Name of Unit	Antidiabetic Agents & Local Anaesthetics
Subject /Course	Medicinal Chemistry-II
Subject/Course ID	BP 501T
Class: B.Pharm. Semester	5th
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Learning Outcome of Module 05

LO	Learning Outcome	Course Outcome Code
LO1	To understand the classification, uses & mechanism of action of Antidiabetic Agents & Local Anaesthetics	BP501.1
LO2	To understand the chemical synthesis of selected drugs.	BP501.2
LO3	To understand the Structural Activity Relationship of different class of drugs.	BP501.3
LO4	To understand the insulin and its preparation	BP501.6

Content Table

Topic
Antidiabetic Agents • Insulin and its preparations. • Sulfonyl ureas: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride. Biguanides: • Metformin. • Thiazolidinediones: Pioglitazone, Rosiglitazone. Meglitinides: Repaglinide, Nateglinide. • Glucosidase inhibitors: Acrabose, Voglibose. **Local Anaesthetics** • SAR of local anaesthetics. • Benzoic Acid derivatives: Cocaine, Hexylcaine, Meprylcaine, Cyclomethycaine, Piperocaine. • Amino Benzoic acid derivatives: Benzocaine*, Butamben, Procaine*, Butacaine, Propoxycaine, • Tetracaine, Benoxinate. • Lidocaine/Anilide derivatives: Lignocaine, Mepivacaine, Prilocaine, Etidocaine. • Miscellaneous: Phenacaine, Diperodon and Dibucaine.*

ANTI –DIABETIC AGENTS

Insulin and its preparations.

- Sulfonyl ureas: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride.
- Biguanides: Metformin.
- Thiazolidinediones: Pioglitazone, Rosiglitazone.
- Meglitinides: Repaglinide, Nateglinide.
- Glucosidase inhibitors: Acrabose, Voglibose.

ANTIDIABETIC AGENTS

Agents which are used in the treatment of diabetes are called as antidiabetic agents. They used to lower the blood sugar level in patients suffering from hyperglycaemia. These are also called as anti-hyperglycaemic agents. Diabetes mellitus: It is a chronic metabolic disorder which is characterized by hyperglycaemia (increased blood sugar level). The common symptoms are polydipsia (excess thirst), polyphagia (excess hunger), and polyurea (excess urination). The classification of diabetes has been presented in Table-1

Table-1: Classification of diabetes mellitus

Type-1 (IDDM)	Type-2 (IDDM)
Insulin dependent diabetes mellitus	Non-insulin dependent diabetes mellitus
Juvenile onset diabetes mellitus	Adult onset diabetes mellitus
Occurs in children	Occurs in adults
Pancreatic β-cells are destroyed No insulin secretion	Less insulin secretion or insulin resistance (cells don't respond to insulin)
Treatment: insulin injection	Treatment: oral hypoglycemic agents

Insulin: It is a peptidic hormone secreted by β-cells of pancreas. It was discovered by Banting & Best in 1921. It regulates metabolism of carbohydrate, lipids and proteins. It decreases blood sugar level by decreasing gluconeogenesis, increasing glucose uptake and increasing glycogen synthesis. Insulin structure: Its full structure was elucidated by Sanger in 1956. It is a polypeptide hormone with a molecular weight of 6000 Da. Inside body, the inactive pro-insulin is converted into active insulin which is composed of 2 chains (A & B). A chain has 21 amino acid residues, whereas B

chain has 30 amino acid residues and both the chains are attached to each other by 2 disulphide (-S-S-) bonds. The structure of insulin has been depicted in

Figure-1. Sources of insulin: Bovine, Porcine, Recombinant human insulin.

Figure-1: Structure of insulin

Table-2: Classification of various insulin preparations

Short acting	Intermediate acting	Long acting
Regular	Isophane (NPH)	Protamine zinc
Lispro	Lente	Ultra Lente
Insulin zinc	Biphasic insulin aspart	Insulin glargine
Insulin aspart		Insulin detemir
		Insulin degludec

[A] RAPID-ACTING INSULIN

INSULIN LISPRO

Insulin lispro was the first available rapid-acting insulin analog. The natural amino acid sequence of the insulin B chain at positions 28 (proline) and 29 (lysine) is inverted to form lispro. This change results in an insulin molecule that more loosely self-associates into hexamers than does regular human insulin. The active monomeric form is more readily available, resulting in an onset of activity (15minutes), peak action (60-90 minutes), and duration (3-4 hours) that more closely simulates physiological insulin secretion relative to meals. Because it can be injected shortly before eating (0-15 minutes), lispro, and all rapid-acting insulins, provide patients greater flexibility in lifestyle

2. INSULIN ASPART

Insulin as part is a rapid-acting insulin analog that differs from human insulin by substitution of aspartic acid at chain B-28. Insulin as part is approved for use in pediatric patients, age 2 and older. It is pregnancy category B.

3. INSULIN GLULISINE

Insulin glulisine is a rapid-acting insulin analog that differs from human insulin by substitution of lysine for asparagines at position B-3 and glutamic acid for lysine at position B-23.

[B] SHORT-ACTING INSULIN

1. Regular insulin has an onset of action of 30 to 60 minutes, a peak effect at 2 to 4 hours, and duration of action of 5 to 7 hours.

(C) INTERMEDIATE-ACTING INSULIN

1. NPH - NEUTRAL PROTAMINE HAGEDORN OR ISOPHANE

NPH (neutral protamine Hagedorn or isophane) is intermediate-acting insulin. Its onset of action is approximately 2 hours (range, 1-3 hours), peak effects occur at approximately 6 to 14 hours, and the duration of action of NPH is approximately 16 to 24 hours

(D) LONG-ACTING INSULIN

INSULIN GLARGINE

1insulin Glargine is insulin analog in which asparagine in position A21 is substituted with glycine and two arginines are added to the C-terminus of the B chain. This change in the amino acid sequence causes a shift in the isoelectric point from pH 5.4 to 6.7, making it more soluble at an acidic pH. Insulin glargine (Lantus) is a long-acting insulin that serves to provide a basal level of insulin.

