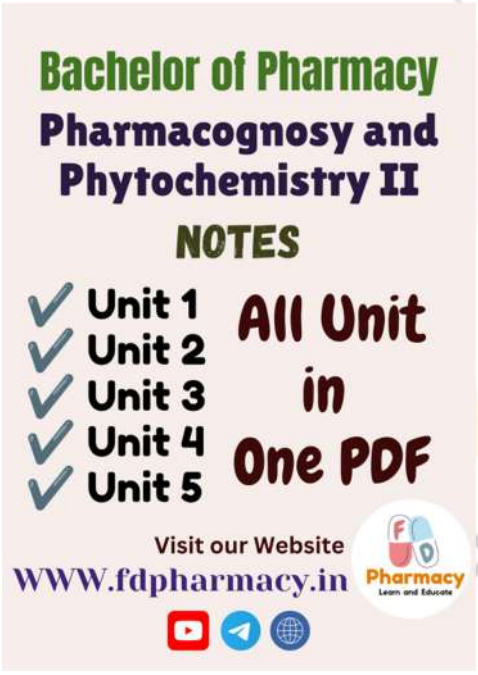
WELCOME

TO


Bachelor of Pharmacy
Pharmaceutical Jurisprudence
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Industrial Pharmacy I
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Medicinal Chemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmacognosy and Phytochemistry II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmacology II
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate

MEDICINAL CHEMISTRY - II

UNIT 3

TOPIC :

- **Anti-arrhythmic Drugs :** Quinidine sulphate, Procainamide hydrochloride, Disopyramide phosphate*, Phenytoin sodium, Lidocaine hydrochloride, Tocainide hydrochloride, Mexiletine hydrochloride, Lorcainide hydrochloride, Amiodarone, Sotalol.

Anti-arrhythmic drugs

- Anti-arrhythmic drugs are agents used to prevent or treat cardiac arrhythmias, which are abnormal rhythms of the heartbeat.
- Cardiac arrhythmia refers to any disturbance in the rate, rhythm, or sequence of heartbeats.
- These disturbances may arise due to:
  - Abnormal impulse generation (ectopic pacemaker)
  - Abnormal impulse conduction (re-entry circuits)
  - Combination of both mechanisms
- The aim of anti-arrhythmic therapy is to:
  - Restore normal sinus rhythm
  - Control heart rate
  - Prevent recurrence of arrhythmias
  - Reduce the risk of sudden cardiac death

Classification of Anti-arrhythmic Drugs (Vaughan Williams Classification)

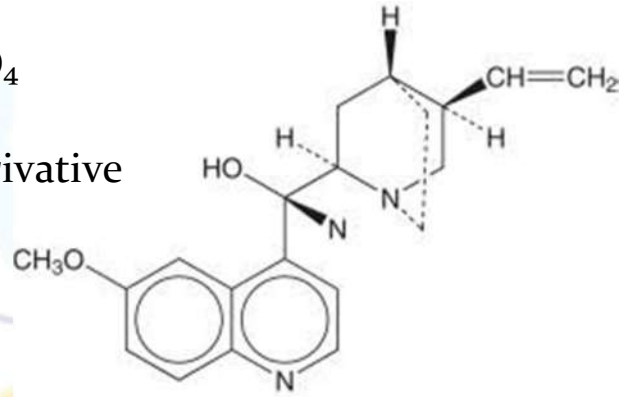
Class	Drug Examples	Mechanism of Action	Main Effect on ECG/Heart
Class I *Sodium channel blockers*	Quinidine, Procainamide, Lidocaine, Phenytoin, Flecainide	Block voltage-gated Na^+ channels → ↓ conduction velocity	Prolong QRS, may affect QT
Class II *β-Blockers*	Propranolol, Metoprolol, Esmolol	Block β-adrenergic receptors → ↓ sympathetic activity	↓ heart rate, ↓ AV conduction
Class III *Potassium channel blockers*	Amiodarone, Sotalol, Dofetilide	Block K^+ channels → prolong repolarization	Prolong action potential & QT interval
Class IV *Calcium channel blockers*	Verapamil, Diltiazem	Block L-type Ca^{2+} channels → slow AV node conduction	Prolong PR interval
Others	Adenosine, Digoxin, Magnesium sulfate	Various mechanisms	Used for specific arrhythmias

Quinidine Sulphate

- Quinidine sulphate is a Class IA antiarrhythmic agent used in the treatment of cardiac arrhythmias.
- It is a stereoisomer of quinine, an alkaloid obtained from the bark of the Cinchona tree (*Cinchona officinalis*).
- Quinidine acts as a membrane-stabilizing agent and is known for its sodium channel blocking activity.
- It reduces the excitability of cardiac muscle, slows conduction, and helps to maintain a normal sinus rhythm.

