Read To Lead

Medicinal Chemistry-II

AS PER (PCI) SYLLABUS
B.Pharm
5th Semester

Dr. Selvakumar. S
Dr. Sachin J. Dighade
Dr. R. Srinivasan

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MEDICINAL CHEMISTRY-II

B.Pharm, Semester-V

According to the syllabus based on **'Pharmacy Council of India'**

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to
my Beloved ***Students****"*

-Dr.Selvakumar.S

"Dedicated
to
my Beloved ***Parents****"*

-Dr. Sachin J. Dighade

"Dedicated
to
my ***Family, Teachers,***
Colleagues *&* *Beloved* ***Students****"*

-Dr. R. Srinivasan

Preface

It gives us immense pleasure to place before the **B.Pharm Fifth Semester** pharmacy students the book on **"Medicinal Chemistry-II"**.

This book has been written strictly in accordance with the current syllabus prescribed by Pharmacy Council of India, for B.Pharm students. Keeping in view the requirements of students and teachers, this book has been written to cover all the topics in an easy -to-comprehend manner within desired limits of the prescribed syllabus, and it provides the students fundamentals of differ ent categories of drugs like anti -anginal, anti -hypertensives, anti -hyperlipidemics, anticoagulants, antineoplastic agents, anti -diabetics, local anaesthetics, gastric PPIs, etc. which are required by them during their pharmaceutical career.

All efforts have been made to keep the text error -free and to present the subject in a student friendly and easy to understand. However, any suggestions and constructive comments would be highly appreciated and incorporated in the future edition.

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Acknowledgement

I am taking deep pleasure to put on my heartiest gratitude to **Dr. S. Ravichandran,** M.Pharmacy., Ph.D, Principal, PSV College of Pharmacy, Dharmapuri and **Dr. K.Prabhu** , Principal, Cherraan's C ollege of Pharmacy, Coimbatore. M.Pharmacy, Ph .D for their encouragement and suggestions by them during all stages of this entire text book work.

I express my deep sense of gratitude and indebtedness to my friends **Dr. P. Kumarnallasivan**, M.Pharmacy, Ph .D., **Dr. Kathiravan** M.Pharmacy, Ph.D and **Dr. A. Arunachalam,** M.Pharmacy, Ph .D for their affection, active cooperation and moral support.

Families are always listed last by some strange custom even though they are the most i mportant people to acknowledge. I would like to extend my heart -felt gratitude to my parents, **Mr. K. Sivananacha Perumal** and **Mrs. N. S. Roja**.

-Dr. Selvakumar. S

First and foremost, I would like to thank **Almighty God**. In the process of putting this book together in front of you, I realized how precious gift **God** has given to me by giving me the capability and the power to believe in my passion and pursue my dreams. "I could never have done this without the faith, which I have in you."

I would also like to thank the **Management** of VYWS, Amravati's Institute of Pharmacy And Research Amravati, for their constant motivation and support.

Finally, I thank **Thakur Publication Pvt. Ltd** ., especially, **Ms. Tuhina Banerjee** (Copy Editor) and **Mr. Sharad Kushwaha** (Marketing Coordinator), for providing me an opportunity to be a part of this book.

-Dr. Sachin J. Dighade

I owe great thanks to Great People, who are working and contributing their findings in the pharmacy profession

I extend my heartful thanks to **Managing Director** of **Thakur Publication Pvt Ltd**., **Dr. Saroj Kumar** (Director), **Ms. Tuhina Banerjee** (Copy Editor) & **Mr. Sharad Kushwaha** (Marketing Coordinator), for giving this wonderful opportunity.

-Dr. R. Srinivasan

Syllabus

Study of the development of the following classes of drugs, Classification, mechanism of action, uses of drugs mentioned in the course, Structure activity relationship of selective class of drugs as specified in the course and synthesis of drugs superscripted (*)

Module 01 **10 Hours**

Antihistaminic Agents

- Histamine, receptors and their distribution in the human body.
- **H_1–Antagonists:** Diphenhydramine hydrochloride*, Dimenhydrinate, Doxylaminescuccinate, Clemastine fumarate, Diphenylphyraline hydroc hloride, Tripelenamine hydrochloride, Chlorcyclizine hydrochloride, Meclizine hydrochloride, Buclizine hydrochloride, Chlorpheniramine maleate, Triprolidine hydrochloride*, Phenidamine tartarate, Promethazine hydrochloride*, Trimeprazine tartrate, Cyprohep tadine hydrochloride, Azatidine maleate, Astemizole, Loratadine, Cetirizine, Levocetrazine Cromolyn sodium.
- H_2-Antagonists: Cimetidine*, Famotidine, Ranitidin.

Gastric Proton Pump Inhibitors

- Omeprazole, Lansoprazole, Rabeprazole, Pantoprazole.

Anti-Neoplastic Agents

- Alkylating Agents: Meclorethamine*, Cyclophosphamide, Melphalan, Chlorambucil, Busulfan, Thiotepa.
- Antimetabolites: Mercaptopurine*, Thioguanine, Fluorouracil, Floxuridine, Cytarabine, Methotrexate*, Azathioprine.
- Antibiotics: Dactinomycin, Daunorubicin, Doxorubicin, Bleomycin.
- Plant products: Etoposide, Vinblastin sulphate, Vincristin sulphate
- Miscellaneous: Cisplatin, Mitotane.

Module 02 **10Hours**

Anti-Anginal

- Vasodilators: Amyl nitrite, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbide dinitrite*, Dipyridamole.
- Calcium Channel Blockers :Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine.

Diuretics

- Carbonic anhydrase inhibitors: Acetazolamide*, Methazolamide, Dichlorphenamide.
- Thiazides: Chlorthiazide*, Hydrochlorothiazide, Hydroflumethiazide, Cyclothiazide.
- Loop diuretics: Furosemide*, Bumetanide, Ethacrynic acid.
- Potassium sparing Diuretics: Spironolactone, Triamterene, Amiloride.
- Osmotic Diuretics: Mannitol.

Anti-Hypertensive Agents

- Timolol, Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride, Methyldopate hydrochloride,* Clonidine hydrochloride, Guanethidine monosulphate, Guanabenz acetate, Sodium nitroprusside, Diazoxide, Minoxidil, Reserpine, Hydralazine hydrochloride.

Module 03 **10 Hours**

Anti-Arrhythmic Drugs

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

Anti-Hyperlipidemic Agents

- Clofibrate, Lovastatin, Cholesteramine and Cholestipol.

Coagulant and Anticoagulants

- Menadione, Acetomenadione, Warfarin*, Anisindione, clopidogrel.

Drugs used in Congestive Heart Failure

- Digoxin, Digitoxin, Nesiritide, Bosentan, Tezosentan.

Module 04 **08 Hours**

Drugs acting on Endocrine System

- Nomenclature, Stereochemistry and metabolism of steroids. Sex Hormones
- Testosterone, Nandralone, Progestrones, Oestriol, Oestradiol, Oestrione, Diethyl stilbestrol.

Drugs for Erectile Dysfunction

- Sildenafil, Tadalafil.

Oral Contraceptives

- Mifepristone, Norgestril, Levonorgestrol

Corticosteroids

- Cortisone, Hydrocortisone, Prednisolone, Betamethasone, Dexamethasone

Thyroid and Anti-Thyroid Drugs

- L-Thyroxine, L-Thyronine, Propylthiouracil, Methimazole.

Module 05 **07 Hours**

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, Dibucaine.*

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CHAPTER 1

Antihistaminic Agents

1.1. ANTIHISTAMINIC AGENTS

1.1.1. Introduction

Histamine, a biologically active substance potentiates the inflammatory and immune responses of the body. It also regulates the physiological functions in the gut, and behaves as neurotransmitter. Anti-histaminic agents (or **histamine antagonists**) are the drugs that antagonise the action of histamine. On the basis of the type of H receptor targeted, antihistamines are divided into:

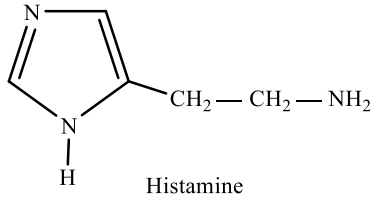
1) **H_1-Antihistamines:** They are used for treating allergic reactions and disorders mediated by mast cells. H_1-antihistamines are sub-divided into two generations. The **first generation H_1-antihistamines** have a central effect so are used as sedatives. The **second generation H_1-antihistamines** have low central effects so are used as anti-allergenic drugs.

2) **H_2-Antihistamines:** They can reduce the production of stomach acid by reversibly blocking the H_2-histamine receptors found in the parietal cells of gastric mucosa; thus, they are used in gastric reflux diseases.

The pregnant women and children should avoid using most H_1- and H_2-antihistamines. First-generation H_1-antihistamines are contraindicated in patients having angle-closure glaucoma and pyloric stenosis.

1.1.2. Histamine

Histamines are nitrogen containing organic compounds belonging to the group of amines. Histamines are produced in almost all the cells (present in an animal) during a local immune response. They regulate various physiological functions of the gut. In addition, histamines have also be en known to play a role in neurotransmission. Release of histamines is the initiating factor of any inflammatory response.



Histamine

Histamines are synthesised and released by basophils and mast cells (found in the nearby connective tissues) on stimulation (as a part of an immune response against foreign pathogens). They cause increased vascular (capillary) permeability for WBCs and other proteins to facilitate adequate invasion of foreign bodies within the tissues.

1.1.3. Histamine Receptors and their Distribution in the Human Body

The biological effects produced by histamine are mediated through histaminergic receptors (H_1, H_2 and H_3 types). Histamine was identified and anti-histamines (H_1 blockers) were synthesised in the beginning of this century. Since then it was known that these anti-histamines cannot block all the histamine actions.

H_4 receptors are linked to the pathology of allergy and asthma; and regulate the changes in cellular shape, chemotaxis, and up-regulation of adhesion molecules (CD11b/CD18 and ICAM, P-selectin). H_4-receptors present on haematopoietic cells (neutrophils and eosinophils) have been recognised lately.

Table 1.1: Histamine Receptor Sub-Types, their Location, Mechanisms of Action, and Effects

Types of Receptor	Location	Mechanism of Action	Effects
H_1	Throughout the body, especially in smooth muscles, on vascular endothelial cells, in heart, and CNS.	G-protein linked to intercellular G_q that activates phospholipase C.	Increased vascular permeability induced by histamine at inflammation sites; bronchoconstriction; increased gut motility; triple response and oedema formation; stimulation of sensory nerve endings.
H_2	Gastric parietal cells, vascular smooth muscles, neutrophils, CNS, heart, and uterus.	G-protein coupled; linked to intercellular G_s that stimulates adenylcyclase and increases cAMP.	Increase in gastric acid secretion; vasodilatation.
H_3	Mostly in the CNS with high levels in thalamus, caudate nucleus and cortex; also in intestine, testis and prostate to a small extent.	G-protein coupled; linked to intercellular G_i that inhibits adenylcyclase and decreases cAMP.	Inhibition of synthesis and release of histamine acting on the presynaptic sites in CNS; modulates the release of 5-HT, dopamine, NAD, ACh and GABA in CNS by acting as heteroreceptor.
H_4	Expressed in various cells of immune system and mast cells and mediate chemotaxis of eosinophils and mast cells.	G-protein coupled; decrease in cAMP.	Immunomodulation.

1.1.4. Classification of Antihistaminic Agents

Following are the **three types** of histamine receptor antagonists:

1) **H_1-Antagonists:** These are classical antihistamines blocking the physiological effects of histamine and used in allergic disorders.

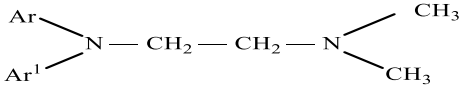
2) **H_2-Antagonists:** Cimetidine, Ranitidine, and Famotidine are H_2-antagonists reducing gastric HCl secretion and used in peptic ulcer diseases.

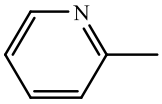
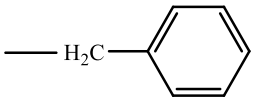
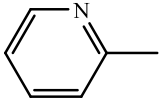
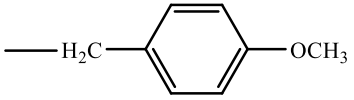
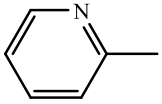
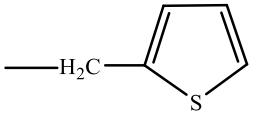
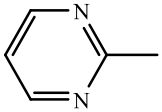
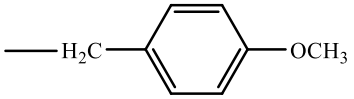
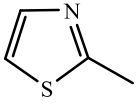
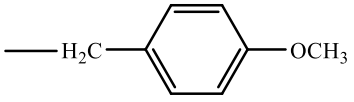
3) **H_3-Antagonists:** Thioperamide is an H_3-antagonist regulating histamine release from histaminergic neurons of CNS by presynaptic auto-regulatory mechanism. It is not recommended to be used therapeutically.

Given below is the classification of antihistaminic agents:

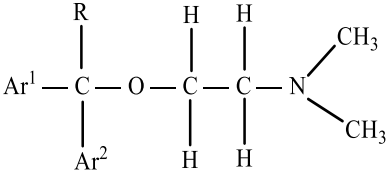
1) **H_1-Receptor Antagonists:** They are grouped into:

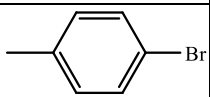
i) **Ethylenediamines**

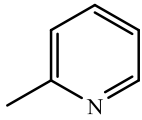
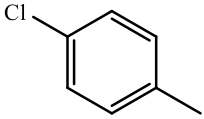
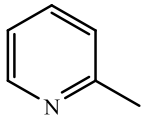
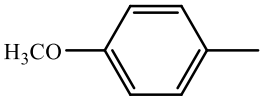
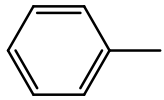


Drugs	Ar	Ar^1
Tripelennamine		
Pyrilamine		
Methapyrilene		
Thonzylamine		
Zolamine		

ii) **Amino Alkyl Ethers**

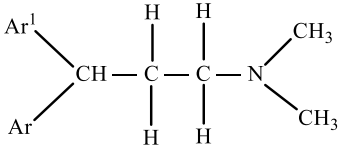


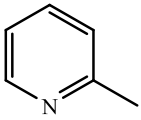
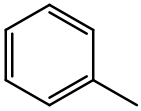
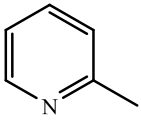
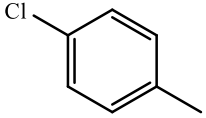
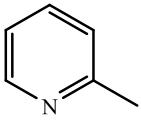
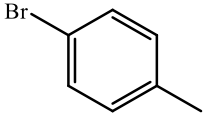
Drugs	Ar^1	Ar^2	R
Diphenhydramine	—C_6H_5	—C_6H_5	—H
Bromodiphenhydramine	—C_6H_5		—H

Doxylamine	—C_6H_5		—CH_3
Carbinoxamine			—H
Medrylamine			—H

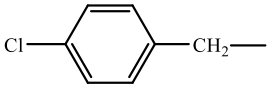
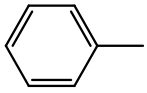
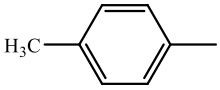
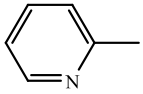
iii) **Mono Amino Propyl Analogues**

a) **Saturated Analogues**

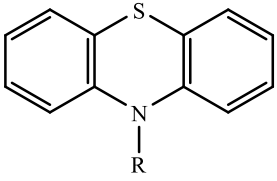


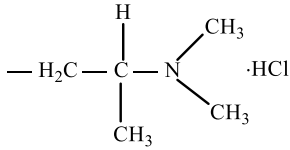
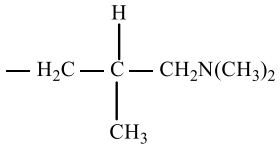
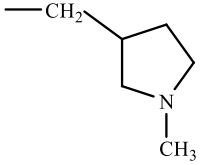
Drugs	Ar	Ar^1
Pheniramine		
Chlorpheniramine		
Bromopheniramine		

b) **Unsaturated Analogues**

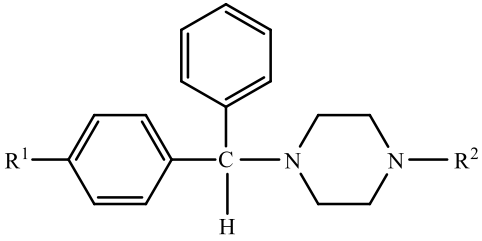
Drugs	Ar	Ar^1
Pyrrobutamine		
Triprolidine		

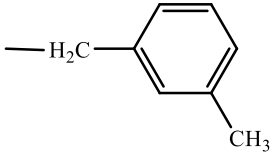
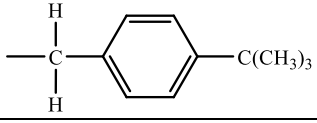
iv) **Tricyclic Ring Systems or Phenothiazine Derivatives**



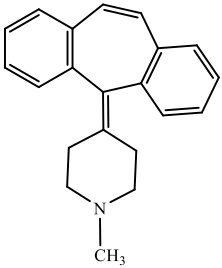
Drugs	R
Promethazine hydrochloride	
Trimeprazine	
Methdilazine	

v) **Cyclic Basic Chain Analogues or Piperazine Derivatives**

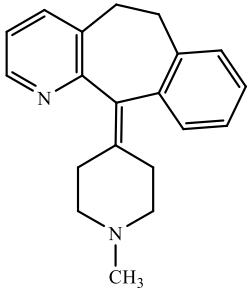


Drugs	R^1	R^2
Cyclizine	—H	—CH_3
Chlorcyclizine	—Cl	—CH_3
Meclizine	—Cl	
Buclizine	—Cl	

vi) **Dibenzocycloheptenes**

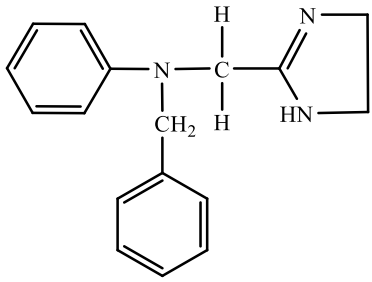


Cyproheptadine (periactin)

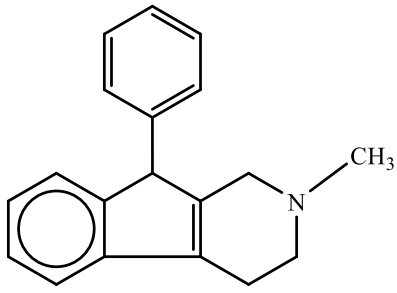


Azatadine

vii) **Miscellaneous**

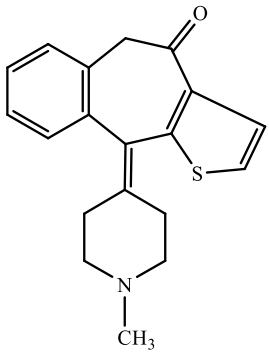


Antazoline

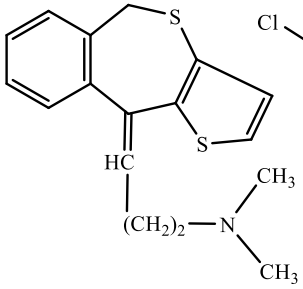


Phenindamine

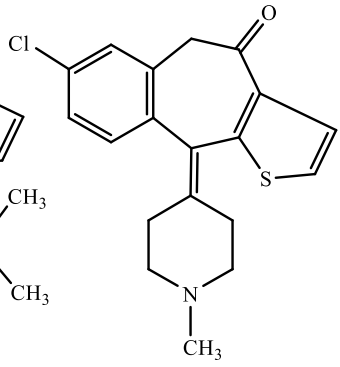
viii) **Newer Agents**



Ketotifene

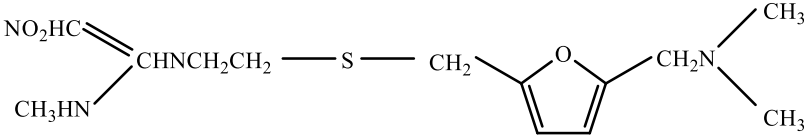


Dithiadene



7-Chloro ketotifene

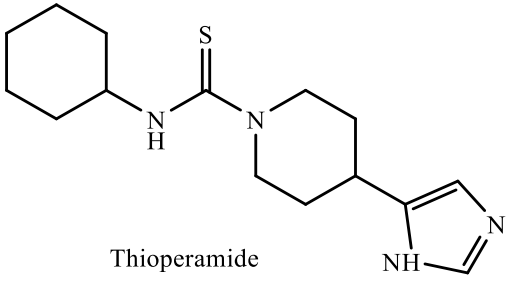
2) **H_2-Receptor Antagonists:** Ranitidine and Cimetidine



Ranitidine

3) **H_3-Receptor Antagonists:** Thioperamide and Impromidine

4) **H_4-Receptor Antagonists:** Thioperamide



Thioperamide

Thioperamide is a potent H_4-antagonist and selective H_3-antagonist. It can cross the blood brain barrier.

1.1.5. Mechanism of Action

Histamine binds with the histaminergic receptors (H_1, H_2, and H_3) after being released by the mast cells. This binding stimulates a series of events that facilitate the characteristic responses by second messenger systems. The histaminergic receptors are G-protein coupled type. Thus, the H_1-receptors are coupled to phospholipase-C and on activation they form inositol phosphate (Ip_3) and diacylglycerol (DAG) from the cell membrane phospholipids.

Ca^{2+} ions are rapidly released from endoplasmic reticulum under the influence of Ip_3. Protein kinase C is activated by DAG. Thus, the turnover of Ca^{2+} ions and protein kinase C stimulates the Ca^{2+}/calmodulin dependent protein kinase and phospholipase A_2. The anti-histaminergic (H_1-antagonist) binds to the H_1-receptors and decreases the production of phospholipase-C and their activation to form IP_3 and DAG. Therefore, it inhibits the characteristic response of histamine.

Histamine forms cAMP-dependent protein kinase (also known as cyclic AMP or 3′-5′-cyclic adenosine monophosphate) on H_2-receptors for producing a response in the GIT. The H_2-antagonist and the H_2-receptors bind reversibly and this decreases cAMP formation. Subsequently, the proton pump is activated and the formation of gastric acid in the GIT decreases.

H_3-receptors are a lso G-protein coupled receptors . They decrease the Ca^{2+} ions influx. H_3-receptors act as feedback inhibitors for histamine a nd other neurotransmitters as they reduce calcium influx in the cells in CNS, decrease gastrin secretion in the GIT, and down-stimulates histamine by auto-regulatory effects. These effects are antagonised by blocking the H_3-receptors, whereas the clinical extendibility is narrow for H_3.

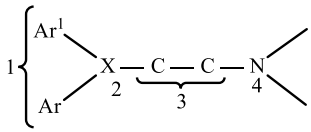
1.1.6. Uses

Following are the therapeutic uses of antihistaminic agents:

1) They have same efficacy when used in suitable doses.
2) The H_2-blockers are used for reducing gastric acid secretion.
3) Sometimes other types of therapy are similarly effective, still the H_2-blockers are chosen due to suitability and good patient acceptability.

1.1.7. Structure-Activity Relationship

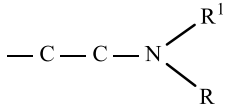
H_1-Receptor Antagonists



1) **Aryl Groups:** Diaryl substitution is required for H_1 affinity, and is found in first-generation and second-generation antihistamines. The co-planarity of two aryl substitutions influences the optimal antihistaminic activity. Active aryl substitutions are as follows:
   i) Ar is phenyl and hetero aryl group (like 2-pyridyl).
   ii) Ar^1 is aryl or aryl methyl group.

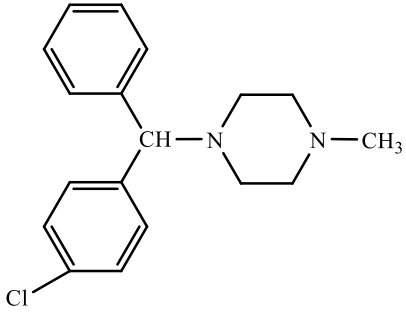
2) **Nature of X:** Antihistamines with X = carbon (pheniramine series) signifies the stereo selective receptor binding to the receptors because of its chirality. The active substitutions of X are as follows:
   i) X = Oxygen (amino alkyl ether analogue)
   ii) X = Nitrogen (ethylene-diamine derivative)
   iii) X = Carbon (mono amino propyl analogue)

3) **Alkyl Chain:** Mostly antihistamines have ethylene chain, t he b ranching of which forms a less active compound.



This general chain is present in all the antihistamines.

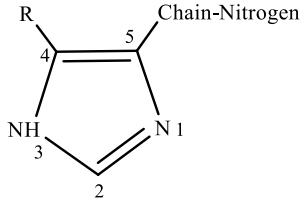
4) **Terminal Nitrogen Atom:** The nitrogen atom at the terminal should be a tertiary amine for maximum activity. The terminal nitrogen can be the part of heterocyclic ring, **for example** , antazoline and chlorcyclizine have a high antihistaminic activity. The am ino moiety on interaction with H_1-receptor shows protonation due to basicity with pka 8.5-10.



Chlorcyclizine

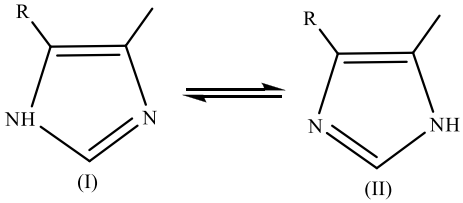
H_2-Receptor Antagonists

H_2-blockers are not like H_1-blockers that are typically lipophilic amines. Instead, they are very polar in nature (**e.g.,** cimetidine). H_2-blockers also have longer uncharged side chains non -related to the protonated dialkylaminoalkyl side chains present in H_1-blockers. The imidazole ring in H_2-blocker structure is important for the identification of the receptor.



H_2-Antagonist

1) **Imidazole Ring Substitutions :** The imidazole ring is found in two tautomeric forms as shown below. The first form (I) is important for maximal H_2-antagonistic activity. Mostly, the activity is potentiated when R is a $-CH_3$ group.



2) **Chain:** Four carbon atoms chain is best for the activity of H_2-blockers. The antagonist activity is extremely reduced in case of a shorter chain. The chain should have an electron withdrawing substituent. An isosteric thioether (─S─) link at the place of methylene group (─CH_2─) gives more active compounds.

3) **Terminal Nitrogen Group:** To achieve maximal antagonist activity the terminal N-group should be a polar, non-basic substituent. A positively charged group binds more firmly to the receptor and this exerts an agonist activity (and not an antagonist activity).

1.1.8. Recent Developments

The effect of first generation sedating H_1-antihistamines in humans has never been investigated. But, most of the second-generation non-sedating H_1-antihistamines are well investigated. The H_1-antihistamines are widely used in the treatment of allergic rhinitis, allergic conjunctivitis, and chronic urticaria. The second generation H_1-antihistamines produce comparatively less CNS and cardiac toxicity if taken in standard doses and even in overdose.

Screening and structural modification of the pre-existing second generation H_1 antihistamines have led to the identification of many new medications of the same class. **For example,** cetirizine is a metabolite of hydroxyzine, levocetirizine is the active R-enantiomer of cetirizine, desloratadine is a metabolite of loratadine, and fexofenadine is a metabolite of terfenadine.

New H_1-antihistamines continue to be developed and introduced for clinical use; however, they should be inspected carefully as they may or may not exhibit clinically important features as compared to the existing second generation H_1-antihistamines. Till date, no second generation H_1-antihistamine is found to have efficacy superior to the others, though some are safer.

The terms **third generation**, **new generation**, or **next generation** are used to market certain new H_1-antihistamines. But, clinically advantageous H_1-antihistamines should be designated by these terms. Some of these medications also have the intrinsic ability to down-regulate histamine at H_2-, H_3-, or H_4-receptors or to down-regulate leukotrienes or cytokines.

Without the discussion of histamine-globulin injection, any discussion on histamine is incomplete. There are no double-blind placebo-controlled, published studies on this formulation, however, it is generally prescribed in India. This combination should be banned.

1.2. H_1-ANTAGONISTS

1.2.1. Introduction

Until the discovery of H_1-receptors, no other histamine receptors had been identified. The H_1-antagonists, termed as **antihistamines** cause a competitive inhibition of only H_1-receptors (they do not block any other histamine receptors). Adrenaline is a physiological antagonist of histamine. It acts via adrenergic receptors and reverses the bronchodilation and vasoconstriction effects of histamine. Cromolyn sodium and corticosteroids block histamine release from mast cells. The H_1-receptor antagonists are employed in the treatment of allergic disorders.

The action of histamines on H_1-receptors is blocked by antihistamines (H_1-blockers) categorised into first and second generations. The **first generation** antihistamines bind to the central and peripheral H_1-receptors, while the **second generation** antihistamines bind to the peripheral H_1-receptors.

Though the sedative effects of second generation antihistamines are lesser as compared to the first generation antihistamines, still they are beneficial for the treatment of allergies.

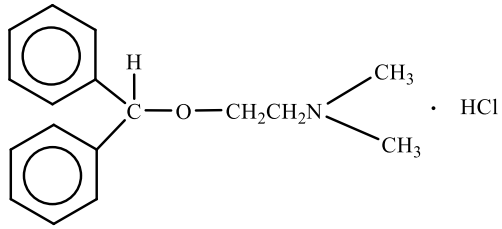
1.2.2. Study of Individual Drugs

The following H_1-antagonists are discussed below:

1) Diphenhydramine hydrochloride,
2) Dimenhydrinate,
3) Doxylamine succinate,
4) Clemastine fumarate,
5) Diphenylpyraline hydrochloride,
6) Tripelennamine hydrochloride,
7) Chlorcyclizine hydrochloride,
8) Meclizine hydrochloride,
9) Buclizine hydrochloride,
10) Chlorpheniramine maleate,
11) Triprolidine hydrochloride,
12) Phenindamine tartrate,
13) Promethazine hydrochloride,
14) Trimeprazine tartrate,
15) Cyproheptadine hydrochloride,
16) Azatadine maleate,
17) Astemizole,
18) Loratadine,
19) Cetirizine,
20) Levocetirizine, and
21) Cromolyn sodium.

1.2.2.1. Diphenhydramine Hydrochloride

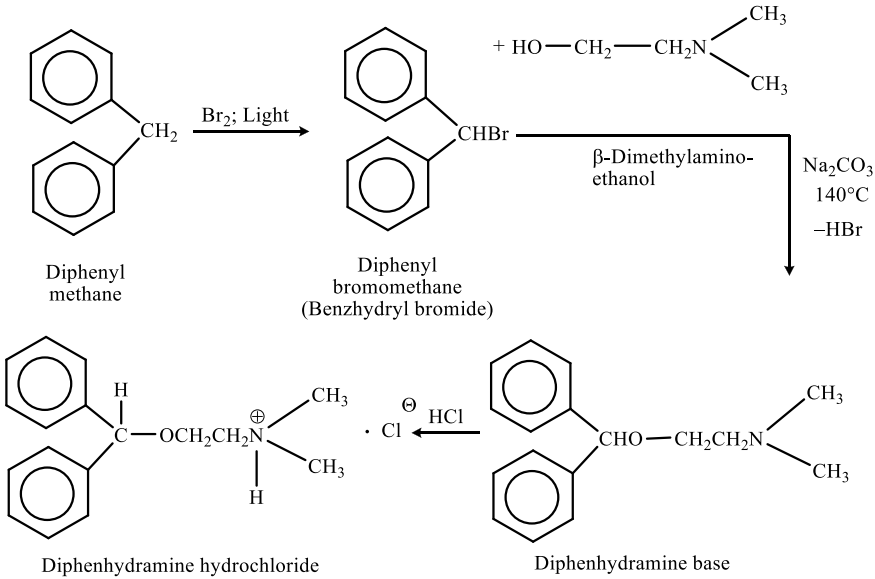
Diphenhydramine is a first generation antihistamine which is mainly used for treating seasonal allergies. But it also exhibits antiemetic, anti -Parkinson, antitussive, and hypnotic properties.



Diphenhydramine Hydrochloride

Synthesis

Firstly, diphenylmethane undergoes bromination in the presence of light to form diphenylbromomethane. Then, diphenylbromomethane, β-dimethyl-amino-ethanol, and sodium carbonate are heated in the presence of toluene to obtain diphenhydramine base. The purified diphenhydramine after distilling-off toluene converts into its hydrochloride form with hydrogen chloride.