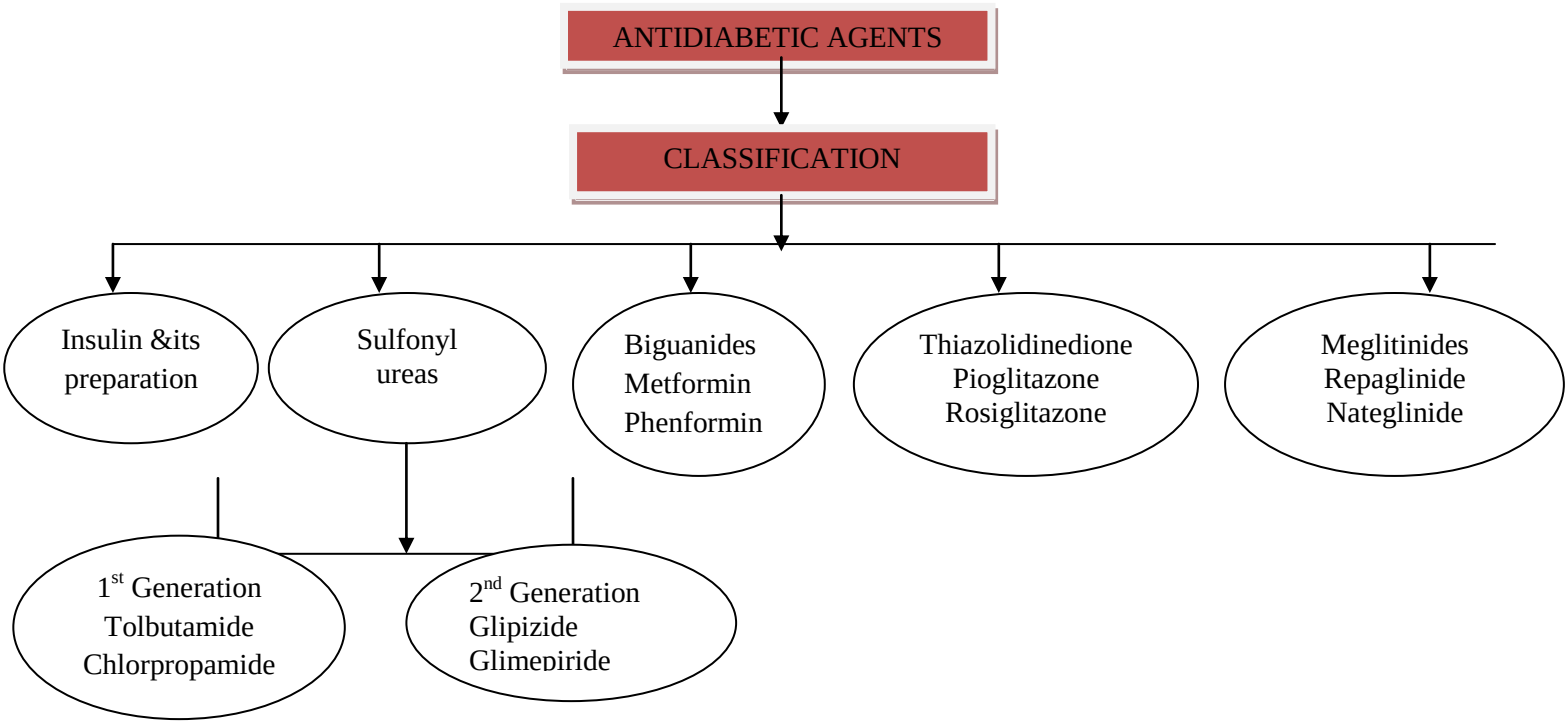
2. INSULIN DETEMIR

Insulin detemir a fatty acid moiety is added to the last amino acid on the end of the B chain. Insulin detemir is a neutral, soluble insulin preparation in which the B30 threonine has been removed and the B29 lysine residue has been covalently bound to a 14-carbon fatty acid. The result is insulin that is more slowly absorbed in the SC tissue because the fatty acid moiety binds to albumin, creating long acting insulin.

3. PREMIXED INSULIN

These premixed insulin's are useful for patients who have difficulty measuring and mixing insulin's and are dosed twice daily. These insulins are compatible when mixed together and retain their individual pharmacodynamics profiles.

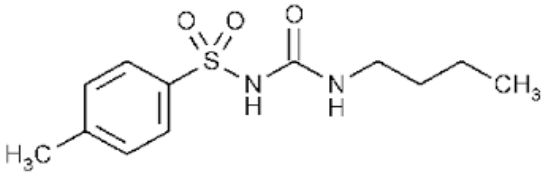
CLASSIFICATION



Oral hypoglycemic agents

a) Sulfonyl ureas: These are the first class of oral hypoglycaemic agents used for treatment of diabetes. They are also called as insulin secretagogues. They bind to the sulfonyl urea receptors present in pancreatic β-cells. It leads to closure of ATP-sensitive K+ channels and depolarises the β-cell membrane. Then it opens voltage gated Ca+2 channels and stimulates β-cells to secrete more insulin.

1. TOLBUTAMIDE



PROPERTIES:

✓ It is white or practically white, practically odourless, crystalline powder.lt is soluble in water; soluble in alcohol and in chloroform.

MECHANISM OF ACTION

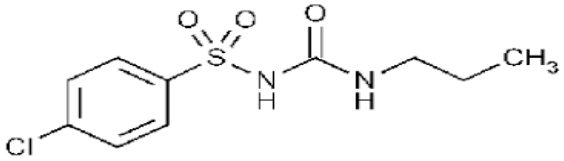
Tolbutamide cause depolarization and the opening of voltage gated calcium channels. The Increased intracellular concentration of calcium ultimately stimulates preformed insulin Secretion.

CLINICAL USES

- ✓ It is given orally in the treatment of type 2 diabetes mellitus and has duration of action of about 10 hours.
- ✓ It is (Tolbutamide sodium) sometimes been used in the diagnosis of insulinoma as well as other pancreatic disorders including diabetes mellitus.

2. CHLORPROPAMIDE

IUPAC NAME:-1-(4-Chlorobenzenesulphonyl)-3-propylurea



PROPERTIES.

- ✓ A white crystalline powder having a slight odour.
- ✓ Chlorpropamide soluble in alcohol and chloroform, insoluble in water.

MECHANISM OF ACTION:

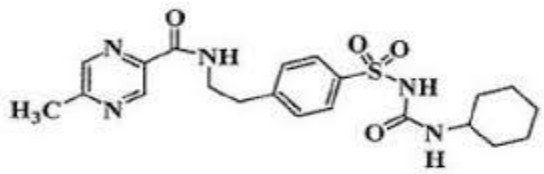
Chlorpropamide is first generation Insulin tropic agents act by closing membrane- bound ATP-sensitive potassium (KAT) channels on the p-cell, which stimulate release of insulin from pancreatic cells.

CLINICAL USES:

- ✓ Chlorpropamide is a sulfonylurea antidiabetic agent used in the treatment of type 2 diabetes mellitus.
- ✓ It has duration of action of at least 24 hours.

3. GLIPIZIDE

IUPAC NAME:-N-(4-(N-(cyclohexylcarbamoyl) sulfamoyl) phenethyl)-5-methylpyrazine-2-carboxamide



Glipizide

PROPERTIES

- ✓ A white or almost white crystalline powder.
- ✓ Practically insoluble in water and in alcohol very slightly soluble in acetone and in dichloromethane.
- ✓ It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

MECHANISM OF ACTION

Glipizide inhibit this potassium ion channel, so efflux of potassium ion blocked and lowering the membrane potential to cause depolarization. The voltage-dependent calcium channels then open, increasing intracellular calcium concentration. The increased intracellular concentration of calcium stimulates preformed insulin secretion.

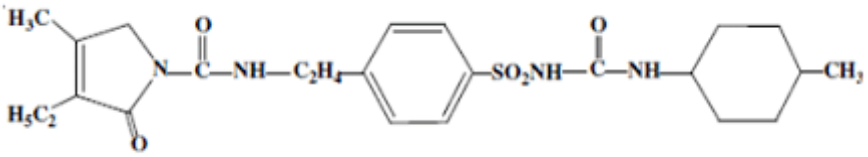
CLINICAL USES:

- ✓ Glipizide is a sulfonylurea's antidiabetic is given orally in the treatment of type 2 diabetes mellitus and duration of action of up to 24 hours.
- ✓ It is given with initial dose 2.5 to 5 mg daily given as a single dose about 30 minutes Before breakfast.

