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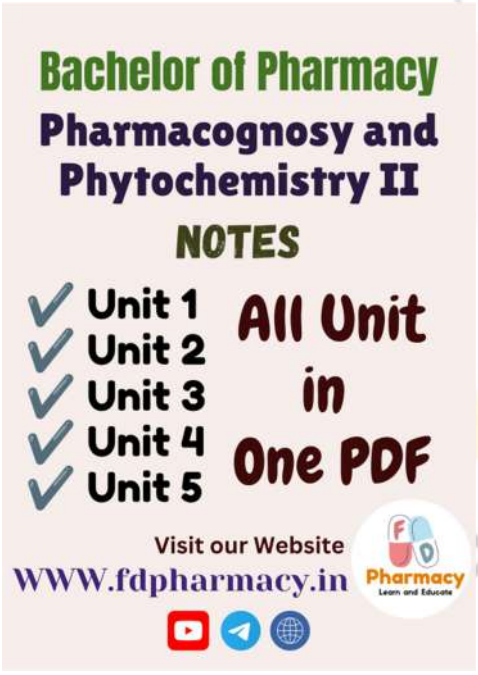
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MEDICINAL CHEMISTRY - II

UNIT 5

TOPIC :

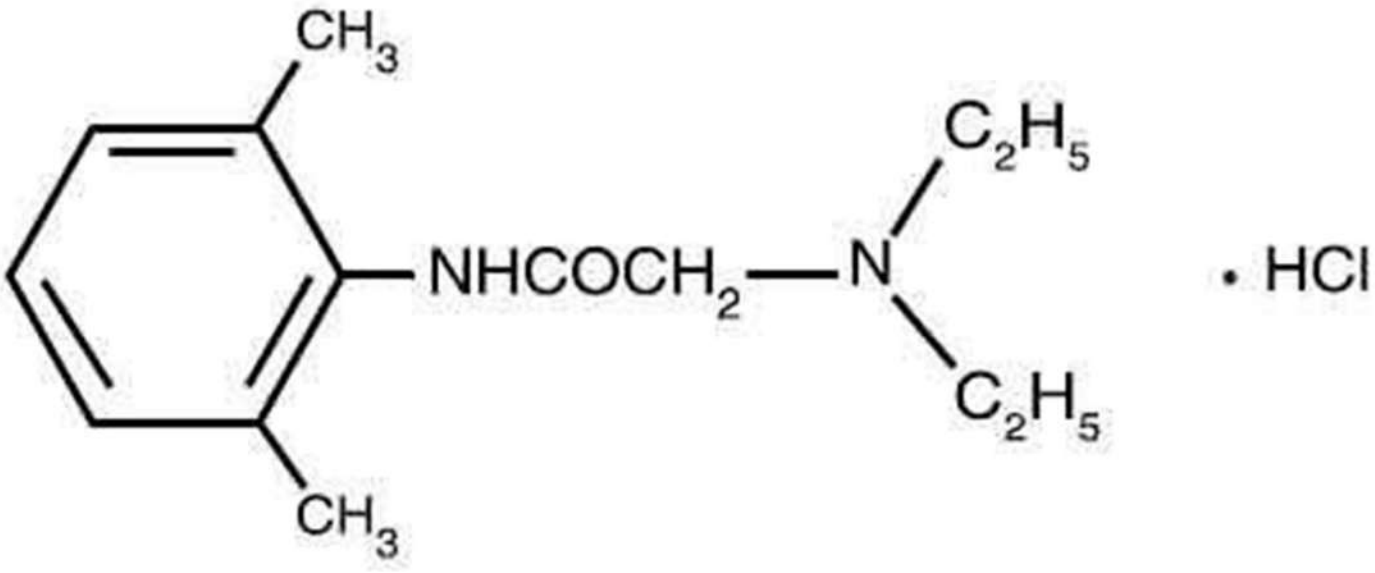
- **Lidocaine/Anilide derivatives :** Lignocaine, Mepivacaine, Prilocaine, Etidocaine.

Lignocaine (Lidocaine)

- Lignocaine, also called Lidocaine, is a widely used amide-type local anesthetic.
- It is used for topical, infiltration, nerve block, spinal, and epidural anesthesia.
- Lignocaine has a rapid onset of action and intermediate duration.
- Unlike ester anesthetics, Lignocaine is metabolized by the liver (hepatic microsomal enzymes) rather than by plasma esterases.
- It is also used as an antiarrhythmic agent (Class 1b) for ventricular arrhythmias.