Diphenyl methane

Diphenyl bromomethane (Benzhydryl bromide)

Diphenhydramine hydrochloride

Diphenhydramine base

Mechanism of Action

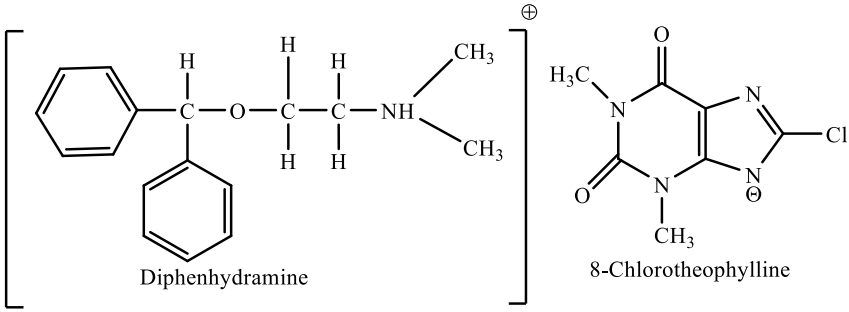
Diphenhydramine works through the antagonism of H_1-receptors found on the respiratory smooth muscles, vascular endothelial cells, GIT, cardiac tissue, immune cells, uterus, and CNS neurons. On stimulating the H_1-receptors in these tissues, they increase vascular permeability, stimulate vasodilation that leads to flushing, decrease the conduction time of atrioventricular (AV) node , stimulate the sensory nerves of a irways that leads to coughing, contract the smooth muscles of bronchi and GIT, and cause eosinophilic chemotaxis that enhances the allergic immune response. Diphenhydramine functions as an inverse agonist at H_1-receptors, and then it converses the histamine effects on capillaries, and decreases the symptoms of allergic reaction.

Uses

1) It is used for preventing and curing nausea, vomiting and dizziness caused by motion sickness.
2) It is used to relax and fall asleep.
3) It is used for relieving the symptoms of a llergy, hay fever, common cold, rashes, itching, watery eyes, itchy eyes/nose/throat, cough, runny nose, and sneezing.

1.2.2.2. Dimenhydrinate

Dimenhydrinate is a combination drug as it comprises of diphenhydramine (53-55.5%) and 8-chlorotheophylline (not less than 44-47%) in a salt form, calculated on the dried basis.



Mechanism of Action

Mechanism of some antihistamines producing antiemetic, anti-motion sickness and anti-vertigo effects is not known ; however, it can be related to their central anticholinergic actions. They reduce the vestibular stimulation and lower the labyrinthine function.

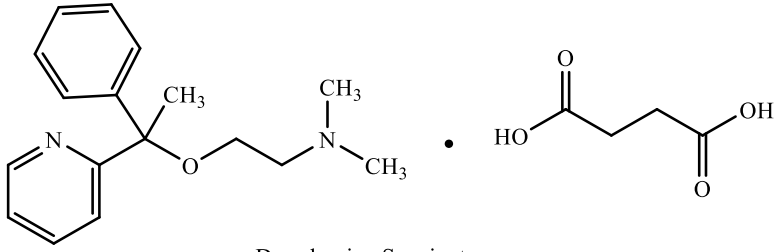
The antiemetic effect may also be the result of a n action on the medullary chemoreceptive trigger zone. Dimenhydrinate is a competitive an tagonist of H_1-receptors found in the human brain. It produces anti-emetic effect because of H_1-antagonism in the vestibular system in the brain.

Uses

1) It is used for preventing motion sickness, nausea, and vomiting.
2) It helps in the treatment of ear congestion.
3) It is used for relieving vertigo and vestibular disorder.

1.2.2.3. Doxylamine Succinate

Doxylamine succinate is a pyridine derivate H $_1$-antagonist having sedative properties. It competitively blocks the H_1-receptor and controls t he allergic and anaphylactic responses, such as bronchoconstriction, vasodilation, increased capillary permeability, and spasmodic contraction of gastrointestinal smooth muscles caused by histamine actions on bronchial and gastrointestinal smooth muscles. Doxylamine succinate also prevents pain and itching of the skin and mucous membranes induced by histamine.



Doxylamine Succinate

Mechanism of Action

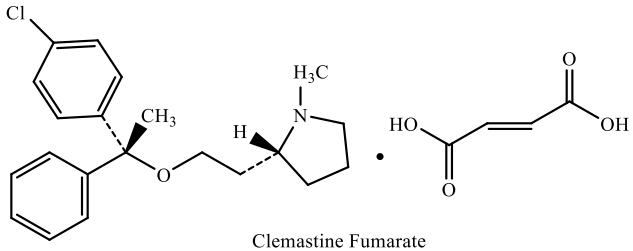
Doxylamine shows antihistaminic and sedative effects because it acts as an antagonist of the H_1-receptors. It also slightly antagonises the muscarinic acetylcholine receptors.

Uses

1) It relieves the symptoms of allergy, hay fever, and common cold.
2) It relieves sneezing, runny nose, watery eyes, hives, and skin rash.
3) It is used for treating insomnia.
4) It is used for preventing morning sickness in pregnant women in combination with vitamin B_6 (pyridoxine).

1.2.2.4. Clemastine Fumarate

Clemastine fumarate is the fumaric acid salt of clemastine. It is an antihistamine having antimuscarinic and moderate sedative properties. It is used for the symptomatic relief of allergic conditions like rhinitis, urticaria, conjunctivitis, and pruritic (severe itching) skin conditions. It is an H_1-receptor antagonist, an anti-allergic agent, a muscarinic antagonist, and an antipruritic drug.



Clemastine Fumarate

Mechanism of Action

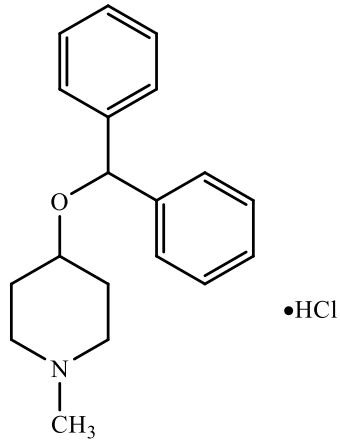
Clemastine is a se lective H_1-antagonist. It binds to the H_1-receptors and blocks the action of histamine, thus temporary relieving the negative symptoms caused due to histamine.

Uses

1) It is used for relieving the symptoms of allergic rhinitis like sneezing, rhinorrhea, pruritus, and acrimation.
2) It is used for the management of mild, uncomplicated allergic skin conditions of urticaria and angioedema.
3) It is u sed as a self-medication for temporary relief of symptoms related to common cold.

1.2.2.5. Diphenylpyraline Hydrochloride

Diphenylpyraline is an antihistamine used for treating allergy by competing with histamine to bind to the H_1-receptor sites found on the effector cells.



Diphenylpyraline Hydrochloride

Mechanism of Action

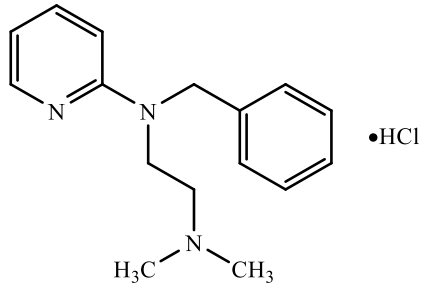
Diphenylpyraline is used for treating allergy as it competes with histamine for binding on the H_1-receptors on effector cells. After binding it suppresses the histamine effects, thus causing temporary relief of the allergic symptoms.

Uses

1) It is used for treating allergic rhinitis.
2) It is used for treating hay fever.
3) It is used for treating allergic skin orders.

1.2.2.6. Tripelennamine Hydrochloride

Tripelennamine is an ethylenediamine derivative having anti -histaminergic property. Tripelennamine hydrochloride is the hydroc hloride salt of tripelennamine.



Tripelennamine Hydrochloride

Mechanism of Action

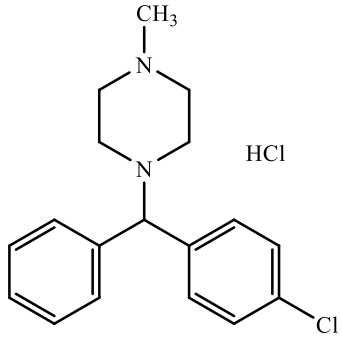
Tripelennamine binds to the H_1-receptor and blocks the action of endogenous histamine, thus temporarily relieving the negative symptoms caused by histamine.

Uses

1) It treats the conditions of upper respiratory tract caused due to illnesses and hay fever.
2) It relieves sneezing, runny nose, itching, watery eyes, hives, rashes, and other symptoms of allergies and common cold.

1.2.2.7. Chlorcyclizine Hydrochloride

Chlorcyclizine is a first generation antihistamine belonging to phenylpiperazine class. It is used for treating urticaria, rhinitis, pruritus, and other allergy symptoms. It also has some local anaesthetic, anticholinergic, antiemetic, and antiserotonergic properties.



Chlorcyclizine Hydrochloride

Mechanism of Action

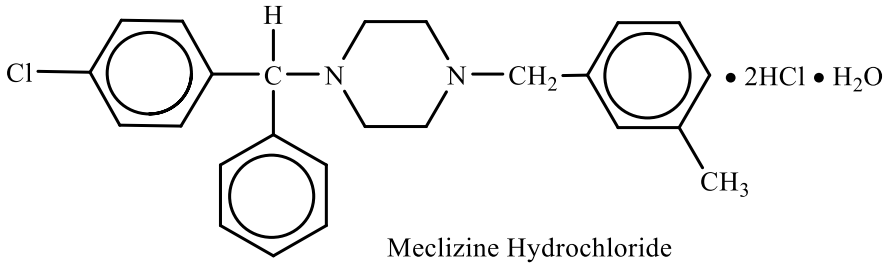
Antihistamines are pharmacological antagonists of histamine acting at most of the histamine receptor sites, but they do not inhibit histamine release. Since chlorcyclizine exhibit hepatic microsomal enzyme-inducing properties, it reduces the duration of action of certain barbiturates due to enzyme induction.

Uses

1) It is used for the treatment of allergic symptoms like rhinitis, urticaria, and pruritus.
2) It is also used for treating hepatitis C.

1.2.2.8. Meclizine Hydrochloride

Meclizine hydrochloride is the hydrochloride salt form of meclizine, which is a synthetic piperazine having anti-emetic, sedative and H_1-antagonistic properties.



Meclizine Hydrochloride

Mechanism of Action

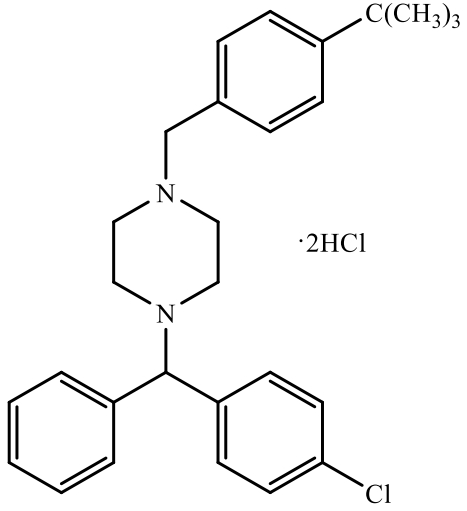
Meclizine hydrochloride inhibits the H_1-receptors. It prevents histamine actions on capillaries, bronchial and gastrointestinal smooth muscles, such as vasodilation, increased capillary permeability, bronchoconstriction, and spasmodic contraction of gastrointestinal smooth muscles. It produces antiemetic effects through its anticholinergic actions or by direct effect on the medullary chemoreceptive trigger zone.

Uses

1) It is used for treating motion sickness.
2) It is safely used in the treatment of nausea in pregnancy.
3) It helps in relieving vertigo.

1.2.2.9. Buclizine Hydrochloride

Buclizine hydrochloride is the hydrochloride salt form of buclizine, which is a piperazine H_1-receptor antagonist having antiemetic and anti-vertigo properties.



Buclizine Hydrochloride

Mechanism of Action

Emesis (vomiting) is a protective mechanism as it removes irritant or harmful substances from the upper GIT. Emesis is regulated by the vomiting centre in the medulla region of brain.

The vomiting centre has neurons which possess many muscarinic cholinergic and histamine-containing synapses. These neurons are involved in transmission from the vestibular apparatus to the vomiting centre.

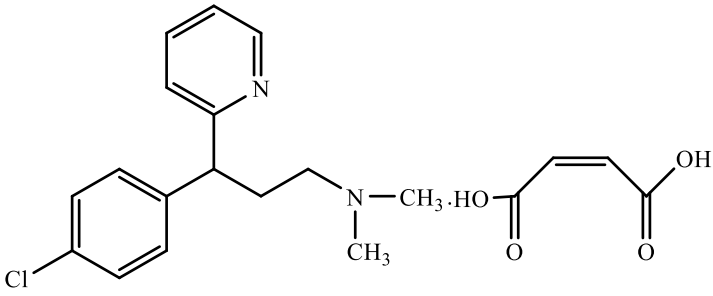
Motion sickness includes overstimulation of these pathways because of various sensory stimuli. Hence, buclizine blocks the histamine receptors in the vomiting centres and decreases the activity along these pathways. Buclizine also has anti-cholinergic properties and blocks the muscarinic receptors.

Uses

1) It is used as an anti-vertigo or antiemetic agent.
2) It is used in the management of vertigo in diseases affecting the vestibular apparatus.
3) It is used for treating nausea, vomiting and dizziness related to motion sickness.

1.2.2.10. Chlorpheniramine Maleate

Chlorpheniramine maleate is a H_1-recpetor antagonist. It is used in allergic reactions, hay fever, rhinitis, urticaria, and asthma. It is also used in veterinary applications.



Chlorpheniramine Maleate

Mechanism of Action

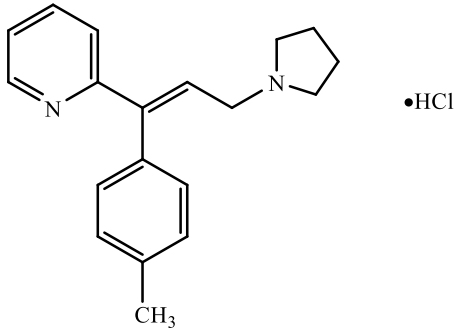
Chloropheniramine binds to H_1-receptors and inhibits the action of histamine, thus temporarily relieving the negative symptoms produced by histamine.

Uses

Chlorpheniramine is used for relieving the symptoms of allergy, hay fever, common cold, rashes, watery eyes, itchy eyes/nose/throat/skin, cough, runny nose, and sneezing.

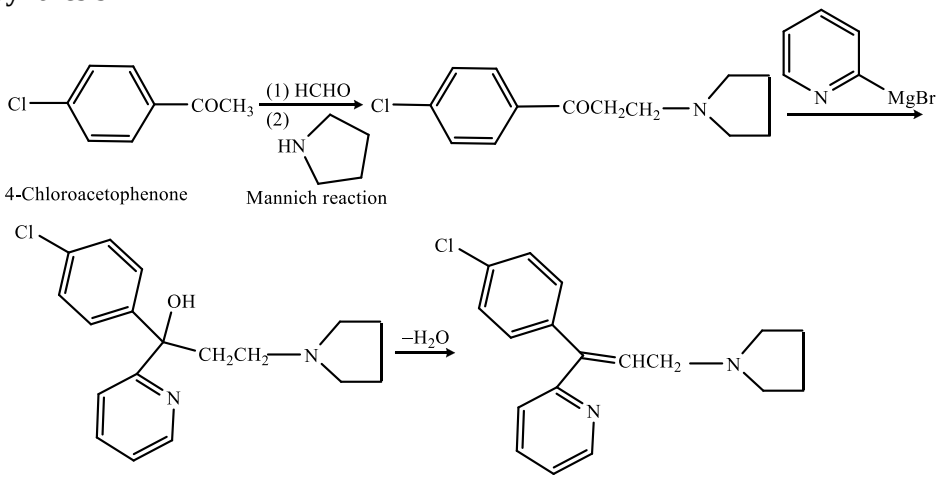
1.2.2.11. Triprolidine Hydrochloride

Triprolidine hydrochloride is obtained by the reaction between equimolar amounts of triprolidine and hydrogen chloride. Its monohy drate form is used for symptomatic relief of urticaria, rhinitis, and many pruritic skin disorders. It is also a H_1-receptor antagonist.



Triprolidine Hydrochloride

Synthesis



Mechanism of Action

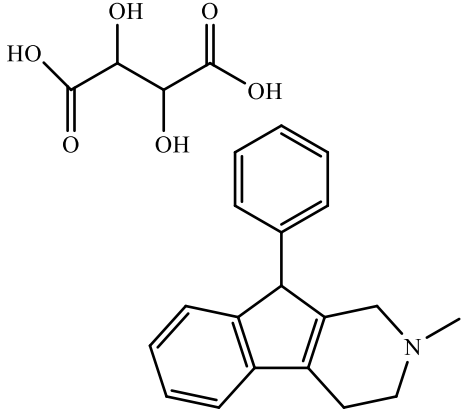
Triprolidine hydrochloride binds to the H_1-receptors and inhibits the action of histamine, thus temporarily relieving the negative symptoms of histamine.

Uses

1) It is used for the symptomatic relief of seasonal or perennial allergic rhinitis or non -allergic rhinitis; allergic conjunctivitis; and mild, uncomplicated allergic skin conditions of urticaria and angioedema.
2) It is used in combination with other agents for the symptomatic relief of symptoms related to common cold.

1.2.2.12. Phenindamine Tartrate

Phenindamine tartrate is a phenylalkylamine sympathomimetic amine. It exhibits appetite depressant property. It inhibits the effects of the naturally occurring histamine in the body.



Phenindamine Tartrate

Mechanism of Action

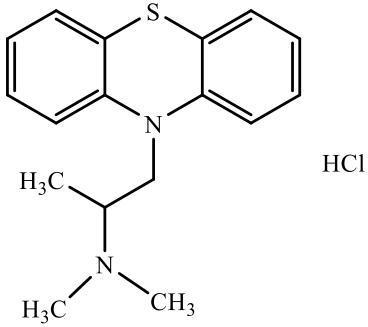
Phenindamine competes with histamine for H_1-receptor sites on effector ce lls. It antagonises those pharmacological effects of histamine that are induced by the activation of H_1-receptor sites. Hence, it decreases the intensity of allergic reactions and tissue injury response that causes histamine release.

Uses

It is used for relieving sneezing, runny nose, itching, watery eyes, hives, rashes, itching, and other symptoms of allergies and common cold.

1.2.2.13. Promethazine Hydrochloride

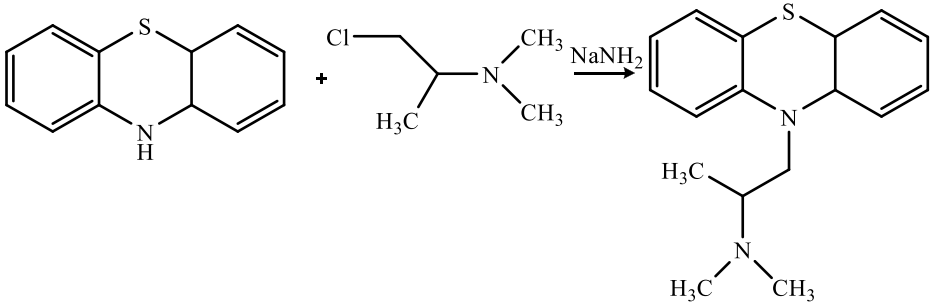
Promethazine hydrochloride is the hydrochloride salt form of promethazine, which is a phenothiazine derivative having antihistaminic, sedative and antiemetic properties.



Promethazine Hydrochloride

Synthesis

Promethazine is form ed by the alkylation of phenothiazine with 1 - dimethylamino-2-chloropropane in the presence of sodium amide.



Mechanism of Action

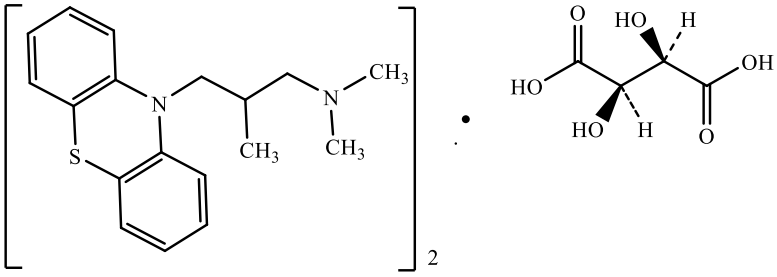
Promethazine hydrochloride selectively inhibits the peripheral H_1-receptors, thus reduces the histamine effects on effector cells. It also inhibits the central histaminergic receptors, thus depresses the reticular system that causes sedative and hypnotic effects. It also exhibits centrally acting anticholinergic properties. It may control nausea and vomiting by acting on the medullary chemoreceptive trigger zone.

Uses

1) It is used for preventing and curin g vertigo and motion sickness. However, it shows marked and long antihistaminic activity.
2) Due to its antiemetic properties, it is added in postoperative nausea and vomiting tablets, elixirs, syrups, suppositories, and injections.
3) It is also used for anaest hetic premedication through intramuscular injection with atropine and meperidine.

1.2.2.14. Trimeprazine Tartrate

Trimeprazine t artrate (or **alimemazine**) is a tartrate salt and a phenothiazine derivative, which is used as an antiprurit ic agent (prevents itching caused due to eczema or poison ivy). It also acts as a sedative, hypnotic, and antiemetic.



Trimeprazine Tartrate

Mechanism of Action

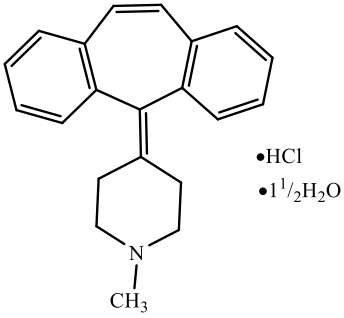
Trimeprazine acts by competing with free histamine f or binding at HA -receptor sites. This antagonis es histamine effects on HA -receptors, thus reducing the negative symptoms caused by binding of histamine to HA-receptors.

Uses

1) It is used alone or along with corticosteroids in controlling inflammatory and allergic problems.
2) It is used for preventing and relie ving the allergic conditions that cause pruritus (itching) and urticaria (some allergic skin reactions).

1.2.2.15. Cyproheptadine Hydrochloride

Cyproheptadine is a first generation antihistamine which is used as an appetite stimulant and for treating allergic rhinitis and urticaria.



Cyproheptadine Hydrochloride

Mechanism of Action

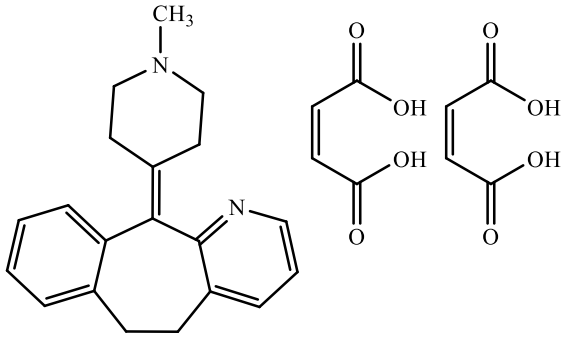
Cyproheptadine acts by competing with free histamine for binding at HA -receptor sites. This antagonises histamine effects on HA -receptors, thus reducing the negative sy mptoms caused by binding of histamine to HA -receptors. It also competes with serotonin for binding to receptor sites in smooth muscle s in intestines and other locations. Antagonism of serotonin on the appetite centre of hypothalamus is responsible for cypr oheptadine's ability to stimulate appetite.

Uses

It is used for treating perennial and seasonal allergic rhinitis, vasomotor rhinitis, allergic conjunctivitis, mild uncomplicated allergic skin manifestations of urticarial and angioedema, amelioration of a llergic reactions to blood or plasma, dermatographism, cold urticaria, and as a treatment for anaphylactic reactions adjuvant to epinephrine.

1.2.2.16. Azatadine Maleate

Azatadine maleate is a first -generation antihistamine. It is the dima leate salt of azatadine. It acts as a H_1-receptor antagonist and an anti-allergic agent.



Azatadine Maleate

Mechanism of Action

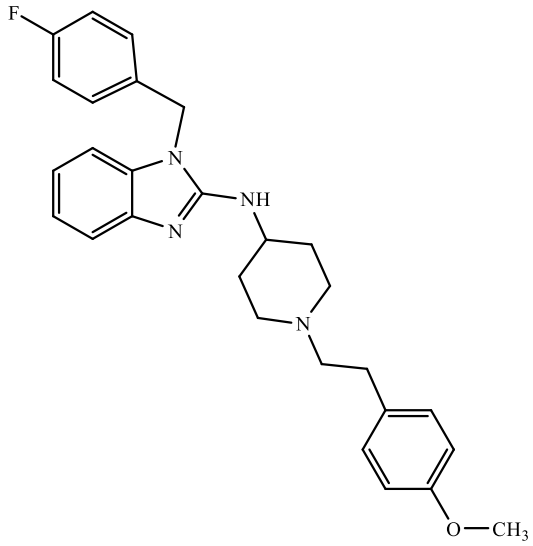
Azatadine competes with histamine for H $_1$-receptor sites on effector cells. It antagonises those pharmacological effects of histamine that are induced by the activation of H $_1$-receptor sites. Hence, it decreases the intensity of allergic reactions and tissue injury response that causes histamine release.

Uses

1) It is used for treating the symptoms of upper respiratory mucosal congestion in perennial and allergic rhinitis.
2) It is also used for treating nasal congestion and eustachian tube congestion.

1.2.2.17. Astemizole

Astemizole is a long -acting, non -sedating second generation antihistamine. It is used for treating the allergic symptoms. At higher doses, it causes arrhythmias due to which it was withdrawn from the market by the manufacturer in 1999.



Astemizole

Mechanism of Action

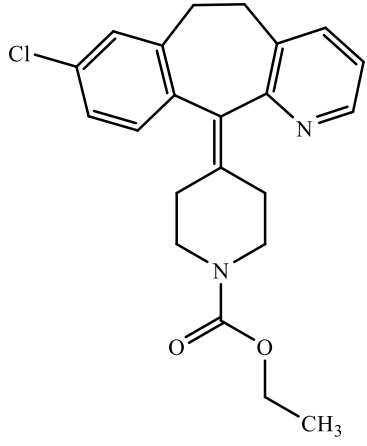
Astemizole acts by competing with histamine for binding reversibly to H_1-receptor sites in the GIT, uterus, large blood vessels, and bronchial muscles. This reversible binding suppresses oedema, flare, and pruritus caused by histaminic activity. Since astemizole does not cross the blood-brain barrier easily, it binds to the peripheral H_1-receptors (and not with those found in the brain); thus, it causes minimal CNS depression. Astemizole also act on H_3-receptors, but produces adverse effects.

Uses

It is used for treating the allergic symptoms such as rhinitis and conjunctivitis.

1.2.2.18. Loratadine

Loratadine is an azatadine derivative and a second generation H_1-receptor antagonist. It is used for relieving the symptoms of allergic rhinitis and urticaria.



Loratadine

Mechanism of Action

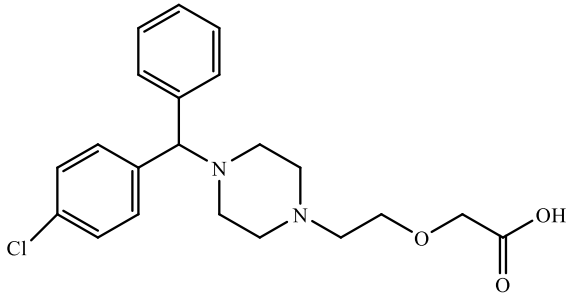
Loratadine competes with free histamine. It shows specific and selective peripheral H_1-antagonistic activity, thus inhibits the action of histamine and temporarily relieves nasal congestion and watery eyes caused by histamine. It has a low affinity for cholinergic receptors and does not show any appreciable *in-vitro* α-adrenergic blocking activity. The clinical use of loratadine is unknown, but it suppresses histamine and leukotrienes release from animal mast cells, and leukotrienes release from human lung fragments.

Uses

1) It is a self-medication and is used alone or along with pseudoephedrine sulphate for the symptomatic treatment of seasonal allergic rhinitis.
2) It is also used for the symptomatic relief of pruritus, erythema, and urticaria related to chronic idiopathic urticaria (it is not used in children below 6 years of age if not directed by a clinician).

1.2.2.19. Cetirizine

Cetirizine (or **zyrtec**) is an orally active second generation H_1-antagonist. It is used for treating the various allergic symptoms like sneezing, coughing, nasal congestion, hives, etc.



Cetirizine

Mechanism of Action

Cetirizine is an antihistamine drug and a hydroxyzine metabolite. It mainly acts by the selective inhibition of peripheral H_1-receptors. Its antihistamine activity is given in a variety of animal and human models. *In vivo* and *ex vivo* animal models have shown insignificant anticholinergic and anti-serotonergic effects. However during clinical studies, dry mouth occurred frequently with cetirizine than with a placebo. *In vitro* receptor binding studies explain that no detectable affinity of cetirizine exists for histamine receptors other than the H_1-receptors. In studies with radiolabeled cetirizine in rats, it was seen that cetirizine insignificantly penetrates into the brain. *Ex vivo* studies in mouse have shown that cetirizine on systemic administration does not occupy the cerebral H_1-receptors.

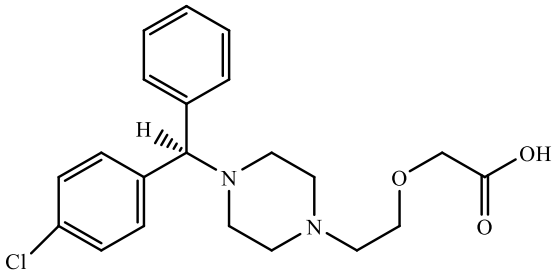
Uses

1) **Seasonal Allergic Rhinitis:** It is used for treating symptoms related to seasonal allergic rhinitis caused by allergens (like ragweed, grass, and tree pollens) in adults and children of 2 years of age and above. Cetirizine is also used for treating sneezing, rhinorrhoea, nasal pruritus, ocular pruritus, tearing, and redness of eyes.

2) **Perennial Allergic Rhinitis:** It is used for treating the symptoms related to perennial allergic rhinitis caused by dust mites, animal dander, and molds in adults and children of 6 months of age and above. Cetirizine is also used for treating sneezing, rhinorrhoea, postnasal discharge, nasal pruritus, ocular pruritus, and tearing.
3) **Chronic Urticaria:** It is used for treating uncomplicated skin conditions of chronic idiopathic urticaria in adults and children of 6 months of age and above. Mainly, cetirizine decreases the occurrence, severity, and duration of hives and pruritus.

1.2.2.20. Levocetirizine

Levocetirizine is a third generation non-sedative antihistamine. It is used for treating the symptoms related to seasonal and perennial allergic rhinitis and uncomplicated skin conditions of chronic idiopathic urticaria.



Levocetirizine

Mechanism of Action

Levocetirizine is the active enantiomer of cetirizine. It produces its major effects by selective inhibition of H_1-receptors. The antihistaminic activity of levocetirizine has been studied in many animal and human models.

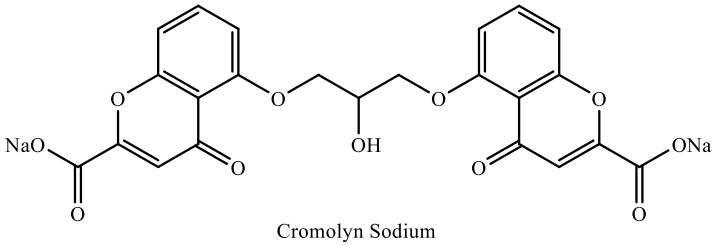
Its affinity for human H_1-receptor is twice than that of cetirizine (Ki=3 nmol/L and 6 nmol/L, respectively), and this has been revealed in the *in vitro* binding studies. However clinical importance of this increased affinity is indefinite.

Uses

1) It is used for treating the symptoms related to seasonal and perennial allergic rhinitis in adults and children of 6 years of age and above.
2) It is used for treating the allergic symptoms like watery eyes, runny nose, itching eyes/nose, and sneezing.
3) It is also used to treat itching and hives.

1.2.2.21. Cromolyn Sodium

Cromolyn sodium is the sodium salt form of cromolyn, which is a mast cell stabiliser having anti-inflammatory activity. It may inhibit the antigen-stimulated calcium transport across the mast cell membrane. Hence, it inhibits the release of histamine, leukotrienes, and other substances that causes hypersensitivity reactions from the mast cells.



Cromolyn Sodium

Mechanism of Action

Cromolyn sodium prevents the degranulation of mast cells, and thus prevents the release of h istamine and Slow-Reacting Substance of Anaphylaxis (SRS -A, mediators of type I allergic reactions). It may also suppress the release of inflammatory leukotrienes. It acts by inhibiting calcium influx.

Uses

1) It used for the management of bronchial asthma.
2) It is used for treating vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis.
3) It is used in the prophylactic treatment of asthma induced by allergy and exercise.
4) On inhalation it prevents bronchial asthma attacks in adults and childre n of 2 years of age.

1.3. H_2-ANTAGONISTS

1.3.1. Introduction

Cimetidine was the first agent to be clinically used as an H_2-blocker. The H_2-receptors present on parietal cells are blocked by cimetidine. The activation of H^+-K^+-ATPase proton pump is prevented by the antagonistic activity against these receptors. Thus, a decrease in the secretion of H^+ ions into the lumen is seen,which in turn decreases the detrimental effects of the acid on mucosal lining.