4. GLIMEPIRIDE

IUPAC NAME:

1 (p 12-(3 Ethyl-4-methyl-2-oxo 3 pyrroline-1-carboxamido) ethyllphenylsulfonyl)-3-(trans-4-methylcyclohexyl) urea



Glimepiride

PROPERTIES:

- ✓ Glimepiride is white powder Glimepiride is Practically insoluble in water, sparingly soluble in dichloromethane; soluble in dimethyl form amide (DMF), slightly soluble in methyl alcohol.
- ✓ Glimepiride is dissolves in dilute alkali hydroxides and in dilute acids. Store at a temperature not exceeding 25.°

MECHANISM OF ACTION:

Glimepiride stimulate the release of insulin from pancreatic ß cells and enhance B cell sensitivity to glucose Glimepiride inhibit this potassium ion channel, inhibit K+ ion efflux which cause depolarization so voltage dependent calcium channels open, increasing intracellular calcium concentration, stimulates preformed insulin secretion.

CLINICAL USES:

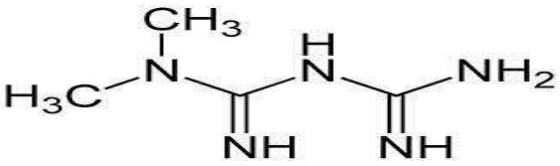
- ✓ Glimepiride is a sulfonylurea agent given orally for the treatment of type 2 diabetes mellitus. Initial doses of 1 to 2 mg daily may be increased if necessary to 4 mg daily for maintenance.
- ✓ Glimepiride is very effective sulfonylurea's antidiabetic agents. It has rapid onset of Effect.

b) Biguanides:

They reduce hepatic gluconeogenesis, decrease intestinal absorption of glucose, increase glucose uptake and utilization to decrease the blood sugar level. As they improve the insulin resistance, they are also known as insulin sensitizers.

5. METFORMIN

IUPAC NAME:-1,1-Dimethylbiguanide hydrochloride



PROPERTIES:

Metformin Hydrochloride is white crystalline powder.

It is freely soluble in water; slightly soluble in alcohol, practically insoluble in acetone and in dichloromethane.

MECHANISM OF ACTION

Metformin acted to activate 5-adenosine monophosphate-activated protein kinase (AMPK).

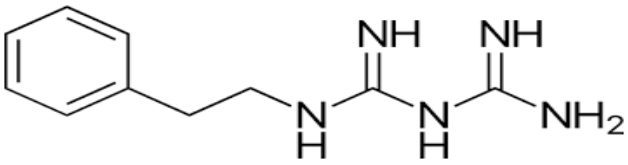
Through AMPK activation, acetyl-CoA carboxylase is inactivated, resulting in decreased lipid synthesis and increased fatty acid oxidation.

CLINICAL USES:

- ✓ It is first choice biguanide antidiabetic agent which given orally in the treatment of type 2 diabetes mellitus for overweight patients.

6. PHENFORMIN

IUPAC NAME: 1-Phenethylbiguanide hydrochloride



PROPERTIES:

- ✓ Phenformin hydrochloride is colorless, crystalline powder.
- ✓ Phenformin hydrochloride is odorless and bitter taste. It is soluble in ether and chloroform It should be stored in airtight containers.

MECHANISM OF ACTION

Phenformin Hydrochloride cause AMPK activation, so acetyl-CoA carboxylase is inactivated, resulting in decreased lipid synthesis and increased fatty acid oxidation (suppress the gluconeogenesis process and stimulate glycolysis which decreases glucose absorption from the intestine). Sterol regulatory element-binding protein-1, a biogenic transcription factor, is suppressed, leading to a reduction in hepatic lipid production.

CLINICAL USES:

- ✓ Phenformin Hydrochloride is biguanide antidiabetic agent which given orally in the treatment of type 2 diabetes mellitus.
- ✓ Phenformin Hydrochloride is used in the treatment of occlusive vascular disease.
- ✓ Phenformin Hydrochloride is used in the treatment of rheumatoid arthritis along with ethylestrenol.

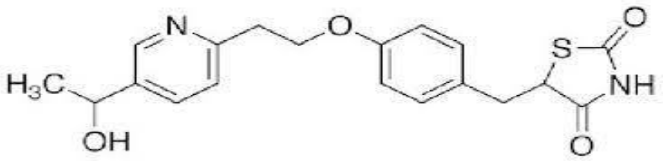
c) Thiazolidinediones:

They binds to and stimulates Peroxisome Proliferator Activated Receptor-γ (PPAR-γ), due to which they are also known as PPAR- γ agonists. They increase the expression of GLUT-1 &

GLUT-4 receptors on cell surface to increase glucose uptake. They reduce insulin resistance and hepatic gluconeogenesis. They decrease the post-prandial glucose level and also HbA1c level.

7. PIOGLITAZONE

IUPAC NAME: 5-{p-12-(5-Ethyl-2-pyridyl)-ethoxy] benzyl}-2,4-thiazolidinedione hydrochloride



PROPERTIES:

- ✓ Pioglitazone hydrochloride is an odorless white or off white crystalline powder. Soluble in water.

MECHANISM OF ACTION

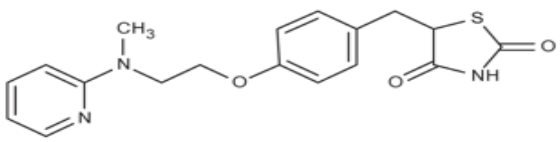
Pioglitazone is a thiazolidinedione oral antidiabetic drug bind to and activate a nuclear receptor (peroxisome proliferator-activated receptor-y[PPAR-yl), which is expressed in many insulin-sensitive tissues, including adipose, skeletal muscle, and liver tissue. PPAR-ϒ regulates transcription of genes that influence glucose and lipid metabolism so called as insulin sensitizers.

CLINICAL USES

- ✓ Pioglitazone is a thiazolidinedione oral antidiabetic used in the management of type 2 diabetes mellitus.
- ✓ It is given orally as monotherapy, particularly in patients who are overweight.
- ✓ Pioglitazone is oral antidiabetic used for whom metformin is contra-indicated or not tolerated.
- ✓ The usual dose is 15 or 30 mg once daily. This may be increased to a maximum of 45 mg once daily if necessary.
- ✓ Pioglitazone is oral antidiabetic may be taken with or without food.

8. ROSIGLITAZONE

IUPAC NAME: 5 (±)-5-1p-[2-(Methyl-2-pyridylamino)ethoxy]benzyl)-2,4-thiazolidinedione



PROPERTIES:

- ✓ Pioglitazone hydrochloride is an odorless white powder. Soluble in water. Protect from light. Store in airtight containers.

MECHANISM OF ACTION

Rosiglitazone is a thiazolidinedione oral antidiabetic drug bind to and activate a nuclear receptor (peroxisome proliferator-activated receptor-y [PPAR-yl), which is expressed in many insulin-sensitive tissues, including adipose, skeletal muscle, and liver tissue PPAR-y regulates transcription of genes that influence glucose and lipid metabolism so called as insulin sensitizers.

