Chapter 7. Anti-Arrhythmic Drugs

Syllabus:

- **Class I (Na+ Channel Blocker):** Quinidine sulphate, Procainamide hydrochloride, Disopyramide phosphate*, Phenytoin sodium, Lidocaine hydrochloride, Tocainide hydrochloride, Mexiletine hydrochloride, Lorcainide hydrochloride
- **K+ Channel Blocker:** Amiodarone,
- **Beta Blocker**: Sotalol.

7.1. ARRHYTHMIA

Disturbance the rhythmicity of the heart (heart rate) is known as cardiac arrhythmia. Many following factors can precipitate or exacerbate arrhythmias:

- ✓ Myocardial ischaemia/hypoxia
- ✓ Heart Failure
- ✓ Acidosis & alkalosis,
- ✓ Electrolyte Imbalance,
- ✓ Over Sympathetic stimulation,
- ✓ Drug toxicity

However, all the arrhythmias result from the following:

1. Disturbances in impulse formation
2. Disturbances in impulse conduction
3. Or both

The different types of cardiac arrhythmias are the following:

1. ***Extrasystoles (ES)*** are premature ectopic beats due to abnormal automaticity or afterdepolarization arising from an ectopic focus in the atrium (AES), A-V node (nodal ES) or ventricle (VES). The QRS complex in VES is broader and abnormal in shape.

2. ***Paroxysmal supraventricular tachycardia (PSVT)*** is sudden onset episodes of atrial tachycardia (rate 150–200/min) with 1:1 atrioventricular conduction: mostly due to circus movement type of reentry occurring within or around the A-V node or using an accessory pathway between atria and ventricle (Wolff-Parkinson-White syndrome or WPW).

3. ***Atrial flutter (AFI)*** Atria beat at a rate of 200–350/min and there is a physiological 2:1 to 4:1 or higher A-V block (because A-V node cannot transmit impulses faster than 200/min).

This is mostly due to a stable re-entrant circuit in the right atrium, but some cases may be due to rapid discharge of an atrial focus.

4. ***Atrial fibrillation (AF)*** Atrial fibres are activated asynchronously at a rate of 350–550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100–160/min) ventricular response. Atria remain dilated and quiver like a bag of worms.

5. ***Ventricular tachycardia (VT)*** is a run of 4 or more consecutive ventricular extrasystoles. It may be a sustained or nonsustained arrhythmia, and is due either to discharges from an ectopic focus, after-depolarizations or single

site (monomorphic) or multiple site (polymorphic) reentry circuits.

6. ***Torsades de pointes*** (French: twisting of points) is a life-threatening form of polymorphic ventricular tachycardia with rapid asynchronous complexes and an undulating baseline on ECG. It is generally associated with long Q-T interval.

7. ***Ventricular fibrillation (VF)*** is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function. It is fatal unless reverted within 2–5 min; is the most common cause of sudden cardiac death.

8. ***Atrio-ventricular (A-V)*** *block* is due to depression of impulse conduction through the A-V node and bundle of His, mostly due to vagal influence or ischaemia.

- ✓ ***First degree A-V block****:* Slowed conduction resulting in prolonged P-R interval.
- ✓ ***Second degree A-V block:*** Some supraventricular complexes are not conducted: drop beats.
- ✓ ***Third degree A-V block:*** No supraventricular complexes are conducted; ventricle generates its own impulse; complete heart block.

Detail Pharmacology:

Arrhythmia basics: https://youtu.be/nmNOyu0iCCQ

Drugs & MOA: https://youtu.be/9JwsnahWdHg

Pharmacology: https://youtu.be/jGZl5teBLis

7.2. ANTIARRHYTHMIC DRUGS

Vaughan Williams & Singh gave a four class system for antiarrhythmic agents. **D.C. Harrison** proposed a modified subgrouping of **class I** agents.

CLASS I: Membrane stabilising agents (Na^+ channel blockers).