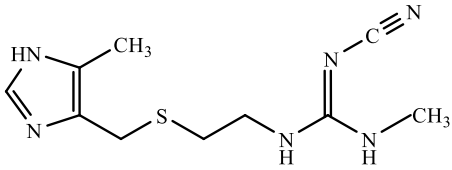
1.3.2. Study of Individual Drugs

The following H_2-antagonists are discussed below:

1) Cimetidine,
2) Famotidine, and
3) Ranitidine.

1.3.2.1. Cimetidine

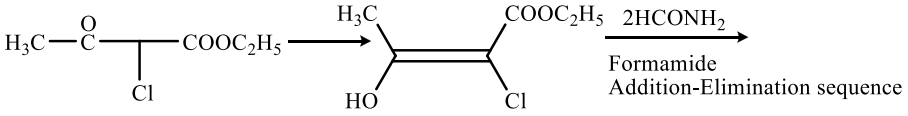
Cimetidine is a histamine congener and competitively inhibits the binding of histamine to histamine H_2-receptors. It prevents gastric acid secretion, pepsin and gastrin output.



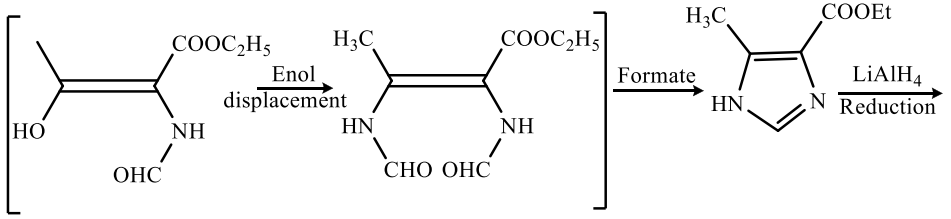
Cimetidine

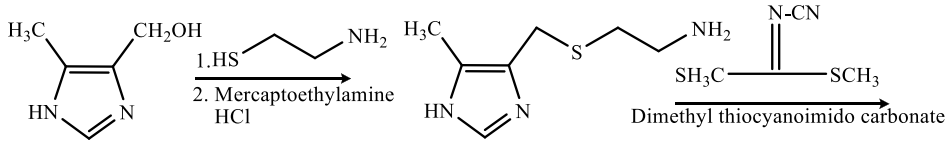
Synthesis (3 mistakes in the reaction)

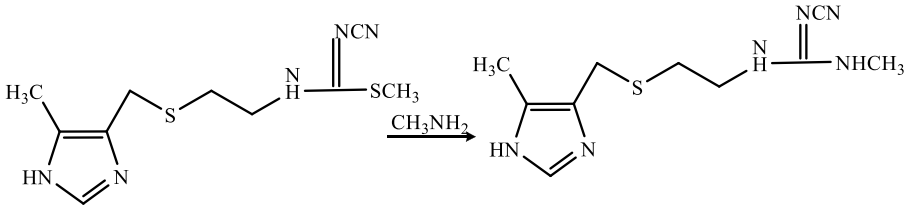
Ethyl-2-chloroacetoacetate on reacting with two moles of formamide forms 4-carbethoxy-5-methylimidazole. This carbethoxy group is reduced with lithium aluminium hydride to form 4-hydroxymethyl-5methylimidazol. The hydrochloride of the resulting alcohol and 2-mercaptoethylamine hydrochloride reacts to form 4-(2-aminomethyl)-thiomethyl-5-methylimidazole dihydrochloride. This compound is reacted with N-cyanimido-S,S-dimethyl dithiocarbonate to form a thiourea derivative, which on reacting with methylamine forms cimetidine.



Ethyl-2-chloroacetoacetate Enolate form







Mechanism of Action

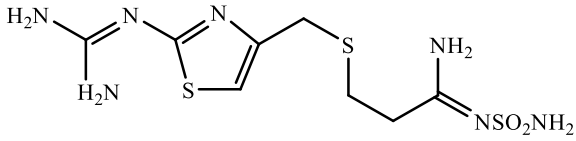
Cimetidine blocks the histamine effects by binding to the H_2-receptors found on the baso lateral membrane of gastric parietal cell. Reduction in gastric acid secretion, gastric volume and acidity are the results of this competitive inhibition.

Uses

1) It is used for treating certain types of ulcer.
2) It is used for treating the conditions in which too much acid is secreted by the stomach.
3) It is also used for treating acid-reflux disorders (like GERD), peptic ulcer disease, heartburn, and acid indigestion.

1.3.2.2. Famotidine

Famotidine is a competitive H_2-receptor antagonist and its main pharmacodynamic effect is the inhibition of gastric secretion.



Famotidine

Mechanism of Action

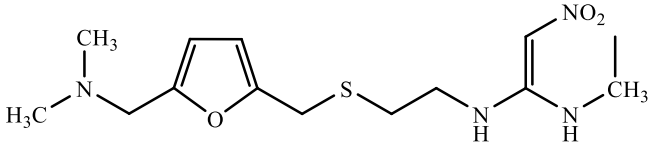
Famotidine blocks the histamine effects by competitively binding to H_2-receptors found on the basolateral membrane of gastric parietal cell. This competitive inhibition reduces basal and nocturnal gastric acid secretion, gastric volume, acidity, and amount of gastric acid produced in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin.

Uses

1) It is used for treating and preventing stomach and intestinal ulcers.
2) It is used in Zollinger-Ellison syndrome (in which excess amounts of acid is produced by the stomach).
3) It is used for treating Peptic Ulcer Disease (PUD) and Gastroesophageal Reflux Disease (GERD).

1.3.2.3. Ranitidine

Ranitidine is a non-imidazole blocker of those histamine receptors which mediate gastric secretion (H_2-receptors). It is used for treating gastrointestinal ulcers.



Ranitidine

Mechanism of Action

Ranitidine reduces the normal as well as the meal-stimulated secretion of acid by parietal cells by two mechanisms:

1) Histamine is released by the ECL cells in stomach is prevented from binding to the H_2-receptors on parietal cells that stimulate acid secretion.
2) When H_2-receptors are blocked, substances promoting acid secretion (**e.g.,** gastrin and acetylcholine) have a decreased effect on parietal cells.

Uses

1) It is used for treating peptic ulcer disease and gastroesophageal reflux disease.
2) It is used in gastric and duodenal ulcer and in conditions in which gastric juice secretion needs to be inhibited.
3) It is given in combination with fexofenadine and other antihistamines for treating skin conditions like hives.

1.4. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Histamine**, a biologically active substance potentiates the inflammatory and immune responses of the body.
2) Anti-histaminic agents (or **histamine antagonists**) are the drugs that antagonise the action of histamine.
3) The **first generation H_1-antihistamines** have a central effect so are used as sedatives.
4) The **second generation H_1-antihistamines** have low central effects so are used as anti-allergenic drugs.
5) **Histamines** are **nitrogen containing** organic co mpounds belonging to the group of **amines**.
6) **Histamines** are synthesised and released by **basophils** and **mast cells** on stimulation.
7) **Diphenhydramine** is a first generation antihistamine which is mainly used for treating seasonal allergies.
8) **Dimenhydrinate** is a comb ination drug as it comprises of diphenhydramine (53-55.5%) and 8-chlorotheophylline (not less than 44 - 47%) in a salt form, calculated on the dried basis.
9) **Clemastine fumarate** is the fumaric acid salt of **clemastine**. It is an antihistamine having antimuscarinic and moderate sedative properties.
10) **Diphenylpyraline** is an antihistamine used for treating allergy by competing with histamine to bind to the H_1-receptor sites found on the effector cells.
11) **Tripelennamine** is an ethylenediamine derivative having anti -histaminergic property.
12) **Chlorcyclizine** is a first generation antihistamine belonging to phenylpiperazine class.
13) **Meclizine hydrochloride** is the hydrochloride salt form of meclizine, which is a synthetic piperazine having anti -emetic, sedative and H_1-antagonistic properties.
14) **Buclizine hydrochloride** is the hydrochloride salt form of buclizine, which is a piperazine H_1-receptor antagonist having antiemetic and anti -vertigo properties.
15) **Chlorpheniramine maleate** is a H_1-recpetor antagonist.
16) **Triprolidine hydrochloride** is obtained by the reaction between equimolar amounts of triprolidine and hydrogen chloride.
17) **Phenindamine tartrate** is a phenylalkylamine sympathomimetic amine.
18) **Promethazine hydrochloride** is the hydrochloride salt form of promethazine, which is a phenothiazine derivative having antihistaminic, sedative and antiemetic properties.

19) **Trimeprazine tartrate** (or **alimemazine**) is a tartrate salt and a phenothiazine derivative, which is used as an antipruritic agent.
20) **Cyproheptadine** is a first generation antihistamine wh ich is used as an appetite stimulant and for treating allergic rhinitis and urticaria.
21) **Azatadine maleate** is a first-generation antihistamine. It is the dimaleate salt of azatadine.
22) **Astemizole** is a long-acting, non-sedating second generation antihistamine.
23) **Loratadine** is an azatadine derivative and a second generation H_1-receptor antagonist.
24) **Cetirizine** (or **zyrtec**) is an orally active second generation H_1-antagonist.
25) **Levocetirizine** is a third generation non-sedative antihistamine.
26) **Cromolyn** sodium is the sodium salt form of cromolyn, which is a mast cell stabiliser having anti-inflammatory activity.
27) **Cimetidine** is a histamine congener and competitively inhibits the binding of histamine to histamine H_2-receptors.
28) **Famotidine** is a competitive H_2-receptor antagonist and its main pharmacodynamic effect is the inhibition of gastric secretion.
29) **Ranitidine** is a non -imidazole blocker of those histamine receptors which mediate gastric secretion (H_2-receptors).

1.5. EXERCISE

1.5.1. True or False

1) Histamine, a biologically active substa nce potentiates the inflammatory and immune responses of the body.
2) The first gene-antihistamines have a central effect so are used as hypnotics.
3) The second generation H_1-antihistamines have low central effects so are used as sedatives.
4) Histamines are nit rogen containing organic compounds belonging to the group of amine
5) Diphenhydramine is a first generation antihistamine which is mainly used for treating seasonal allergies.
6) Chlorcyclizine is a second generation antihistamine belonging to phenylpiperazine class.
7) Buclizine hydrochloride is the hydrochloride salt form of buclizine, which is a piperazine H_2-receptor antagonist.
8) Chlorpheniramine maleate is a H_1-recpetor antagonist.
9) Cimetidine is a histamine congener and competitively inhibits the binding of histamine to histamine H_2-receptors.

1.5.2. Fill in the Blanks

10) Anti-histaminic agents are the drugs that antagonise the action of _____.
11) Histamines are synthesised and released by _____ and _____ on stimulation.

12) _____ is a first gene ration antihistamine which is mainly used for treating seasonal allergies.
13) _____ is a H_1-recpetor antagonist.
14) _____ is a phenylalkylamine sympathomimetic amine.
15) _____ is a long-acting, non-sedating second generation antihistamine.
is an azatadine derivative and a second generation H_1-receptor antagonist.
16) _____ is a non -imidazole blocker of those histamine receptors which mediate gastric secretion.
17) _____ is a third generation non-sedative antihistamine.

Answers

1) True	2) False	3) False	4) True
5) False	6) False	7) True	8) True
9) Histamine,	10) Basophils, Mast cells		11) Diphenhydramine
12) Chlorpheniramine maleate		13) Phenindamine tartrate	
14) Astimazole	15) Losartan	16) Ranitidine	17) Levocetrizine.

1.5.3. Very Short Answer Type Questions

1) Give the structure of histamine
2) What are the types of histamine receptors?
3) Give the structure of diphenhydramine.
4) What is the mechanism of action of clemastine fumarate?
5) Enlist uses of doxylamine succinate.
6) Give the mechanism of action of levocetrizine.

1.5.4. Short Answer Type Questions

1) Write a short note on histamine.
2) Explain histamine receptors and their distribution in the body.
3) Write a note on recent development of antihistaminic agents.
4) Give the synthesis of cimetidine.
5) Write a short note on ranitidine.

1.5.5. Long Answer Type Questions

1) Explain H_1-antagonists and give mechanism of action , uses a nd structure of following drugs:
   i) Doxylamine succinate
   ii) Clemastine fumarate
   iii) Meclizine hydrochloride
   iv) Chlorpheniramine
   v) Levocetrizine
2) Explain antihistaminic agents in detail and give its SAR.
3) Write about H_2-antagonists in d etails and mechanism of action of action, uses of following drugs:
   i) Cimetidine
   ii) Famotidine
   iii) Ranitidine

CHAPTER 2

Gastric Proton Pump Inhibitors

2.1. GASTRIC PROTON PUMP INHIBITORS

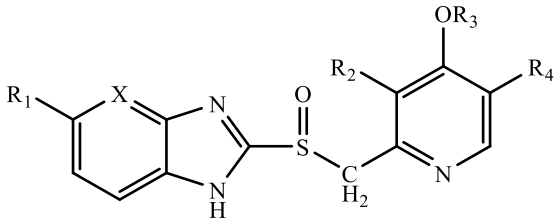
2.1.1. Introduction

Proton Pump Inhibitors (PPIs) are irreversible inhibitors of gastric parietal cell proton pump. This enzyme promotes the exchange of H^+ or K^+ ions, which are required for mediating HCl secretion. PPIs induce 80 -90% inhibition of basal, nocturnal, and food stimulated acid levels after single administration.

PPIs reduce the acid production by blocking the enzyme present in the stomach wall. Reduction in the production of acid by stomach prevents the occurrence of ulcers and also facilitates the healing of ulcers already existing in the oesophagus, stomach, and duodenum.

2.1.2. Classification

Proton pump inhibitors are classified as follows:



Drugs	X	R_1	R_2	R_3	R_4
Omeprazole	CH	OCH_3	CH_3	CH_3	CH_3
Esomeprazole (S-enantiomer)	CH	OCH_3	CH_3	CH_3	CH_3
Tenatoprazole	N	OCH_3	CH_3	CH_3	CH_3
Lansoprazole	CH	H	CH_3	CH_2CF_3	H
Rabeprazole	CH	H	CH_3	$(CH_2)_3OCH_3$	H
Pantoprazole	CH	$OCHF_2$	OCH_3	CH_3	H

2.1.3. Mechanism of Action

The H^+-K^+-ATPase proton pump of the apical membrane of parietal cell is the mediator of acid secretion . The newer substituted benzimidazoles have been developed as specific inhibitors because the H^+-K^+-ATPase proton pump is unique to parietal cells. These benzimidazoles are used in peptic ulcer.

The PPIs have a sulphinyl group in a bridge between substituted benzimidazole and pyridine rings. These agents ar e chemically stable and lipid -soluble weak bases without inhibitory activity at neutral pH. These neutral weak bases reach the parietal cells from the blood and diffuse into the secretory canaliculi.

Here the drugs become protonated and trapped. The protonated agent re-arranges for producing sulphuric acid and sulphonamide, which covalently interacts with sulphhydryl groups of cysteine at critical sites in the extra cellular domain of the H^+- K^+-ATPase. Thus, it irreversibly inhibits gastric acid secretion.

2.1.4. Uses

Proton pump inhibitors are used for treatin g ulcers and haemorrhagic ulcers caused by *Helicobacter pylori* as they inhibit the growth of *H. pylori*. They also allow the continuous use of NSAIDs in a patient with known peptic ulcer.

Proton pump inhib itors are also used for preventing recurrent haemorrhagic ulcers. Clot formation comprises of the processes that weaken in acidic environments, and the clot integrity is maintained in the ulcer bed by the suppression of gastric acid secretion by proton pump inhibitors.

For example, an intravenous infusion o f omeprazole maintains the intragastric pH above 6, thus, it supports platelet aggregation and clot stability.

Proton pump inhibitors are superior to H_2-receptor antagonists (like ranitidine) for heali ng gastric and duodenal ulcers in patients who continue the use of NSAIDs. This is because proton pump inhibitors can withstand a constant increase in gastric pH.

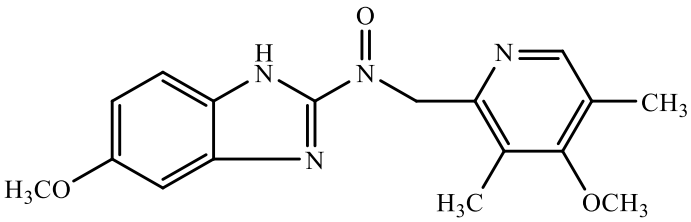
2.1.5. Study of Individual Drugs

The following gastric PPIs are discussed below:

1) Omeprazole,
2) Lansoprazole,
3) Rabeprazole, and
4) Pantoprazole.

2.1.5.1. Omeprazole

Omeprazole inhibits the proton pump and decreases the amount of acid produced in the stomach.



Omeprazole

Mechanism of Action

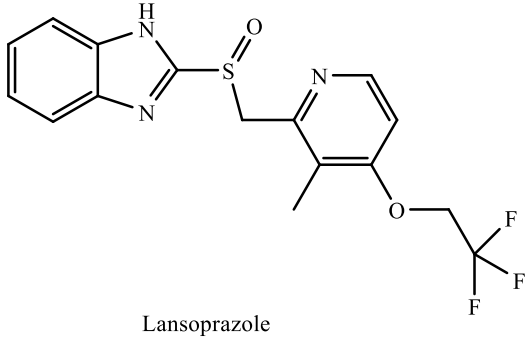
Omeprazole suppresses gastric acid secretion by inhibiting the H^+-K^+-ATPase in the gastric parietal cell. Thus, by acting specifically on the proton pump it blocks the final step in acid production, and reduces gastric acidity.

Uses

1) It is used for t reating GERD and other conditions caused by excessive production of stomach acid.
2) It is used to promote the healing of erosive oesophagitis (damage caused to oesophagus by the stomach acid).
3) It is used to relieve heartburn, difficulty in swallowing, and persistent cough.
4) It is used to prevent oesophageal cancer.
5) It is used along with antibiotics to treat gastric ulcer caused by *H. pylori*.

2.1.5.2. Lansoprazole

Lansoprazole i s a substituted benzimidazole prodrug having the selective and irreversible proton pump inhibitor activity. It prevents the production of acid in the stomach.



Lansoprazole

Mechanism of Action

Lansoprazole is an anti -secretory compound. It is a substituted benzimidazole that is devoid of anticholinergic or H_2-receptor antagonist properties. However, it suppresses gastric acid secretion by inhibiting the H^+-K^+-ATPase enzyme system at the secretory surface of gastric parietal cell.

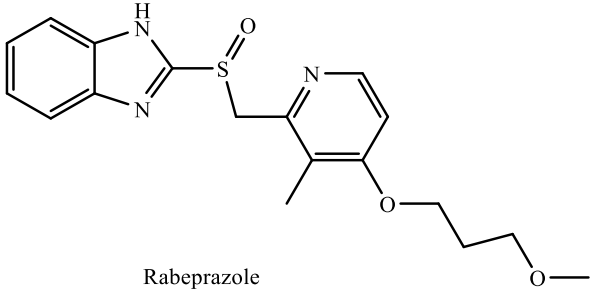
Since this enzyme system i s the acid (proton) pump in the parietal cell, lansoprazole is considered the gastric acid-pump inhibitor which inhibits the final step of acid production . This effect is dose -dependent and inhibits the basal as well as stimulated gastric acid secretion irrespective of the stimulus.

Uses

1) It is used for treating acid -reflux disorders (like GERD) and peptic ulcer disease.
2) It is used for *H. pylori* eradication.
3) It is used in combination with NSAIDs for preventing gastrointestinal bleeding.

2.1.5.3. Rabeprazole

Rabeprazole is an antiulcer drug that blocks the H^+-K^+-ATPase of the coating gastric cells. It also inhibits the dose -dependent oppresses basal and stimulated gastric acid secretion.



Rabeprazole

Mechanism of Action

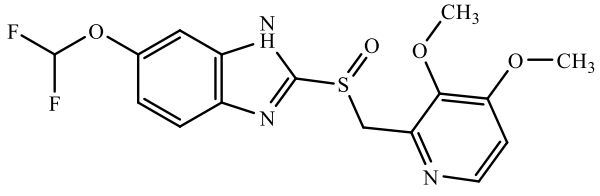
Rabeprazole is an anti -secretory compound. It is a substituted benzimidazole proton-pump inhibitor that suppresses gastric acid secretion by inhibiting the H^+-K^+-ATPase enzyme system at the secretory surface of gastric parietal cell. Since this enzyme system is the acid (proton) pump i n the parietal cell, rabeprazole is considered the gastric acid -pump inhibitor which inhibits the final step of acid production.

Uses

1) It is used in the treatment of Gastroes ophageal reflux disease (GERD) and poorly responsive systemic GERD.
2) It is used in severe erosive esophagitis.
3) It is used in pathol ogic hypersecretory conditions, like Zollinger-Ellison syndrome, systemic mastocytosis, and multiple endocrine adenomas.
4) It is used for treating duodenal ulcers with or without anti -infectives for *Helicobacter pylori.*
5) It is also used for curing the daytime or night time heartburn.

2.1.5.4. Pantoprazole

Pantoprazole is a first generation PPI. It is also used for treating other disorders wherein gastric acid secretion needs to be reduced. Pantoprazole is available in many forms, such as a delayed -release oral capsule, oral suspension, and intravenous injection.



Pantoprazole

Mechanism of Action

Pantoprazole is a substituted benzimidazole derivative and a weak base. It collects in the acidic space of the pa rietal cell and then converts into active sulfenamide derivatives in the acidic environment of the canaliculi of gastric

parietal cell. The active derivatives obtained inhibit the function of gastric acid pump by making disulfide bonds with important cyste ines on the pump. Pantoprazole binds to the sulfhydryl group of H^+-K^+-ATPase (an enzyme that accelerates the final step in acid secretion pathway). This enzyme is inactivated and gastric acid secretion is inhibited.

Uses

1) Pantoprazole injection is given t o patients having GERD and history of erosive esophagitis for short -term treatment (7 -10 days). It is given as an alternate to pantoprazole delayed-release tablets in patients who are not able to swallow the tablets.
2) It is used in the treatment of pathological hypersecretory conditions related to Zollinger-Ellison syndrome or other neoplastic conditions.
3) Pantoprazole delayed-release oral suspension is used for short-term treatment of erosive esophagitis related to GERD.
4) It is also used to promote the healing of erosive esophagitis and decrease the relapse rates of daytime and night time heartburn symptoms in adult patients of GERD.

2.2. SUMMARY

The details given in the chapter are summarised as follows:

1) **Proton Pump Inhibitors** (PPIs) are irreversible inhibitor s of gastric parietal cell proton pump.
2) PPIs induce 80 -90% inhibition of basal, nocturnal, and food stimulated acid levels after single administration.
3) PPIs reduce the acid production by blocking the enzyme present in the stomach wall.
4) Proton pump inhibit ors are used for treating ulcers and haemorrhagic ulcers caused by *Helicobacter pylori* as they inhibit the growth of *H. pylori*.
5) Proton pump inhibitors are superior to H_2-receptor antagonists (like ranitidine) for healing gastric and duodenal ulcers in pati ents who continue the use of NSAIDs.
6) **Omeprazole** inhibits the proton pump and decreases the amount of acid produced in the stomach.
7) **Lansoprazole** is a substituted benzimidazole prodrug having the selective and irreversible proton pump inhibitor activity.
8) **Rabeprazole** is an antiulcer drug that blocks the H^+-K^+-ATPase of the coating gastric cells. It also inhibits the dose -dependent oppresses basal and stimulated gastric acid secretion.
9) **Pantoprazole** is a first generation PPI. It is also used for treating other disorders wherein gastric acid secretion needs to be reduced.
10) Pantoprazole is a substituted benzimidazole derivative and a weak base.

2.3. EXERCISE

2.3.1. True or False

1) Proton Pump Inhibitors are reversible inhibitors of gastric parietal cell proton pump.
2) PPIs induce 80-90% inhibition of basal, nocturnal, and food stimulated acid leve ls after single administration.
3) PPIs reduce the acid production by blocking the enzyme present in the stomach wall.
4) Proton pump inhibitors are superior to H_1-receptor antagonists.
5) Omeprazole inhibits the proton pump and decreases the amount of acid produced in the stomach.

2.3.2. Fill in the Blanks

6) Proton pump inhibitors are superior to _____ for healing gastric and duodenal ulcers in patients who continue the use of NSAIDs.
7) _____ is a substituted benzimidazole prodrug having the selective and irreversible proton pump inhibitor activity.
8) _____ is an antiulcer drug that blocks the H^+-K^+-ATPase of the coating gastric cells.
9) Pantoprazole is a _____ generation PPI.
10) Pantoprazole is a substituted _____ derivative and a weak base.

Answers

1) False 2) True 3) True 4) False
5) False 6) H_2-receptor antagonists 7) Lansoprazole
8) Rabeprazole 9) First 10) Benzimidazole.

2.3.3. Very Short Answer type Questions

1) Define proton pump inhibitors.
2) Classify proton pump inhibitors.
3) What are the uses of proton pump inhibitors?
4) Give structure of omeprazole.
5) Give structure of pantoprazole.

2.3.4. Short Answer Type Questions

1) Give the mechanism of action of proton pump inhibitors.
2) What are the uses of proton pump inhibitors?
3) Give the structure and uses of pantoprazole.

2.3.5. Long Answer Type Question

1) Explain proton pump inhibitor in detail and give structure, mechanism of action and uses of the following drugs:
    i) Omeprazole
    ii) Lansoprazole
    iii) Rabeprazole
    iv) Pantoprazole

CHAPTER 3

Antineoplastic Agents

3.1. ANTI-NEOPLASTIC AGENTS

3.1.1. Introduction

Cancer is a disease characterised by abnormal and uncontrolled cell division attacking the surrounding tissues and organs, and also the distant body parts by circulating with blood and lymph. Cancer is classified into the following categories:

1) **Carcinoma:** This type of cancer starts in the skin or tissues lining the internal organs. There are many sub-types of carcinoma, like adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.
2) **Sarcoma:** This type of cancer starts in the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissues.
3) **Leukaemia:** This type of cancer starts in the blood-forming tissues (i.e., the bone marrow) and produces numerous abnormal blood cells.
4) **Lymphoma and Myeloma:** This type of cancer starts in the cells of immune system.
5) **Central Nervous System Cancers:** This type of cancer starts in the brain and spinal cord tissues.

Antineoplastic or **anticancer drugs** are used for treating malignancies or cancerous growths. Either these drugs are used alone (chemotherapy) or in combination with surgery or radiation therapy.

3.1.2. Classification

The anti-neoplastic agents are classified as follows:

1) **Alkylating agents**	
Nitrogen mustards	Mechlorethamine (Mustine HCl), Ifosfamide, Cyclophosphamide, Chlorambucil, and Melphalan
Ethylenimine	Thiotepa
Alkyl sulfonate	Busulfan
Nitrosoureas	Carmustine (BCNU) and Lomustine (CCNU)
Triazine	Dacarbazine (DTIC)
2) **Antimetabolites**	
Folate antagonist	Methotrexate (Mtx)
Purine antagonist	6-Mercaptopurine (6-MP), 6-Thioguanine (6-TG), and Azathioprine
Pyrimidine antagonist	5-Fluorouracil (5-FU) and Cytarabine (cytosine arabinoside)

3) **Natural Products**	
Vinca alkaloids	Vincristine (Oncovin) and Vinblastine
Taxanes	Paclitaxel and Docetaxel
Epipodophyllo toxin	Etoposide
Camptothecin analogues	Topotecan and Irinotecan
4) **Antibiotics**	Actinomycin D, Dactinomycin, Doxorubicin, Daunorubicin, Rubidomycin, Mitoxantrone, Bleomycin, Mitomycin C, and Mithramycin
5) **Enzymes**	Asparaginase (Elspar)
6) **Miscellaneous**	Hydroxyurea, Procarbazine, L -Asparaginase, Cisplatin, and Carboplatin
7) **Hormones**	
Glucocorticoids	Prednisolone
Estrogens	Fosfestrol and Ethinylestradiol
Antiestrogen	Tamoxifen
Antiandrogen	Flutamide
5-α reductase inhibitor	Finasteride
GnRH analogues	Nafarelin and Goserelin
Progestins	Hydroxyprogesterone Acetate, etc.
8) **Radioactive Isotopes**	Sodium phosphate, Sodium iodide, and Radio gold solution

3.1.3. Mechanism of Action

The cytotoxic drugs mostly affect DNA synthesis and cell division. These drugs are classified as per their site of action affecting the DNA synthesis process in the cancer cell. Therefore, c ytotoxic drugs are most effective against the actively cycling/proliferating cells (both normal and malignant) and are least effective against the non-dividing cells.

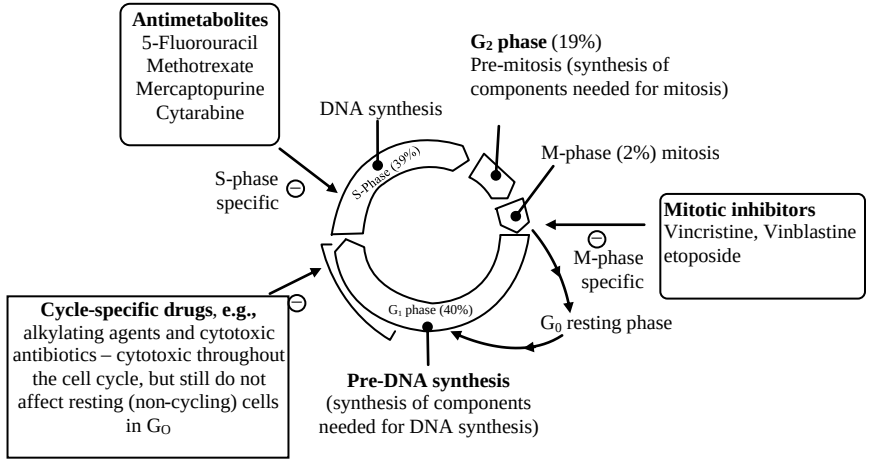


Figure 3.1: Cell Cycle and Point of Action of Phase-Specific Drugs.
DNA, Deoxyribonucleic Acid

Certain drugs effectively kill the cycling cells during specific cell cycle phases; these drugs are called **phase-specific drugs** (**figure 3.1**). Some other drugs like alkylating agents, are cytotoxic towards the cycling cells in the cell cycle; these drugs are called **cycle-specific drugs**.

3.1.4. Recent Developments

The current strategies for drug development involve drugs with novel modes of action, monoclonal antibodies directed against specific cellular targets, drugs modulating or reversing drug resistance, and drugs used for providing supportive care to the cancer patients. Simple and effective antiemetic therapy and hematopoietic growth factors are the supportive therapies due to which the administration and management of chemotherapy has become safer and easier.

The goals of traditional chemotherapy were limited to ease the symptoms only. Increasing the cytotoxic chemotherapy resulted in significant tumour regression and also improved the control of cancer. The development and acceptance of combination chemotherapy improved the outcome for incurable neoplastic diseases. This newer approach to cancer treatment included the theoretical point that targeting multiple biochemical processes produces a greater overall effect on tumour regression and remission. The chemotherapy goals shifted to a curative approach for cancers that showed complete responses to chemotherapy.

Table 3.1: Chemotherapy Sensitive Tumours

Relative Chemosensitivity and Expected Survival Outcome	Types of Cancer
1) **Highly Sensitive:** Normal survival, possible cure	Acute leukaemia in children, Hodgkin's disease, Diffuse large cell lymphoma, Burkitt's lymphoma, Wilms' tumour, Testicular carcinoma, Embryonal carcinoma, Ewing's sarcoma, and Skin cancer.
2) **Moderately Sensitive:** Increase in survival	Ovarian carcinoma, Breast carcinoma, Endometrial carcinoma, Acute leukaemia in adults, Small cell lung cancer, Prostate cancer, Stomach cancer, Cervical cancer, and Neuroblastoma.
3) **Minimally Sensitive:** Some increase in survival	Head and neck cancers, Gastrointestinal cancers, Endocrine gland tumours, Malignant melanoma, Osteogenic sarcoma, and Soft tissue sarcoma.
4) **Marginally Sensitive:** No documented increase in survival	Bladder cancer, Oesophageal cancer, Non-small cell lung cancer, Pancreatic carcinoma, and Hepatocellular carcinoma.

3.2. ALKYLATING AGENTS

3.2.1. Introduction

Alkylating agents exert cytotoxic and radiomimetic actions. Many of these agents act on dividing and resting cells, and thus are cell cycle-non-specific. Some of these agents show CNS stimulant and cholinergic properties. Alkylating agents are chemically reactive compounds. It combines most easily with nucleophilic centres, and a fully saturated carbon atom of the alkylating group attaches to the nucleophile.

The term **alkylating agent** is used for a compound that reacts with a substance by joining with covalent bond and alkylates it. Any antineoplastic agent that acts by such a mechanism is an alkylating agent.

3.2.2. Mechanism of Action

Alkylating agents shows three different mechanisms:

1) The alkyl groups attach to DNA bases , and the DNA fragment by repair enzymes in their attempt to replace the alkylated bases, thus inhibiting DNA synthesis and RNA transcription from the affected DNA.
2) Cross-links (bonds between atoms in the DNA) are formed that stop DNA from getting separated for synthesis or transcription, thus damaging the DNA.
3) Mis-pairing of nucleotides occurs that causes mutations.