CLINICAL USES

- ✓ Rosiglitazone is a thiazolidinedione oral antidiabetic that improves insulin sensitivity and used in the management of type 2 diabetes mellitus.
- ✓ It is given orally as monotherapy, particularly in patients who are overweight.
- ✓ Rosiglitazone is also used for whom metformin is contraindicated..
- ✓ Rosiglitazone is may be taken with or without food.

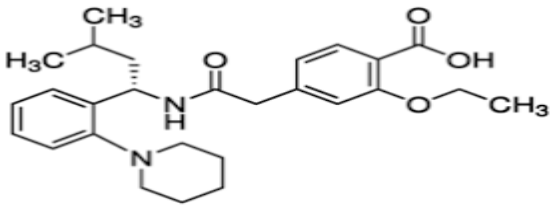
d) Meglitinides:

Same as that of sulfonylureas. They bind to the sulfonyl urea receptors present in pancreatic β-cells. It leads to closure of ATP-sensitive K+ channels and depolarises the β-cell membrane. Then it opens voltage gated Ca+2 channels and stimulates β-cells to secrete more insulin. These agents are also known as insulin secretagogues.

9. REPAGLINIDE

IUPAC NAME:

(S)-2-Ethoxy-4-{[1-(o-piperidinophenyl)-3-methylbutyl] carbamoylmethyl} benzoic acid.



PROPERTIES:

- ✓ A white or almost white powder. Practically insoluble in water, freely soluble in dichloromethane and in methyl alcohol. It exhibits polymorphism. Protect from light. Store in airtight containers.

MECHANISM OF ACTION

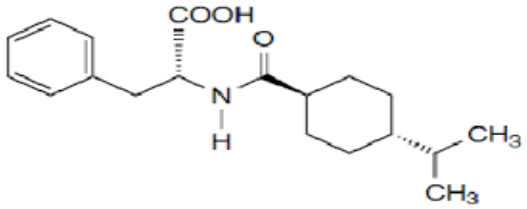
Repaglinide close the adenosine triphosphate (ATP)-sensitive potassium channels in the B cell, Which leads to cell membrane depolarization, an influx of calcium, and secretion of insulin?

CLINICAL USES

- ✓ Repaglinide is a meglitinide antidiabetic and used in the management of type diabetes mellitus.
- ✓ It is given orally for treatment of type 2 diabetes mellitus or with metformin/TZs inadequate their monotherapy.
- ✓ Repaglinide is given up to 30 minutes before meals.

10. NATEGLINIDE

IUPAC NAME: N-[(trans-4-Isopropylcyclohexyl) carbonyl]-D-phenylalanine



PROPERTIES:

- ✓ Nateglinide is white powder. Nateglinide is practically insoluble in water, freely soluble in organic solvent-DCM and methanol Protect from light. Store in airtight containers.

MECHANISM OF ACTION

Nateglinide causes cell membrane depolarization via inhibiting adenosine triphosphate (ATP)-sensitive potassium channels in the B cell, which leads to an influx of calcium and secretion of insulin. Unlike the sulfonylureas, Nateglinide has rapid onset and shorter duration of action

CLINICAL USES

- ✓ Nateglinide is a meglitinide antidiabetic and used in the management of type diabetes mellitus.
- ✓ Nateglinide is given with meals to enhance postprandial glucose utilization.

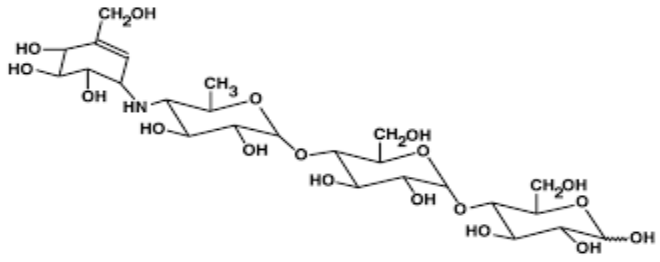
e) Glucosidase inhibitors:

They delays the absorption and metabolism of carbohydrates by inhibiting α-glucosidase enzyme found in the brush border epithelium of small intestine. A glucosidase helps in hydrolysing polysaccharides and oligosaccharides into monosaccharides and helps in their absorption. Flatulence and loose motion are the common side effects of this class of drugs. These drugs produce anti-hyperglycaemic effect but do not produce hypoglycaemia.

11. ACRABOSE

IUPAC NAME:

O-14-Amino-4,6-dideoxy-N-[(18,4R,58,6S)- 4,5,6-trihydroxy-3-hydroxymethylcyclohex-2-enyl)-a-D-glucopyranosyl)-(14)-O a-D-glucopyranosyl-(1-4)-a-D-glucopyranose



PROPERTIES:

- ✓ A white or yellowish, amorphous, hygroscopic powder. Acrabose is very soluble in water and methyl alcohol, practically insoluble in dichloromethane Store in airtight containers.

MECHANISM OF ACTION

Acarbose is glucosidase inhibitors; reversibly inhibit glucosidase present in the brush border of the mucosa of the small intestine. These enzymes break down complex polysaccharides and disaccharides into glucose and other absorbable monosaccharide's. This slows digestion and absorption of carbohydrates in the small intestine reduces the increase blood-glucose concentrations after a carbohydrate load.

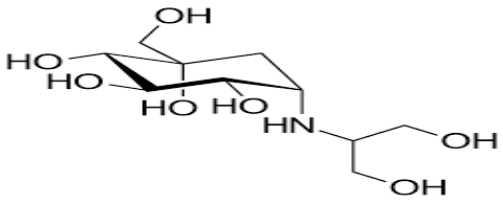
CLINICAL USES:

- ✓ Acarbose is given in the treatment of type 2 diabetes mellitus either alone or with a sulfonylurea, biguanide, or insuli
- ✓ Acarbose treatment may be started with a low oral dose of 25 or 50 mg daily to minimize gastrointestinal disturbance.
- ✓ Acarbose play significant role when it is used to supplement insulin therapy in type-I diabetes mellitus.

12. VOGILOBOSE

IUPAC NAME:

3,4-Dideoxy-4-{[2-hydroxy-1-(hydroxymethyl)ethyl)amino}-2-C (hydroxymethyl)- D-epi-inositol



PROPERTIES

- ✓ Voglibose is white. Hygroscopic in nature powder.
- ✓ Acrabose is very soluble in water, insoluble in dichloromethane. Voglibose should be protected from light and store in airtight containers.

MECHANISM OF ACTION

Voglibose act in similar way as Acarbose, a-glucosidase inhibitor, reversibly inhibit glucosidases. These enzymes break down complex polysaccharides and disaccharides into glucose and other absorbable monosaccharide's.

CLINICAL USES:

- ✓ Voglibose is an α-glucosidase inhibitor given in the treatment of type 2 diabetes mellitus either alone or with a sulfonylurea or insulin.
- ✓ Voglibose is used in the treatment of diabetes mellitus in oral doses of 200 to 300 micrograms three times daily before meals.
- ✓ Voglibose has been researched in the treatment of hepatic encephalopathy (liver dysfunction).