Chemical Structure

- Chemical name: (S)-(2R,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-ylmethanol sulfate
- Molecular formula: $C_{20}H_{24}N_2O_2 \cdot H_2SO_4$
- Molecular weight: 480.55 g/mol
- Chemical class: Cinchona alkaloid derivative
- Structure



Mechanism of Action

- Quinidine is a Class IA antiarrhythmic drug that acts primarily on the cardiac sodium (Na^+) channels and secondarily on potassium (K^+) channels.
- Main actions:
  1. Blocks fast Na^+ channels in phase 0 of the cardiac action potential → slows depolarization and conduction velocity.
  2. Inhibits K^+ efflux → prolongs repolarization (phase 3) and increases action potential duration and refractory period.
  3. Decreases myocardial excitability and suppresses ectopic pacemaker activity.
  4. Has mild anticholinergic and α-adrenergic blocking effects → may cause vasodilation and reflex tachycardia.

Synthesis of Quinidine Sulphate

1. Natural Source Extraction:
    - Quinidine is isolated from Cinchona bark, which also contains related alkaloids like quinine, cinchonine, and cinchonidine.
2. Separation and Purification:
    - The bark is powdered and extracted with an acidified solvent (e.g., dilute H_2SO_4 or HCl).
    - The extract contains a mixture of alkaloids, which are then basified (with ammonia or sodium hydroxide) to liberate the free bases.
    - The free bases are separated by fractional crystallization or chromatography.
3. Conversion to Sulphate Salt:
    - The purified quinidine base is reacted with dilute sulfuric acid (H_2SO_4) to form quinidine sulphate, a crystalline and water-soluble salt.

Uses

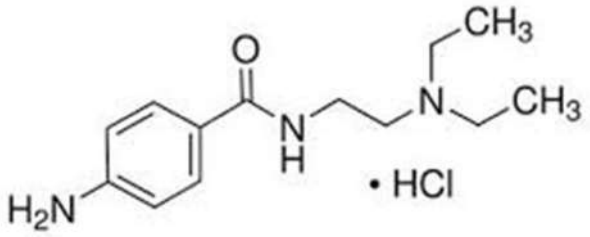
- Therapeutic Uses:
    1. Treatment of cardiac arrhythmias (atrial fibrillation, flutter, and ventricular arrhythmias).
    2. Conversion and maintenance of normal sinus rhythm after cardioversion.
    3. Occasionally used as an antimalarial agent (though less effective than quinine).
    4. Used in research to study cardiac ion channel physiology.

Procainamide Hydrochloride

- Procainamide hydrochloride is a Class IA antiarrhythmic drug, chemically related to procaine (a local anesthetic).
- It was developed as a more stable and orally active analog of procaine, used primarily for the treatment of cardiac arrhythmias.
- It acts mainly by blocking sodium (Na^+) channels in cardiac tissues, thereby reducing excitability and conduction velocity.
- Procainamide stabilizes the cardiac membrane and helps restore normal rhythm in abnormal heartbeats.

Chemical Structure

- Chemical name: 4-Amino-N-(2-diethylaminoethyl)benzamide hydrochloride
- Molecular formula: $C_{13}H_{21}N_3O{\cdot}HCl$
- Molecular weight: 271.79 g/mol
- Chemical class: Synthetic derivative of procaine (an amide-type antiarrhythmic).
- structure



Mechanism of Action

- Procainamide is a Class IA antiarrhythmic agent that affects cardiac action potentials.
- Main actions:
  1. Blocks fast Na^+ channels → slows phase 0 depolarization → reduces conduction velocity.
  2. Inhibits K^+ channels → prolongs repolarization (phase 3) and increases the effective refractory period.
  3. Reduces myocardial excitability and suppresses ectopic pacemaker activity.
  4. Slight anticholinergic activity, which may increase heart rate slightly.