Chemical Structure

- Chemical Name: 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide
- Molecular Formula: $C_{14}H_{22}N_2O$
- Molecular Weight: 234.34 g/mol
- Chemical Class: Amide-type local anesthetic
- Structural



Mechanism of Action

- Lignocaine blocks voltage-gated sodium (Na^+) channels in neuronal membranes.
- This prevents depolarization, inhibiting the propagation of nerve impulses, resulting in reversible anesthesia.
- Primarily affects sensory neurons, sparing motor function at lower concentrations.
- In cardiac tissue, it stabilizes the membrane by reducing automaticity and conduction velocity, making it useful in ventricular arrhythmias.
- Onset is rapid (2–5 minutes), and duration is 30–60 minutes (shorter with infiltration, longer with nerve block).

Synthesis

Starting Materials: 2,6-Dimethylaniline and Chloroacetyl chloride

Steps:

1. Acylation: 2,6-Dimethylaniline reacts with chloroacetyl chloride to form 2-chloro-N-(2,6-dimethylphenyl)acetamide.
2. Amination: The chloro group is displaced by diethylamine, yielding Lignocaine (Lidocaine) base.
3. Salt Formation: The base can be converted into Lignocaine hydrochloride for water-soluble clinical formulations.

Uses

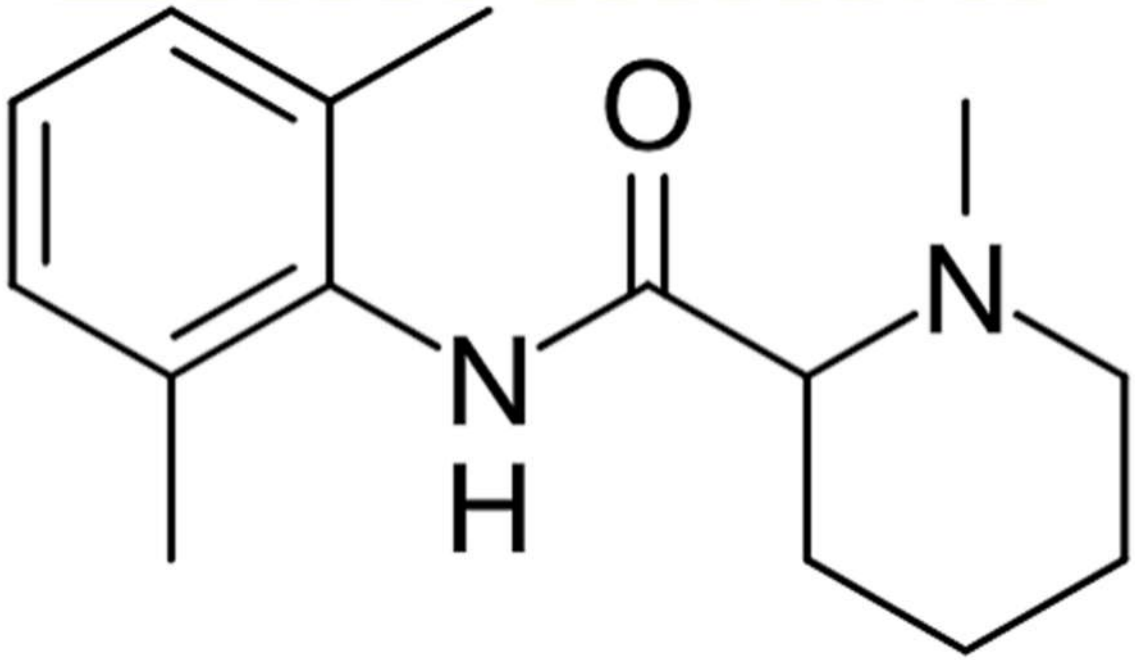
- Local anesthesia: Topical, infiltration, nerve block, spinal, epidural.
- Dental anesthesia: Commonly used for dental procedures.
- Antiarrhythmic agent: Treats ventricular arrhythmias (Class 1b).
- Topical analgesia: For minor burns, cuts, or mucous membrane irritation.
- Sometimes combined with epinephrine to prolong action and reduce bleeding.

Mepivacaine

- Mepivacaine is an amide-type local anesthetic commonly used for infiltration, nerve block, and epidural anesthesia.
- It is structurally related to Lidocaine, but has a slightly longer duration of action and less vasodilation, which reduces the need for vasoconstrictors.
- Mepivacaine is used as Mepivacaine hydrochloride in injectable form for clinical applications.
- It is favored in dental procedures and minor surgical procedures due to its rapid onset and intermediate duration.