3.2.3. Classification

Alkylating agents are classified as follows:

1) **Nitrogen Mustards**
   i) Mechlorethamine
   ii) Cyclophosphamide
   iii) Ifosfamide
   iv) Chlorambucil
   v) Melphalan
2) **Ethylenimine**
   i) Thiotepa
   ii) Altretamine
   iii) Carboquone
   iv) Triaziquone
3) **Alkyl Sulfonate**
   i) Busulfan
   ii) Treosulfan
   iii) Mannosulfan
4) **Nitrosoureas**
   i) Carmustine
   ii) Lomustine
   iii) Semustine
   iv) Streptozocin
5) **Triazine**
   i) Dacarbazine
   ii) Temozolomide

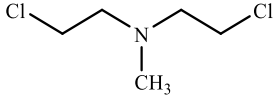
3.2.4. Study of Individual Drugs

The following alkylating agents are discussed below:

1) Mechlorethamine,
2) Cyclophosphamide,
3) Melphalan,
4) Chlorambucil,
5) Busulfan, and
6) Thiotepa.

3.2.4.1. Mechlorethamine

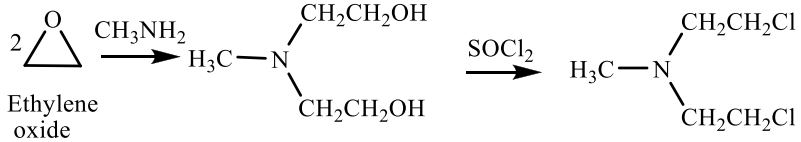
Mechlorethamine is the first nitrogen mustard. It is highly reactive and is administered intravenously. It is a vesicant and necrotis ing irritant that is destructive to mucous membranes.



Mechlorethamine

Synthesis

Mechlorethamine is synthesised when 2,2′-(methylimino) diethanol is chlorinated with thion yl chlo ride; the reaction also involves elimination of sulphurous acid.



Ethylene oxide

Mechlorethamine

Mechanism of Action

Mechlorethamine forms highly reactive carbonium ion interm ediates that react with strong nucleophilic substituents (**e.g.,** phosphate, amino, –SH, –OH, –COOH and imi dazole groups) to form covalent bonds, thus alkylating the target molecule. Guanine in DNA is very susceptible at its N-7 position.

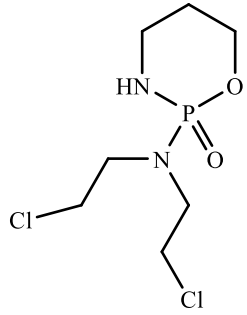
Therefore, alkylation of guanine results in cross-linking of DNA strands, linking of DNA to a closely related protein, base pairing of guanine with thymine (and not with cytosine), or breakage of DNA strand.

Uses

1) It is used for the treatment of stages III and IV of Hodgkin' s disease, lymphosarcoma, chronic myelocytic or chronic lymphocytic leukaemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma.
2) It is also used for the treatment of metastatic carcinoma.

3.2.4.2. Cyclophosphamide

Cyclophosphamide is a precursor of alkylating nitrogen mustard antineoplastic and immunosuppressive agent. It activates in the liver to form the active aldophosphamide.



Cyclophosphamide

Mechanism of Action

Cyclophosphamide is a cell cycle-non-specific cytotoxic agent. It acts against the cells that are actively dividing and resting before entering the cell cycle. The hepatic cytochrome P-450 enzyme system activates cyclophosphamide to make it cytotoxic. It alkylates DNA and forms cross-links between DNA strands.

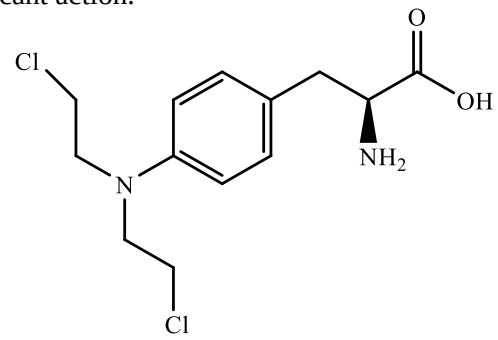
These cross -links interfere with DNA replication and transcription, thus cell proliferation is inhibited ult imately resulting in c ell death. The activity of cyclophosphamide is maximum when a cell is replicating its DNA. This is because at this stage the unpairing of DNA strands makes the nucleotide residues more susceptible to alkylation.

Uses

1) It is used in the treatment of malignant lymphomas, multiple myeloma, leukaemia, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, and carcinoma of breast.
2) It is also used in biopsy -proven minimal change nephrotic syndrome in paediatrics.

3.2.4.3. Melphalan

Melphalan is an alkylating nitrogen mustard, whose levo isomer (melphalan), racemic mixture (merphalan), and the dextro isomer (medphalan) are used as antineoplastic agents. It is toxic to bone marrow, but is a potential carcinogen and has a little vesicant action.



Melphalan

Mechanism of Action

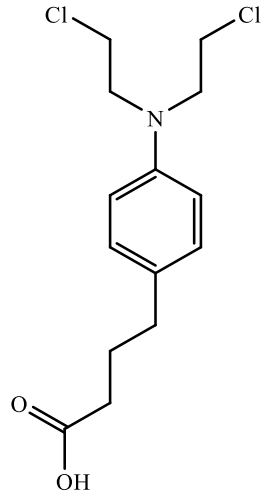
Melphalan causes breaks and cross -linkages in DNA strands along with miscoding and breakage, thus prevents cell replication.

Uses

1) It is used for the treatment of multiple myeloma and non-resectable epithelial carcinoma of ovaries.
2) It is used alone or as part of many chemotherapeutic regimens as an adjunct to surgery for treating breast cancer.
3) It is used alone or in combination regimens in the treatment of locally recurrent or unresectable in-transit metastatic melanoma of the extremities.
4) It is used with prednisone in the treatment of amyloidosis.

3.2.4.4. Chlorambucil

Chlorambucil is a nitrogen mustard alkylating agent that is used as an antineoplastic agent for treating many malignant and non-malignant diseases.



Chlorambucil

Mechanism of Action

Chlorambucil is a bifunctional alkylating agent, an analogue of nitrogen mustard, and cell cycle -non-specific. It cross -linkages with DNA, and inhibits DNA synthesis and function.

During all the phases of cell cycle, c hlorambucil alkylates and cross -links DNA, and induces DNA damage by the following methods of covalent adduct generation with double-helical DNA:

1) The alkyl groups attach to DNA bases, and the DNA fragment by re pair enzymes in their attempt to replace the alkylated bases, thus inhibiting DNA synthesis and RNA transcription from the affected DNA.
2) Cross-links (bonds between atoms in the DNA) are formed that stop DNA from getting separated for synthesis or transcrip tion, thus damaging the DNA.
3) Mis-pairing of nucleotides occurs that causes mutations.

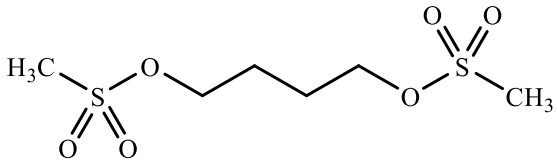
The exact mechanism of action of chlorambucil to kill the tumour cells is still not understood clearly.

Uses

Chlorambucil is used in the treatment of chronic lymphatic leukaemia, childhood minimal-change nephrotic syndrome, and malignant lymphomas including lymphosarcoma, giant follicular lymphoma, Hodgkin's disease, non -Hodgkin's lymphomas, and Waldenström's Macroglobulinemia.

3.2.4.5. Busulfan

Busulfan is a b ifunctional alkylating agent. It exerts a selective immunosuppressive effect on bone marrow. It is not a structural analogue of nitrogen mustards. It is used in the treatment of chronic myeloid leukaemia; however, it provides only symptomatic relief and no permanent cure.



Busulfan

Mechanism of Action

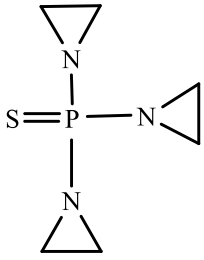
Busulfan is a bifunctional alkylating agent and cell cycle -non-specific. It interacts with the thiol groups of proteins and nucleic acids and forms DNA-protein and DNA -DNA cross-links. These cross -linkages prevent the synthesis and function of DNA.

Uses

1) It is used with cyclophosphamide as a conditioning regimen before allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous (myeloid, myelocytic, and granulocytic) leukaemia.
2) It is also a component of pre-transplant conditioning regimen in bone marrow transplantation for acute myeloid leukaemia and non-malignant diseases.

3.2.4.6. Thiotepa

Thiotepa is a cancer chemotherapeutic member of the alkylating agent group. It is in use since 50 years. It is a stable derivative of N,N',N'' -triethylenephosphoramide (TEPA), and its main toxicity is myelosuppression.



Thiotepa

Mechanism of Action

Thiotepa attaches to the guanine base of DNA at the N 7 position of the imidazole ring. It stops the tumour growth by cross-linking guanine nucleobases in DNA double-helix strands. As a result, DNA replication is inhibited because the strands fail to uncoil and separate. Thus, the cells fail to divide.

Uses

1) It is used for treating breast, ovarian and bladder cancer.
2) It is also used as conditioning for bone marrow transplantation.
3) It is used as a conditioning treatment before allogeneic or autologous Haematopoietic Progenitor Cell Transplantation (HPCT) in adult and paediatric patients having haematological diseases.

3.3. ANTIMETABOLITES

3.3.1. Introduction

Antimetabolites show interference with the availability of normal purine or pyrimidine nucleotide precursors either by inhibiting their synthesis, or by competing with them in DNA or RNA synthesis.

Antimetabolite drugs are the first effective chemotherapeutic agents. These drugs are low molecular weighed analogues of folic acid, pyrimidine or purine. Th eir structures are similar to those of naturally occurring molecules involved in nucleic acid (DNA and RNA) synthesis. Antimetabolites are identical to the chemicals required for normal biochemical activity. However, they are sufficiently different to interfere with normal cell functioning.

3.3.2. Mechanism of Action

Antimetabolites are structurally similar to norma l metabolic constituents, like folic acid, pyrimidines, or purines. The y act by inhibiting the enzymes required for folic acid regeneration or pyrimidine or purine activation of DNA or RNA synthesis in neoplastic cells. Antimetabolites commonly kill the cells in S phase.

3.3.3. Classification

Antimetabolites are classified as follows:

1) **Folate Antagonist:** Methotrexate
2) **Purine Antagonist s:** 6-Mercaptopurine, 6-Thioguanine, Azathioprine, and Fludarabine.
3) **Pyrimidine Antagonist s:** 5-Fluorouracil, Cytarabine, Gemcitabine, and Decitabine.

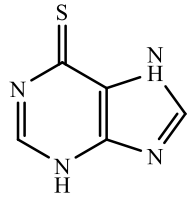
3.3.4. Study of Individual Drugs

The following antimetabolites are discussed below:

1) Mercaptopurine,
2) Thioguanine,
3) Fluorouracil,
4) Floxuridine,
5) Cytarabine,
6) Methotrexate, and
7) Azathioprine.

3.3.4.1. Mercaptopurine

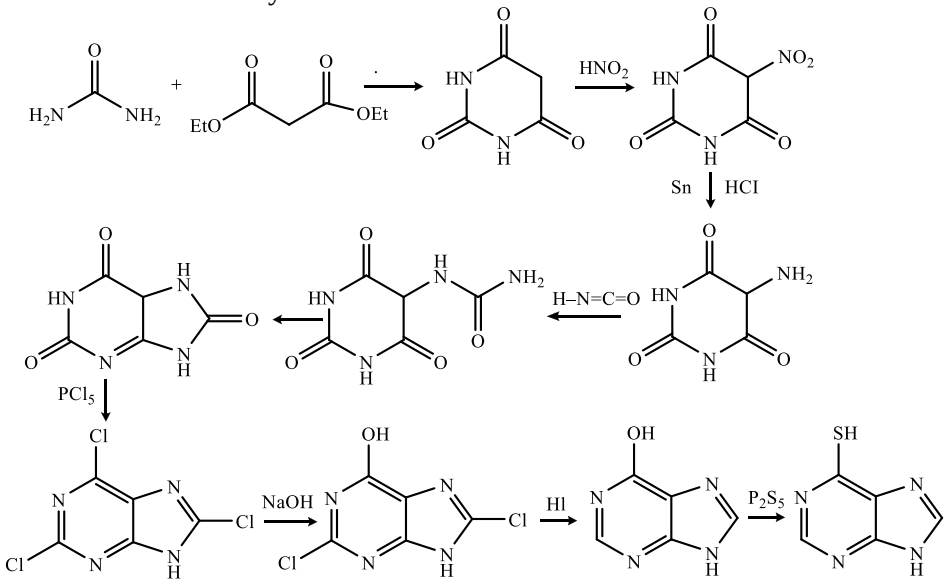
Mercaptopurine is an an timetabolite antineoplastic drug having immunosuppressant properties. It prevents purine metabolism, thus inhibits nucleic acid synthesis . It is used with other drugs for the treatment of or in remission maintenance programs for leukaemia.



Mercaptopurine

Synthesis

Mercaptopurine is synthesised by mercaptopurine metabolism by hypoxanthine - guanine phosphoribosyltransferase (HGPRTase). The metabolites of mercaptopurine are 6-thioguanosine-5'-phosphate (6-thioGMP) and 6 - thioinosine monophosphate (T-IMP). These metabolites prevent nucleotide inter-conversions and *de novo* purine synthesis, thus prevent the formation of purine nucleotides and DNA synthesis.



Mechanism of Action

Mercaptopurine competes with hypoxanthine and guanine for hypoxanthine - guanine phosphoribosyltransferase (HGPRTase). It converts into thioinosinic acid (TIMP). This intracellular nucleotide blocks the reactions in which inosinic acid (IMP) is involved, such as IMP conversion into xanthylic acid (XMP) and IMP conversion into adenylic acid (AMP) by adenylosuccinate (SAMP).

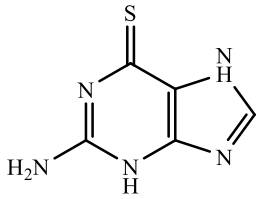
TIMP undergoes methylation to form 6-methylthioinosinate (MTIMP). TIMP along with MTIMP block glutamine-5-phosphoribosylpyrophosphate amidotransferase (first enzyme unique to the *de novo* pathway for purine ribonucleotide synthesis).

Some mercaptopurine converts into nucleotide derivatives of 6 -thioguanine (6-TG) through the sequential actions of inosinate (IMP) dehydrogenase and xanthylate (XMP) aminase, converting TIMP to thioguanylic acid (TGMP).

Uses
It is used for remission induction and maintenance therapy of acute lymphatic leukaemia.

3.3.4.2. Thioguanine

Thioguanine is an antineoplastic compound, also having antimetabolite action. It is used in the therapy of acute leukaemia.



Thioguanine

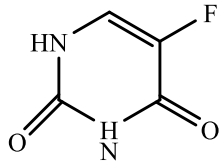
Mechanism of Action
Thioguanine is a cell cycle -specific purine analogue that acts in the S -phase. Its cytotoxic monophosphate form interferes with purine synthesis and is utilised in the following three ways:

1) Feedback inhibition of *de novo* purine synthesis,
2) Inhibition of inter-conversions of purine nucleotide, and
3) Incorporation into DNA and RNA.

Uses
It is used for remission induction and remission consolidation treatment of acute non-lymphocytic leukaemia.

3.3.4.3. Fluorouracil

Fluorouracil is a pyrimidine analogue which is an antineoplastic antimetabolite. It inhibits DNA synthesis by preventing the conversion of thymidylate synthetase of deoxyuridylic acid into thymidylic acid.



Fluorouracil

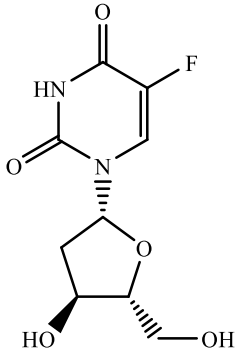
Mechanism of Action
The exact mechanism of action of fluoro uracil is not clearly understood; however, it is thought to act by the binding of deoxyribonucleotide of the drug (FdUMP) and N5 –10-methylenetetrahydrofolate (the folate cofactor) to Thymidylate Synthase (TS) to form a covalently bound ternary complex. Thi s prevents the formation of thymidylate from uracil, thus inhibiting DNA and RNA synthesis and ultimately causing cell death. Fluorouracil can also be incorporated into RNA in place of Uridine Triphosphate (UTP), thus forming a false RNA and interfering with RNA processing and protein synthesis.

Uses

1) It is used in acute lymphocytic leukaemia , Crohn's disease , and ulcerative colitis.
2) It is used for treating the slowly growing solid tumours (**e.g.,** colorectal, breast, ovarian, pancreatic, and gastric carcinomas).
3) It is used with levamisole (a veterinary anthelmintic agent) in patients having colon cancer.
4) On topical application, it is effective in superficial basal cell carcinomas.

3.3.4.4. Floxuridine

Floxuridine is an antineoplastic antimetabolite that on rapid administration through injections metabolise into fluorouracil. It is available as a s terile, non-pyrogenic, lyophilised powder for reconstitution.



Floxuridine

Mechanism of Action

Floxuridine metabolises in to the active 5-fluorouracil. It mainly interferes with DNA s ynthesis and also inhibits RNA formation (to a lesser extent) by incorporating into it and producing a false RNA . Fluorouracil also blocks uracil riboside phosphorylase that inhibits the utilisation of pre-formed uracil in RNA synthesis.

The monophosphate of floxuridine, i.e., 5-fluoro-2'-deoxyuridine-5'-phosphate (FUDR-MP) blocks thymidylate synthetase enzyme, thus preventing DNA synthesis by blocking the methylation of deoxyuridylic acid to thymidylic acid.

Uses

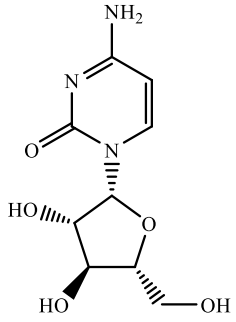
1) It is given by continuous regional intra -arterial infusion (in patients that cannot be cured by surgery or other methods) for the management of gastrointestinal adenocarcinoma metastatic to the liver.
2) It is given through hepatic intra-arterial infusion for the management of liver cancer.

3.3.4.5. Cytarabine

Cytarabine is a pyrimidine nucleoside analogue used for treating leukaemia, especially acute non-lymphoblastic leukaemia.

Mechanism of Action

Cytarabine acts by direct ly incorp orating into and damaging DNA. It is cytotoxic to various proliferating mammalian cells in culture. It shows cell phase specificity, and kill cells undergoing DNA synthesis (S - phase) and under conditions that block the progression of cells from the G1 phase to S-phase.



Cytarabine

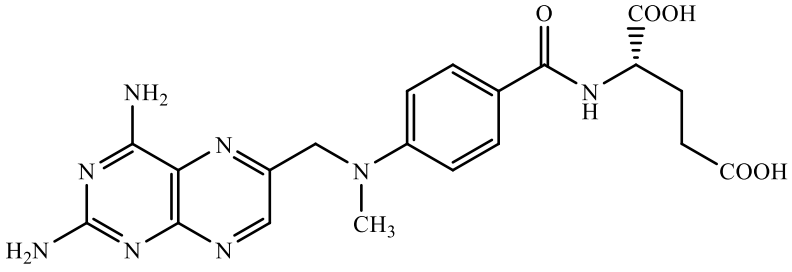
While, the mechanism of action of cytarabine is not completely understood, it is thought to act by inhibiting DNA polymerase.

Uses

It is used for treating acute non -lymphocytic leukaemia, acute lymphocytic leukaemia, and the last phase of chronic myelocytic leukaemia.

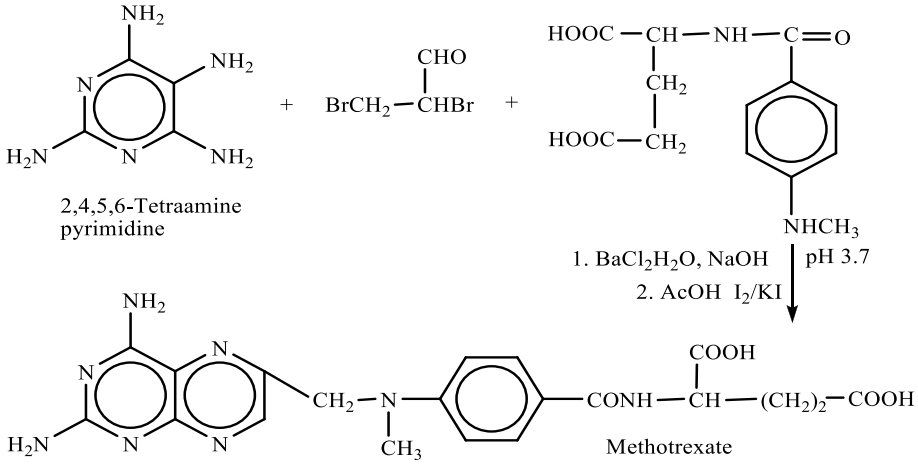
3.3.4.6. Methotrexate

Methotrexate (MTX) is an antineoplastic antimetabolite with immunosuppressant properties. It inhibits the formation of tetrahydrofolate dehydrogenase, which is required for the synthesis of thymidylate (an important DNA component).



Methotrexate

Synthesis



2,4,5,6-Tetraamine pyrimidine

Methotrexate

Mechanism of Action

MTX binds to the active catalytic site of dihydrofolate reductase, and disrupts the synthesis of the reduced form that accepts a carbon. Due to the non -availability of this cofactor, synthesis of thymidylate, purine nucleotides, amino acids, serine, and methionine is blocked; this in turn prevents the formation of DNA , RNA, and proteins.

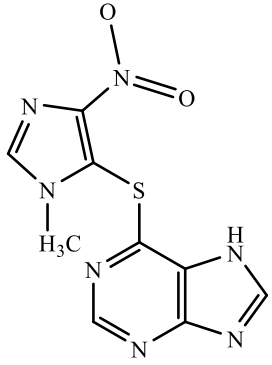
Inhibition of dihydrofolate reductase can be reversed by dihydrofolate , or by administration of leucovorin, which bypasses the blocked enzyme, replenishing the folate pool.

Uses

1) It is effectively used with other drugs in acute lymphocytic leukaemia, choriocarcinoma, Burkitt lymphoma in children, breast cancer, and head and neck carcinomas.
2) It is alone effective in low doses against certain inflammatory diseases (**e.g.,** severe psoriasis).

3.3.4.7. Azathioprine

Azathioprine is an immunosuppressive antimetabolite prodrug and an imidazolyl derivative of 6 -mercaptopurine. Most of its biological effects are similar to that of the parent compound. Azathioprine converts into 6 -mercaptopurine in the body and inhibits purine metabolism and DNA synthesis.



Azathioprine

Mechanism of Action

Azathioprine antagonises purine metabolism. It prevents the synthesis of DNA, RNA, and proteins. It also interferes with cellular metabolism and prevents mitosis. It acts due to the incorporation of thiopurine analogues into the DNA structure, thus terminating the chain and causing cytotoxicity.

Uses

1) It is used for treating rheumatoid arthritis, Crohn,s disease, and colitis.
2) It is used for preventing renal transplant rejection.
3) It is mostly used as an adjunct for the management and prevention towards the rejection of renal homotransplants.

3.4. ANTIBIOTICS

3.4.1. Introduction

Antibiotics have been recently recognised as an important class of antineoplastic agents. Thus, the antineoplastic agents should be produced by proper strain selection and controlled microbial fermentation conditions to optimise the development of a specific component in an antibiotic mixture. Antibiotics act by binding to DNA or fit ting into the helical lattice between specific bases, thus blocking the transcription of new RNA and DNA and cell replication.

For certain types of c ancer, therapeutic antibiotics have become an accepted treatment. They bind to primary and metastatic cancer cells to inhibit the growth of cancer cells, and limiting the effects on surrounding healthy cells. They are also known as the **antitumour** or **anticancer antibiotics**, and can also be used to treat or prevent infections caused due to cancer treatments.

3.4.2. Study of Individual Drugs

The following anticancer antibiotics are discussed below:

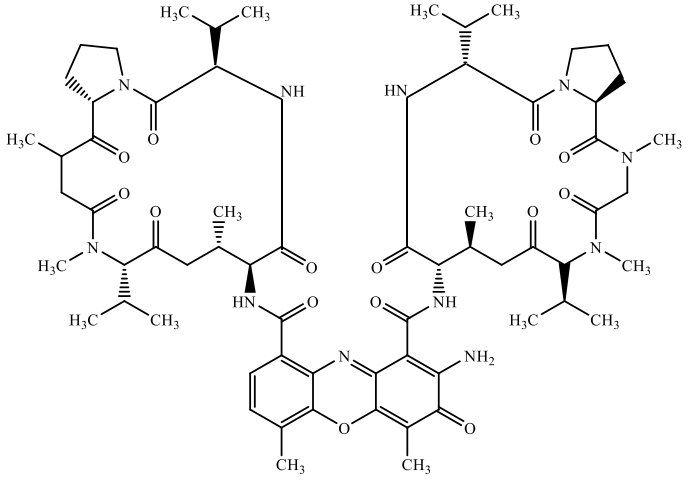
1) Dactinomycin,
2) Daunorubicin,
3) Doxorubicin, and
4) Bleomycin.

3.4.2.1. Dactinomycin

Dactinomycin is a high molecular weight antineoplastic antibiotic, which is isolated from *Streptomyces parvulus*.

Mechanism of Action

Dactinomycin binds to DNA and blocks the RNA transcription with chain elongation more sensitive th an initiation, termination, or release. This impaired mRNA production also declines the protein synthesis.



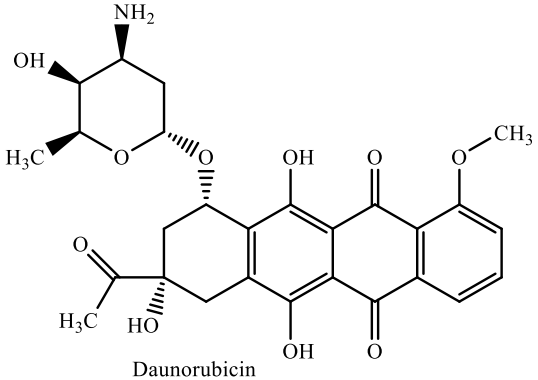
Dactinomycin

Uses

It is used as a part of combination chemotherapy and/or multi-modality treatment regimen for treating Wilms' tumour, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic, non-seminomatous testicular cancer.

3.4.2.2. Daunorubicin

Daunorubicin is a toxic anthracycline aminoglycoside antineoplastic obtained from *Streptomyces peucetius*. It is used for the treatment of leukaemia and other neoplasms.



Daunorubicin

Mechanism of Action

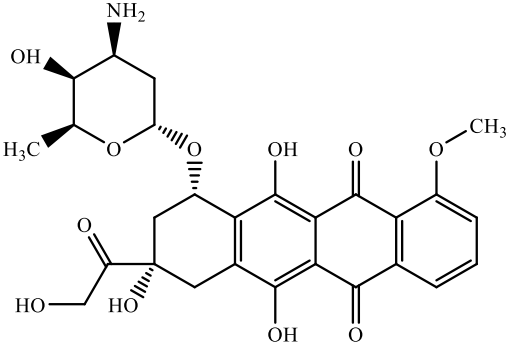
Daunorubicin exerts its antimitotic and cytotoxic activity by forming complexes with DNA through intercalation between base pairs. It blocks the activity of topoisomerase II by stabilising DNA-topoisomerase II complex, inhibiting the religation portion of the ligation-religation reaction catalysed by topoisomerase II.

Uses

1) It is used for remission induction in acute non-lymphocytic leukaemia (myelogenous, monocytic, and erythroid) in adults.
2) It is also used for remission induction in acute lymphocytic leukaemia in children and adults.

3.4.2.3. Doxorubicin

Doxorubicin is a cytotoxic anthracycline antibiotic. It is obtained from cultures of *Streptomyces peucetius* var. caesius. It binds to nucleic acids by intercalation of the planar anthracycline nucleus with the DNA double helix.



Doxorubicin

Mechanism of Action

Doxorubicin exerts its antimitotic and cytotoxic activity by forming complexes with DNA through intercalation between bas e pairs. It blocks the activity of topoisomerase II by stabilising DNA -topoisomerase II complex, inhibiting the religation portion of the ligation-religation reaction catalysed by topoisomerase II.

Uses

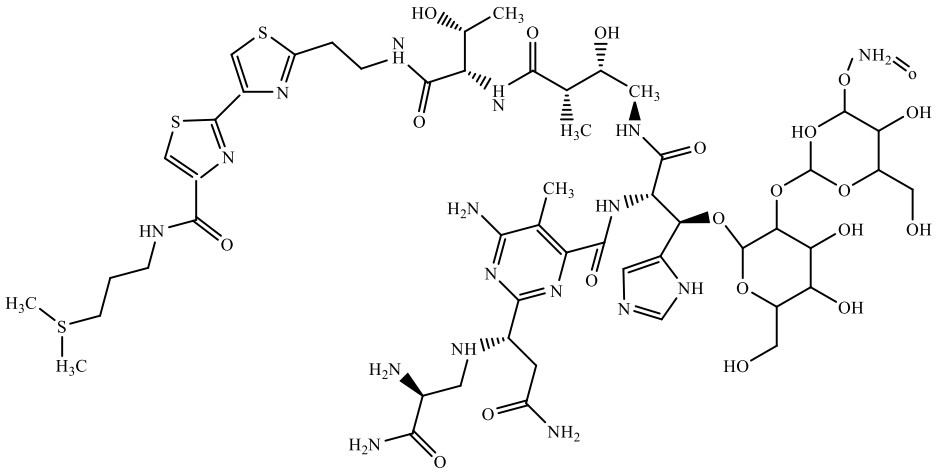
1) It is used for producing regression in disseminated neoplastic conditions such as acute lymphoblastic leukaemia, acute myeloblastic leukaemia, Wilms ' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive
2) It is also used as a part of adjuvant therapy in women showing signs of axillary lymph node involvement after the resection of primary breast cancer.

3.4.2.4. Bleomycin

Bleomycin is a complex of related glycopeptide antibiotics obtained from *Streptomyces verticillus* and consisting of bleomycin A2 and B2. It inhibits DNA metabolism and is used as an antineoplastic for treating solid tumours.

Mechanism of Action

The exact mechanism action of bleomycin is unknown, but the available evidence indicates that it inhibits DNA synthesis and also RNA and protein synthesis (to a lesser extent). Cleavage of DNA by bleomycin depends on *in vitro* oxygen and metal ions. Bleomycin chelates metal ions (chiefly iron) and forms a pseudoenzyme that reacts with oxygen to form superoxide and hydroxide free radicals that cleave DNA.



Bleomycin

Uses

It is used for the treatment of malignant neoplasm (trachea, bronchus, and lungs), squamous cell carcinoma, and lymphomas.

3.5. PLANT PRODUCTS

3.5.1. Introduction

For centuries herbal medicines have been used for treat ing various health problems in India . Herbal medicines comprise of plants or mixture of plant extracts used for treating illness and promoting health. People suffering from cancer used h erbal medicines as the most commonly used complemen tary and alternative methods . Medicinal plants relieve and treat cancer with the help of compounds having antioxidant and anticancer activities so that the carcinogenic cells can be destroyed . Some plants have a natural property to inhibit the spreading or risk of developing various forms of cancer. Some plants that are used for treating cancer are given in **table 3.2** along with their advancements:

Table 3.2: List of Medicinally Important Plants Towards Therapy

Plants	Species	Common Names	Compounds	Mechanism of Action
Autumn crocus	*Colchicum autumnale*	Naked ladies, colchicum, and meadown saffron	Colchicine	Used to treat inflammatory disorders; also valued for its chemotherapeutic properties.
Birch	*Betula alba*	Birch	Betulinic acid	Prostate cancer.
Camptotheca	*Camptotheca acuminata*	Xi Shu and happy tree	Camptothecia, topotecan, CPT -11, and 9 - aminocamptothecin	Used as drugs for cancer treatment.
Docetaxel	*Taxus baccata*	Yew	Docetaxel and taxol	Breast and lung cancer.
Hemp	*Cannabis sativa*	Marijuana, bhang, ganja, and hashish	Delta-9-tetrahydrocannabino	Widely used as a drug, co mmonly known as marijuana.
Lapacho tree	*Tabebuia impetiginosa* and *T. avellanedae*	Lapacho, pau D'arco, taheebo, and ipe roxo	β-Lapachone and lapachol	Promoted as a treatment for a number of human ailments, including cancer.
Mayapple	*Podophyllum peltatum*	Devil's apple, hog apple, Indian apple, umbrella plant, and wild lemon	Podophyllotoxin, etoposide, podophyllin acid, and teniposide	Lung and testicular cancer.
Nothapodytes tree	*Nothapodytes foetida*	Nothapodytes tree	Acetycamptothecin, camptothecin, and scopoletin.	To make anti - leukaemia and anti - tumoural.
Pacific yew	*Taxus brevifolia*	Yew	Paclitaxel	Refractory ovarian cancer.
Periwinkle	*Catharanthus roseus*	Madagascar periwinkle	Vinblastine, vincristine, vindesine, and vinorelbine.	Leukaemia, lymphoma breast, lung, and pediatric solid cancers.

