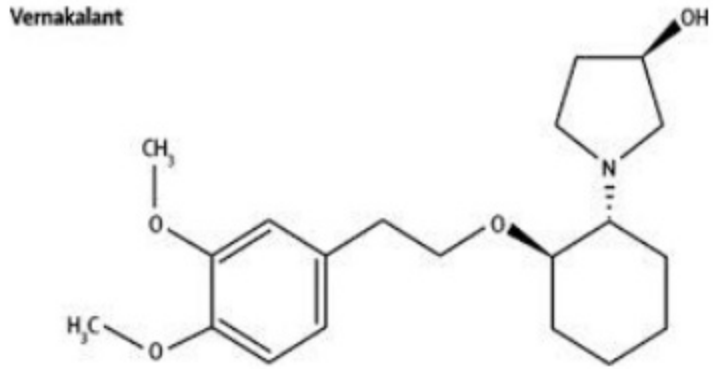
Verapamil



Diltiazem

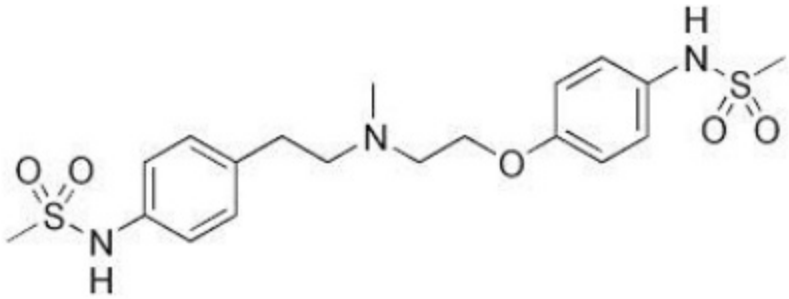
Recent advance in arrhythmia

Vernakalant



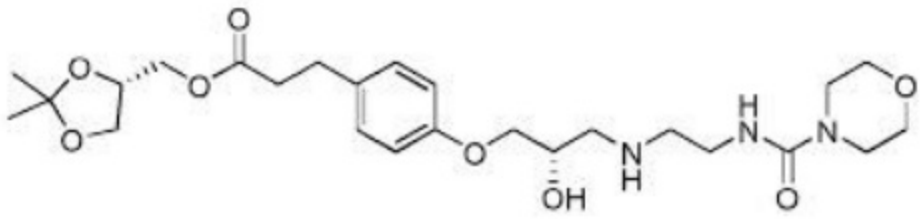
- It act selectively on atrium by only delaying atrial repolarization.
- It does this by selectively acting on K^+ channels that exist primarily in atrium,thus resulting in atrial specific prolongation of effective refractory period.

❑ Dofetilide



- Novel Class III antiarrhythmic agent.
- It act by selective prolongation of cardiac action potantial duration.
- It works by selectively blocking the rapid component of delayed rectified outward potassium current.
- USE-atrial fibrillation,atrial flutter & PSVT.

LANDIOLOL



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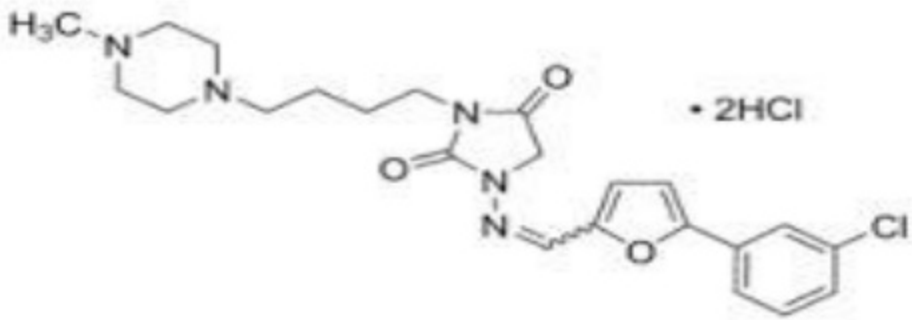
LANDIOLOL