Chemical Structure

- Chemical Name: 1-Methyl-2′,6′-pipecoloxylidide
- IUPAC Name: N-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide
- Molecular Formula: C15H22N2O
- Molecular Weight: 246.35 g/mol
- Chemical Class: Amide-type local anesthetic
- Structural



Mechanism of Action

- Mepivacaine blocks voltage-gated sodium (Na^+) channels in neuronal membranes.
- This prevents depolarization, inhibiting nerve impulse propagation, resulting in reversible local anesthesia.
- Primarily affects sensory nerves, sparing motor function at lower concentrations.
- Metabolized by the liver (hepatic microsomal enzymes).
- Its slower vasodilation prolongs duration of action compared to other amide anesthetics.

Synthesis

Starting Materials: 2,6-Dimethylaniline and 2-chloro-1-methylpiperidine-4-carboxylic acid derivative

Steps:

1. Acylation: 2,6-Dimethylaniline is reacted with a piperidine carboxylic acid derivative to form the amide linkage.
2. Purification: The base is purified and converted into Mepivacaine hydrochloride for water-soluble injectable forms.

Uses

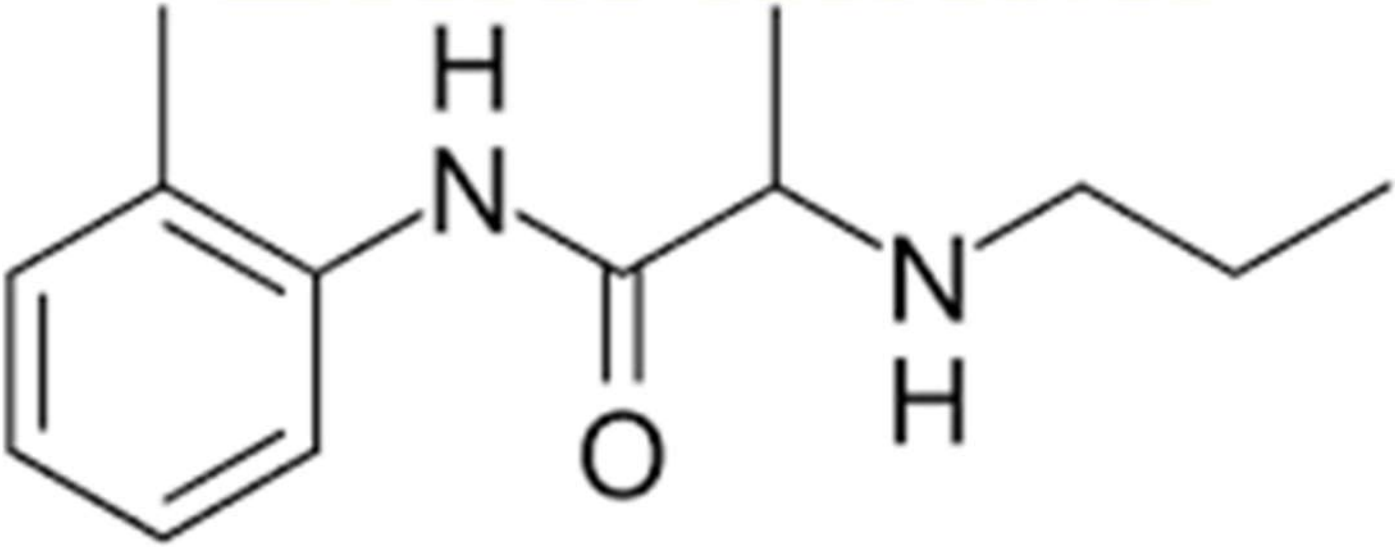
- Infiltration anesthesia for minor surgeries.
- Peripheral nerve block and epidural anesthesia.
- Dental anesthesia, especially in procedures requiring medium-duration anesthesia.
- Sometimes combined with vasoconstrictors to prolong effect further.

Prilocaine

- Prilocaine is an amide-type local anesthetic, structurally related to Lidocaine, but with less vasodilatory activity, which allows it to act longer without a vasoconstrictor.
- Commonly used in infiltration, nerve block, epidural, and topical anesthesia.
- Often combined with Lidocaine in a 1:1 mixture known as EMLA cream for surface anesthesia.
- Metabolized primarily in the liver, with renal excretion of metabolites.
- Its main advantage is low systemic toxicity and suitability for patients sensitive to vasoconstrictors.

Chemical Structure

- Chemical Name: N-(2-Methylphenyl)-2-(propylamino)propanamide
- IUPAC Name: N-(2-Methylphenyl)-2-propylaminopropionamide
- Molecular Formula: $C_{13}H_{20}N_2O$
- Molecular Weight: 220.31 g/mol
- Chemical Class: Amide-type local anesthetic
- Structural



Mechanism of Action

- Prilocaine blocks voltage-gated sodium (Na^+) channels in neuronal membranes.
- This prevents depolarization, inhibiting nerve impulse conduction, resulting in reversible anesthesia.
- Primarily affects sensory neurons, sparing motor function at lower concentrations.
- Metabolism occurs mainly in the liver, producing metabolites including orthotoluidine, which can induce methemoglobinemia in high doses.