Synthesis of Procainamide Hydrochloride

Stepwise synthetic route:

1. Starting material: *p-Aminobenzoic acid* (PABA)
2. Amide formation:
    - PABA is reacted with 2-diethylaminoethylamine in the presence of a dehydrating agent (e.g., DCC or $SOCl_2$).
    - This results in the formation of 4-amino-N-(2-diethylaminoethyl)benzamide (Procainamide base).
3. Formation of hydrochloride salt:
    - The base is treated with hydrochloric acid (HCl) to form Procainamide hydrochloride, which is water-soluble and stable.

Uses

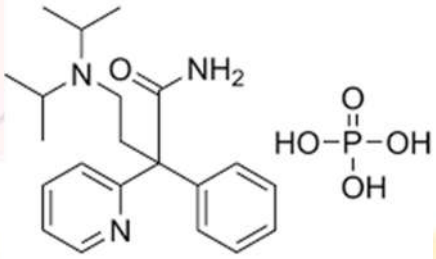
- Therapeutic Uses:
    1. Treatment of cardiac arrhythmias:
        - Atrial fibrillation and flutter
        - Ventricular tachycardia
        - Premature ventricular contractions
    2. Post-myocardial infarction arrhythmias
    3. Alternative to quinidine in patients who cannot tolerate it.
- Other Uses:
    - Occasionally used in diagnostic electrophysiologic studies of the heart.

Disopyramide Phosphate

- Disopyramide phosphate is a Class IA antiarrhythmic agent, used for the management of ventricular and supraventricular arrhythmias.
- It is a synthetic derivative of 2-pyridyl disubstituted amide, structurally and pharmacologically related to quinidine and procainamide.
- The drug acts by blocking sodium (Na^+) channels and prolonging the cardiac action potential, thereby stabilizing the cardiac membrane.
- It exhibits additional anticholinergic (antimuscarinic) activity, which distinguishes it from other Class IA agents.

Chemical Structure

- Chemical name: (RS)-α-[diisopropylamino]-2-phenyl-2-(2-pyridyl)acetamide phosphate
- Molecular formula: $C_{21}H_{29}N_3O_4 \cdot H_3PO_4$
- Molecular weight: 505.47 g/mol
- Chemical class: Synthetic amide derivative (Class IA antiarrhythmic).
- Structural



Mechanism of Action

- Disopyramide is a Class IA antiarrhythmic agent that primarily affects cardiac electrophysiology.

Actions:

1. Blocks fast Na^+ channels during phase 0 depolarization of the cardiac action potential → slows conduction velocity.
2. Inhibits K^+ efflux, leading to prolonged repolarization and extended refractory period.
3. Decreases myocardial excitability and suppresses ectopic pacemaker activity.
4. Exhibits anticholinergic (antimuscarinic) effects → decreases vagal tone and may cause slight tachycardia.
5. Has negative inotropic action (reduces cardiac contractility).

Synthesis of Disopyramide Phosphate

Stepwise synthetic route (simplified):

1. Starting materials:
    - 2-cyanopyridine
    - Benzyl chloride
    - Diisopropylamine
2. Reaction Steps:
    - Step 1: Condensation of 2-cyanopyridine with benzyl chloride to form 2-phenyl-2-(2-pyridyl)acetonitrile.
    - Step 2: The nitrile group is converted to an amide by reaction with diisopropylamine and suitable dehydrating/condensing agent.
    - Step 3: The resultant disopyramide base is then treated with phosphoric acid (H_3PO_4) to form disopyramide phosphate salt, which is crystalline and water-soluble.

Uses

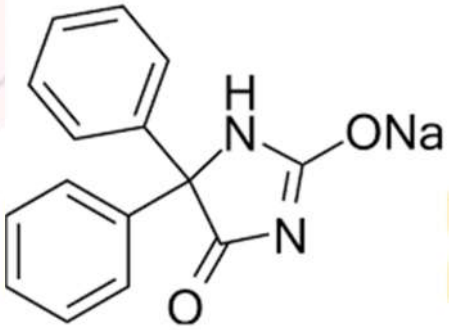
- Therapeutic Uses:
    1. Ventricular arrhythmias (especially life-threatening or sustained ventricular tachycardia).
    2. Supraventricular arrhythmias, including atrial fibrillation and flutter.
    3. Maintenance of normal sinus rhythm after conversion from arrhythmia.
    4. Occasionally used in hypertrophic cardiomyopathy due to its negative inotropic effect.