Class 1A: The drugs of this group prolong action potential duration. e.g. Quinidine, Procainamide, Disopyramide & Moricizine.

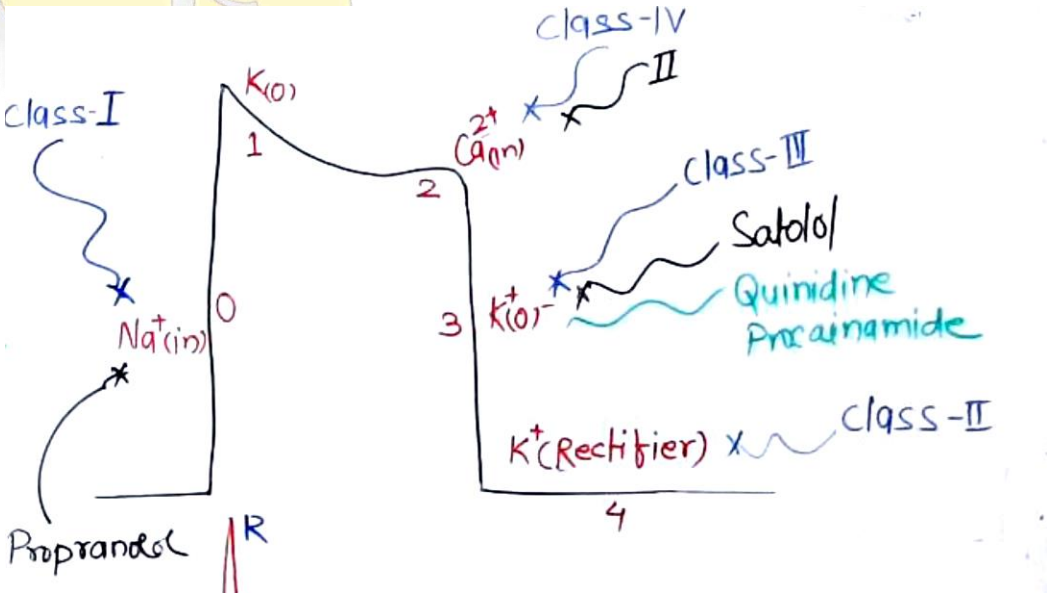
Class I B : The drugs of this group shorten action potential duration e.g. Lidocain, Phenytoin, Tocainide And Mexiletine.

Class 1C : The drugs of this group have no effect on action potential duration. (*i.e.*, slow phase O depolarisation e.g. Lorcainide, Encainide, Flecainide, Indecainide And Propaferone.

CLASS II : 'β' adrenergic blockers e.g. Propranolol, Metoprolol, Sotalol.

CLASS III : Drugs that prolongs the action potential duration (potacium channel blockers) e.g. Amiodarone, Bretylium Tosylate.

CLASS IV : Calcium channel blockers, e.g. Verapamil, Diltiazem, Nifedipine.



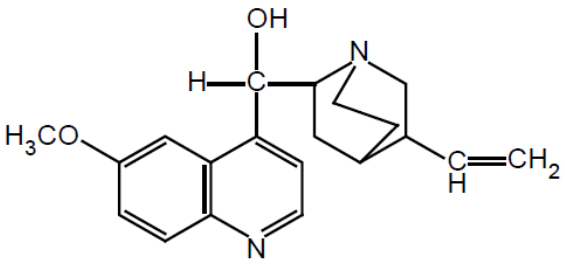
Drug of Choice (imp for GPAT)

- PSVT- Adenosine
- Atrial flutter- Cardioversion
- Atrial Fibrillation - Cardioversion
- Atrial extra systole- Quinidine
- Ventricular extrasystole
  - Due to MI------- Lignocaine
  - Due to Digitalis---Lignocaine
- Ventricular tachycardia- Ligocaine, CaCl2
- Wolff-Parkinson-White syndrome- Cardioversion, procainamide
- Sinus bradycardia- Atropine
- Cardiac arrest- Adrenaline, dobutamine
- Heart block- Isoprenaline
- Atrial fluter - Digoxine
- Ventricular fibrillation/digitalis arrhythmia - MgCl2
- Torsades de point: MgSO4