Synthesis

Starting Materials: 2-Methylacetanilide and Propylamine

Steps:

1. Acylation: 2-Methylacetanilide is reacted with propylamine to form the amide linkage.
2. Purification: The base is purified and converted into Prilocaine hydrochloride for water-soluble injectable form.

Uses

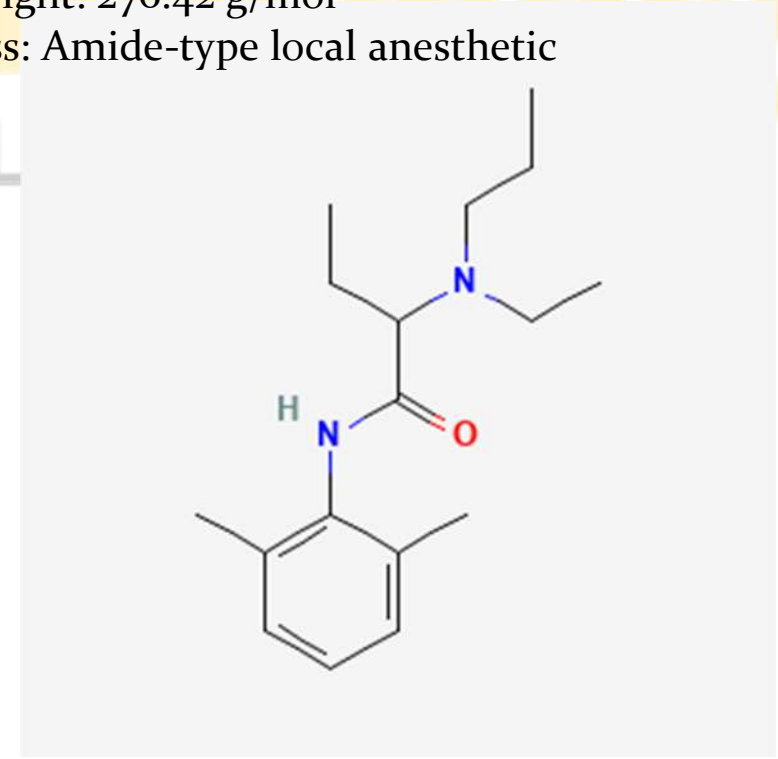
- Infiltration anesthesia for minor surgical procedures.
- Peripheral nerve block and epidural anesthesia.
- Topical anesthesia: Often combined with Lidocaine as EMLA cream for skin procedures.
- Dental anesthesia for patients sensitive to epinephrine.
- Can be combined with vasoconstrictors if longer duration is required.

Etidocaine

- Etidocaine is a long-acting amide-type local anesthetic used for infiltration, nerve block, and epidural anesthesia.
- It is chemically and pharmacologically related to Lidocaine, but provides a longer duration of anesthesia and more profound motor block.
- It is available as Etidocaine hydrochloride for injectable use.
- Etidocaine shows rapid onset of action (similar to lidocaine) but with extended duration, making it ideal for major surgical procedures requiring prolonged anesthesia.
- It is metabolized mainly in the liver and excreted in urine as metabolites.

Chemical Structure

- Chemical Name: N-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide
- IUPAC Name: N-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide
- Molecular Formula: C17H28N2O
- Molecular Weight: 276.42 g/mol
- Chemical Class: Amide-type local anesthetic
- Structural



Mechanism of Action

- Etidocaine blocks voltage-gated sodium (Na^+) channels in the neuronal membrane.
- This inhibits sodium ion influx, preventing depolarization and propagation of action potentials, resulting in reversible loss of sensation.
- It affects both sensory and motor fibers, often producing a more pronounced motor block than other local anesthetics.
- Onset is rapid, and duration is long (3–8 hours) due to high lipid solubility and protein binding.

Synthesis

Starting Materials: 2,6-Dimethylaniline and 2-butyryl chloride derivative

Steps:

1. Acylation: 2,6-Dimethylaniline is acylated with an appropriate chloroalkylbutanoyl chloride derivative to form an intermediate amide.
2. Amine substitution: The intermediate is reacted with ethylpropylamine to introduce the tertiary amino side chain.
3. Conversion to salt: The base is converted to Etidocaine hydrochloride to increase solubility and stability for injection.

Uses

- Infiltration anesthesia for surgical procedures.
- Peripheral nerve block anesthesia (brachial plexus, intercostal blocks).
- Epidural anesthesia for obstetric and postoperative pain management.
- Suitable for long-duration procedures where prolonged anesthesia is required.