Phenytoin Sodium

- Phenytoin sodium is a hydantoin derivative and a widely used antiepileptic (anticonvulsant) drug.
- It is primarily used in the management of generalized tonic–clonic (grand mal) seizures and partial seizures.
- The drug was first synthesized in 1908 by Heinrich Biltz and introduced clinically in 1938 as an effective non-sedative anticonvulsant.
- It acts by stabilizing neuronal membranes and reducing excessive electrical activity in the brain.

Chemical Structure

- Chemical name: Sodium 5,5-diphenylimidazolidine-2,4-dione
- Molecular formula: $C_{15}H_{11}N_2NaO_2$
- Molecular weight: 274.25 g/mol
- Chemical class: Hydantoin derivative
- IUPAC name: Sodium 5,5-diphenylimidazolidine-2,4-dione
- Structural



Mechanism of Action

Phenytoin acts mainly by modulating voltage-gated sodium (Na^+) channels in neurons.

Stepwise Action :

1. Blocks voltage-gated Na^+ channels in their inactive state.
2. Prevents repetitive and sustained firing of action potentials by stabilizing neuronal membranes.
3. Limits the spread of seizure activity by reducing electrical excitability in cortical motor areas.
4. Does not cause general CNS depression (unlike older sedative anticonvulsants).

Synthesis of Phenytoin Sodium

Stepwise Synthesis Route (Simplified):

1. Starting material: *Benzil* and *Urea*
2. Condensation Reaction:
    - Benzil (1,2-diphenylethane-1,2-dione) is condensed with urea in the presence of basic catalyst (e.g., NaOH or KOH).
    - This results in cyclization forming 5,5-diphenylhydantoin (phenytoin).
3. Formation of Sodium Salt:
    - Phenytoin is treated with sodium hydroxide (NaOH) to yield phenytoin sodium, the water-soluble salt form.

Uses

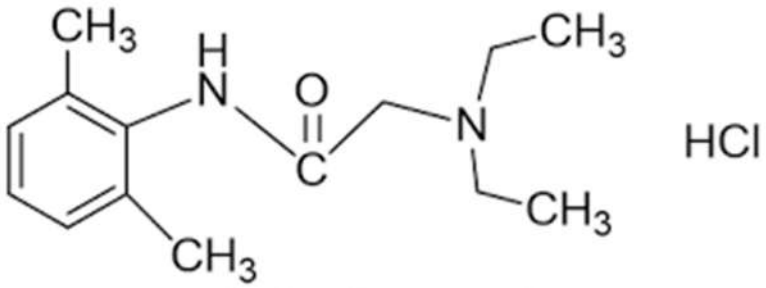
- Therapeutic Uses:
    1. Epilepsy (Anticonvulsant):
        - Generalized tonic–clonic seizures (grand mal)
        - Partial (focal) seizures
    2. Status epilepticus (IV use for acute control).
    3. Cardiac arrhythmias (especially digitalis-induced arrhythmias).
    4. Trigeminal neuralgia (occasionally as adjunct therapy).

Lidocaine Hydrochloride

- Lidocaine hydrochloride (also known as lignocaine) is a local anesthetic and a Class IB antiarrhythmic agent.
- It was the first amide-type local anesthetic developed (in 1943 by Löfgren and Lundqvist).
- The drug provides rapid onset and intermediate duration of anesthesia.
- It acts by blocking voltage-gated sodium (Na^+) channels in neuronal and cardiac membranes.
- Lidocaine hydrochloride is more stable, less allergenic, and longer-acting than ester-type anesthetics (like procaine).

Chemical Structure

- Chemical name: 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide hydrochloride
- Molecular formula: $C_{14}H_{22}N_2O{\cdot}HCl$
- Molecular weight: 270.80 g/mol
- Chemical class: Amide-type local anesthetic; Class IB antiarrhythmic
- IUPAC Name: N-(2,6-dimethylphenyl)-2-(diethylamino)acetamide hydrochloride
- Structural



Mechanism of Action

Lidocaine acts as both a local anesthetic and antiarrhythmic by blocking voltage-gated sodium channels (Na^+ channels).