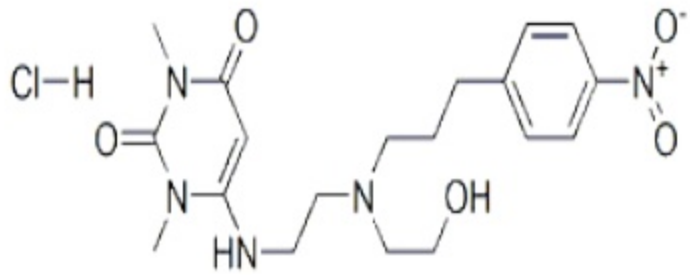
- It is a new ultra-short acting beta blocker,in patient with cardiac tachyarrhythmias.

AZIMILIDE DIHYDROCHLORIDE



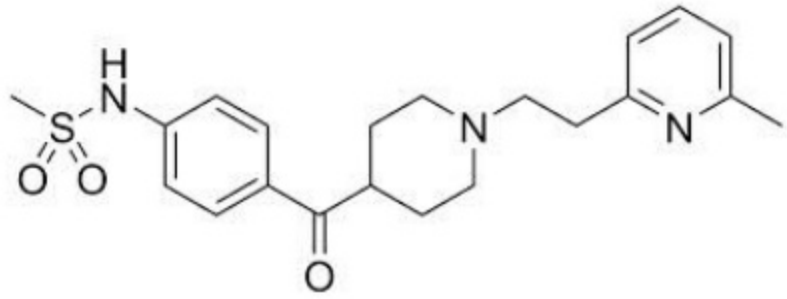
- Novel Class III antiarrhythmic agent.
- USE;atrial fibrillation,atrial flutter & paroxysmal supraventricular tachycardia in patient with and without structural heart disease.

Nifekalant hydrochloride



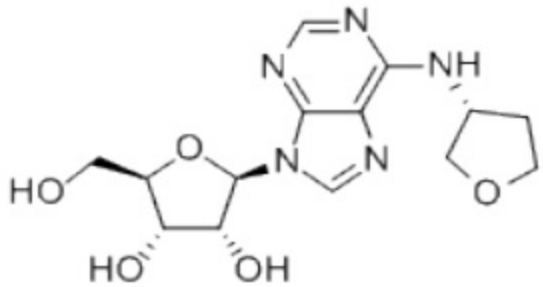
- Novel Class III antiarrhythmic agent.
- No selective blocker of myocardial repolarising pottasium currents & completely devoid of ß adrenergic effect.

•E-4031



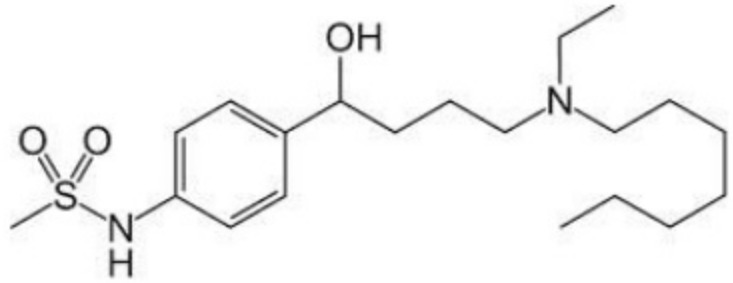
- Novel Class III antiarrhythmic agent.
- It is synthesized toxin that is methane sulfonamide.

❖ Tecadenoson(CVT-510)



- It is novel selective adenosine recepter antagonist,selectively activates A1 adenosine recepter & prolongs AV nodel conduction at doses lower than those required to cause A2 adenosine recepter mediated coronary & peripheral vasodilation.

❖ Ibutilide



- Novel Class III antiarrhythmic agent.
- At a cellular level it exert two action ; induction of a persistent Na^{+} current sensitive to dihydropyridine Ca^{2+} channel blockers & potent inhibition of cardiac rapid delayed rectifier K^{+} current ,by binding within the channel pore cavity upon channel gating.


THANK YOU