7.3. MEDICINAL CHEMISTRY OF SELECTED ANTIARRHYTHMIC DRUGS

CLASS 1A: Stabilize the membrane of myocardiocyte by blocking the Na+ Channel in open state and moderately delay the channel recovery

(1) Quinidine



(8*R*, 9*S*)-6'-Methoxycinchonan–9-ol

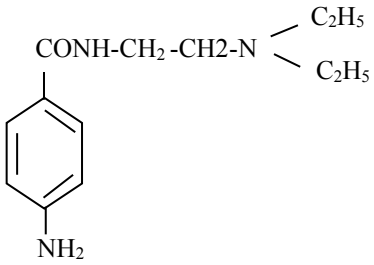
Quinidine is a d-isomer of quinine. It is obtained from bark of various species of cinchona and from *Remijia pedunculata*. Quinidine has a direct myocardial depressant action. It increases

the refractory period, depresses contractility, depresses excitability and slows speed of conduction in cardiac muscle. It also having the K+ channel blocking activity

Dose: 100 – 200 mg 3 times a day (oral).

Uses: Used in atrial flutter, atrial fibrillation, paroxysmal tachycardia & ventricular arrhythmias.

(2) Procainamide



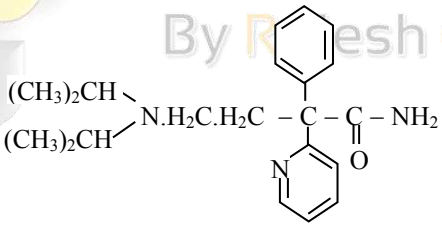
4-Amino-N-(2-diethylamino ethyl) benzamide

MOA: Actions are similar to quinidine, but less potent myocardial depressant than quinidine. It also having the K+ channel blocking activity

Dose : 0.5 to 1.5 g (oral).

Uses : In atrial and ventricular arrhythmias.