Mechanism (Local Anesthetic Action):

1. Penetrates the neuronal membrane in its unionized form.
2. Inside the axoplasm, it becomes ionized and binds to Na^+ channels on the inner side of the membrane.
3. This prevents Na^+ influx, inhibiting depolarization and blocking conduction of nerve impulses.
4. As a result, pain signals are not transmitted to the central nervous system.

Synthesis of Lidocaine Hydrochloride

Stepwise synthetic pathway (simplified):

1. Starting material: *2,6-Dimethylaniline* (xylidine)
2. Step 1 – Acylation:
   - React *2,6-dimethylaniline* with chloroacetyl chloride in the presence of a base (e.g., NaOH or pyridine)
   - Forms 2-(chloroacetylamino)-2,6-dimethylbenzene (chloroacetyl derivative).

$$\text{2,6-Dimethylaniline} + ClCH_2COCl \rightarrow \text{2,6-Dimethylphenyl-2-chloroacetamide}$$

3. Step 2 – Alkylation:
   - The chloroacetamide is reacted with diethylamine to substitute the chlorine atom with a diethylamino group.
   - This yields Lidocaine (base).

$$\text{2,6-Dimethylphenyl-2-chloroacetamide} + (C_2H_5)_2NH \rightarrow \text{Lidocaine}$$

4. Step 3 – Formation of Hydrochloride Salt:
   - The base is treated with hydrochloric acid (HCl) to form Lidocaine hydrochloride, which is crystalline and water-soluble.

Uses

As a Local Anesthetic

1. Topical anesthesia: Skin, mucous membranes, burns, insect bites.
2. Infiltration anesthesia: For minor surgical and dental procedures.
3. Nerve block and epidural anesthesia: For surgical and obstetric procedures.

As an Antiarrhythmic

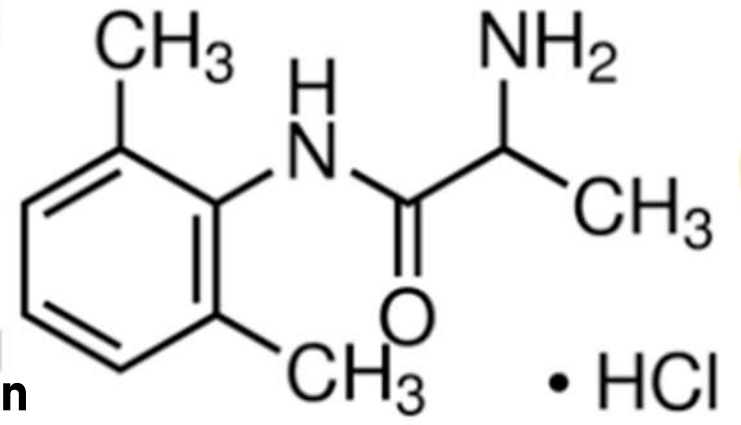
1. Ventricular arrhythmias, especially after myocardial infarction.
2. Digitalis-induced arrhythmias.
3. Emergency management of ventricular tachycardia or fibrillation (IV form).

Tocainide Hydrochloride

- Tocainide hydrochloride is a Class IB antiarrhythmic agent, structurally related to lidocaine, but unlike lidocaine, it is orally active.
- It is primarily used for the management of ventricular arrhythmias, especially in patients intolerant to other antiarrhythmics.
- Tocainide has rapid absorption, moderate half-life, and acts by stabilizing cardiac membranes and suppressing abnormal electrical activity.
- Being an amide-type local anesthetic derivative, it exhibits less CNS toxicity compared to lidocaine when used systemically.

Chemical Structure

- Chemical name: N-(2,6-Dimethylphenyl)-2-(methylamino)propionamide hydrochloride
- Molecular formula: $C_{12}H_{18}N_2O{\cdot}HCl$
- Molecular weight: 235.74 g/mol
- Chemical class: Amide derivative, Class IB antiarrhythmic
- Structura



Mechanism of Action

- Tocainide is a Class IB antiarrhythmic, primarily acting on ventricular myocardial cells.

Actions:

1. Blocks voltage-gated Na^+ channels in their inactive state → reduces phase 0 depolarization in ischemic or depolarized cardiac tissue.
2. Shortens action potential duration (APD) and refractory period, especially in ventricular myocardium.
3. Suppresses abnormal automaticity and ectopic pacemaker activity.
4. Minimal effect on atrial tissue and conduction through the AV node.