LOCAL ANAESTHETICS

LOCAL ANAESTHETICS: These are agents which upon topical application or local injection cause reversible loss of pain sensation in a restricted area of the body. They act by blocking both sensory and motor nerve conduction to produce temporary loss of sensation without loss of consciousness.

Mechanism of action- These drugs reversibly prevent the generation and propagation of impulses in all excitable membranes including nerve fibre by stabilising the membrane. Local anaesthetics block the nerve conduction by decreasing the entry of Na+ during action potential. They interact with a receptor situated within the voltage sensitive Na+ channel and raise the threshold of Na+ channel opening. Therefore, Na+ can't enter into the cell in response to an impulse which prevents depolarization. Thus, action potential is not generated. This action affecting the depolarization which

leads to failure of conduction of impulse without affecting the resting membrane potential (RMP) is known as membrane stabilizing effect.

Uses- These are used for

i) Temporary relief of localised pain

ii) Itching due to minor burns, insect bites & allergy

iii) Minor surgery and in dentistry

Methods or sites of administration:

1. Surface anaesthesia- Applied directly to the mucosal surfaces of nose, mouth, bronchial tree, oesophagus & genito-urinary tract

2. Infiltration anaesthesia- It is injected under the skin in the area of operation

3. Nerve block anaesthesia- It is injected around the nerve trunks or plexuses. Used for peripheral anaesthesia.

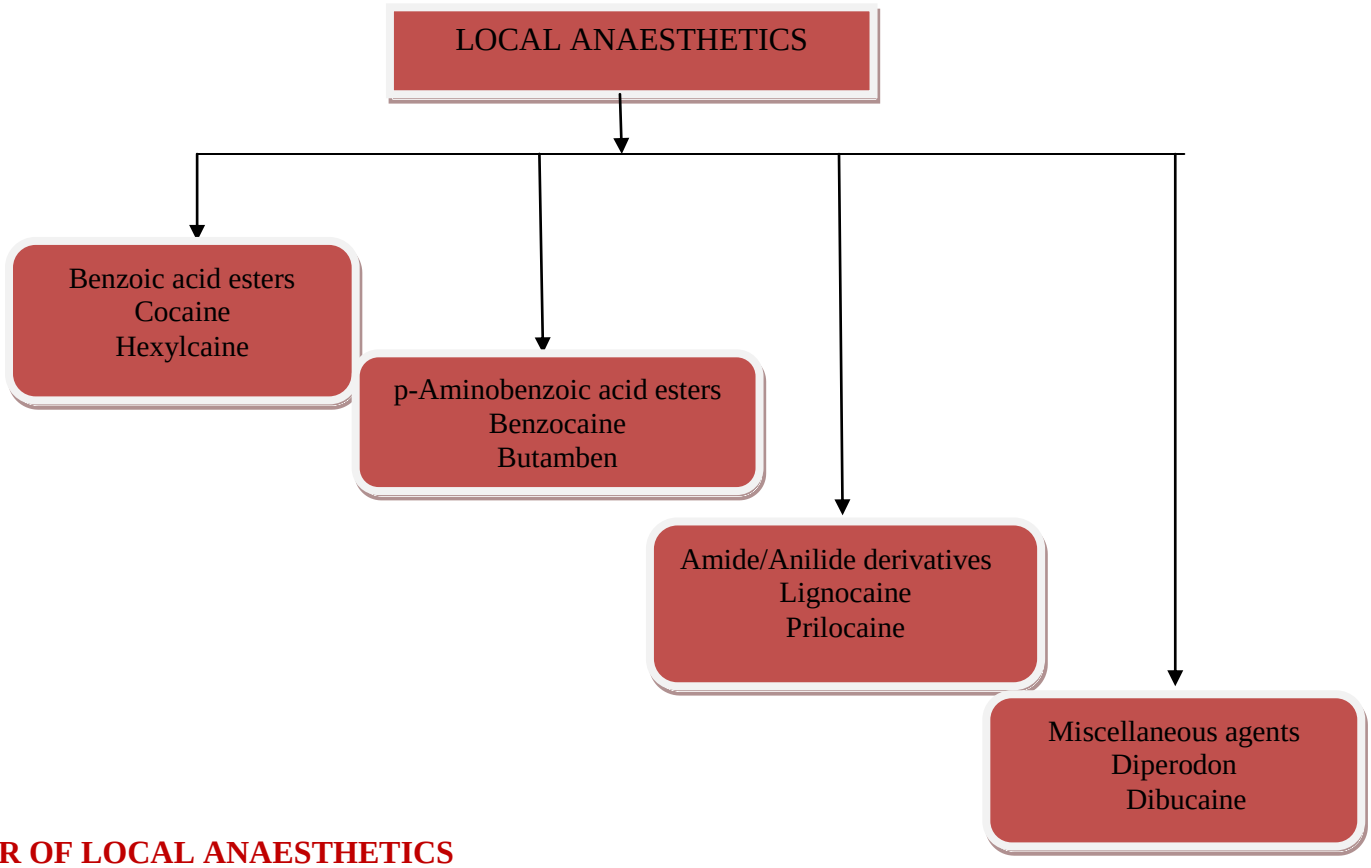
4**. Spinal anaesthesia-** It is injected into the sub-arachnoid space so that the local anaesthetic mixes with the spinal fluid. Lower abdomen and hind limbs are paralysed. Used for operation in lower limbs, pelvis, abdomen, prostatectomy, fracture setting, obstetric procedures, caesarean surgery etc.

5. Epidural anaesthesia- It is injected into a narrow spinal dural space containing semi liquid fat where the nerve roots pass.

Ideal characteristics of Local anaesthetics:

1. Non-irritating to the tissue.
2. Doesn't cause damage to the nerve structure.
3. Rapid onset & short duration of action.
4. Low systemic toxicity.
5. Must be effective whether injected or topically applied.

Classification of Local Anesthetics Drugs



SAR OF LOCAL ANAESTHETICS

1. Ester derivatives

i) Presence of electron withdrawing group at 2nd position of aryl moiety provides rapid onset of action. Eg- Chloroprocaine has more rapid onset of action because it is 4 times faster hydrolysed than procaine.

ii) Presence of non-polar groups on aromatic N atom imparts greater lipid solubility and good absorption. Eg- Tetracaine.

iii) Aryl group- It is attached directly to the carbonyl moiety.

- Conjugation of aromatic moiety with carbonyl group enhances local anesthetic activity.
- Substituent's like amino, alkoxy, alkyl amino groups increase the electron density on carbonyl oxygen and enhances the activity.
- Presence of alkyl group in between aryl and carbonyl results in inactive compounds.

iv) Bridge X- X may be C, O, N, or S Anaesthetic potency: S > O > C > N Amides (X=N) are resistant to metabolic hydrolysis. v) Amino alkyl group- Tertiary amines have longer

duration of action, but they are more irritating than primary amines. Alkyl groups also influence the lipid solubility.