(3) Disopyramide



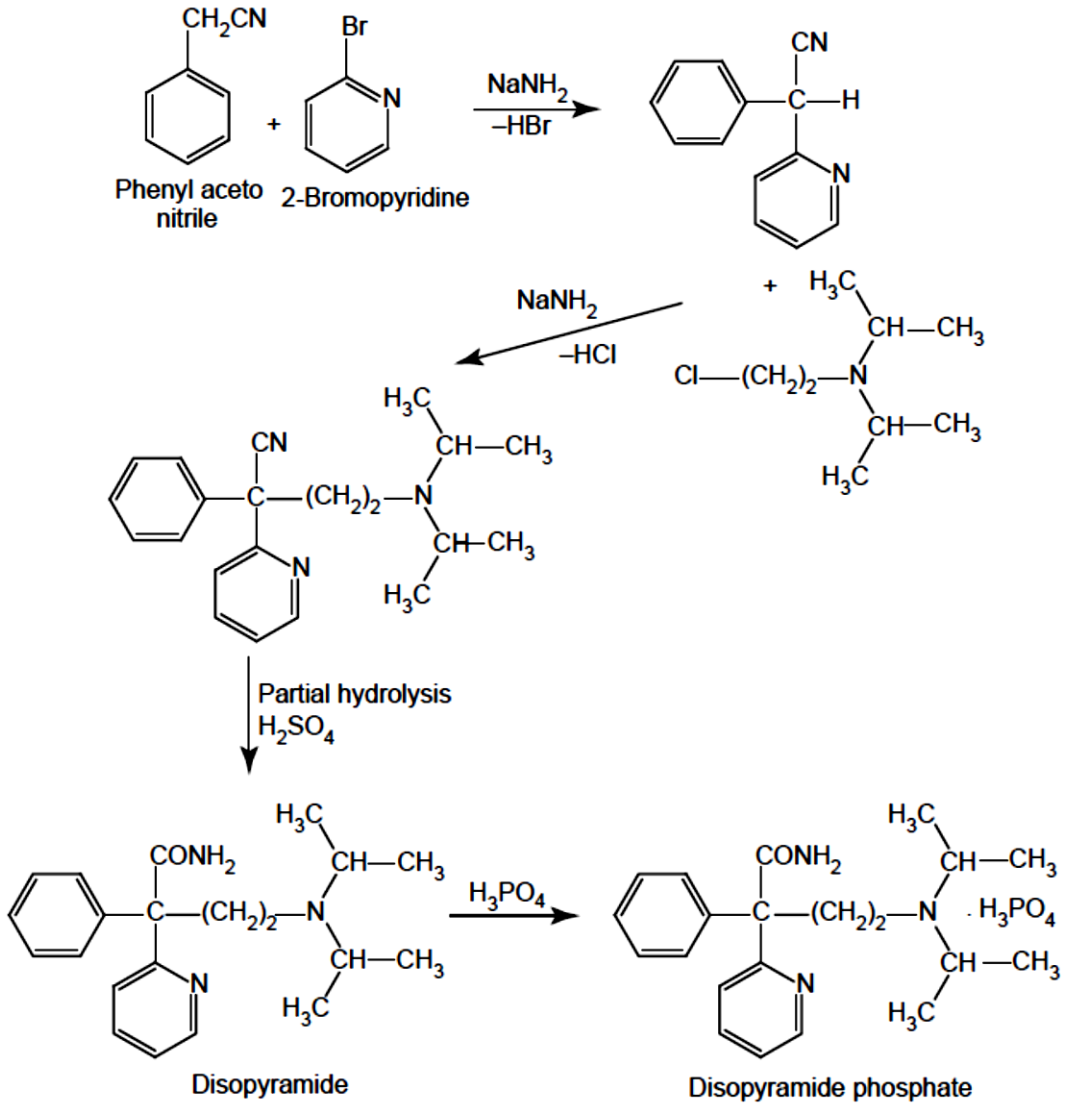
4-Diisopropylamino-2-phenyl-2-(2-pyridyl) butyramide

MOA: Actions are similar to quinidine. Its cardiac vagolytic action is more marked than that of quinidine and hence digitalisation is a must with disopyramide in the treatment of atrial flutter and fibrillation. It also has negative inotropic effect.

Dose: 100 – 150 mg 3–4 times a day (oral).

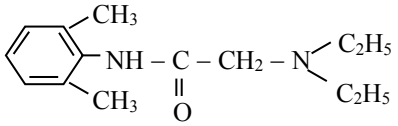
Uses: Premature ventricular contractions and ventricular arrhythmias.

Synthesis



CLASS 1B: Stabilize the membrane by blockimg the Na+ channel in both state but not delay the channel recovery.

(1) Lidocaine (Lignocaine)



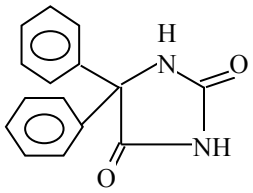
2-(diethylamino)-*N*-(2,6-dimethyl phenyl) acetamide

MOA: Lidocaine is a local anesthetic agent. It blocks both active and inactive sodium channels. It shortens the ventricular action potential duration. It undergoes Ist pass metabolism and hence it is given by parenteral route.

Dose : 150 – 200 mg i.v. as loading dose, 1- 4 mg/min by i.v. infusion as maintenance dose.

Uses : Used in ventricular arrhythmias and ventricular fibrillation (specially after myocardial infarction and cardic surgery).