Synthesis of Tocainide Hydrochloride

1. Starting material: *2,6-Dimethylaniline* (xylidine)
2. Step 1 – Acylation:
    - 2,6-Dimethylaniline is reacted with 2-bromopropionyl chloride to form 2,6-dimethylphenyl-2-bromopropionamide.
3. Step 2 – Amination:
    - Bromopropionamide is reacted with methylamine to replace the bromine with a methylamino group, forming tocainide base.
4. Step 3 – Formation of Hydrochloride Salt:
    - The base is treated with HCl to obtain tocainide hydrochloride, which is crystalline and water-soluble.

Uses

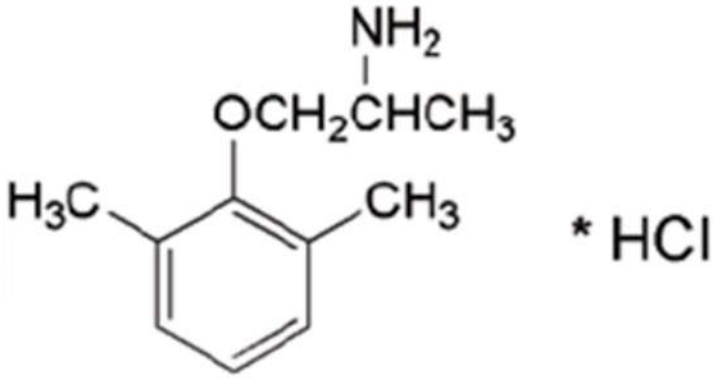
- Therapeutic Uses:
    1. Management of ventricular arrhythmias, including:
        - Ventricular tachycardia
        - Premature ventricular contractions (PVCs)
    2. Prevention of life-threatening arrhythmias in post-myocardial infarction patients.
    3. Alternative for oral antiarrhythmic therapy when lidocaine (IV) is unsuitable.

Mexiletine Hydrochloride

- Mexiletine hydrochloride is a Class IB antiarrhythmic agent and an orally active analog of lidocaine.
- It is primarily used for the management of ventricular arrhythmias and occasionally for chronic pain syndromes (off-label use).
- Unlike lidocaine, mexiletine is stable in the gastrointestinal tract and has good oral bioavailability, making it suitable for long-term therapy.
- It acts by blocking sodium (Na^+) channels, stabilizing cardiac membranes, and suppressing abnormal ventricular excitability.

Chemical Structure

- Chemical name: 1-(2,6-Dimethylphenyl)-2-methylaminopropane hydrochloride
- Molecular formula: $C_{12}H_{20}N{\cdot}HCl$
- Molecular weight: 211.76 g/mol
- Chemical class: Amine derivative; Class IB antiarrhythmic
- Structural



Mechanism of Action

Mexiletine is a Class IB antiarrhythmic, similar to lidocaine, acting predominantly on ventricular myocardial cells.

Actions:

1. Blocks voltage-gated Na^+ channels during the inactivated state, reducing phase 0 depolarization in ischemic or depolarized tissue.
2. Shortens action potential duration (APD) and refractory period in ventricular myocardium.
3. Suppresses abnormal automaticity and ectopic pacemaker activity.
4. Minimal effect on atrial tissue or AV nodal conduction.

Synthesis of Mexiletine Hydrochloride

1. Starting material: *2,6-Dimethylaniline* (xylidine)
2. Step 1 – Alkylation:
    - 2,6-Dimethylaniline is reacted with 2-chloro-2-methylpropane or a similar halide to introduce a methylaminopropyl side chain, forming mexiletine base.
3. Step 2 – Formation of Hydrochloride Salt:
    - The base is treated with hydrochloric acid (HCl) to yield mexiletine hydrochloride, which is crystalline and water-soluble.

Uses

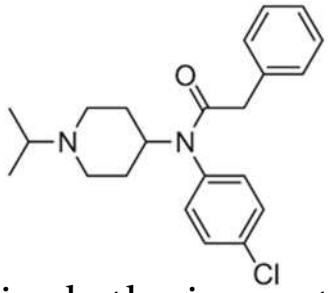
- Therapeutic Uses:
    1. Ventricular arrhythmias (premature ventricular contractions, ventricular tachycardia)
    2. Chronic pain syndromes (neuropathic pain, off-label use)
    3. Prevention of arrhythmias in patients with ischemic heart disease

Lorcainide Hydrochloride

- Lorcainide hydrochloride is a Class IC antiarrhythmic agent, structurally related to lidocaine, and an oral antiarrhythmic.
- It is used for the management of serious ventricular arrhythmias, including ventricular tachycardia and premature ventricular contractions.
- Lorcainide has high potency, slow dissociation from sodium channels, and minimal effect on repolarization, which is characteristic of Class IC agents.
- The drug is mainly used when patients are intolerant to other antiarrhythmics or when long-term oral therapy is required.