3.5.2. Mechanism of Action

The medicinal herbs act against cancer through the following mechanisms:

1) **Disruption in Cell Signal Transduction Pathways:** Cancer is related to defects in signal transduction proteins that cause uncontrolled or abnormal cell growth. Following are the various pathways through which the herbal drugs block signal transduction in cancer patients:
   i) **Nuclear Factor (NF -kB) Pathways with Activator Protein -1 (Ap-1):** Nuclear factor with activator protein-1 is a transcription factor controlling various gene expressions involved in oncogenesis, apoptosis, etc. by extracellular signals. It is a protein complex that regulates DNA transcription, cytokine production , and cell survival. Inappropriate regulation of NF-kB is related to cancer, inflammatory and autoimmune diseases. Plant products block the growth of cancer ous cells by this mechanism; **for example**, botanical extract of mountain ginsengblocks the growth of lung cancer cells through regulating NF-kB signalling pathway.
   ii) **Protein Tyrosine Kinase (PTK) Pathways:** PTK enzyme is named so because it transfers a phosphate group to a protein in the cell. It may function as an active and in active form in various cellular reactions. It causes growth in signal transduction to cells.
2) **Modification in Cell Cycle:** Natural and constant balance of cell cycle safeguards standard cell escalation. Tumour is formed due to any change in cell cycle. The cell cycle elongates due to the existence in the control points in G1 and G2 phases. Neoplastic cells cannot prevent cell division at the control points (G1/S and G2/M), andthus cell proliferation becomes deregulated.
3) **Mitogen-Activated Protein Kinase (MAPK) Signal Pathways:** MAPK signalling pathway induces signals for cell division. Th erefore, carcinogenesis occurs due to the deregulation of MAPK signal pathways. These techniques are used to induce apoptosis.
4) **Cyclooxygenase (Cox-2) Pathways:** Cox-2 inhibitor catalysed prostaglandin synthesis. Its inhibition blocks cell proliferation, thus affects the growth of tumour cells.
5) **Intervention with Microtubules:** These tubules are microscopically small and found in the cell cytoplasm. They prevent the alignment of the daughter chromosomes and stop mitosis at anaphase which is lastly followed by apoptosis. Herbaceous plant phytochemicals like vinca alkaloids (vincristine and vinblastine) and taxanes are essential microtubulin-binding factors.
6) **Topoisomerase Inhibitor:** Herbal drugs have an important role in cancer treatment with balancing capacity of topoisomerases. Camptothecins block topoisomerase-I, and epipodophyllotoxins blocks topoisomerase II.

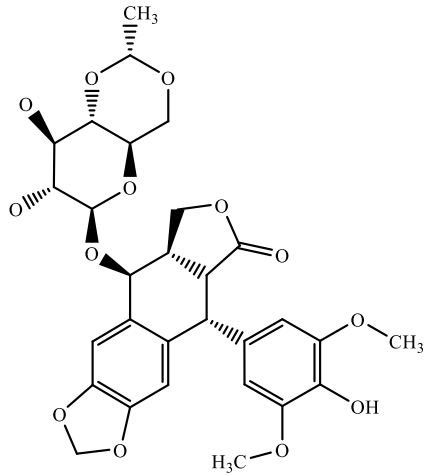
3.5.3. Study of Individual Drugs

The following plant products are discussed below:

1) Etoposide,
2) Vinblastine sulphate, and
3) Vincristine sulphate.

3.5.3.1. Etoposide

Etoposide is a semi-synthetic derivative of podophyllotoxin. It is a chemotherapy medication used for treating various forms of cancer, like testicular cancer, lung cancer, lymphoma, leukaemia, neuroblastoma, and ovarian cancer. It is administered through oral or intravenous route.



Etoposide

Mechanism of Action

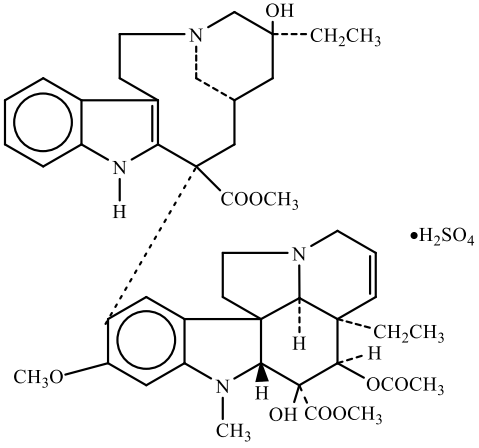
Etoposide blocks DNA topoisomerase II, hence, inhibits DNA re-ligation. It causes critical errors in DNA synthesis at the pre-mitotic stage of cell division. It also leads to apoptosis of the cancer cell. Etoposide is cell cycle dependent and also phase specific. It mainly affects the S and G2 phases of cell division. Etoposide exerts its anti-tumour activity by inhibiting topoisomerase II alpha isoform. It also inhibits the beta isoform but inhibition of this target is not related to anti-tumour activity, but to carcinogenic effect.

Uses

1) It is used in combination with other chemotherapeutic agents for treating refractory testicular tumours.
2) It is used as first line treatment in small cell lung cancer.
3) It is also used for treating other malignancies like lymphoma, non-lymphocytic leukaemia, and glioblastoma multiforme.

3.5.3.2. Vinblastine Sulphate

Vinblastine sulphate is the sulphate salt of vinblastine, which is a natural alkaloid, obtained from *Catharanthus roseus* (Madagascar periwinkle). This plant possesses antineoplastic properties.



Vinblastine sulphate

Mechanism of Action

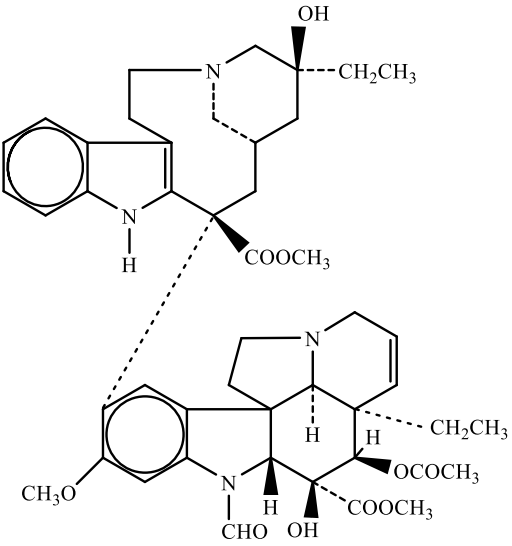
Vinblastine sulphate exerts its antitumour activity by interacting with tubulin and inhibiting mitosis at metaphase. Vinblastine binds to the microtubular proteins of the mitotic spindle and causes crystallis ation of the microtubule and mitotic arrest or cell death.

Uses

It is used in the treatment of breast cancer, testicular cancer, lym phomas, neuroblastoma, Hodgkin's and non -Hodgkin's lymphomas, mycosis fungoides, histiocytosis, and Kaposi's sarcoma.

3.5.3.3. Vincristine Sulphate

Vincristine sulphate is the sulphate salt of a natural alkaloid, which is obtained from *Catharanthus roseus* (*Vinca rosea* L.). This plant has antimitotic and antineoplastic activities.



Vincristine sulphate

Mechanism of Action

Vincristine sulphate exerts its antitumour activity by interacting with tubulin and inhibiting mitosis at metaphase. It also interferes with:

1) Metabolism of amino acid, cAMP, and glutathione,
2) Calmodulin-dependent Ca^{2+}-transport ATPase activity,
3) Cellular respiration, and
4) Biosynthesis of nucleic acid and lipid.

Uses

1) It is used for treating the Acute Lymphocytic Leukaemia (ALL), Hodgkin's lymphoma, non -Hodgkin's lymphomas, Wilms' tumo ur, n euroblastoma, rhabdomyosarcoma.
2) Liposomal vincristine is used for treating relapsed Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukaemia.

3.6. MISCELLANEOUS AGENTS

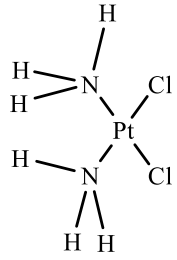
3.6.1. Study of Individual Drugs

The following drugs have been discussed below:

1) Cisplatin and
2) Mitotane.

3.6.2. Cisplatin

Cisplatin, cisplatinum or cis -diamminedichloroplatinum (II) (CDDP) is a platinum based chemotherapy drug. It is used for treating many types of cancers, such as sarcomas, some carcinomas (**e.g.,** small cell lung cancer and ovarian cancer), lymphomas, and germ cell tumours.



Cisplatin

Mechanism of Action

Cisplatin destroys the cancerous cells by binding to DNA and interfering with its repair mecha nism, thus ultimately causing cell death. When cisplatin molecule penetrates the cell membrane intact, one of its chloride ions is replaced by a water molecule. The structure obtained then binds to the single nitrogen on a DNA nucleotide. Another water mol ecule replaces the second chloride ion and the platinum binds to a second nucleotide. Studies of cisplatin binding to DNA have shown a preference for N7 on two adjacent guanines in the same strand. It also binds to adenine and across the strands to a lesser extent.

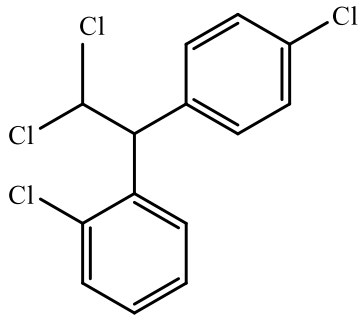
The complex of cisplatin and DNA attracts HMG (High Mobility Group)-1 and other DNA repair proteins that get irreversibly bound. It causes distortion to the DNA shape, thus inhibits effective repair , i.e., the *trans* isomer of cisplatin cannot form 1,2 intrastrand links and also do not exhibit antineoplastic activity.

Uses

It is used for treating metastatic testicular tumo urs, metastatic ovarian tumo urs, and advanced bladder cancer.

3.6.3. Mitotane

Mitotane is the derivative of dichlorodiphenyldichloroethane, which is an insecticide and blocks the cells of adrenal cortex and production of their hormones. It is used in the treatment of adrenocortical tumours and causes CNS damage.



Mitotane

Mechanism of Action

The biochemical mecha nism of action of mitotane is still not known . But, according to the present data, it changes the peripheral metabolism of steroids and directly supresses the adrenal cortex.

Uses

It is used for treating inoperable adrenocortical tumours and Cushing's syndrome.

3.7. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Cancer** is a disease characterised by abnormal and uncontrolled cell division attacking the surrounding tissues and organs, and also the distant body parts by circulating with blood and lymph.
2) **Carcinoma** starts in the skin or tissues lining the internal organs. There are many sub -types of carcinoma, like adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.
3) **Sarcoma** starts in the bone, cart ilage, fat, muscle, blood vessels, or other connective or supportive tissues.
4) **Leukaemia** starts in the blood -forming tissues (i.e., the bone marrow) and produces numerous abnormal blood cells.
5) **Lymphoma** and **myeloma** starts in the cells of immune system.
6) **Central Nervous System Cancers** start in the brain and spinal cord tissues.
7) **Antineoplastic** or **anticancer drugs** are used for treating malignancies or cancerous growths.
8) **Alkylating agents** exert cytotoxic and radiomimetic actions. Many of these agents act on dividi ng and resting cells, and thus are cell cycle -non-specific. Some of these agents show CNS stimulant and cholinergic properties.
9) The term **alkylating agent** is used for a compound that reacts with a substance by joining with covalent bond and alkylates it.

10) **Mechlorethamine** is the first nitrogen mustard. It is highly reactive and is administered intravenously.

11) **Cyclophosphamide** is a precursor of alkylating nitrogen mustard antineoplastic and immunosuppressive agent.

12) **Melphalan** is alkylating nitrogen mustard, whos e levo isomer (melphalan), racemic mixture (merphalan), and the dextro isomer (medphalan) are used as antineoplastic agents.

13) **Chlorambucil** is a nitrogen mustard alkylating agent that is used as an antineoplastic agent for treating many malignant and non -malignant diseases.

14) **Antimetabolites** show interference with the availability of normal purine or pyrimidine nucleotide precursors either by inhibiting their synthesis, or by competing with them in DNA or RNA synthesis.

15) **Mercaptopurine** is an antimetabolite anti neoplastic drug having immunosuppressant properties.

16) **Thioguanine** is an antineoplastic compound, also having antimetabolite action. It is used in the therapy of acute leukaemia.

17) **Floxuridine** is an antineoplastic antimetabolite that on rapid administration through injections metabolise into fluorouracil.

18) **Cytarabine** is a pyrimidine nucleoside analogue used for treating leukaemia, especially acute non-lymphoblastic leukaemia.

19) **Methotrexate** inhibits the formation of tetrahydrofolate dehydrogenase, which is require d for the synthesis of thymidylate (an important DNA component).

20) **Azathioprine** is an immunosuppressive antimetabolite prodrug and an imidazolyl derivative of 6-mercaptopurine.

21) **Antibiotics** act by binding to DNA or fitting into the helical lattice between specific bases, thus blocking the transcription of new RNA and DNA and cell replication.

22) **Medicinal plants** relieve and treat cancer with the help of compounds having antioxidant and anticancer activities so that the carcinogenic cells can be destroyed.

23) **Etoposide** is a semi -synthetic derivative of podophyllotoxin. It is a chemotherapy medication used for treating various forms of cancer, like testicular cancer, lung cancer, lymphoma, leukaemia, neuroblastoma, and ovarian cancer.

24) **Mitotane** is the derivative of dich lorodiphenyldichloroethane, which is an insecticide and blocks the cells of adrenal cortex and production of their hormones.

3.8. EXERCISE

3.8.1. True or False

1) Central nervous system cancers start in the brain and spinal cord tissues.
2) Mercaptopurine is a nitrogen mustard alkylating agent.
3) Lymphoma and myeloma starts in the cells of immune system.
4) Etoposide is an insecticide and blocks the cells of adrenal cortex and production of their hormones.
5) Antineoplastic drugs are used for treating malignancies or cancerous growths.
6) Leukaemia starts in the blood-forming tissues.

3.8.2. Fill in the Blanks

7) _____ is a pyrimidine nucleoside analogue used for treating leukaemia.
8) _____ is a nitrogen mustard alkylating agent.
9) _____ is a disease characterised by abnormal a nd uncontrolled cell division attacking the surrounding tissues and organs.
10) _____ is a precursor of alkylating nitrogen mustard.
11) _____ and _____ starts in the cells of immune system.
12) _____ exert cytotoxic and radiomimetic actions.

Answers

1) True 2) False 3) True 4) False
5) True 6) True 7) Cytarabine 8) Chlorambucil
9) Cancer 10) Cyclophosphamide 11) Lymphoma, Myeloma
12) Alkylating agents

3.8.3. Very Short Answer Type Questions

1) Classify cancer.
2) Give the mechanism of action of antineoplastic agents.
3) Give the uses of cyclophosphamide and melphalan.
4) Write a short note on antibiotics.
5) Discuss floxuridine.
6) Write a short note on vinblastine sulphate.

3.8.4. Short Answer Type Questions

1) Briefly discuss anticancer antibiotics.
2) Discuss mercaptopurine and thioguanine in detail.
3) Write a short note on methotrexate.
4) Discuss the recent developments in anti-neoplastic agents.
5) Give the classification of alkylating agents.

3.8.5. Long Answer Type Questions

1) Discuss the use of plant products as anticancer agents.
2) Write a detailed note on antimetabolites.
3) Discuss alkylating agents.
4) What are anti-neoplastic agents? Classify and also give recent developments.

CHAPTER 4

Anti-Anginal

4.1. ANTI-ANGINAL

4.1.1. Introduction

Angina pectoris, usually referred to as **angina**, denotes severe chest pain which may be caused by **ischemia** (lack of blood, and hence lack of oxygen supply) of heart muscle. This ischemia is the result of **obstruction** or **spasm of coronary artery** (vessels supplying blood to heart). Thus, the main cause of angina is coronary artery disease which results from atherosclerosis of the cardiac arteries.

Unstable angina (usually grouped with similar conditions as the acute coronary syndrome) may have symptoms like:

1) Worsening ("crescendo") of angina attacks,
2) Sudden onset of angina at rest, and
3) Angina lasting more than 15 minutes.

Presence of these conditions may lead to myocardial infarction (a heart attack), thus, needs medical aid on an urgent basis. Anti-anginal drug therapy aims at restoring the balance between the supply and demand of oxygen in the ischemic area of the myocardium.

4.1.2. Classification

The anti-anginal drugs are classified as follows:

1) **Vasodilators (Organic Nitrites and Nitrates):** Amyl nitrite, Sodium nitrite, Nitroprusside sodium, Isosorbide dinitrate, Isosorbide mononitrate, Erythrityl tetranitrate, and Nitroglycerine.
2) **Calcium Channel Blockers**
   i) **Arylalkylamines:** Bencyclane, Bepridil hydrochloride, Caroverine, Cetiedil citrate, Diltiazem hydrochloride, Doprenilamine, Etafenone, Fendiline, Mecinarone, Prenylamine, Proadifen, and Terodiline.
   ii) **Phenyldihydropyridine Derivatives:** Amlodipine, Darodipine, Felodipine, Flordipine, Isrodipine, Mesudipine, Nicardipine, Nifedipine, Niludipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Oxodipine, and Riodipine.
   iii) **Piperazine Derivatives:** Cinnarizine, Flunarizine, and Lidoflazine.
   iv) **Verapamil and Related Drugs:** Anipamil, Dagapamil, Devapamil, Emopamil, Falipamil, Gallopamil, Methoxyverapamil, Ronipamil , Tiapamil, and Verapamil hydrochloride.
   v) **Miscellaneous Agents:**Flutonidine, Fostedil, Perhexiline, and Piprofurol.

3) **Potassium Channel Opener**: Nicorandil.
4) **β-Adrenoceptor Antagonists (β-Blockers):** Atenolol, Metoprolol, Nadolol, and Propranolol.
5) **Metabolic Modifiers:** Ranolazine and Trimetazidine.

4.1.3. Uses

The different classes of anti-anginal drugs have the following therapeutic uses:

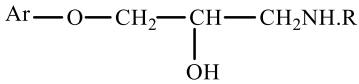
1) **Organic Nitrates:** These are one of the several classes of drugs employed for treating ischemic symptoms of angina. These are also employed in the treatment of congestive heart failure by acting through nitric oxide (NO) replacement therapy so that the bioavailability of impaired NO can be overpowered.
2) **Calcium Channel Blockers:** Both the forms of angina (i.e., stable and variant) are treated using calcium channel blockers. In **stable angina**, these drugs stimulate peripheral arteriolar relaxation. As a result, the afterload decreases which in turn diminishes oxygen demand of the heart. In **variant angina**, these drugs stimulate relaxation of coronary artery spasm. As a result, oxygen supply to the heart increases. Verapamil and diltiazem suppress the heart rate and contractility, thereby, further decreasing oxygen demand moderately.
3) **Potassium Channel Openers:** These drugs are administered to symptomatic patients waiting to undergo surgery or angioplasty and in whom ideal management with other drugs has already been carried out.
4) **β-Adrenergic Blockers:** These drugs are administered in combination with nitrates for treating angina patients. Drugs from two or more classes are employed in the treatment of persistent angina, **e.g.,** a combination of β-adrenergic blockers with long-acting nitrates or calcium channel blockers.

   The anti-hypertensive action of β-adrenergic blockers makes them the most ideal drug for patients suffering from both hypertension and coronary artery disease. The β-adrenergic blockers are also the drugs of choice for prophylactic treatment of chronic angina. Once a patient has suffered an acute myocardial infarction, propranolol is employed for prophylactic treatment for 1.5-3 years, so that ischemic damage could be decreased.

4.1.4. Structure-Activity Relationship

In most of the anti-anginal drugs, the lipophilicity and steric factors play an important role. The electronic factors are important in some cases. Lipophilicity is the most common factor regulating the anti-anginal activity of β-blockers and nitrates; while steric factors are responsible for the activity of calcium channel blockers. The steric factors hold importance in drug-receptor interactions involving hydrophobic interactions as well as electronic interactions (to a lesser extent). The **requirements for anti-anginal activity** are:

1) **β-Blockers:** The structural features which are responsible for the activity of β-blockers are:



General Structure

i) The O-CH_2 group between the aromatic ring and ethylamino side chain is responsible for the antagonistic property.

ii) Replacement of c atechol hydroxyl group with chlorine or phenyl ring retains the β-blocking activity.

iii) N,N-di-substitution decrease β-blocking activity. Activity is maintained when phenylethyl, hydroxyl phenylethyl or methoxy phenyl ethyl groups are added to amine as a part of molecule.

iv) The two carbon side chains are essential for the activity.

v) Nitrogen atom should be of secondary amine for optimum β-blocking activity.

vi) The carbon side chain having hydroxyl group must be S -configuration for optimum affinity to β-receptor. (**e.g.,** Levobunolol and Timolol).

vii) The aryloxypropanolamines are more potent than aryl ethanolamines.

viii) Replacement of ethereal oxygen in aryloxy propanolamines with S, CH_2 or N–CH_3 decreases the β-blocking activity.

ix) The most effective substituents at amino group are isopropyl and tertiary butyl group.

x) The aromatic portion of the molecules could be varied with good activity.

xi) Converting the aromatic portion to phenanthrene or anthracene decreases the activity.

xii) Cyclic alkyl substituents are better than corresponding open chain substituents at nitrogen atom of amine.

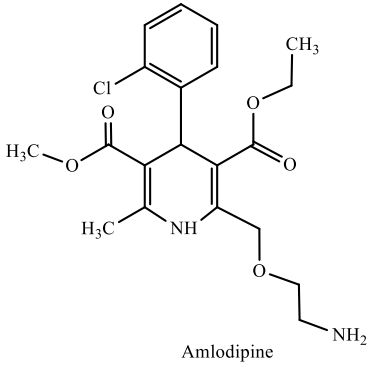
xiii) The α-methyl group at side chain decreases the activity.

2) **Calcium Channel Blockers:** The structural features responsible for the activity of **phenyl-dihydropyridine derivatives** are:

i) The dihydropyridine ring,

ii) The secondary nitrogen in the ring which remains un altered at physiological pH, and

iii) A bulky substituent (such as phenyl) in the 4-position of the heterocyclic compound.

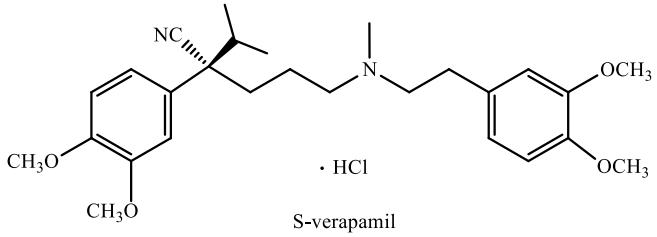


Amlodipine

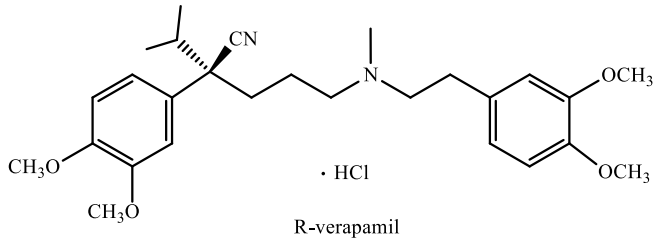
The nitro group and ester moieties are not essential for the activity. The structural features responsible for the activity of **verapamil** and related drugs are:

i) The benzene ring, and
ii) The tertiary amino nitrogen which is almost completely charged at physiological pH.

The isopropyl group and the ring substituents are not essential for activity.



S-verapamil



R-verapamil

$C_{27}H_{38}N_2O_4 \cdot HCl$ M.W. = 491.07

Verapamil hydrochloride

4.1.5. Recent Developments

The β-blockers, calcium channel blockers, and Long-Acting Nitrates (LANs) are the various classes of drugs available for **angina treatment**. However, many patients remain symptomatic, though they are treated with **conventional agents** and/or **revascularisation**. The anti-ischemic effect of conventional pharmacological therapies is based on the mechanism that involves lowering the determinants of myocardial oxygen demand, i.e., heart rate, myocardial contractility, or wall stress. Though combination therapy may increase the efficiency of these drugs, at the same time it may also decrease the anti-ischemic efficacy or may result in excessive side effects.

Some agents that have recently been discovered after a long time are **ranolazine**, **ivabradine**, and **fasudil**. It would be of great help if these agents could be used safely in combination with other anti-anginal drugs without decreasing the determinants of myocardial oxygen demand excessively. A metabolic modulator, **trimetazidine** improves cardiac energy availability and cardiac metabolism in patients with chronic stable angina.

1) **Ranolazine:** It is a recently discovered anti-anginal agent. It is derived from piperazine and is active on oral administration. Its mechanism of action involves selective inhibition of the late sodium current, thereby,

reducing the extent of ischemia -induced sodium and calcium overload. In turn, it improves myocardial perfusion and functions. Decrease in heart rate or blood pressure, or increase in coronary blood flow does not determine the anti-anginal effects of ranolazine. This drug inhibits the oxidation of fatty acids in myocardium, leading to preferential glucose oxidation.

2) **Trimetazidine:** It is an agent added to the standard therapy for angina (along with conventional long-acting nitrates, calcium channel blockers, and β-blockers). It inhibits oxidation of fatty acids. Its mechanism of action involves selective inhibition of 3-ketoacyl CoA thiolase. Trimetazidine is effective in treating angina when administered alone (mono therapy) or in combination (with other anti-anginal drugs). Angina pectoris in diabetic patients can be efficaciously treated by trimetazidine, since it inhibits oxidation of fatty acids, and hence facilitates glucose utilisation (by metabolising glucose and helping in its uptake by tissues).

3) **Fasudil:** It is an agent inhibiting Rho-kinase which is an intracellular signalling molecule involved in the contractile response of vascular smooth muscles to agonists like ACh, angiotensin II, endothelin, nor-epinephrine, platelet-derived growth factor, and serotonin. Thus, Fasudil has been suggested as a therapeutic target that can be employed for the treatment of stable angina.

4) **Ivabradine:** Tachycardia has been found to be a risk factor for ischemic cardiac disorders; thus decreasing heart rate may improve the results. Heart rate is decreased by the administration of β-blockers and some calcium channel blockers. However, they have negative inotropic effects and a number of contraindications, which may limit their use. Ivabradine is an I_f channel (selective found in sinoatrial node) inhibitor which is a beneficial advancement for treating ischemia. It decreases heart rate without disturbing cardiac systolic function. This implies that inhibition of I_f may be an effective mechanism that minimises both angina and the underlying ischemia.

4.2. VASODILATORS (ORGANIC NITRITES AND NITRATES)

4.2.1. Introduction

Organic nitrates and nitrites are simple nitric and nitrous acid esters of glycerol having different volatilities (**e.g.,** isosorbide dinitrate and isosorbide mononitrate are solids at room temperature, nitroglycerine is moderately volatile, and amyl nitrite is highly volatile). These compounds are used in angina pectoris. They rapidly reduce the myocardial oxygen demand, followed by rapid relief of symptoms. They are effective in classic as well as in variant angina pectoris.

Organic nitrates cause arterial and venous vasodilation by directly acting on the arterial and vascular smooth muscles. Nitroglycerine and isosorbide dinitrate decrease the oxygen consumption and restore the balance between oxygen supply

and oxygen demand by decreasing the preload and afterload. Coronary blood flow remains unchanged . Reduction in mean blood pressure activates the sympathetic nervous system. The decrease in oxygen consumption due to arterial and venous vasodilation is partly reversed by the i ncrease in heart rate and contractility. Organic nitrates inhibit or reverse coronary artery spasm in variant angina patients.

Organic nitrates get rapidly metabolised in the liver. A small portion of the orally administered dose appears in the peripheral blood in unchanged form. The drugs are lipid-soluble and get absorbed by the skin and mucous membranes.

4.2.2. Mechanism of Action

Nitrates principally act by direct non -specific relaxation of smooth muscles. The principle of action for all organic nitrates is the same; they only differ in their duration of action.

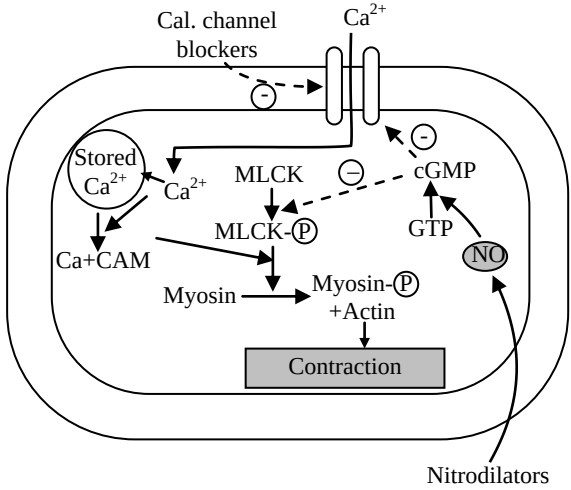


Figure 4.1: Mechanism of Vascular Smooth Muscle Relaxant Action of Nitrodilators like Glyceryl Trinitrate and Calcium Channel Blockers; (- - →) Inhibition; CAM - Calmodulin; NO - Nitric Oxide; MLCK – Myosin Light Chain Kinase; MLCK-P - Phosphorylated MLCK; GTP - Guanosine Triphosphate; cGMP - Cyclic Guanosine Monophosphate

The mechanism can be explained as follows:

1) Enzymatic de -nitration of organic nitrates occurs rapidly in the smooth muscle cells, which releases the reactive free radical nitric oxide (NO).
2) This radical activates the cytosolic guanylyl cyclase , which in turn increases cGMP. This dephosphorylates Myosin Light Chain Kinase (MLCK) via cGMP dependent protein kinase (**figure 4.1**).
3) Thus, the availability of pho sphorylated (active) MLCK is decreased, which in turn interrupts myosin activation.
4) It does not interact with actin and thus does not cause contraction. Hence, relaxation occurs.
5) Concentration of cGMP within the cells is also increased which may decrease the entry of Ca^{2+} ions, contributing to relaxation.

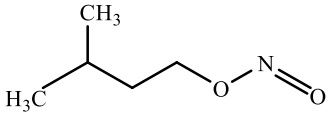
4.2.3. Study of Individual Drugs

The following vasodilators are discussed below:

1) Amyl nitrite,
2) Nitroglycerine,
3) Pentaerythritol tetranitrate,
4) Isosorbide dinitrate, and
5) Dipyridamole.

4.2.3.1. Amyl Nitrite

Amyl nitrite is an antihypertensive drug. It is used for treating heart diseases like angina. It is also used for the treatment of cyanide poisoning.



Amyl Nitrite

Mechanism of Action

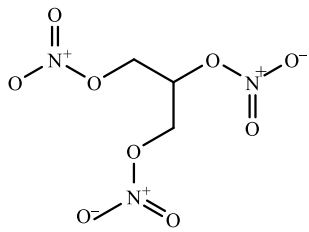
The anti-anginal activity of amyl nitrite is due to the reduction in systemic and pulmonary arterial pressure (afterload) and decreased the cardiac output due to peripheral vasodilation (and not coronary artery dilation). Amyl nitrite is a source of nitric acid that is responsible for the above mentioned mechanism. Amyl nitrite when used as an antidote to cyanide poisoning stimulates the formation of methemoglobin that combines with cyanide to form cyanmethemoglobin (non-toxic).

Uses

1) It is used in the treatment of heart diseases and angina.
2) Sometimes, it is used as an antidote to cyanide poisoning. To aid the formation of methemoglobin, amyl nitrite acts as an oxidant. The formed methemoglobin in turn sequesters cyanide as cyanomethemoglobin.
3) It used as a cleaning agent and solvent in industrial and household applications. It replaced dichlorodifluoromethane, an industrial chemical used as a printed circuit board cleaner that was banned in 1996 due to the damage to ozone layer.
4) It is added in some perfumes in a very small quantity.

4.2.3.2. Nitroglycerine

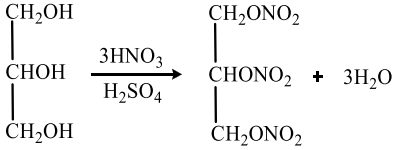
Nitroglycerine is the drug of choice for angina pectoris since it is effective, fast acting, and economic. If taken via sub-lingual route, it acts rapidly and its action lasts for an hour.



Nitroglycerine

Synthesis

Nitroglycerine is synthesised by treating dehydrated glycerine with a mixture of fuming nitric acid and sulphuric acid.



Mechanism of Action

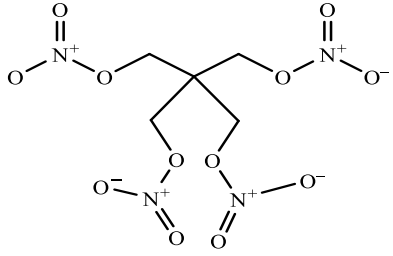
Nitroglycerine acts by dilating the blood vessels , thus affecting the vascular smooth muscles. It decreases the cardiac oxygen demand in case of stable angina, and increases the oxygen supply in variant angina.