(2) Phenytoin



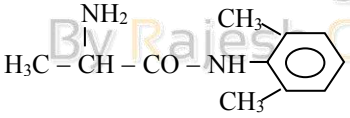
5, 5-diphenylhydantoin

Actions are similar to lidocaine. It is mainly used as an antiepileptic agent in grand mal epilepsy.

Dose : 200 – 600 mg (oral).

Uses : Drug of choice in the treatment of digitalis induced arrhythmias.

(3) Tocainide



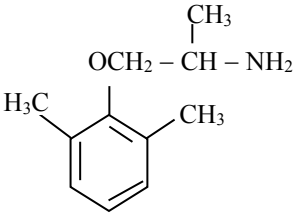
2-amino-N-(2, 6-dimethylphenyl)-propanamide

Actions are similar to lidocaine.

Dose: 400 mg every 8 hr. (oral).

Uses: It is used to prevent and supress premature ventricular depolarisations and ventricular tachydysarrhythmias.

(4) Mexiletine



1-Methyl-2-(2, 6-xylyloxy) ethylamine

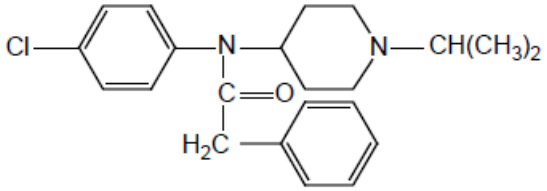
Actions are similar to lidocaine but undergoes little hepatic first pass metabolism.

Dose: 400 mg loading dose, followed by 200 – 250 mg three to four times daily.

Uses: Used in post-infarction ventricular arrhythmias as an alternative to lignocaine and in resistant cases.

CLASS IC: Block the Na+ channel and prolong the recovery time.

(1) Lorcainide hydrochloride

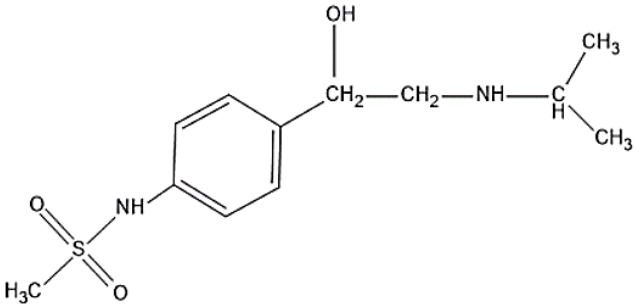


N-(4-chlorophenyl)-N-(1-isopropyl piperidin-4yl)-2-phenyl acetamide

Uses: Treatment of ventricular and supraventricular arrhythmia.

CLASS II: β-Adrenergic Blockers

(1) Sotalol



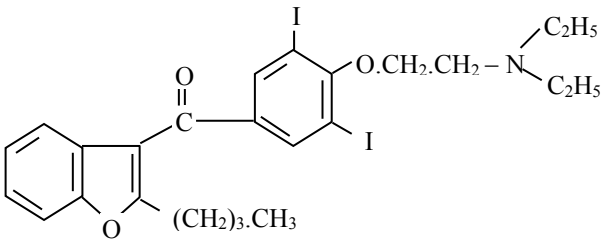
***N*-[4-[1-hydroxy-2-(propan-2-yl amino) ethyl] phenyl] methane sulfonamide**

MOA: It is adrenergic beta blocker, also having the K+ channel blocking property and cause delayed in repolarization and resting phase

Uses: Used in cardiac arrhythmia, hypertension, and angina.

CLASS III: K+ Channel Blocker

(1) Amiodarone



(2-butyl-1-benzofuran-3-yl)-[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone

It is a long acting antiarrhythmic agent.

Dose: 400 – 600 mg (oral).

Uses: Used in ventricular and supraventicular arrhythmias.

Amiodarone is a broad spectrum antiarrhythmic agent belonging to class IA, II, III and IV

CLASS IV: Calcium Channel Blockers

Refer topic Antianginal Vasodilators.

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