Amide derivatives

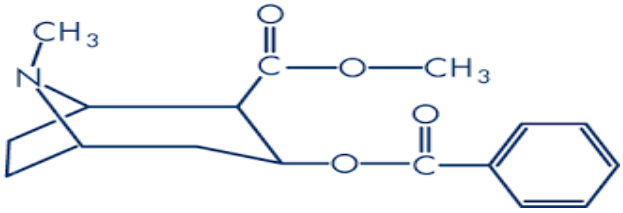
These are essentially anilide derivatives having the general structure:

Aryl group- Phenyl group is attached to the sp2 'C' atom through nitrogen bridge. Substitution of phenyl group with a methyl in 2 or 6 position enhances the activity. It provides steric hindrance to hydrolysis and also increases the coefficient of distribution.

The amide bond is more stable to hydrolysis than esters. Substituent X- X may be C (eg- isogramine), O (eg- lidocaine), N (eg- phenacaine) Amino alkyl group- It is the hydrophilic part which helps in salt formation. 1° and 2° amines are more irritating than 3° amines.

a) Benzoic acid esters

1. Cocaine



PROPERTIES

- ✓ Cocaine is natural ester of benzoic acid and nitrogen containing base and alkaloid obtained from the leaves of Erythroxylon coca.
- ✓ Coca leaves contain about 0.7 to 1.5%of total alkaloids, of which cocaine, cinnamyl-cocaine, and a-truxilline are the most important.
- ✓ Cocaine is colorless, odorless, bitter taste crystalline powder. Cocaine forms a hydrochloride salt due to the presence of a tertiary nitrogen atom and this salt form is freely soluble in water, Cocaine insoluble in water but soluble in alcohol, ether. Cocaine melting point is 98°C.

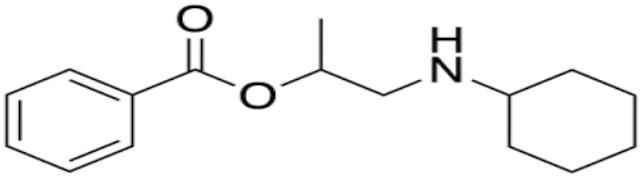
MECANISM OF ACTION

Cocaine is reversibly bind to Sodium ion channel and prevent sodium ion entry, which is (Sodium influx) necessary for the depolarization of nerve cell membranes. When the influx of sodium is blocked, an action potential will decrease and nerve signal conduction has been stopped. Cocaine is the only local anesthetic with vasoconstrictive properties.

CLINICAL USES

- ✓ Cocaine has vasoconstrictive properties, so it is uses to decrease bleeding and swelling from minor injuries (wound cleaning and stitches)
- ✓ It is uses to anesthetized the inner lining of the mouth during oral surgery (wound cleaning, biopsy, stitches etc).

2. Hexylcaine



PROPERTIES

- ✓ Hexylcaine is short-acting local anesthetic of Benzoic Acid derivatives.
- ✓ Hexylcaine is colorless, odorless, bitter taste crystalline powder.

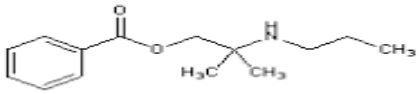
MECANISM OF ACTION

Hexylcaine acts mainly by prevent (Blocked) sodium ion entry through sodium channels voltage gated in the neuronal cell membrane. When the influx of sodium is blocked, an action potential will decrease and nerve signal conduction is thus stopped.

CLINICAL USES

- ✓ It is uses in oral surgery.
- ✓ It is used as a surface anesthetic or Useful for topical anaesthesia.
- ✓ Dose: Hexylcaine in concentrations of up to 10%-20% have been used for surface anaesthesia of the mouth and throat.

3. MEPRYLCAINE



PROPERTIES

- ✓ A white or almost while crystalline powder or colorless crystals.
- ✓ Very soluble in water; soluble in alcohol. A 2% solution in water has a pH of 5.0 to 6.5. Protect from light.

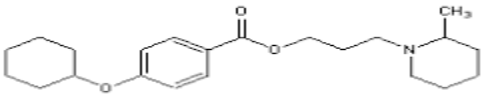
MECANISM OF ACTION

Meprylcaine acts on sodium channels and inhibit influx of sodium ion which decreases signal propagation in to neuronal cell membrane so depolarization has been prevented.

CLINICAL USES

- ✓ Meprylcaine used in dentistry (surface or infiltration anesthesia).
- ✓ Meprylcaine used in acute pain due to trauma, surgery, infection etc.
- ✓ Meprylcaine is useful for topical anaesthesia.
- ✓

4. CYCLOMETHYLCAINE



PROPERTIES

- ✓ Cyclomethylaine is white odourless crystalline, odourless powder, mildly Soluable in water and It is soluable in organic solvents and alcohol and organic acid.

MECANISM OF ACTION

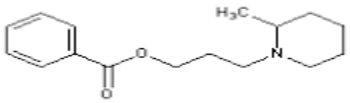
Cyclomethylaine is an benzoic acid-type local anesthetic agent. Cyclomethylaine block sodium ion channels entry and depolarization inhibited.

CLINICAL USES

Cyclomethylaine used topical anesthetic in minor surgeries.

Cyclomethylaine used in veterinary practices as surface anesthetic.

5. PIPEROCAINE



PROPERTIES:

- ✓ A white odourless crystalline solid. It discolors on prolonged exposure to light and air.
- ✓ Soluble 1 in 2 of water, 1 in 10 of alcohol, and 1 in 80 of ether; practically insoluble in acetone and in chloroform. Protect from light.

MECANISM OF ACTION

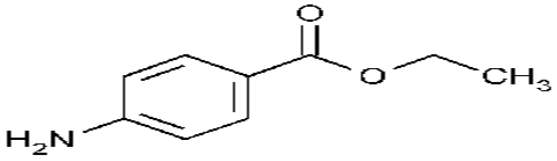
Propipocaine block sodium ion channels entry and prevent depolarization inside cell membrane and nerve signal conduction has been stopped and hence anesthetic action achieved.

CLINICAL USES

- ✓ Propipocaine is used for surface anaesthesia in ophthalmology in a concentration of 0.5%
- ✓ Propipocaine is in the management of mouth ulceration as surface anesthetic agent
- ✓ Drug is also used in dentistry in small dose regimen.

b) Amino Benzoic acid derivatives:

6. BENZOCAINE



PROPERTIES:

- ✓ Benzocaine is para-aminobenzoic acid ester, is a local anaesthetic agent.
- ✓ It is white crystals or a white odourless crystalline powder having M.p. 88° to 92^{0}C.
- ✓ It is Soluble 1 in 2500 of water, 1 in 5 of alcohol and 1 in 30 to 50 of almond oil or olive oil; it is completely dissolves in dilute acids.

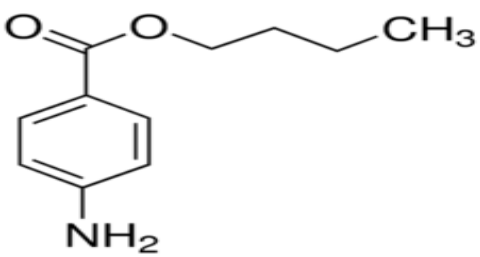
MECANISM OF ACTION

Benzocaine reversibly bind to Na+ ion channel and inhibit entry of sodium ion, which decreases its permeability i.e depolarisazation stopped.