Uses

1) It is administered sublingually for treating angina and left ventricular failure.
2) Its intravenous administration helps in controlling hypertension during heart surgery, and in congestive heart fai lure (unrespons iveness to general treatments).
3) As a result of improved left ventricular function and reduced pulmonary arterial pressure, it provides sudden relief of paroxysmal nocturnal dyspnoea.

4.2.3.3. Pentaerythritol Tetranitrate

Pentaerythritol tetranitrate is the nitrate ester of pentaerythritol that has explosive properties. It is a vasodilator with general properties similar to nitroglycerine but a more prolonged duration of action. All the four hydroxy groups of pentaerythritol have changed to the corresponding nitrate ester.



Pentaerythritol Tetranitrate

Mechanism of Action

Pentaerythritol tetranitrate is a lipid -soluble polyol ester of nitric acid of nitro-vasodilators class. After the de -nitration reaction, pentaerythritol tetranitra te releases free nitric oxide (NO) that triggers NO -dependent signalling transduction that involves the soluble guanylate cyclase (sGC).

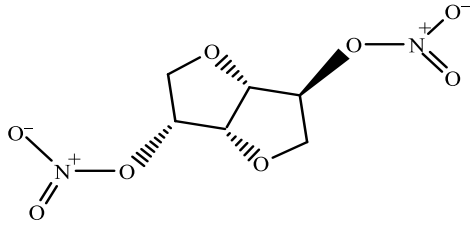
Nitric oxide and ferrous-heme centre of sGC reversibly bind to each other, and cause conformational change and enzyme activation. This increases the cellular concentrations of cGMP in the vascular smooth muscles, thus causes vasodilation mediated by cGMP-dependent protein kinases.

Uses

1) It is used as a vasodilator just like nitroglycerine (glyceryl trinitrate) and other nitrates for treating heart conditions.
2) It is used in the treatment of angina pectoris.

4.2.3.4. Isosorbide Dinitrate

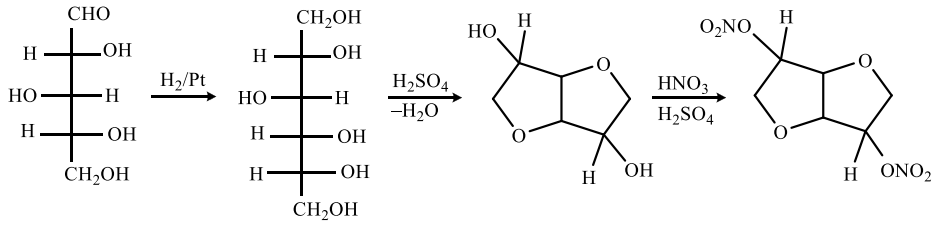
Isosorbide dinitrate is a vasodilator. It is used for treating angina pectoris. It has actions similar to nitroglycerine, however it has a slower onset of action.



Isosorbide Dinitrate

Synthesis

Sorbitol is obtained by c hemical or ferm entative reduction of glucose. The obtained sorbitol forms a cyclic intermediate on dehydration with sulphuric acid. Nitration of isosorbide produces isosorbide dinitrate.



Glucose D-Sorbitol Isosorbide

Mechanism of Action

Isosorbide dinitrate is converted to nitric oxide (NO) just like the other nitrites and organic nitrates. Nitric oxide is an active intermediate that activates guanylate cyclase (atrial natriuretic pept ide receptor A) enzyme, and stimulates the synthesis of cyclic guanosine 3',5'-monophosphate (cGMP).

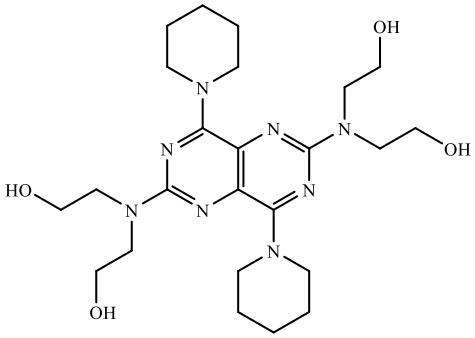
The obtained cGMP activates a series of protein kinase -dependent phosphorylations in the smooth muscle cells . This results in the dephosphorylation of th e myosin light chain of the smooth muscle fibre. The resultant release of calcium ions causes relaxation of the smooth muscle cells and vasodilation.

Uses

1) It is used for treating angina, congestive heart failure and oesophageal spasms.
2) It is also used for treating or preventing the angina attacks.
3) It dilates the blood vessels so that the blood flow easily through them and the heart also pumps blood easily.

4.2.3.5. Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor. It blocks the uptake and metabolism of adenosine by erythrocytes and vascular endothelial cells. It also potentiates the anti-aggregating action of prostacyclin.



Dipyridamole

Mechanism of Action

Dipyridamole inhibits adenosine deaminase and phosphodiesterase, thus prevents the degradation of cAMP (inhibitor of platelet function). This increase in cAMP concentration inhibits the release of arachidonic acid from membrane phospholipids and reduces the activity of thromboxane A2. Dipyridamole also stimulates the release of prosta cyclin that potentiates the activity of adenylate cyclase. Hence, the intra-platelet concentration of cAMP increases and platelet aggregation is blocked.

Uses

1) It is used as an adjunct to coumarin anticoagulants for preventing post - operative thromboembolic complications of cardiac valve replacement.
2) It also used for treating angina.

4.3. CALCIUM CHANNEL BLOCKERS

4.3.1. Introduction

Four chemically distinct classes of calcium channel blockers are currently used to treat angina. These are:

1) **Phenylalkylamines:** Verapamil.
2) **Benzothiazepines:** Diltiazem.
3) **Dihydropyridines:** Nifedipine, Nimodipine, and Nicardipine.
4) **Diarylaminopropylamine Ethers:** Bepridil.

4.3.2. Mechanism of Action

Calcium channel blockers (**e.g.,** verapamil, diltiazem, and nifedipine) are used as an alternative to β-blockers for treating stable angina. They directly slow down the heart rate, thus decrease the myocardial oxygen demand and blunt reflex responses to arteriolar dilatation. The calcium influx in ischemic myocardial cells is prevented and this directly decreases the myocardial oxygen demand by

preserving the myocardial ATP. Calcium channel blockers are used for improving exercise tolerance in chronic stable angina patients due to c oronary atherosclerosis or in patients having abnormally small coronary arteries and limited vasodilator reserve.

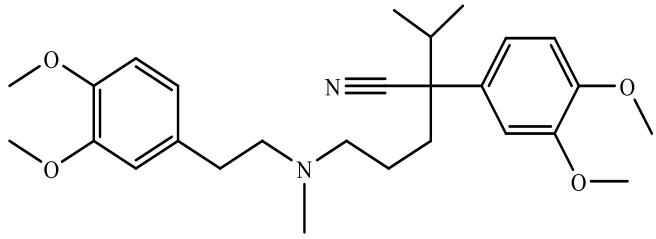
4.3.3. Study of Individual Drugs

The following calcium channel blockers are discussed below:

1) Verapamil,
2) Bepridil hydrochloride,
3) Diltiazem hydrochloride,
4) Nifedipine,
5) Amlodipine,
6) Felodipine,
7) Nicardipine, and
8) Nimodipine.

4.3.3.1. Verapamil

Verapamil is a calcium channel blocker of class IV anti -arrhythmic agent. It acts by inhibiting voltage -dependent calcium channels. Due to its effect on L -type calcium channels in the heart, ionotropy and chronotropy is reduced, which further reduces heart rate and blood pressure.



Verapamil

Mechanism of Action

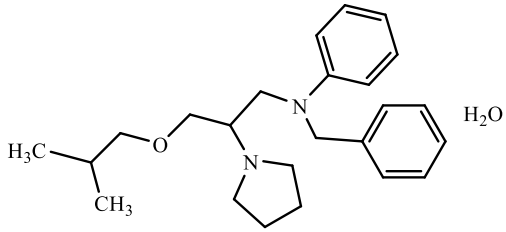
Verapamil blocks the voltage-dependent calcium channels. Its effect on L -type calcium channels in the heart decreases ionotropy and chronotropy, thus lowering the heart rat e and bl ood pressure. The mode of action of verapamil in cluster headache is linked to its calc ium channel blocking activity; however, the channel sub-types involved is still unknown.

Uses

It is the first generation calcium channel blocker used for treating hyper tension, supraventricular tachyarrhythmias, cluster headache prophylaxis, and angina pectoris.

4.3.3.2. Bepridil Hydrochloride

Bepridil hydrochloride is the hydrochloride salt of bepridil, which is a calcium antagonist. It i s a long -acting calcium blocker having anti -anginal activity.



Bepridil Hydrochloride

Mechanism of Action

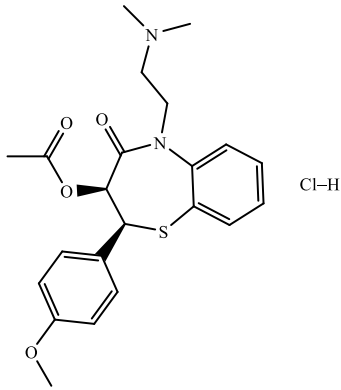
Bepridil has inhibitory effects on slow calcium (L-type) as well as on fast sodium inward currents in myocardial and vascular smooth muscle s. It interrupts the binding of calcium to calmodulin, and inhibits voltage and receptor operated calcium channels. Bepridil blocks the transmembrane influx of calcium ions into cardiac and vascular smooth muscles. It lowers the heart rate and arterial pressure at rest and at a given level of exercise by causing peripheral arteriole dilation and reducing the total peripheral resistance (afterload) against which the heart works.

Uses

It is used for treating hypertension and chronic stable angina (classic effort - associated angina).

4.3.3.3. Diltiazem Hydrochloride

Diltiazem hydrochloride is a benzothiazepine derivative whose vasodilating action is due to its antagonism of calcium ion actions on membrane functions.



Diltiazem Hydrochloride

Mechanism of Action

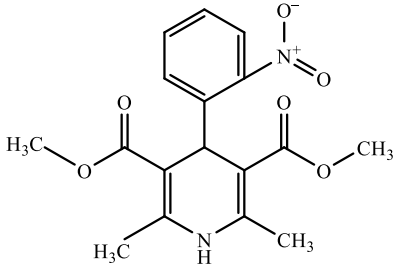
Diltiazem hydroch loride blocks the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. It does so by deforming the channel, blocking ion-control gating mechanisms, and/or inhibiting calcium release from sarcoplasmic reticulum. As a result, the contractile processes of the myocardial smooth muscle cells are inhibited, and this causes the dilation of coronary and systemic arteries, and enhances oxygen delivery to the myocardial tissue.

Uses

1) It is used for treating angina and hypertension.
2) It is used for treating supr aventricular tachycardias (PSVT) as effectively as verapamil.

4.3.3.4. Nifedipine

Nifedipine is a calcium channel blocker that relaxes the blood vessels (veins and arteries) so that the heart easily pumps blood and its workload is reduced.



Nifedipine

Mechanism of Action

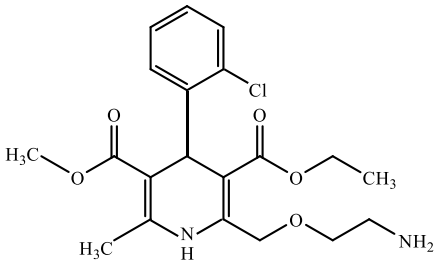
Nifedipine blocks the influx of extracellular calcium through the myocardial and vascular membrane pores by physically plugging the channel. The decrease in intracellular calcium blocks the con tractile pr ocesses of smooth muscle cells. This causes dilation of the coronary and systemic arteries, increases oxygen delivery to myocardial tissue s, decreases total peripheral resistance, decreases systemic blood pressure, and decreases afterload.

Uses

1) It is used in the treatment of vasospastic angina, chronic stable angina, hypertension, and Raynaud's phenomenon.
2) It is also used as a first line agent for left ventricular hypertrophy and for isolated systolic hypertension (long-acting agents).

4.3.3.5. Amlodipine

Amlodipine preferentially binds to vascular smooth muscle c ells over cardiac muscle cells, and thus it acts as a peripheral arterial vasodilator. It is highly protein bound and gets heavily metabolis ed like most other calcium channel blocker dihydropyridines. Amlodipine is not influenced by grapefruit juice (as felodipine) and shows fewer drug-drug interactions.



Amlodipine

Mechanism of Action

Amlodipine inhibits the influx of calcium ions through L -type calcium channels, thus reduces the contractility and vasoconstriction of arterial smooth muscle s. Calcium ions enter the cell s through L-type calcium channels and bind to calmodulin. The resultant complex binds to and activates Myosin Light Chain Kinase (MLCK). Phosphorylation of the regulatory light chain subunit of myosin is catalysed by the activated MLCK; this is a key step in muscle contraction.

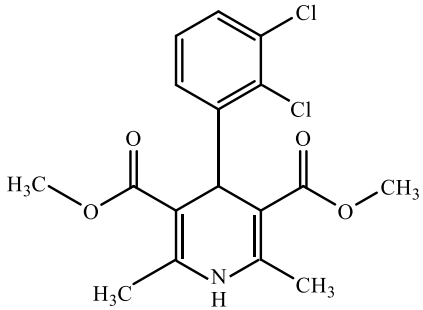
Signal amplification occurs by calcium -induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. When the initial influx of calcium is inhibited, the contractile activity of arterial smooth muscle cells decreases and causes vasodilation and decrease in blood pressure. Amlodipine may also act by inhibiting the activity of vascular smo oth muscle carbonic anhydrase I. This increases the cellular pH which may be involved in regulating intracellular calcium influx through calcium channels.

Uses

1) It is a long-acting calcium channel blocker used for treating mild to moderate essential hypertension and exertion-related angina (chronic stable angina).
2) It is used alone or with other antihypertensive and anti -anginal drugs for treating coronary artery disease , c hronic stable angina , and v asospastic angina (Prinzmetal's or variant angina).

4.3.3.6. Felodipine

Felodipine is a long-acting 1,4-dihydropyridine calcium channel blocker used for treating mild to moderate essential hypertension.



Felodipine

Mechanism of Action

Felodipine inhibits the influx of calcium ions through voltage -gated L -type calcium channels, thus decreases arterial smooth muscle contractility and vasoconstriction. It reversibly competes to nitrendipine and other dihydropyridine calcium channel blockers for dihydropyridine binding sites present on vascular smooth muscle and cultured rabbit atrial cel ls. Calcium ions on entering the cell s through L-type calcium channels bind to calmodulin. The resultant complex binds to and activates Myosin Light Chain Kinase (MLCK). Phosphorylation of the regulatory light chain subunit of myosin is catalysed by the activated MLCK; this is a key step in muscle contraction.

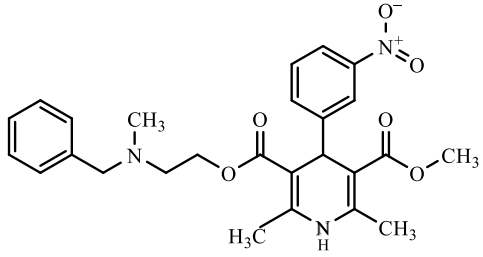
Signal amplification occurs by calcium -induced calcium release from the sarcoplasmic reticulum through ryanodine receptors. When the initial influx of calcium is inhibited, the contractile activity of arterial smooth muscle cells decreases and causes vasodilation and decrease in blood pressure.

Uses

1) It is used for treating hypertension.
2) It lowers high blood pressure and prevents strokes, heart attacks, and kidney problems.
3) It is used for treating angina.

4.3.3.7. Nicardipine

Nicardipine is a potent calcium channel blocker having vasodilator action and antihypertensive properties. It is used for treating angina and coronary spasms without presenting cardio depressant effects. It is also used for treating asthma and improves the action of specific antineoplastic agents.



Nicardipine

Mechanism of Action

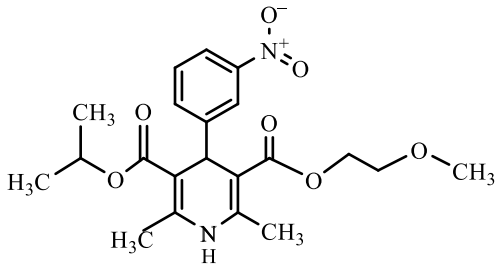
Nicardipine blocks the influx of extracellular calcium across the myocardial and vascular smooth muscle cell membranes. It does so by deforming the channel, inhibiting ion -control gating mechanisms, and/or interrupting calcium release from the sarcoplasmic reticulum. As a result of reduced intracellular calcium, the contractile processes of myocardial smooth muscle cells are inhibited. This leads to the dilation of coronary and systemic arteries, increased oxygen delivery to myocardial tissues, decreased total peripheral resistance, decreased systemic blood pressure, and decreased afterload.

Uses

1) It is used for treating chronic stable angina.
2) It is also used in the treatment of hypertension.

4.3.3.8. Nimodipine

Nimodipine is a 1, 4-dihydropyridine calcium channel blocker. It is used as an adjunct for improving the neurologic outcome following subarachnoid haemorrhage from ruptured intracranial aneurysm.



Nimodipine

Mechanism of Action

The detailed mechanism of action of nimodipine is not known, but it is believed to inhibit intracellular influx of calcium across the myocardial, vascular smooth muscle, and neuronal cell membranes through voltage-dependent and receptor-operated slow calcium channels. It does so by binding itself to these calcium channels. Inhibition of calcium ion transfer further inhibits vascular smooth muscle contraction. Nimodipine's clinical action in subarachnoid haemorrhage condition is due to the dilation of small cerebral resistance vessels, increase in collateral circulation, and/or prevention of calcium overload in neurons.

Uses

It is used as an adjunct to improve neurologic outcome following Subarachnoid Haemorrhage (SAH) from ruptured intracranial berry aneurysms by decreasing the occurrence and severity of ischemic deficits.

4.4. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Angina pectoris**, usually referred to as **angina**, denotes severe chest pain which may be caused by **ischemia** (lack of blood, and hence lack of oxygen supply) of heart muscle.
2) This ischemia is the result of **obstruction** or **spasm of coronary artery** (vessels supplying blood to heart).
3) **Anti-anginal drug** therapy aims at restoring the balance between the supply and demand of oxygen in the ischemic area of the myocardium.
4) **Organic Nitrates** are one of the several classes of drugs employed for treating ischemic symptoms of angina.
5) **Potassium Channel Openers** are administered to symptomatic patients waiting to undergo surgery or angioplasty.
6) **β-Adrenergic Blockers** are administered in combination with nitrates for treating angina patients.
7) **Ranolazine** is derived from piperazine and is active on oral administration.
8) **Trimetazidine** is an agent added to the standard therapy for angina (along with conventional long-acting nitrates, calcium channel blockers, and β-blockers).

9) **Fasudil** is an agent inhibiting Rho-kinase which is an intracellular signalling molecule involved in the contractile response of vascular smooth muscles to agonists like ACh, angiotensin II, endothelin, nor-epinephrine.
10) **Vasodilators** (organic nitrates and nitrites) are simple nitric and nitrous acid esters of glycerol having different volatilities.
11) **Amyl nitrite** is an antihypertensive drug. It is used for treating heart diseases like angina.
12) **Nitroglycerine** is the drug of choice for angina pectoris since it is effective, fast acting, and economic.
13) **Pentaerythritol tetranitrate** is the nitrate ester of pentaerythritol that has explosive properties. It is a vasodilator with general properti es similar to nitroglycerine but a more prolonged duration of action.
14) **Isosorbide dinitrate** has actions similar to nitroglycerine, however it has a slower onset of action.
15) **Calcium channel blockers** (**e.g.,** verapamil, diltiazem, and nifedipine) are used as an alternative to β-blockers for treating stable angina.
16) **Verapamil** is a calcium channel blocker of class IV anti-arrhythmic agent. It acts by inhibiting voltage-dependent calcium channels.
17) **Bepridil hydrochloride** is the hydrochloride salt of bepridil, which is a calcium antagonist.
18) **Diltiazem hydrochloride** is a benzothiazepine derivative whose vasodilating action is due to its antagonism of calcium ion actions on membrane functions.
19) **Nifedipine** is a calcium channel blocker that relaxes the blood vessels (veins and arteries) so that the heart easily pumps blood and its workload is reduced.
20) **Amlodipine** preferentially binds to vascular smooth muscle cells over cardiac muscle cells, and thus it acts as a peripheral arterial vasodilator.
21) **Nicardipine** is a potent calcium channel blocker having vasodilator action and antihypertensive properties.
22) **Nimodipine** is a 1,4-dihydropyridine calcium channel blocker. It is used as an adjunct for improving the neurologic outcome following subarachnoid haemorrhage from ruptured intracranial aneurysm.

4.5. EXERCISE

4.5.1. True or False

1) Organic nitrates treat the ischemic symptoms of angina.
2) Bepridil is a calcium antagonist.
3) Amyl nitrite is an antineoplastic drug.
4) Isosorbide dinitrate has a faster onset of action.
5) Ischemia is the result of obstruction or spasm of coronary artery.
6) Calcium channel blockers cannot be used for treating stable angina.

4.5.2. Fill in the Blanks

7) _____ is a calcium channel blocker that relaxes the blood vessels (veins and arteries).
8) _____ is a 1,4-dihydropyridine calcium channel blocker.
9) _____ preferentially binds to vascular smooth muscle cells over cardiac muscle cells.
10) _____ is an antihypertensive drug that is used for treating heart diseases like angina.
11) _____ are simple nitric and nitrous acid esters of glycerol having different volatilities.

Answers

1) True 2) True 3) False 4) False
5) True 6) False 7) Nifedipine 8) Nimodipine
9) Amlodipine 10) Amyl nitrite 11) Vasodilators

4.5.3. Very Short Answer Type Questions

1) Write a short note on vasodilators.
2) Give the uses of amyl nitrite.
3) Classify calcium channel blockers.
4) Give the mechanism of action of bepridil hydrochloride.
5) Write short note nitroglycerine.
6) Give the mechanism of action of felodipine.

4.5.4. Short Answer Type Questions

1) What are anti-anginal drugs? Give their classification.
2) Write short note on verapamil and nifedipine.
3) Discuss nicardipine and nimodipine.
4) Write short note on nitroglycerine and pentaerythritol tetranitrate.
5) Give the classification of anti-anginal drugs.

4.5.5. Long Answer Type Questions

1) Give the uses and SAR of anti-anginal drugs.
2) Write a detailed note on vasodilators.
3) Give a detailed account on calcium channel blockers.
4) What are the recent developments in anti-anginal drugs?

CHAPTER 5

Diuretics

5.1. DIURETICS

5.1.1. Introduction

Drugs promoting urine output are known as **diuretic drugs**, which refer only to those agents that act directly on the kidneys. These drugs primarily increase the excretion of water and ions like sodium (Na^+), chloride (Cl^-), or bicarbonates (HCO_3^-) from the body. **Glomerular filtration**, **tubular reabsorption**, and **tubular secretion** in kidneys determine the excretion of substances.

Tubular reabsorption is a process which involves active transport of electrolytes and other solutes from tubular urine to tubular cells, and then to extracellular fluid. As a result, glomerular filtration is increased. The mechanism of action of diuretic drugs also involves a decrease in tubular reabsorption.

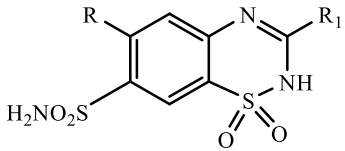
However, these drugs have no effect on glomerular filtration rate or on the action of Anti-Diuretic Hormone (ADH) on the distal portion of nephron. Diuretics effectively treat cardiac oedema (accumulation of fluid in extra vascular tissues), especially the one which is associated with congestive heart failure.

It is also employed in the treatment of various disorders like nephrotic syndrome, diabetes insipidus, hypertension, nutritional oedema, oedema of pregnancy, and liver cirrhosis. They also decrease the intracellular and cerebrospinal fluid pressure.

5.1.2. Classification

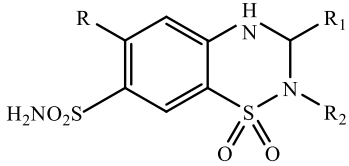
Diuretics are classified as follows:

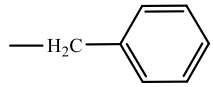
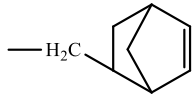
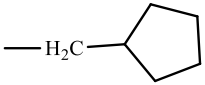
1) **Carbonic Anhydrase Inhibitors:** Acetazolamide, Methazolamide, and Dichlorphenamide.
2) **Thiazide Derivatives:**
   i) Chlorothiazide and Analogues:



Drugs	R	R_1
Chlorothiazide	—Cl	H
Benzthiazide	—Cl	$—CH_2SCH_2C_6H_5$

ii) Hydrochlorothiazide and Analogues:



Drugs	R	R_1	R_2
Hydrochlorothiazide	—Cl	—H	—H
Hydroflumethiazide	—CF_3	—H	—H
Bendroflumethiazide	—CF_3		—H
Trichlormethiazide	—Cl	—$CHCl_2$	—H
Methyclothiazide	—Cl	—CH_2Cl	—CH_3
Polythiazide	—Cl	—$CH_2SCH_2CF_3$	—CH_3
Cyclothiazide	—Cl		—H
Cyclopenthiazide	—Cl		—H

3) **Loop Diuretics:** Furosemide, Bumetanide, and Ethacrynic acid.
4) **Potassium Sparing Diuretics:** Amiloride, Triamterene, and Spironolactone.
5) **Osmotic Diuretics:** Isosorbide, Mannitol, Glycerol, and Urea.
6) **Miscellaneous:** Indapamide, Xipamide, Clopamide, Quinethazone, Metolazone, Chlorthalidone, and Clorexolone.

5.1.3. Uses

Diuretics have the following uses:

1) They are used for preventing and easing oedema and ascites that may occur in the diseased conditions of heart, kidney and liver. Thus, the diuretics are used for treating oedema related to chronic congestive heart fai lure, acute pulmonary oedema, oedema caused due to pregnancy, brain oedema , and cirrhosis related with ascites.
2) They are also used in the treatment of hypertension, diabetes insipidus, renal calculi, hypocalcaemia, acute and renal failure, and nephritic syndrome.
3) Some diuretics are used in glaucoma, hyperpotassemia, bromide intoxication, anginal syndrome, epilepsy, migraine, and pre-menstrual depression conditions.

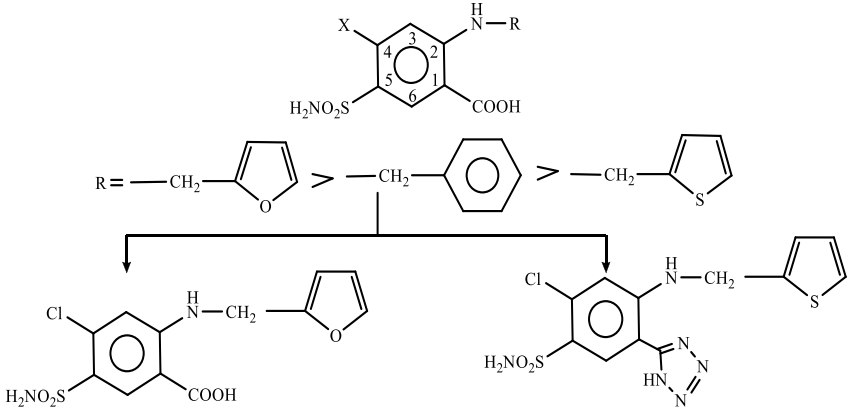
5.1.1. Structure-Activity Relationship

The SAR of diuretics can be studied as follows:

1) **Structure-Activity Relationship of High Efficacy Diuretics:** Development of loop diuretics is the result of a research in which thiazide and thiazide-like diuretics were involved. The 5-sulfamoyl-2-aminobenzoic acid derivatives and the 5-sulfamoyl-3-aminobenzoic acid derivatives (**figure 5.1**) require some common structural features.

First, an acidic substituent should be present at 1 -position. **Optimum diuretic activity** is achieved by the carboxyl group, while other groups (such as a tetrazole) impart a respectable diuretic activity.

Second, in order to achieve **optimum high -ceiling diuretic activity** , a sulfamoyl group should be present in the 5-position.
Third, the activating group (—X) present in the 4 -position can b e Cl^- or CF_3^- (as in thiazides and thiazide -like diuretics) or a phenoxy, alkoxy, anilino, benzyl, or benzoyl group. The **diuretic activity of thiazides** or **thiazide-like diuretics decreases** if their Cl^- or CF_3^- group is replaced with one of the latter five functional groups.



5-Sulfamoyl-3-aminobenzoic acids

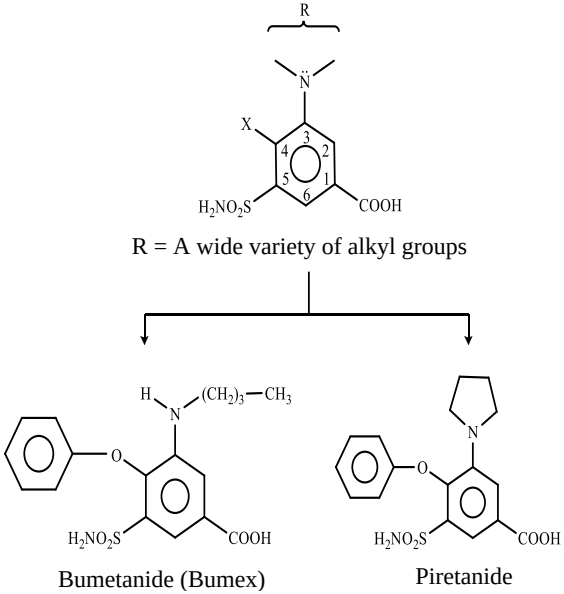


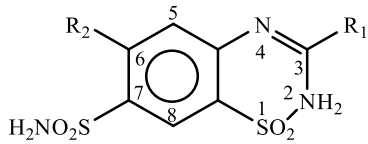
Figure 5.1: Results from Structure-Activity Relationship Studies that Led to the Development of Furosemide and Bumetanide

The functional groups substituted in the 2 - and 3 - positions of these two series of 5-sulfamoylbenzoic acids are different in nature and also retains the **maximum diuretic activity** (**figure 5.1**). Very limited substituents can be placed on the 2 -amino group of the 5 -sulfamoyl-2-aminobenzoic acids, and deviations are not allowed on the few moieties.

For example, the diuretic activity is maximum for derivatives of furfuryl, benzyl, and thienylmethyl (in decreasing order) moieties. The substituents that can be placed on the 3 -amino group of the 5 -sulfamoyl-3-aminobenzoic acids widely differ; however, without affecting the optimal diuretic activity.

Furosemide and azosemide are the high -ceiling diuretics derived from the 5-sulfamoyl-2-aminobenzoic acid series; while bumetanide and piretanide are those derived from the 5-sulfamoyl-3-aminobenzoic acid series.

2) **Structure Activity Relationship of Medium Efficacy Diuretics (Thiazide and Thiazide-like Diuretics)**



Generic Name (Trade Name)	R_1	R_2
Chlorothiazide	H	Cl
Benzthiazide	$-CH_2-SCH_2-C_6H_5$	Cl
Flumethiazide	H	CF_3

i) The diuretic activity can be increased by replacing the SO 2 group with CO group.

ii) The diuretic activity can be increased by replacing the ri ng nitrogen atoms at 2-position with methyl. However, if the N -atom at 4-position is replaced with methyl group , the diuretic activity declines, making the heterocyclic ring more susceptible to hydrolytic cleavage.

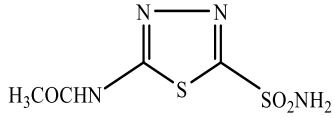
iii) The saluretic activity is increased 1000 folds by adding hydrophobic substituents in 3-position, **e.g.,** $-CH_2Cl$, $-CHCl_2$, $-CH_2C_6H_5$, $-CH_2$, and $CH_2S-CH_2-C_6H_5$. The resultant increased activity correlates with the lipid solubility.

iv) The diuretic activity increases with the saturation of the 3,4-double bond.

v) The diuretic activity increases by adding Cl, Br, or CF_3 substituents in the 6-position, whereas H or NH_2 are weakly active.

vi) The diuretic activity is m aintained by adding a free sulf amoyl or potentially free sulfamoyl group at 7-position. N^7-caproylchlorthiazide is excreted as chlorothiazide. Removal of sulfamoyl group results in diminished diuretic activity, but the hypertensive action (**e.g.,** diazoxide) is still retained.

3) **Structure Activity Relationship of Carbonic Anhydrase Inhibitors**



Acetazolamide

i) The diuretic activity can be maintained with free sulfamoyl nitrogen. While, the mono- and di- substituents at SO_2NH_2 eliminate the diuretic activity.

ii) The diuretic activity is maintained by adding methyl group on one of the ring nitrogen (methazolamide).

iii) The heterocyclic sulphonamides exhibit highest lipid/water partition coefficient, lowest pK_a values, and greatest carbonic anhydrase inhibitory and diuretic activity.

iv) The benzene *meta*-sulphonamide derivatives are active when substituted with chlorine or methyl groups.