Chemical Structure

- Chemical name: N-(2,6-Dimethylphenyl)-2-methoxy-N-propylacetamide hydrochloride
- Molecular formula: $C_{14}H_{22}N_2O_2 \cdot HCl$
- Molecular weight: 276.79 g/mol
- Chemical class: Amide derivative; Class IC antiarrhythmic
- Structural



Mechanism of Action

- Lorcainide is a Class IC antiarrhythmic agent, primarily acting on ventricular myocardium.

Actions:

1. Blocks fast voltage-gated Na^+ channels → markedly slows phase 0 depolarization and conduction velocity in the His-Purkinje system and ventricular myocardium.
2. Slow dissociation from Na^+ channels → persistent sodium channel blockade even at normal heart rates.
3. Minimal effect on action potential duration (APD) or refractory period.
4. Suppresses abnormal automaticity and prevents re-entry ventricular arrhythmias.

Synthesis of Lorcainide Hydrochloride

Stepwise synthesis (simplified):

1. Starting material: *2,6-Dimethylaniline*
2. Step 1 – Acylation:
    - React 2,6-dimethylaniline with 2-chloroacetyl chloride to form 2-chloro-N-(2,6-dimethylphenyl)acetamide.
3. Step 2 – Alkylation:
    - React the chloroacetamide with N-propylmethoxyamine to introduce the methoxy-N-propyl side chain, forming lorcainide base.
4. Step 3 – Formation of Hydrochloride Salt:
    - Treat the base with HCl to yield lorcainide hydrochloride, a water-soluble crystalline salt.

Uses

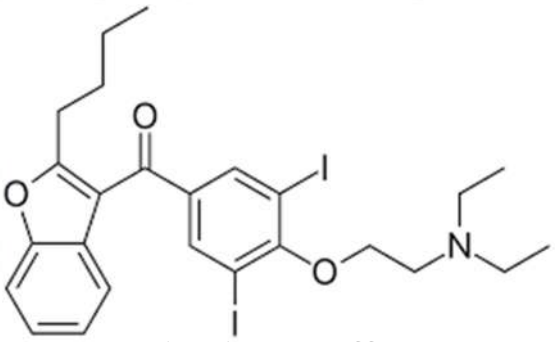
- Therapeutic Uses:
    1. Management of serious ventricular arrhythmias (ventricular tachycardia, PVCs).
    2. Long-term oral therapy for patients intolerant to other antiarrhythmics.
    3. Prevention of recurrent ventricular arrhythmias post-myocardial infarction.

Amiodarone

- Amiodarone is a Class III antiarrhythmic drug, widely used for the management of life-threatening ventricular arrhythmias and certain supraventricular arrhythmias.
- It was developed in the 1960s and is highly effective due to multiple electrophysiological effects on the heart.
- Amiodarone is iodinated, lipophilic, and has a very long half-life (30–100 days), which allows for sustained antiarrhythmic effects.
- Available as oral tablets, intravenous injection, and as solution for infusion.

Chemical Structure

- Chemical name: 2-Butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3,5-diiodobenzyl ether
- Molecular formula: $C_{25}H_{29}I_2NO_3$
- Molecular weight: 645.32 g/mol
- Chemical class: Benzofuran derivative; Class III antiarrhythmic
- Structural



Mechanism of Action

Amiodarone exhibits multiple antiarrhythmic effects:

1. Class III action:
    - Blocks potassium (K^+) channels → prolongs repolarization and action potential duration (APD) in atrial and ventricular tissue.
2. Class I action:
    - Blocks sodium (Na^+) channels, reducing phase 0 depolarization.
3. Class II action:
    - Mild noncompetitive antiadrenergic effect, decreasing sympathetic activity.
4. Class IV action:
    - Blocks calcium (Ca^{2+}) channels, slowing AV nodal conduction.