CLINICAL USES

- ✓ It is used for surface anaesthesia.
- ✓ It is used for temporary local relief of pain associated with dental conditions.
- ✓ Lozenges containing benzocaine in usual doses of up to 10 mg are used for the relief of sore throat.
- ✓ Benzocaine is used in ear drops, creams, ointments, lotions, solutions, sprays, gels, and suppositories in concentrations up to 20% for topical analgesia and Anaesthesia.

7. BUTAMBEN



PROPERTIES

It is white odourless crystalline powder. Butamben is mildly soluble in water. It is soluble in organic solvents and alcohol and organic acid.

MECANISM OF ACTION

Butamben is an inhibitor of the sodium channels and delayed rectifier of potassium currents due to Butamben reduced the electrical excitability.

CLINICAL USES:-

- ✓ Butamben is used in treatment of chronic pain.
- ✓ It is also used as surface anesthetic for skin mucous membrane.

8. PROCAINE

PROPERTIES

- ✓ Procaine is odorless, while crystals or white, crystalline powder.
- ✓ Soluble 1 in 1 of water and 1 in 15 of alcohol; slightly soluble in chloroform; practically insoluble in ether. It should be protected from light. Procaine hydrochloride has been reported to be incompatible with barbiturates, magnesium sulfate.

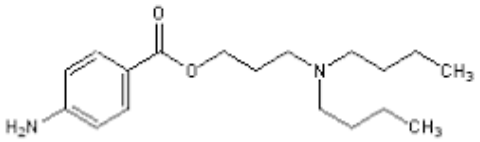
MECANISM OF ACTION

Procaine inhibit sodium influx through voltage gated sodium channels in the neuronal cell membrane which causes slower the signal conduction in the neuronal cell, due to this Depolarization stopped and anesthetic action achieved.

CLINICAL USES:-

- ✓ It is mainly used for infiltration anaesthesia

9. BUTACAINE



PROPERTIES

- ✓ It is a white crystalline powder of amino benzoic acid ester.
- ✓ It is insoluble in water, soluble in organic acids. It should be protected from light.

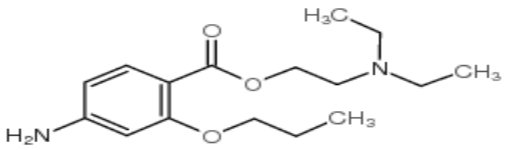
MECANISM OF ACTION

Butacaine sulphate inhibits irreversibly sodium influx and decrease cellular excitability and conductibility. So depolarization stopped and pharmacological response achieved.

CLINICAL USES

- ✓ Butacaine sulphate is used for surface anaesthesia.
- ✓ It has been used topically, as the sulfate, in solutions for dental pain and in ear and nasal drops.

10. PROPOXYCAINE



PROPERTIES:

- ✓ Propoxycaine is white, odorless, bitter taste crystalline powder, insoluble in water but soluble in organic solvent.

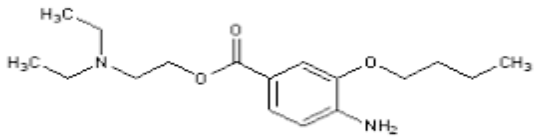
MECANISM OF ACTION

Propoxycaine is ester of para-aminobenzoic acid having anesthetic activity .Propoxycaine binds to and blocks voltage-gated sodium channels and inhibiting the Na+ ion influx which is essential for the conduction of nerve impulses. So it causes loss of sensation and provides anaesthetic effect.

CLINICAL USES

- ✓ Potent local anesthetic
- ✓ Profound anesthesia of long duration when injected close to nerve sheath.

11. BENOXINATE



PROPERTIES

- ✓ Benoxinate is white, odorless, bitter taste crystalline powder, insoluble in water but soluble in organic solvent.

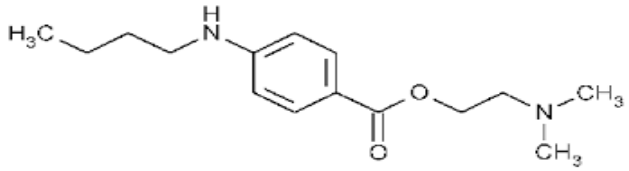
MECANISM OF ACTION

Benoxinate inhibit sodium influx through voltage gated sodium channels in the neuronal cell membrane which causes slower the signal conduction in the neuronal cell, due to this depolarization stopped and anesthetic action achieved.

CLINICAL USES:

- ✓ It is used as surface anesthetic agent.
- ✓ It is used in ophthalmology to anesthetized surface of the eye and minor operations
- ✓ It is used in bronchoscopy to anesthetized surface of mucous membranes of bronchi and mucous membranes of the nostrils and pharynx.

12. TETRACAINE



PROPERTIES:

- ✓ It is white, odorless powder soluble in water. It is rapidly decompose by alkali. The pH of Tetracaine is 5.9.

MECANISM OF ACTION

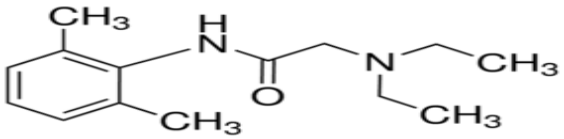
Tetracaine is an ester-type local anesthetic drug. Tetracaine block entry of Sodium ion which causes conduction of neuronal impulses), depolarization stopped and anaesthetic effect arises.

CLINICAL USES:

- ✓ It is used for spinal anesthesia.
- ✓ It is potent topical anesthetic.

c) ANILIDE DERIVATIVES

13. LIGNOCAINE



PROPERTIES:

- ✓ A white to slightly yellow crystalline powder with a characteristic odour. Mp. 66° to 69º

- ✓ Practically insoluble in water, very soluble in alcohol and in chloroform; freely soluble in ether and in benzene; dissolves in oils.

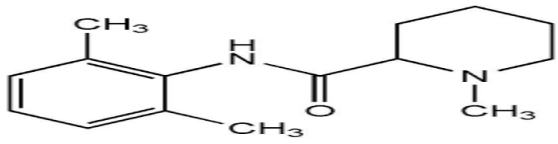
MECANISM OF ACTION

It has a rapid onset of action Lidocaine blocked the sodium (Na+) channels in the neuronal cell membrane so signal transduction stopped and depolarization of neuronal membrane prevented, It has a rapid onset of action.

CLINICAL USES:

- ✓ It is used for surface anaesthesia
- ✓ A local anesthetic and cardiac depressant used as an antiarrhythmia agent.
- ✓ It is used for Sympathetic nerve block & It is used for Cervical block
- ✓ It is used for lumbar block.
- ✓ It is used for Eye drops for lonometry.

14. MEPIVACAINE



PROPERTIES:-

- ✓ It is a white crystalline powder. It is freely soluble in water and alcohol but very slightly soluble in methylene chloride. M.P - 150.5 °C, pKa – 77.