4) **Structure Activity Relationship of 5-Sulfamoyl Benzoic Acid Derivatives (High Ceiling or Loop Diuretics)**

i) For an efficient diuretic activity, 5-sulfamoyl and 2-aminobenzoic acid group is required.

ii) For an efficient diuretic activity, an acidic group should be added at 1-position.

iii) The diuretic activity is increased if the activating group at 4-position is Cl or CF_3.

iv) The diuretic activity is decreased if the activating group at 4-position is phenoxy, alkoxy, anilino, benzyl, or benzoyl.

v) The diuretic activity is increased if furfuryl, benzyl, and thienyl methyl groups are added at 2-position.

5.1.2. Recent Developments

During the past decade, new diuretics having better efficiency and lesser side effects have been introduced. These agents have been recommended for the management of hypertension and include new loop diuretics like bumetanide and piretanide, which have more potential than the older loop diuretics; uricosuric indanyloxyacetic acid derivative (indacrinone) and a new generation of sulfamoyl diuretics like indapamide and xipamide.

The diuretic and natriuretic responses of newer agents have been found to follow the plasma drug concentration–time curve and urinary excretion rate of these drugs. Thus, in most of the patients with hypertension or oedema, therapeutic monitoring of these drugs may be accomplished by observing the patients closely and by using laboratory analyses for the determination of concentration of electrolytes and creatinine in the plasma along with the excretion rate of electrolytes in urine. The mechanisms involved in the actions of newer diuretics on both, renal as well as extra-renal vessels have involved a better understanding of the contributions of alterations in venous compliance, peripheral vascular resistance, and distribution of

renal blood flow on the total therapeutic response of a patient to these agents. This is particularly true in patients with severe CHF, renal insufficiency with low glomerular filtration rates, and hypertension with cardiorenal complications.

The pharmacodynamic effects of the modern diuretics on kidneys are responsible for the adverse reactions these drugs show. These agents have minimal adverse effects when the dose is properly calibrated depending upon the individual requirements of the patient. Yet, researchers are still investigating the long -term consequences of the diuretic -induced alterations in plasma potassium levels and the metabolic effects including increased levels of lipids in blood, when these diuretics are administered for prolonged periods.

5.2. CARBONIC ANHYDRASE INHIBITORS

5.2.1. Introduction

Carbonic anhydrase inhibitors are derived from sulphonamide antibacterial. This type of diuretics inhibit carbonic anhydrase enzyme in the membrane and cytoplasm of the epithelial cell. Carbonic anhydr ase influence tubular reabsorption of sodium at the **proximal tubule** (where bicarbonate absorption occurs) and in the **distal tubule** (where sodium is exchanged for potassium or hydrogen ion and bicarbonate is formed as an accompanying anion).

5.2.2. Mechanism of Action

Carbonic anhydrase inhibitors inhibit the carbonic anhydrase enzyme found in the membrane and cytoplasm of epithelial cells. These diuretics primarily act in the proximal tubules. Carbonic anhydrase enzyme is found in the renal tubular cells. It immediately converts the CO_2 formed metabolically in the cells of renal tubules into carbonic acid.

$$CO_2 + H_2O \underset{}{\overset{CA}{\rightleftharpoons}} H^+ + HCO_3^-$$

The hydrogen ion obtained from carbonic acid produced in the proximal tubular cells is exchanged for sodium ions.

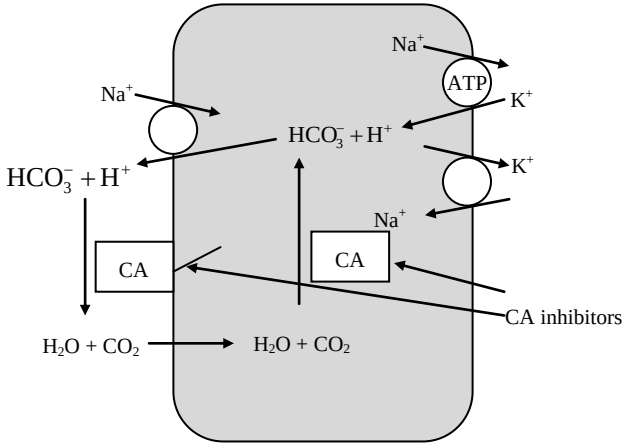


Figure 5.2: Mechanism of Action of CA Inhibitors

The Na^+—H^+ anti-port present in the apical membrane of epithelial cells in proximal tubule transports H^+ ion into the tubular lumen in exchange for Na^+ ion movement in the cytoplasm. The Na^+ ion is pumped out of the cytoplasm into the interstitium by sodium pump. In the lumen, the H^+ and HCO_3^- ions react to form H_2CO_3 (carbonic acid), which undergoes dehydration (catalysed by carbonic anhydrase in the luminal membrane) and forms CO_2 and H_2O. The obtained CO_2 and H_2O permeate into the cells, undergo rehydration (catalysed by cytoplasmic carbonic anhydrase) and form H_2CO_3. This obtained H_2CO_3 dissociates into H^+ ion (that is secreted into the lumen) and HCO_3 (that is transported into interstitium). Thus, inhibition of anhydrase blocks the reabsorption of HCO_3^- ion and results in its accumulation in the tubular lumen, ultimately inhibiting Na^+-H^+ ion exchange and Na^+ ion reabsorption.

Stimulation of adenyl cylase inhibits the carbonic anhydrase enzyme , and the amount of H^+ ions available for exchange with Na^+ ions is reduced. Excess ive Na^+ ions that accumulated in the tubule combine with HCO_3^- ion, and is excreted by the kidney s with an increased volume of water and loss of potassium. The increased concentration of Na^+ ions in the tubular fluid is partially compensated by increased reabsorption of NaCl in the later segments of tubule. Hence, the diuretic effect of carbonic anhydrase inhibitors is low.

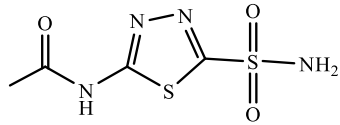
5.2.3. Study of Individual Drugs

The following carbonic anhydrase inhibitors are discussed below:

1) Acetazolamide,
2) Methazolamide, and
3) Dichlorphenamide.

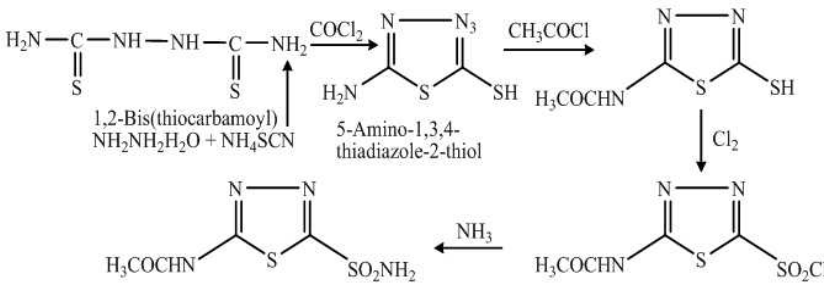
5.2.3.1. Acetazolamide

Acetazolamide is the prototype carbonic anhydrase inhibitor. This type of diuretics inhibit carbonic anhydrase enzy me in the membrane and cytoplasm of epithelial cell.



Acetazolamide

Synthesis



Mechanism of Action

Carbonic anhydrase enzyme is inhibited by acetazolamide; thus, preventing the formation of H^+ ions. As a result, the exchange of Na^+ ions with H^+ ions does not take place. The Na^+ and HCO_3^- ions undergo urinary excretion. Increased exchange of Na^+ and K^+ ions in the distal convoluted tubule resulted in the loss of K^+ ions. On the whole, the urine produced is alkaline in nature as the Na^+, K^+, and HCO_3^- ions are lost.

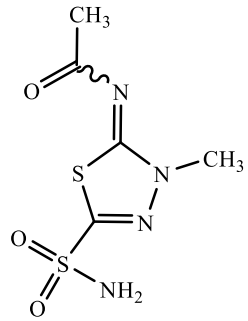
Uses

Acetazolamide is self-limiting in nature. It produces adverse effects like acidosis and hypokalaemia. Thus, it is not used as a diuretic anymore; instead, it is currently being employed in the treatment of:

1) **Glaucoma:** As an adjuvant to other ocular hypotensives.
2) **Alkalinising Urine:** For urinary tract infection or to promote excretion of certain acidic drugs.
3) **Epilepsy:** As an adjuvant in absence seizures when primary drugs are not fully effective.
4) **Acute Mountain Sickness:** Symptomatic relief as well as prophylaxis.

5.2.3.2. Methazolamide

Methazolamide is a carbonic anhydrase inhibitor. It is used as a diuretic and for treating glaucoma.



Methazolamide

Mechanism of Action

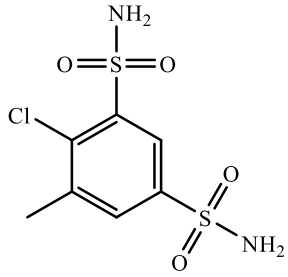
Methazolamide is a potent inhibitor of carbonic anhydrase enzyme. It inhibits the enzyme in the ciliary processes of eye , thus reduces aqueous humor secretion by delaying the formation of bicarbonate ions and reducing sodium and fluid transport.

Uses

1) It is used for treating chronic op en-angle glaucoma an d acute angle -closure glaucoma.
2) It is used in cystoid macular oedema and pseudotumour cerebri.

5.2.3.3. Dichlorphenamide

Dichlorphenamide is a carbonic anhydrase inhibitor. It is used for treating glaucoma.



Dichlorphenamide

Mechanism of Action

Carbonic anhydrase inhibitors decrease intraocular pressure by partially suppressing aqueous humor secretion. The mechanism behind this is however not known completely. It has been proved that HCO^{3-} ions are formed in the ciliary body by hydration of carbon dioxide catalysed by carbonic anhydrase. The HCO^{3-} ions formed diffuse into the hypertonic posterior chamber containing more Na^{+} and HCO^{3-} ions than the plasma. Then, water is attracted to the posterior chamber by osmosis, thereby causing a pressure drop.

Uses

1) It is used for adjunctive treatment of chronic simple (open-angle) glaucoma and secondary glaucoma.
2) It is used pre-operatively in acute angle closure glaucoma in which surgery is delayed so that the intraocular pressure decreases.

5.3. THIAZIDES

5.3.1. Introduction

Thiazide diuretics are referred to as moderately efficacious diuretics as a majority (nearly 90%) of the filtered sodium is already re-absorbed before it reaches the distal tubule. These diuretics comprise of **two distinct groups**:

1) Diuretics **containing a benzothiadiazine ring**; these agents are referred to as **thiazide diuretics** and include agents like chlorothiazide, hydrochlorothiazide, polythiazide, etc.
2) Diuretics **not containing benzothiadiazine ring**, but **containing an un-substituted sulphonamide group**; these agents are termed as **thiazide-like diuretics** and include chlorthalidone, indapamide, metolazone, etc.

5.3.2. Mechanism of Action

Thiazide diuretics inhibit the reabsorption of Na^{+} and Cl^{-} ions at the first portion of the distal tubules. They block a Na^{+}-Cl^{-} symport in the luminal membrane of the epithelial cells in the distal convoluted tubule, thus, blocking the reabsorption of NaCl. Thiazide diuretics exert a minor effect on NaCl reabsorption in the proximal tubule. They block the entry of Na^{+} ions and enhance the activity of Na^{+}-Ca^{++} exchanger in the basolateral membrane of epithelial cells. Thus, the reabsorption of Ca^{++} ions in the distal convoluted tubule is enhanced. Thiazide

diuretics also inhibit the carbonic anhydrase enzyme. The resulting diuretics are supplemented by increased excretion of potassium, bicarbonates, chloride, and water.

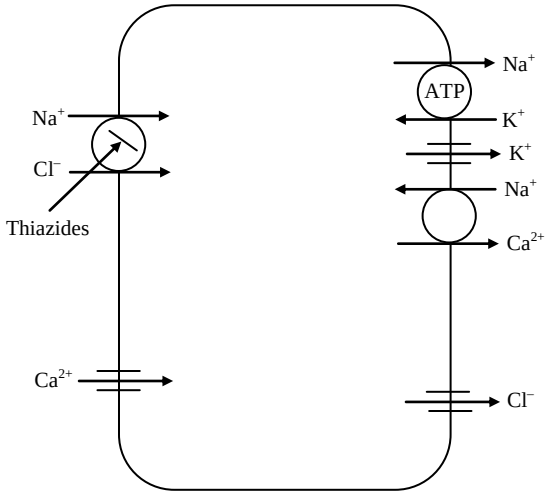


Figure 5.3: Mechanism of Action of Thiazides

The anti-hypertensive action of thiazide diuretics is influenced by the following two factors:

1) Reduced plasma concentration of sodium due to its depletion, and
2) Decrease in peripheral resistance.

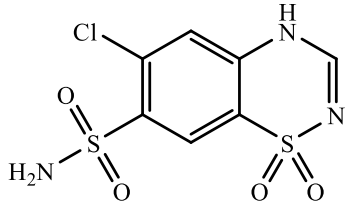
5.3.3. Study of Individual Drugs

The following thiazide diuretics are discussed below:

1) Chlorothiazide,
2) Hydrochlorothiazide,
3) Hydroflumethiazide, and
4) Cyclothiazide.

5.3.3.1. Chlorothiazide

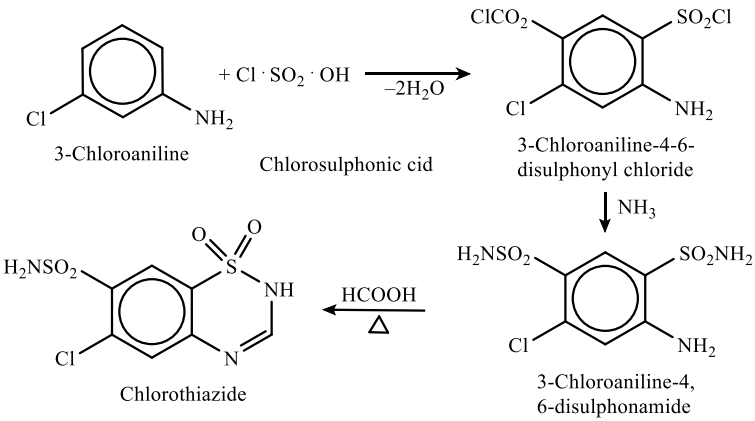
Chlorothiazide is a short -acting, benzothiadiazine sulfonamide derivative and prototypical thiazide diuretic. It gets excreted via kidneys in unchanged form.



Chlorothiazide

Synthesis

Chlorination of 3-chloroaniline with chlorosulphonic acid forms 3-chloroaniline-4,6-disulphonyl chloride. This compound is amidated with ammonia to yield 3-chloroaniline-4,6-disulphonamide analogue, which on heating with formic acid undergoes cyclisation by double condensation and forms chlorothiazide.



Mechanism of Action

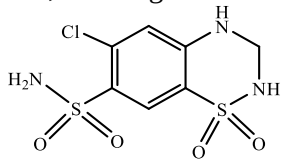
Chlorothiazide blocks reabsorption of active Cl^- ions in the first portion of distal convoluted tubule through the Na^+-Cl^- cotransporter. This causes an increase in the excretion of Na^+ and Cl^- ions, and water. Chlorothiazide also blocks the transport of Na^+ ions across the renal tubular epithelium by binding to the thiazide sensitive Na^+-Cl^- transporter. This causes an increase in excretion K^+ ions through Na^+-K^+ exchange mechanism. The antihypertensive mechanism of chlorothiazide is not clearly understood, but it is believed to act on carbonic anhydrase enzyme in the smooth muscles or on the large -conductance calcium-activated potassium (KCa) channel in the smooth muscles.

Uses

1) It is used as an adjunct in oedema related to congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.
2) It is used alone in the management of hypertension, but in combination with other antihypertensive drugs in the more severe forms of hypertension.

5.3.3.2. Hydrochlorothiazide

Hydrochlorothiazide reduces the reabsorption of electrolytes from renal tubules. This causes an increase in the excretion of water and electrolytes, including sodium, potassium, chloride, and magnesium.



Hydrochlorothiazid

Mechanism of Action

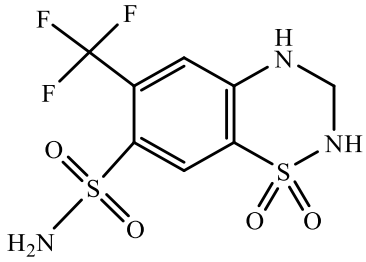
Hydrochlorothiazide inhibits the Na^+-Cl^- symporter in the distal convoluted tubule (responsible for 5% of total sodium reabsorption), thus blocks the reabsorption of water in nephrons. The Na^+-Cl^- symporter transports Na^+ and Cl^- ions from the lumen into the epithelial cell lining the distal convoluted tubuleA sodium gradient established by Na^+-K^+ ATPases on the basolateral membrane provides energy for transporting Na^+ and Cl^- ions. Once the Na^+ ions enter the cell, they are transported into the basolateral interstitium via Na^+-K^+ ATPase, and the osmolarity of the interstitium increases. This establishes an osmotic gradient for water reabsorption.

Uses

1) It reduces sodium and water retention in preeclampsia during pregnancy.
2) It is u sed for the management of hypertension, and as an adjunct in oedema related to congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

5.3.3.3. Hydroflumethiazide

Hydroflumethiazide is an intermediate -acting benzothiadiazine sulfonamide derivative. Its actions and uses are similar to those of hydrochlorothiazide.



Hydroflumethiazide

Mechanism of Action

Hydroflumethiazide inhibits the Na^+-Cl^- symporter in the distal convoluted tubule (responsible for 5% of total sodium reabsorption), thus blocks the reabsorption of water in nephrons. The Na^+-Cl^- symporter transports Na^+ and Cl^- ions from the lumen into the epithelial cell lining the distal convoluted tubule. A sodium gradient established by Na^+-K^+ ATPases on the basolat eral membrane provides energy for transporting Na^+ and Cl^- ions.

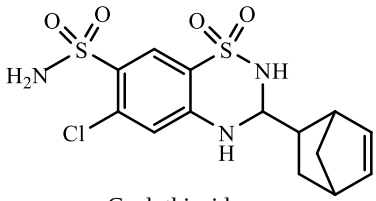
Once the Na^+ ions enter the cell, they are transported into the basolateral interstitium via Na^+-K^+ ATPase, and the osmolarity of the interstitium increases. This establishes an osmotic gradient for water reabsorption.

Uses

1) It is used as an adjunct in oedema related to congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.
2) It is used alone in the management of hypertension, but in combination with other antihypertensive drugs in the more severe forms of hypertension.

5.3.3.4. Cyclothiazide

Cyclothiazide is a benzothiadiazide of thiazide diuretics. It is used as an adjunct in oedema. It is also used for treating hypertension.



Cyclothiazide

Mechanism of Action

Cyclothiazide blocks reabsorption of active Cl^- ions in the first portion of distal convoluted tubule through the Na^+-Cl^- cotransporter. This causes an increase in the excretion of Na^+ and Cl^- ions, and water. Cyclothiazide also blocks the transport of Na^+ ions across the renal tubular epithelium by binding to the thiazide sensitive Na^+-Cl^- transporter. This causes an increase in excretion K^+ ions through Na^+-K^+ exchange mechanism. The antihypertensive mechanism of cyclothiazide is not clearly understood, but it is believed to act on carbonic anhydrase enzyme in the smooth muscles or on the large-conductance calcium-activated potassium (KCa) channel in the smooth muscles.

Uses

1) It is used as an adjunctive therapy in oedema related to congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.
2) It is used alone in the management of hypertension, but in combination with other antihypertensive drugs in the more severe forms of hypertension.

5.4. LOOP DIURETICS

5.4.1. Introduction

Loop or high efficacy diuretics exhibit their effects by acting on the ascending limb of the loop of Henle. They are the most effective of all diuretic agents since the reabsorptive capacity of the ascending limb of the loop of Henle is very high. The loop diuretics are also known as **high ceiling diuretics**, or **Na^+-K^+-$2Cl^-$ co-transporter inhibitors**.

5.4.2. Mechanism of Action

Loop diuretics inhibit the Na^+-K^+-$2Cl^-$ symport in the luminal membrane of the Thick Ascending Limb (TAL) of loop of Henle, thus inhibit the reabsorption of NaCl and KCl. The TAL is responsible for the reabsorption of 35% of filtered sodium and there no downstream compensatory reabsorption mechanisms, thus the loop diuretics are highly efficacious and are also termed as high ceiling diuretics.

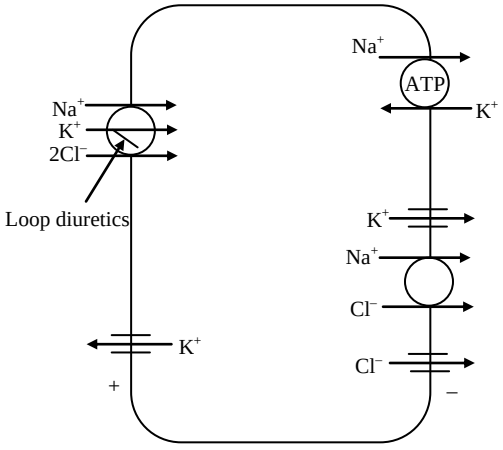


Figure 5.4: Mechanism of Action of Loop Diuretics

The Na^+-K^+-$2Cl^-$ symport along with the sodium pump generate a positive lumen potential that initiates the reabsorption of Ca^{++} and Mg^{++} ions. Therefore, the inhibition of Na^+-K^+-$2Cl^-$ symport also results in the inhibition of Ca^{++} and Mg^{++} ions reabsorption. Loop diuretics also have direct effect on vasculature including increased renal blood flow and increased systemic venous capacitance through unknown mechanisms (prostaglandin-mediated probably).

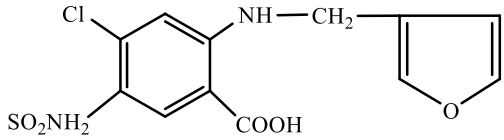
5.4.3. Study of Individual Drugs

The following loop diuretics are discussed below:

1) Furosemide,
2) Bumetanide, and
3) Ethacrynic acid.

5.4.3.1. Furosemide

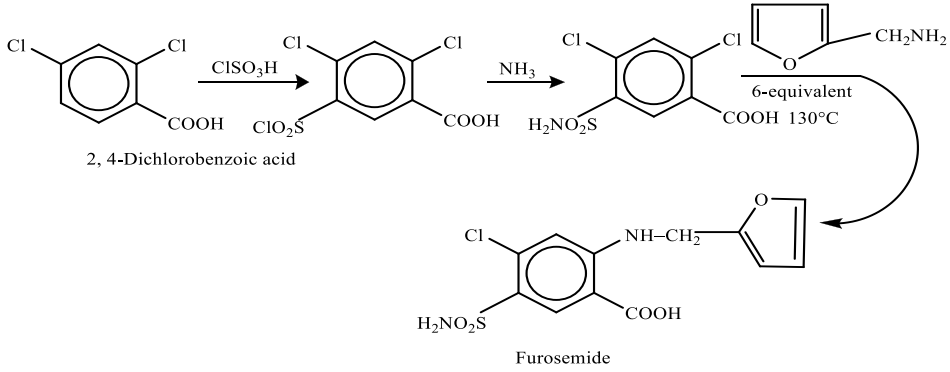
Furosemide is a benzoic -sulfonamide-furan with fast onset and short duration of action. It is used for treating oedema and chronic renal insufficiency.



Furosemide

Synthesis

Chemically furosemide is 4 -chloro-N-furfuryl-5-sulfamoylanthranylic acid. It is synthesised by reacting 2,4-dichlorobenzoic acid with chlorosulphonic acid. The resultant product is further reacted with ammonia to yield 5 -aminosulphonyl-4,6-dichorobenzoic acid, which is reacted with furfurylamine to yield furosemide.



Mechanism of Action

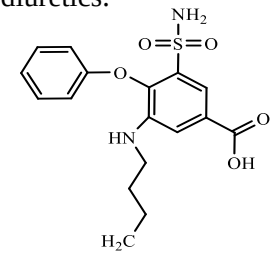
Furosemide competitively inhibits the binding of Cl^- ions at the Na^+-K^+-$2Cl^-$ co-transporter in the thick ascending limb of Henl e's Loop. This in turn inhibits the reabsorption of water in nephron. As a result, the sodium transport from the lumen of the loop of Henle into the basolateral interstitium is prevented. Hence, the hypertonicity of lumen increases (due to more sodium) while that of the interstitium decreases (as the sodium is lesser). This altered concentration of sodium reduces the osmotic gradient for the reabsorption of water all over the nephron.

Uses

1) It is used for the treatment of oedema related to congestive heart failure, liver cirrhosis, and renal disease.
2) It is also used either alone or with other antihypertensive agents for the management of hypertension.

5.4.3.2. Bumetanide

Bumetanide is a loop diuretic of sulfamyl category. It is used for treating heart failure. It is used by the people who are not responding to high doses of furosemide or other diuretics.



Bumetanide

Mechanism of Action

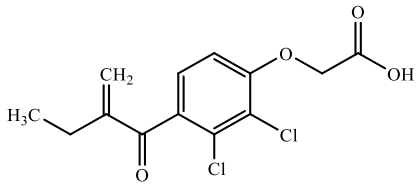
Bumetanide inhibits renal cAMP and/or the Na^+-K^+ ATPase pump. It also inhibits the active reabsorption of Cl^- and Na^+ ions in the ascending loop of Henle, thus disturbing the electrolyte transfer in proximal tubule. This causes excretion of Cl^- and Na^+ ions, and water, and results in diuresis.

Uses

It is used for treating oedema related to congestive heart failure, hepatic and renal disease including nephrotic syndrome.

5.4.3.3. Ethacrynic Acid

Ethacrynic acid is an unsaturated ketone derivative of aryloxyacetic acid without a sulfonamide substituent. It belongs to the class of loop diuretics.



Ethacrynic Acid

Mechanism of Action

Ethacrynic acid blocks Na^+-K^+-$2Cl^-$ symport in the ascending limb of Henle loop and in the proximal and distal tubules. This causes excretion of Na^+, K^+, and $2Cl^-$ ions, increases urinary output, and decreased extracellular fluid. Ethacrynic acid also reduces the blood pressure by lowering the plasma and extracellular fluid volume, which in turn reduces the cardiac output. Ultimately, the cardiac output returns to normal with a reduction in peripheral resistance.

Uses

It is used in the treatment of high blood pressure and oedema caused by diseases like congestive heart failure, liver failure, and kidney failure.

5.5. POTASSIUM SPARING DIURETICS

5.5.1. Introduction

Potassium sparing diuretics include triamterene and amiloride. Only less than 5% of total filtered (amount of a substance filtered per unit time) Na^+ load is excreted by the use of these agents, and this is its maximal effect. As the name suggests, these agents (triamterene and amiloride) form sparing diuretics for K^+ ions contrary to loop and thiazide diuretics, which are K^+ ion depleting agents.

5.5.2. Mechanism of Action

The late distal tubule and the collecting duct comprise of **principal cells** and **intercalated cells**. A Na^+ ion channel, present in the luminal membrane of the principal cells, forms a pathway for the entry of Na^+ ions into the cells mediated by the basolateral Na^+ ion pump, against the electrochemical gradient.

The luminal membrane is highly permeable to Na^+ ions, thereby, creating a lumen negative trans-epithelial potential difference. This potential difference between the lumen and epithelium forms an important driving force enabling the secretion of K^+ ions into the lumen.

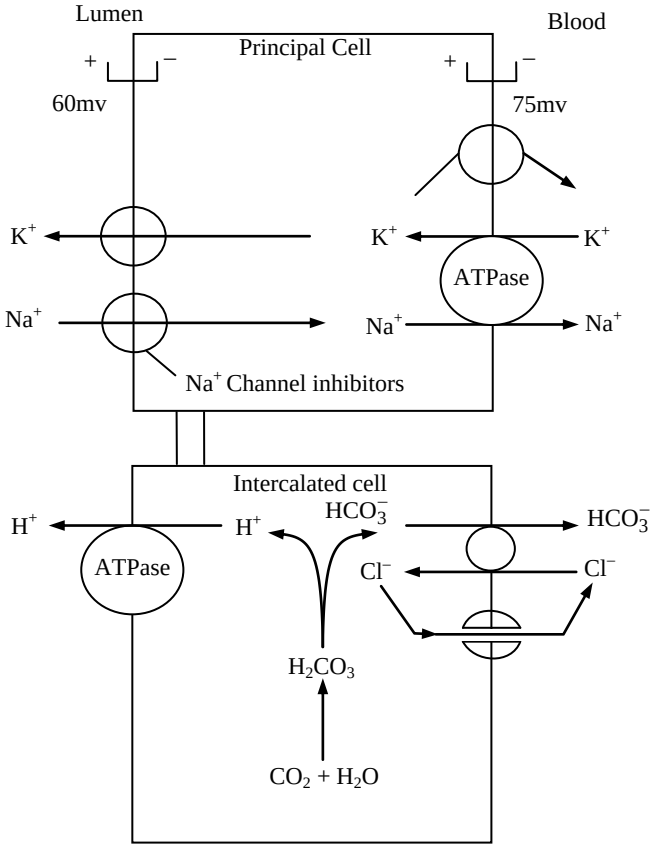


Figure 5.5: Mechanism of Action of Potassium Sparing Diuretics

The H^+ ion is secreted into the tubular lumen by the intercalated cells. This secretion is med iated by the H^+-ATPase pump or proton pump and the lumen negative trans-epithelial voltage difference acts as the driving force.

The potassium sparing diuretics (triamterene and amiloride) act by blocking the Na^+ ion channels in the luminal membrane of th e principal cells (within the late distal tubule and collecting duct). This inhibits the transport of Na^+ ions through the cells, thereby, reducing the luminal secretion of H^+ ions from the intercalated cells and K^+ ions from the principal cells. The net e ffect is increase in the excretion of Na^+ ions through urine, and retention of K^+ and H^+ ions.

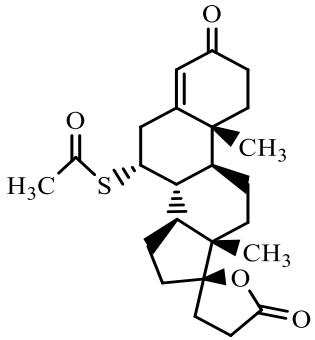
5.5.3. Study of Individual Drugs

The following potassium sparing diuretics are discussed below:

1) Spironolactone,
2) Triamterene, and
3) Amiloride.

5.5.3.1. Spironolactone

Spironolactone is a potassium sparing diuretic which acts by antagonising aldosterone in the distal renal tubules.



Spironolactone

Mechanism of Action

Spironolactone is a specific pharmacologic antagonist of aldosterone. It acts by competitive binding of receptors at the aldosterone -dependent Na^+- K^+ exchange site in the distal convoluted renal tubule. Spironolactone increases the amounts of Na^+ ions and water to be excreted, while retaining the K^+ ions. Through this mechanism, spironolactone acts as a diuretic as well as an antihypertensive drug.

It is administered either alone or along with other diuretics that act more proximally in the renal tubule. Aldosterone improves the expression of Na^+-K^+-ATPase and the Na^+ ion channel involved in Na^+-K^+ transport in the distal tubule by interacting with a cytoplasmic mineralocorticoid receptor.

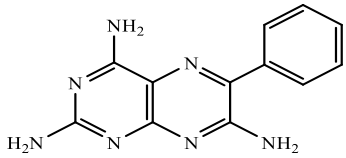
Spironolactone binds to t his receptor and inhibits aldosterone actions on gene expression. Aldosterone hormone retains Na^+ ions and excrete s K^+ ions in the kidneys.

Uses

1) It is used for treating refractory oedema in patients having failure, nephrotic syndrome, or hepatic cirrhosis.
2) It is also used for treating hypokalaemia, Conn's syndrome, and low -renin hypertension.

5.5.3.2. Triamterene

Triamterene is a potassium-sparing diuretic. It is used with thiazide diuretics in the treatment of hypertension and swelling.



Triamterene

Mechanism of Action

Triamterene blocks the epithelial sodium channels on principal cells in the late distal convoluted tubule and collecting tubule (responsible for 1-2% of total sodium reabsorption). It increases the osmolarity in nephron lumen and reduces the osmolarity of interstitium by inhibiting sodium reabsorption. Sodium concentration is the major driving force for water reabsorption, therefore triamterene attains a modest amount of diuresis by decreasing the osmotic gradient required for water reabsorption from lumen to interstitium.

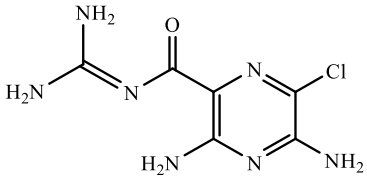
Triamterene also has a potassium-sparing effect. The potassium excretion process is driven by the electrochemical gradient formed by sodium reabsorption. Sodium on reabsorption, leaves a negative potential in the lumen, whereas forms a positive potential in the principal cell. This potential helps in potassium excretion through apical potassium channels. Triamterene also blocks potassium excretion by blocking sodium reabsorption.

Uses

1) It is used for treating oedema related to congestive heart failure, liver cirrhosis, and nephrotic syndrome.
2) It is also used for treating steroid-induced oedema, idiopathic oedema, and oedema caused by secondary hyperaldosteronism.