Synthesis of Amiodarone

1. Starting material: 2,3-dibromobenzyl bromide or diiodobenzyl derivatives
2. Step 1 – Ether formation:
    - React with 2-butylbenzofuran in the presence of base to form benzofuran-diiodobenzyl ether.
3. Step 2 – Side chain introduction:
    - Attach 2-(diethylamino)ethanol to the benzene ring via nucleophilic substitution to yield Amiodarone base.
4. Step 3 – Purification:
    - The product is purified, sometimes converted into hydrochloride salt for solubility (injectable forms).

Uses

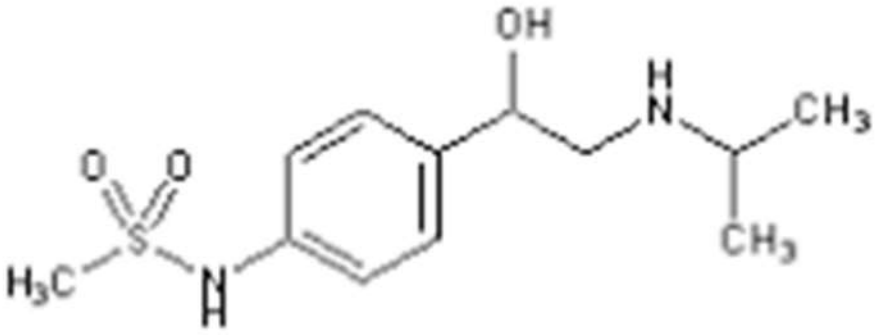
- Therapeutic Uses:
    1. Ventricular arrhythmias:
        - Ventricular tachycardia (sustained or nonsustained)
        - Ventricular fibrillation
    2. Supraventricular arrhythmias:
        - Atrial fibrillation and flutter
        - Paroxysmal supraventricular tachycardia
    3. Emergency settings: IV infusion for life-threatening arrhythmias.
    4. Occasionally used for prevention of recurrent arrhythmias in high-risk patients.

Sotalol

- Sotalol is a non-selective beta-adrenergic blocker (β-blocker) with Class III antiarrhythmic activity.
- Unlike typical beta-blockers, sotalol also prolongs the action potential duration and refractory period in cardiac tissue, giving it dual action.
- It is used for the treatment of atrial and ventricular arrhythmias, including life-threatening ventricular tachycardia.
- Sotalol is water-soluble and available as oral tablets and IV injections.

Chemical Structure

- Chemical name: (RS)-1-[4-(β-hydroxy-β-phenyl-ethyl)aminophenyl]sulfonyl-3-propanol
- Molecular formula: $C_{12}H_{21}NO_3S$
- Molecular weight: 272.36 g/mol
- Chemical class: Non-selective β-blocker with Class III antiarrhythmic property
- Structural



Mechanism of Action

- Dual antiarrhythmic activity:

A. Beta-blocker effect (Class II):

1. Non-selectively blocks β_1 and β_2 adrenergic receptors.
2. Reduces sympathetic stimulation of the heart → decreases heart rate, AV nodal conduction, and myocardial oxygen demand.

B. Class III antiarrhythmic effect:

1. Blocks potassium (K^+) channels, prolonging repolarization and action potential duration (APD).
2. Increases refractory period in atrial and ventricular tissue.

Synthesis of Sotalol

Stepwise Synthesis (Simplified Overview):

1. Starting materials:
    - 4-chlorophenol
    - Epichlorohydrin
2. Step 1 – Epoxide formation:
    - React 4-chlorophenol with epichlorohydrin → forms glycidyl ether intermediate.
3. Step 2 – Amination:
    - Glycidyl ether reacts with propanolamine derivative to yield the sotalol base.
4. Step 3 – Sulfonamide formation:
    - Introduce sulfonamide group via reaction with sulfonyl chloride to obtain sotalol.
5. Step 4 – Racemic mixture:
    - The final product is a racemic mixture of D- and L-enantiomers, both contributing to its dual pharmacological activity.

Uses

- Therapeutic Uses:
    1. Ventricular arrhythmias: Sustained and nonsustained ventricular tachycardia
    2. Supraventricular arrhythmias: Atrial fibrillation, atrial flutter
    3. Prevention of sudden cardiac death in high-risk patients with ventricular arrhythmias
    4. Sometimes used in combination therapy for refractory arrhythmias