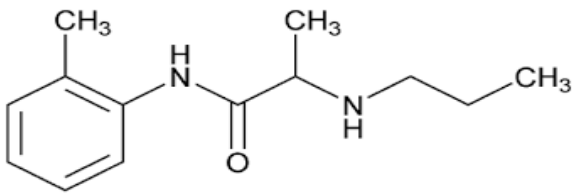
MECANISM OF ACTION

It blocks the nerve impulse generation and conduction by blocking Na+ ion influx and by reducing the rate of rise of the action potential. It arise anesthetic effects.

CLINICAL USES:

- ✓ It is used as a local anesthetic for an epidural or spinal block.
- ✓ It is also used as an anesthetic for dental procedures.

15. PRILOCAINE



PROPERTIES:-

- ✓ It is a white crystalline powder or colorless, odorless compound, initially acidic to bitter taste, slightly soluble in acetone, practically insoluble in ether, freely soluble in water and alcohol.
- ✓ Melting point is 37-38 °C.

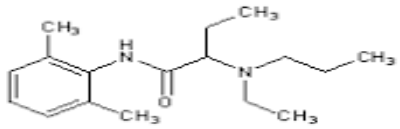
MECANISM OF ACTION

Prilocaine acts as sodium channels blocker on the neuronal cell membrane, Its causes anesthetic effects and prevent seizure propagation.

CLINICAL USES:-

- ✓ It is used for intravenous regional anesthesia.
- ✓ Prilocaine used topical administration to decrease painful needle sticks in children.
- ✓ It possesses less vaso-dilator activity than lidocaine.

16. ETIDOCAINE



PROPERTIES:-

- ✓ It is white crystalline powder, soluble in water, freely soluble in alcohol.

MECANISM OF ACTION

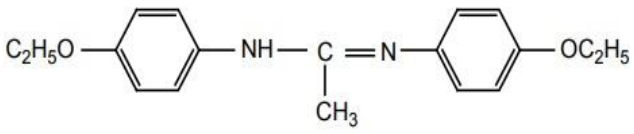
It is completely reversible act on influx Na+ ion and blocked depolarization. In contact with a nerve trunk, these anesthetics can cause both sensory and motor paralysis in the innervated area.

CLINICAL USES:-

- ✓ It is used for epidural anesthesia.
- ✓ It is used for topical anesthesia
- ✓ It is used for peripheral nerve or plexus block.

d) MISCELLANEOUS DRUGS

17. PHENACAINE



N, N'-bis(4-Ethoxyphenyl ethanindamide)

PROPERTIES:-

- ✓ A white or almost white powder. Practically insoluble in water; freely soluble in methyl alcohol, very soluble in chloroform; soluble in ethyl acetate.

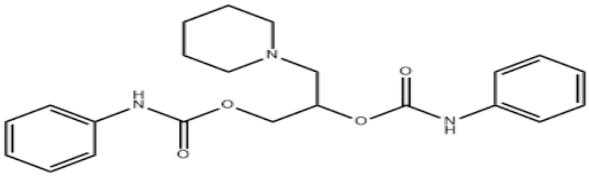
MECANISM OF ACTION

Phenacaine act as nerve impulse conduction blocker via binding to sodium ion channels and stabilizes the neuronal membrane which decreases permeability to sodium ions to the neuronal membrane.

CLINICAL USES:

- ✓ Phenacaine used as 1% solution for local anaesthetic effects in eye operation Procedures.
- ✓ Phenacaine used as used treatment of skin operative procedures.
- ✓ Phenacaine used to cause topically numbness.
- ✓ Phenacaine used in dental and other minor surgical procedures.

18. DIPERODON



PROPERTIES:-

- ✓ Diperodon is a white-off white crystalline powder and odorless compound.
- ✓ It is acidic to bitter taste, slightly soluble in acetone, practically insoluble in ether, freely soluble in water and alcohol.

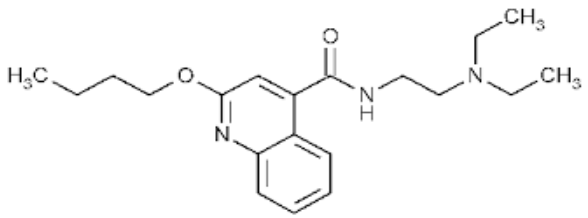
MECANISM OF ACTION

Diperodon prevents entry of sodium ion into sodium channels and blocked depolarization or conductance in neuronal cell through membrane membrane.

CLINICAL USES:-

- ✓ Diperodon hydrochloride is used to nerve block.
- ✓ Diperodon hydrochloride is used to topical application: To skin for analgesia or Surgery of skin.
- ✓ Diperodon hydrochloride is used in Dentistry practices.
- ✓ Diperodon hydrochloride is used treatment of foot, ankle disorders.

19. DIBUCAINE



PROPERTIES:-

- ✓ Dibucaine is Colorless or white to off white crystals or white to off-white, crystalline powder.
- ✓ It is odorless, hygroscopic, and darkens on exposure to light (Protect from light). Freely soluble in water, in alcohol, in acetone, and in chloroform.
- ✓ Its solutions have a pH of about 5.5 Store in airtight containers. It is one of the most potent and toxic of the long-acting local anaesthetics and its parenteral use was restricted to spinal anaesthesia.
- ✓ Melting point 99-101 °C.

MECANISM OF ACTION

Dibucaine Hydrochloride acts as sodium ion blocker on initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability the neuronal cell membrane which causes anesthetic effects.

CLINICAL USES:

- ✓ Dibucaine is used as surface anaesthetics.
- ✓ Dibucaine is used in hemorrhoid.
- ✓ Dibucaine is used to numb pain and relieve itching
- ✓ Dibucaine is used in purities of skin.
- ✓ Dibucaine is used to reduce swelling.

VERY SHORT ANSWER TYPE QUESTIONS

1) Define antidiabetic agents.
2) What is insulin?
3) What are oral hypoglycaemic agents?
4) Give the structure of tolbutamide.
5) What are biguanides?
6) What are thiazolidinediones?

7) Give the structure of rosiglitazone.

8) Define local anaesthetics.

9) What are benzoic acid derivative.

10) Give the structure of cocaine.

11) What is the mechanism of action of butaben?

12) Give the structure of propoxycaine

13) Write the uses of benoxinate

14) Write the mechanism of action of lignocaine

15) What are the uses of diperodon?

SHORT ANSWER TYPE QUESTIONS

1) Give the synthesis of insulin.

2) Write some common insulin preparation.

3) Give the classification of oral hypoglycaemic agents.

4) Write the SAR of sulphonylureas.

5) What is the mechanism of action and uses of thiazolidinediones?

6) Give the structure and mechanism of action of acarbose.

7) Classify local anaesthetics.

8) Give the mechanism of action of local anaesthetics.

9) Write short note on benzoic acid derivative.

LONG ANSWER TYPE QUESTIONS

1) Write a note on insulin in detail.

2) What are oral hypoglycaemic agents and give its classification and explain sulphonylureas.

3) Write detailed notes on biguanides, meglitinides, and □-glucosidase inhibitors.

4) Give the SAR and write about recent developments of local anaesthetics.

5) Write a detailed note on benzoic acid derivatives.

6) give the mechanism of action structure and uses of following drugs:

i) Benzocaine iv) Tetracaine vii) Phenacaine

ii) Butamben v) Lignocaine viii) Dibucaine

iii) Procaine vi) Prilocaine