5.5.3.3. Amiloride

Amiloride is a pyrazine compound that inhibits sodium reabsorption through sodium channels in renal epithelial cells.



Amiloride

Mechanism of Action

Amiloride binds to the amiloride -sensitive sodium channels and inhibits sodium reabsorption in the distal convoluted tubules and collecting ducts in the kidneys. As a result, sodium and water loss from the body occurs, while retaining potassium. Amiloride inhibits sodium reabsorption at the distal convoluted tubule, cortical collecting tubule, and collecting duct; and this explains its potassium sparing effect. This effect of amiloride reduces the net negative potential of the tubular lumen and decreases the secretion and excretion of potassium and hydrogen. Amiloride is not an aldosterone antagonist, and can act even in the absence of aldosterone.

Uses

It is used with thiazide diuretics or other kaliuretic -diuretic agents in the treatment of congestive heart failure or hypertension.

5.6. OSMOTIC DIURETICS

5.6.1. Introduction

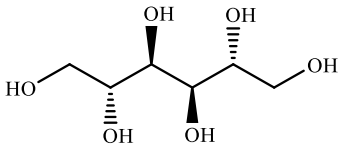
Osmotic diuretics are pharmacologically inert agents. They are comparatively large in size (though they are smaller than albumin); yet, they are filtered freely through the glomerulus. They show poor reabsorption by the renal tubules.

5.6.2. Mechanism of Action

Osmotic diuretics are filtered at the glomerulus. They are not reabsorbed by the renal tubule. The primary sites of action for osmotic diuretics are the loop of Henle and the proximal tubule (membrane is most permeable to water). They prevent water absorption due to its osmotic action in the proximal tubules and impair sodium reabsorption by decreasing sodium concentration in the tubular fluid. Osmotic diuretics decrease medullary hypertonicity in the loop of Henle by raising the medullary blood flow. They decrease sodium and water reabsorption in the collecting duct due to papillary washout and high flow rate.

5.6.3. Mannitol

Mannitol is a naturally occurring alcohol found in fruits and vegetables. It is used as an osmotic diuretic. It undergoes glomerulus filtration and poor renal tubule reabsorption, thus increases osmolarity of the glomerular filtrate.



Mannitol

Mechanism of Action

Mannitol is metabolically inert in humans and occurs naturally as a sugar or sugar alcohol in fruits and vegetables. It raises the osmolality of blood plasma, thus enhancing the flow of water from tissues (brain and cerebrospinal fluid) to interstitial fluid and plasma. This results in cerebral oedema, increased intracranial pressure, and reduced cerebrospinal fluid volume and pressure.

Mannitol causes diuresis by not getting reabsorbed in the renal tubule. Hence, it increases the osmolality of the glomerular filtrate, facilitates excretion of water, and inhibits reabsorption of sodium, chloride, and other solutes in the renal tubules. Mannitol induces urinary excretion of toxic materials. It also provides protection against nephrotoxicity by preventing the concentration of toxic substances in the tubular fluid.

Mannitol as an anti-glaucoma agent increases the osmolarity of blood plasma, thus increasing flow of water from the eye into the plasma and reducing the intraocular pressure.

Mannitol as a renal function diagnostic aid is freely filtered by the glomeruli with less than 10% tubular reabsorption. Hence, its urinary excretion rate is a measurement of its Glomerular Filtration Rate (GFR).

Uses

1) It is used for producing diuresis before irreversible renal failure becomes established.
2) It is also used for reducing intracranial pressure, in treating cerebral oedema, and for facilitating urinary excretion of toxic substances.

5.7. SUMMARY

The details given in the chapter can be summarised as follows:

1) Drugs promoting urine output are known as **diuretic drugs**, which refer only to those agents that act directly on the kidneys.
2) **Carbonic anhydrase inhibitors** are derived from sulphonamide antibacterial. This type of diuretics inhibit carbonic anhydrase enzyme in the membrane and cytoplasm of the epithelial cell.
3) **Acetazolamide** is the pro totype carbonic anhydrase inhibitor. This type of diuretics inhibit carbonic anhydrase enzyme in the membrane and cytoplasm of epithelial cell.
4) **Methazolamide** is a carbonic anhydrase inhibitor. It is used as a diuretic and for treating glaucoma.
5) **Dichlorphenamide** is a carbonic anhydrase inhibitor. It is used for treating glaucoma.
6) **Thiazide diuretics** are referred to as moderately efficacious diuretics as a majority (nearly 90%) of the filtered sodium is already re-absorbed before it reaches the distal tubule.
7) **Chlorothiazide** is a short-acting, benzothiadiazine sulfonamide derivative and prototypical thiazide diuretic.
8) **Hydrochlorothiazide** reduces the reabsorption of electrolytes from renal tubules.
9) **Hydroflumethiazide** is an intermediate-acting benzothiadiazine sulfonamide derivative.

10) **Cyclothiazide** is a benzothiadiazide of thiazide diuretics. It is used as an adjunct in oedema. It is also used for treating hypertension.

11) **Loop** or **high efficacy diuretics** exhibit their effects by acting on the ascending limb of the loop of Henle.

12) The loop diuretics are also known as **high ceiling diuretics**, or **Na^+-K^+-2Cl^- co-transporter inhibitors**.

13) **Furosemide** is a benzoic -sulfonamide-furan with fast onset and short duration of action.

14) **Bumetanide** is a loop diuretic of sulfamyl category. It is used for treating heart failure. It is used by the people who are not responding to high doses of furosemide or other diuretics.

15) **Ethacrynic acid** is an unsaturated ketone derivative of aryloxyacetic acid without a sulphonamide substituent.

16) **Potassium sparing diuretics** include triamterene and amiloride. Only less than 5% of total filtered (amount of a substance filtered per unit time) Na^+ load is excreted by the use of these agents, and this is its maximal effect.

17) **Spironolactone** is a potassium sparing diuretic which acts by antagonising aldosterone in the distal renal tubules.

18) **Triamterene** is a potassium -sparing diuretic that is used with thiazide diuretics in the treatment of hypertension and swelling.

19) **Amiloride** is a pyrazine compound that inhibits sodium reabsorption through sodium channels in renal epithelial cells.

20) **Osmotic diuretics** are pharmacologically inert agents. They are comparatively large in size (though they are smaller than albumin); yet, they are filtered freely through the glomerulus.

21) **Mannitol** is a naturally occurring alcohol found in fruits and vegetables. It is used as an osmotic diuretic.

5.8. EXERCISE

5.8.1. True or False

1) Hydrochlorothiazide increases the reabsorption of electrolytes from renal tubules.
2) Spironolactone acts by antagonising aldosterone in the distal renal tubules.
3) Furosemide is a benzoic -sulphonamide-furan with slow onset and long duration of action.
4) Osmotic diuretics are pharmacologically active agents.
5) Methazolamide is used as a diuretic and for treating glaucoma.

5.8.2. Fill in the Blanks

6) _____ is a pyrazine compound that inhibits sodium reabsorption through sodium channels in renal epithelial cells.
7) _____ is a naturally occurring alcohol found in fruits and vegetables.

8) _____ is a potassium-sparing diuretic that is used with thiazide diuretics in the treatment of hypertension and swelling.
9) The loop diuretics are also known as _____.
10) _____ reduces the reabsorption of electrolytes from renal tubules.
11) _____ is a benzoic -sulphonamide-furan with fast onset and short duration of action.

Answers

1) False	2) True	3) False	4) False
5) True	6) Amiloride	7) Mannitol	8) Triamterene
9) High ceiling diuretics		10) Hydrochlorothiazide	11) Furosemide

5.8.3. Very Short Answer Type Questions

1) Give a brief introduction of diuretics.
2) Write a short note on methazolamide.
3) Discuss thiazides.
4) Write a short note on loop diuretics.
5) Discuss amiloride.
6) Write a note on hydroflumethiazide.

5.8.4. Short Answer Type Questions

1) Give the classification and uses of diuretics.
2) Discuss the SAR of diuretics.
3) Write a short note on carbonic anhydrase inhibitors.
4) Discuss loop diuretics.

5.8.5. Long Answer Type Questions

1) Discuss potassium sparing diuretics.
2) Give a detailed note on thiazides in detail.
3) What are diuretics? Give their classification, uses and SAR.

CHAPTER 6

Anti-Hypertensive Agents

6.1. ANTI-HYPERTENSIVE AGENTS

6.1.1. Introduction

A condition in which the blood pressure of systemic artery increases beyond the normal pressure is known as **hypertension** Therefore to deliver blood to tissues, the heart works harder to overcome the increased systemic pressure. This increased systemic arterial pressure puts strain on heart and other arteries, thus resulting **high blood pressure** Based on the degree of severity, hypertension can be graded as:

1) **Mild:** Diastole up to 104 mmHg,
2) **Moderate:** Diastole105-114 mmHg, and
3) **Severe:** Diastole more than 115 mmHg.

Therapy for hypertensive patients aims at reducing the increased blood pressure. This is accomplished by administration of drugs from different classes; treatment is often given in the form of a combination of several agents. If left untreated, it would result in end organ damage, an increased risk for MI and stroke.

6.1.2. Classification

Antihypertensive drugs are classified as follows:

1) **Diuretics**
   i) **Thiazides:** Hydrochlorothiazide, Chlorthalidone, and Indapamide.
   ii) **Loop Diuretics:** Furosemide, Bumetanide, and Torsemide.
   iii) **Potassium Sparing Diuretics:** Spironolactone, Amiloride, and Triamterene.
2) **Angiotensin Converting Enzyme Inhibitors:** Captopril, Enalapril, Lisinopril, Ramipril, Perindopril, Fosinopril, Trandolapril, Quinapril, and Benazepril.
3) **Angiotensin II Receptor Antagonists:** Losartan, Candesartan, Valsartan, Eprosartan, and Irbesartan.
4) **Ganglion Blockers:** Trimethaphan.
5) **Adrenergic Drugs**
   i) **Centrally Acting Drugs:** Clonidine, Methyldopa, Guanabenz & Guanfacine.
   ii) **Adrenergic Neuron Blockers:** Guanethidine and Reserpine.
   iii) **Sympatholytics (Adrenergic Receptor Blockers)**
      a) **α-Blockers:** Prazosin, Terazosin, Doxazin, Phenoxybenzamine, and Phentolamine.
      b) **β-Blockers:** Propranolol, Atenolol, Esmolol, and Metoprolol.
      c) **α & β-Blockers:** Labetalol and Carvedilol.
6) **Calcium Channel Blockers:** Verapamil, Nifedipine, Nicardipine, Nimodipine, Amlodipine, and Felodipine.

7) **Vasodilators**
   i) **Arteriolar Dilators:** Hydralazine, Minoxidil, and Diazoxide.
   ii) **Arteriolar and Venular Dilators:** Sodium nitroprusside.

6.1.3. Mechanism of Action

Anti-hypertensive drugs involve the following mechanisms:

1) **Diuretics:** These drugs are secreted into the urine by the proximal tubule cells. The three diuretic types used for treating hypertension are:
   i) **Thiazide Diuretics:** These diuretics work initially by increasing urinary sodium excretion by inhibiting the Na^+-Cl^- pump in the early segment of the distal convoluted tubule. This causes an initial reduction in plasma volume, which increases plasma renin activity and aldosterone. Eventually, vascular resistance decreases by unknown mechanisms because plasma volume approaches pre-treatment levels.
   ii) **Loop Diuretics:** These diuretics act at the thick ascending loop of Henle to prevent sodium and chloride reabsorption from urine. They have a rapid onset of action compared to thiazide diuretics. **Torsemide** is the longest-acting loop diuretic.
   iii) **Potassium-Sparing Diuretics:** These diuretics decrease the excretion of magnesium and potassium. **Amiloride** and **triamterene** inhibit the Na^+-proton exchanger in the distal and collecting tubules. They block the epithelial sodium transport channel. **Spironolactone** inhibits the Na^+-K^+ exchanger affected by aldosterone, and it is particularly effective in hyperaldosteronism. It is a potent non-selective aldosterone blocker that also interacts with androgen and progesterone receptors.

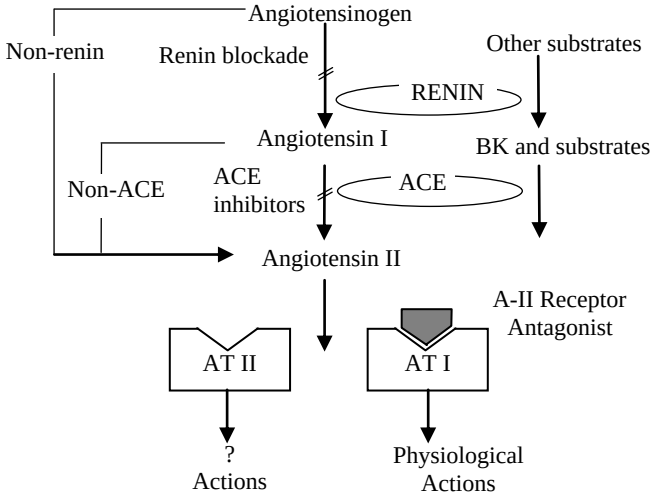


Figure 6.1: ACE inhibitors block the conversion of angiotensin I and angiotensin II via angiotensin converting enzyme, but do not prevent the formation of angiotensin II via alternate pathways. Angiotensin II Receptor Blockers (ARBs) work at the receptor level to block the binding of angiotensin II to its Type 1 receptor (AT_1), which mediates all known pressor effects of angiotensin II. (BK, Bradykinin)

2) **Angiotensin-Converting Enzyme (ACE) Inhibitors:** These drugs slow down the formation of angiotensin II, which reduces vascular resistance, blood volume, and blood pressure. Renin enzyme is released by the kidneys in response to reduced renal blood circulation or hypernatremia. This enzyme acts in the plasma angiotensinogen to produce angiotensin I which is then converted to angiotensin II, mostly in the lungs. Angiotensin II is a vasoconstricting agent. It causes sodium retention via aldosterone release. In adrenal gland, angiotensin II is converted to angiotensin III. Both of them stimulate the release of aldosterone.

3) **Angiotensin II Receptor Blockers (ARBs):** These drugs inhibit the final step of renin-angiotensin cascade, i.e., the interaction between angiotensin II and the angiotensin II type 1 receptor (AT_1) – which is thought to mediate all effects of this hormone and some of its effects that promote atherosclerosis. ARBs result in more complete antagonism of angiotensin II than ACE inhibitors, because angiotensin II can be produced by non-ACE pathways (**figure 6.1**). ARBs do not cause elevations in bradykinin, which may be responsible for the dry cough seen with ACE inhibitors.

4) **β-Blockers:** These drugs decrease the cardiac output by blocking β-adrenergic receptors in the heart, resulting in negative chronotropic (heart rate) and inotropic (contractility) effects. The β-blockers also decrease renin release from the kidney and are thought to decrease sympathetic outflow to the periphery via central effect. Over-activity of the sympathetic nervous system increases blood pressure by increasing cardiac output.

5) **Calcium Channel Blockers:** These drugs block or alter cell membrane calcium flux. Dihydropyridine calcium channel blockers (**e.g.,** amlodipine, felodipine, and nifedipine) lower the blood pressure via arteriolar and venous vasodilation; non-dihydropyridine calcium channel blockers (**e.g.,** verapamil and diltiazem) are less potent vasodilators and lower the blood pressure through peripheral vasodilation and a negative inotropic effect.

6) **Vasodilators:** Available evidence suggests that a single mechanism does not exist; instead various vasodilators act at different places in a series of processes that couple excitation of vascular smooth muscle cells with contraction. **For example,** the vasodilators known as **calcium channel antagonists** block or limit the entry of calcium through voltage-dependent channels in the membrane of vascular smooth muscle cells. In this way, the calcium channel blockers limit the amount of free intracellular calcium available to interact with smooth muscle contractile proteins. Other vasodilators, such as **diazoxide** and **minoxidil**, cause dilation of blood vessels by activating potassium channels in vascular smooth muscle. An increase in potassium conductance results in hyperpolarisation of the cell membrane, which will cause relaxation of vascular smooth muscle.

   Another group of drugs, called **nitrovasodilators** (**e.g.,** nitroprusside) activate soluble guanylate cyclase in vascular smooth muscle to increase the intracellular levels of cGMP. This increase in cGMP is associated with vascular smooth muscle relaxation.

6.1.4. Uses

Therapeutic uses of anti-hypertensive agents are:

1) **Angiotensin-Converting Enzyme (ACE) Inhibitors:** They are employed in the following cases:
   i) **Hypertension:** Currently, ACE inhibitors are the first line of drugs employed in the treatment of all grades of hypertension. Nearly 50% of the patients are treated using the ACE inhibitors alone (**monotherapy**) while majority of the remaining p atients are treated using combination s of ACE inhibitors with diuretics or β-blockers (**combinational therapy**). When this group of drugs is administered in lower doses, the hypotensive effect develops progressively in 2-3 weeks.

      Advantages of ACE inhibitors include:
      a) Lack of postural hypoten sion, electrolyte disturbances, feeling of weakness, and CNS effects.
      b) Safe in asthmatics, diabetics, and peripheral vascular disease patients.
      c) Prevention of secondary hyperaldosteronism and potassium loss due to diuretics.
      d) Maintenance of renal blood flow.
      e) Reverse left ventricular hypertrophy and increased wall -to-lumen ratio of blood vessels that occurs in hypertensive patients.
      f) No hyperuricemia, no deleterious effect on plasma lipid profile.
      g) No rebound hypertension on withdrawal.
      h) Minimum worsening of quali ty of life parameters like general well -being, work performance, sleep, sexual performance, etc.

   ii) **Congestive Heart Failure (CHF):** ACE inhibitors exhibit a property of dilatation of arteries as well as vessels; and this property is effective in CHF patients. When ACE inhibitors are administered, the after -load and pre-load in CHF patients is reduced. These agents do not exhibit any direct effects on myocardium; yet, they increase the stroke volume and cardiac output and decrease the heart rate. Renal perfusio n is improved and sodium retention (facilitated by mineralocorticoids) is eliminated. As a result, the accumulated salt and water are excreted out. Cardiac load is decreased, and thus, the capacity to exercisein CHF patients is improved.

   iii) **Myocardial Infarc tion (MI):** Administering ACE inhibitors orally during the development of MI (within 24 hours of an attack), and continuing for 6 weeks after the initial attack, decreases early and long -term mortality in such patients. Presence or absence of systolic dysfunction does not affect the action of these drugs, until hypotension does not occur. If this therapy is extended in patients who are at high risk for MI and patients with latent or overt ventricular dysfunction (CHF), their survival rate is increased by some years.

   iv) **Prophylaxis in High Cardiovascular Risk Subjects:** ACE inhibitors have also been found to decrease the risk of development of heart failure

or diabetes. Therefore, these agents play a protective role in patients with a high risk of cardiovascular d iseases even when they do not have hypertension or left ventricular dysfunction.

v) **Diabetic Nephropathy:** In patients with type -I and type -II diabetes, administration of ACE inhibitor therapy for prolong period either delays or prevents the end stage renal d isease. Diabetic patients who are treated with ACE inhibitors present with stable albuminuria (an index of glomerulopathy). On the other hand, albuminuria is found to be aggravated in diabetic patients not been treated with ACE inhibitors.

vi) **Scleroderma Crisi s:** Angiotensin II mediates a noticeable increase in blood pressure and deteriorates renal function during scleroderma crisis. In such patients, ACE inhibitors show an intense improvement and form life-saving drugs.

2) **Angiotensin II Receptor Blockers (ARBs):** These drugs are employed in the following cases:
   i) In patients who cannot tolerate ACE inhibitor therapy, hypertension is mainly treated using Angiotensin II receptor antagonists.
   ii) They do not inhibit the breakdown of bradykinin or other kinins, thus, are rarely associated with persistent dry cough; however, this limits ACE inhibitor therapy.
   iii) Patients with heart failure and who cannot tolerate ACE inhibitor therapy can be treated using ARBs (like candesartan). Data from clinical trials using irbesartan and los artan have shown beneficial results in type II diabetic patients having hypertension. These drugs also seem to postpone the progression of diabetic nephropathy.

3) **Calcium Channel Blockers (CCBs):** Patients in whom β-blockers are contraindicated and who are affected with peripheral vascular disease and obstructive lung disease can be treated safely using CCBs. It is beneficial over β-blockers as the problem of rebound worsening of angina (seen on withdrawal of these drugs) after chronic use is lesser in these drugs. These drugs can be therapeutically used in:
   i) **Angina Pectoris:** All the CCBs effectively decrease the frequency and severity of both forms of angina (classical and variant). Cardiac performance is decreased due to a decrease in after-load, and this appears to be the primary benefit in patients with classical angina. In normal individuals, though the CCBs can increase coronary flow, yet this increase is insignificant in patients with fixed art erial obstruction. Also, tolerance to exercise is increased.

   CCBs have the ability to prevent arterial spasm. The therapeutic effects of CCBs in variant angina are due to this action of CCBs. They also decrease the cardiac oxygen demand. In the treatment of angina pectoris, no significant difference has been observed in the efficiency even when different CCBs are used. For unstable angina, CCBs are not the first drugs of choice; and can just be employed as an additional therapy to patients who are not responsive to nitrates and β-blockers.

ii) **Hypertension:** DHPs, diltiazem, and verapamil are now recognised CCBs for hypertension.

iii) **Arrhythmias:** In conditions like Paroxysmal Supraventricular Tachycardia (PSVT), verapamil proves to be highly efficacious (diltiazem to a lesser extent). Verapamil is also an effective agent for supraventricular arrhythmias as it controls the ventricular rate.

iv) **Hypertrophic Cardiomyopathy:** In this condition, the beneficial effects of verapamil are due to its negative inotropic action.

v) **Other Uses:** Premature labour can be alternatively treated using nifedipine; nocturnal leg cramps can be suppressed by the administration of verapamil; the severity of Raynaud's episodes can be reduced by Dihydropyridines **(**DHPs).

4) **Vasodilators:** They are employed in the following cases:
   i) Hypertensive emergencies employ nitroprusside as the drug of choice.
   ii) Vasodilator action of anti -hypertensives is used in conditions of MI for decreasing myocardial work load (for a short period of time).

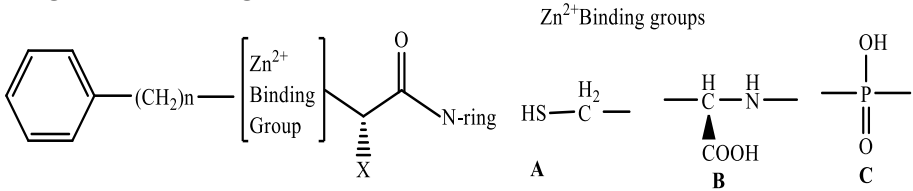
6.1.5. Structure-Activity Relationship

The SAR of some important classes of anti -hypertensive agents is described below:

1) Structure-activity relationship of ACE inhibitors,
2) Structure-activity relationship of angiotensin II antagonists,
3) Structure-activity relationship of dihydropyridines (calcium channel blockers), and
4) Structure-activity relationship of β-adrenergic antagonist.

6.1.5.1. Structure-Activity Relationship of ACE Inhibitors

All commercially available inhibitors of angiotensin converting enzyme are the analogues of following structure:

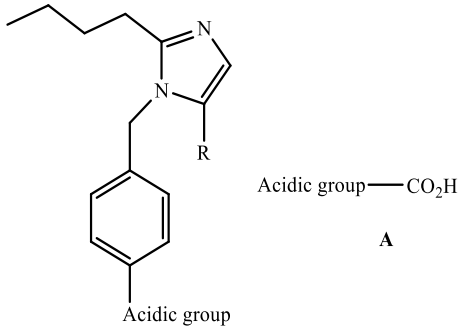


1) A carboxylic acid should be present in the N -ring to mimic the C -terminal carboxylate of ACE substrates.
2) The potency is enhanced and the pharmacokinetic parameters are alter ed by the large hydrophobic heterocyclic rings present in the N-ring.
3) Groups A, B, or C are the zinc binding groups.
4) The sulfhydryl group binds superiorly to zinc (Phe in carboxylate and phosphinic acid side-chain compensates for sulfhydryl group).
5) Sulfhydryl-containing compounds form disulphides which shorten the duration of action.

6.1.5.2. Structure-Activity Relationship of Angiotensin II Antagonists

All commercially available angiotensin II antagonists are analogues of the following structure:

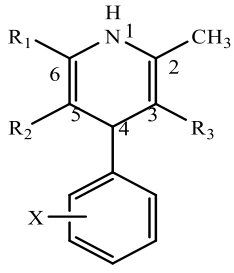
1) The acidic groups, such as carboxylic acid (A), a phenyl tetrazole (B), or a phenyl carboxylate (C) mimic either the Tyr_4 phenol or the A-sp, carboxylate of angiotensin II.
2) To achieve optimum activity, the tetrazole and carboxylate groups in the biphenyl series should be in the ortho position (the tetrazole group is superior in terms of metabolic stability, lipophilicity, and oral bioavailability).
3) The n-butyl group of the model compound provides hydrophobic interaction and mimics the side chain of angiotensin II. In candesa rtan and telmisartan, this n-butyl group is replaced with a substituted benzimidazole ring.
4) The imidazole ring or an isosteric equivalent can mimic the side chain of angiotensin II.
5) In order to mimic the Phe of angiotensin II, substitution with a variety o f R groups (including a carboxylic acid, methyl alcohol, ether, or an alkyl chain) is required. These groups interact with the angiotensin receptor, some through ionic or ion-dipole bonds and others through hydrophobic interactions.



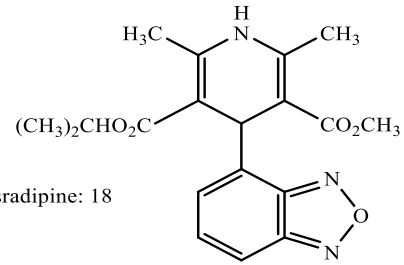
6.1.5.3. Structure-Activity Relationship of Dihydropyridines (Calcium Channel Blockers)

The SAR for 1,4-DHP derivatives indicates that the following structural features are essential for activity:

1) Activity is optimised by substituting a phenyl ring at C -4 (heteroaromatic rings, such as pyridine, produce similar therapeutic effects; but are not used due to observed animal toxicity). Activity is decreased by substituting with a small non-planar alkyl or cycloalkyl group at C-4.



Key to general structure: 105



Isradipine: 18

Table 6.1: Structures of the Dihydropyridine Calcium Channel Blockers

Compounds	R_1	R_2	R_3	X
Amlodipine	$CH_2OH_2CH_2NH_2$	$CO_2CH_2CH_3$	CO_2CH_3	2-Cl
2-Felodipine	CH_3	$CO_2CH_2CH_3$	CO_2CH_3	2,3-Cl_2
Nicardipine	CH_3	$CO_2(CH_2)_2$—NH(Me)CH_2—Ph	CO_2CH_3	3-NO_2
Nifedipine	CH_3	$CO_2CH_2CH_3$	CO_2CH_3	2-NO_2
Nimodipine	CH_3	CO_2CH_2 CH_2OCH_3	$CO_2CH(CH_3)_2$	3-NO_2
Nisoldipine	CH	$CO_2CH_2CH(CH_3)_2$	CO_2CH_3	2-NO_2

2) Substitution of phenyl ring (X) is essential for size and position, but not for electronic nature. The compounds with *ortho*- or *meta*-substitutions are active, while the unsubstitu ted compounds or those containing a *para*-substitution are less active. The compounds are optimally active if *ortho* or *meta*-substituents are electron withdrawing or donating groups. The se substituents provide sufficient bulk to "lock" the conformation of 1, 4-DHP so that the C-4 aromatic ring is perpendicular to the 1,4-dihydropyridine ring. This perpendicular conformation is important for the activity of 1,4-DHPs.

3) The 1,4 -dihydropyridine ring is important for activity. Substitution at N_1 position or the use of oxidised (piperidine) or reduced (pyridine) ring systems either reduces or eliminates the activity.

4) Optimum activity is achieved by substituting ester groups at C -3 and C -5 positions. The antagonist activity decreases and may even show agonist activity if electron withdrawing groups are used for substitution. **For example,** a calcium channel activator or an agonist is obtained by replacing the C -3 ester of isradipine with a NO_2 group. Thus, the term **calcium channel modulator** is a more appropriate classification for the 1,4-DHPs.

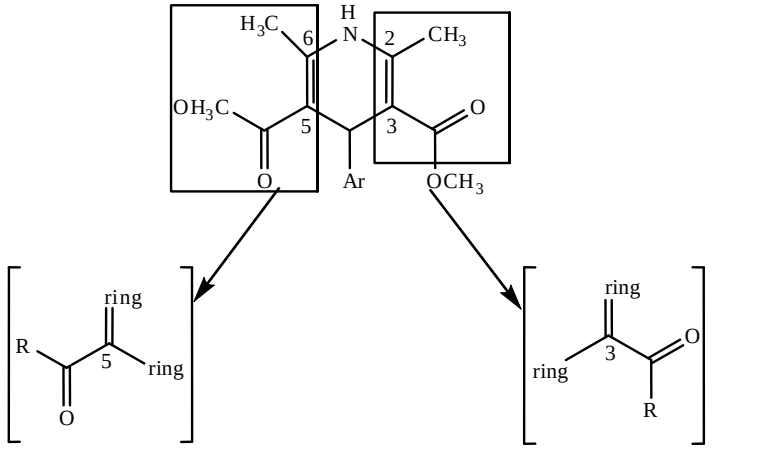


Figure 6.2: Conformation of the C3 and C5, Esters of Nifedipine (Ar = 2-nitrophenyl). The C3, Carbonyl is Synplanar to the C2-C3 Bond, and the C5 Carbonyl Anti-Periplanar to the C5-C6 Bond

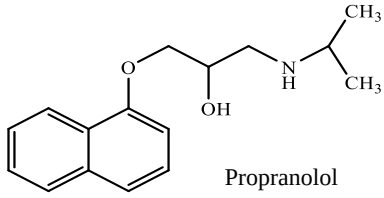
5) Non-identical esters are substituted at C -3 and C -5. The C -4 becomes chiral and stereoselectivity is observe d between the enantiomers. Also, there is evidence that the C -3 and C -5 positions of the dihydropyridi ne ring are not

equivalent. The crystal structures of nifedipine (first marketed symmetrical 1,4-DHP) indicate the C-3 carbonyl to be synplanar to the C2-C3 bond, but the C-5 carbonyl to be anti-planar to C5-C6 bond. The selectivity of asymmetrical compounds for specific blood vessels is optimum, thus are being developed. Nifedipine is the only symmetrical compound in this chemical class.

6) All 1,4-DHPs, except amlodipine, have methyl groups at C-2 and C-6 positions. The enhanced potency of amlodipine (*versus* nifedipine) indicates that large groups can be substituted at the 1,4-DHP receptor and altering these groups is the result of enhanced activity.

6.1.5.4. Structure-Activity Relationship of β-Adrenergic Antagonists

Soon another major advancement was introduced in drug development for β-adrenergic antagonists. As per this advancement, by introducing an oxymethylene bridge (OCH_2) into the arylethanolamine structure of pronethalol, an aryl-substituted phenyloxypropanololamines, i.e., propranolol can be yielded. It is the first clinically used practolol which selectively inhibits sympathetic β-blocker. Along with this advancement (i.e., introduction of oxymethylene bridge), the side chain has also been shifted from C-2 of the naphthyl group to Cl position.



Propranolol

The potency of aryloxypropanolamines as β-blockers is more than that of the corresponding arylethanolamines. Aryloxypropanolamines are the β-blockers which at the current time are in clinical use. The β-blockers are widely used as anti-hypertensive agents.

6.1.6. Recent Developments

For cardiovascular diseases, hypertension forms the most common risk factor. It is one of the most prevalent cardiovascular diseases and is the primary cause of mortality all over the world. The currently used anti-hypertensive agents have numerous limitations, thus, led to the research and development of new classes of anti-hypertensive agents, which act by different mechanisms providing a better patient tolerability, better control over blood pressure, greater protection against damage to the organs, and prevention against cardiovascular diseases in a more efficient manner.

Various drugs that form the current first-line anti-hypertensive agents have different glycometabolic effects. **For example**, while the calcium channel blockers are neutral, β-blockers or diuretics decrease insulin sensitivity and consequently worsen the states of **Insulin Resistance** (IR). According to a recent meta-analysis, only the ACE inhibitors and angiotensin II (Ang II) type 1 (AT_1) receptor antagonists increase the sensitivity to insulin and decrease the onset of type II diabetes in hypertensive patients.

Insulin resistance in patients suffering from metabolic syndrome as well as hypertension, have not been found to be affected by the effects of **telmisartan**. Though extensive research on drugs has been carried out and is still going on, drugs able to improve hypertension and IR and/or hyperinsulinemia have not yet been developed. It is thus required that a new generation of anti -hypertensive drugs be developed such that it improves the metabolic disorders.

Dysfunction of the endothelium related to Insulin Resistance (IR) states is characterised by the release of NO (stimulated by injured insulin) from the endothelium, along with a decrease in the blood flow and de livery of hormones and substrates to the insulin target tissues. Further, the imbalance between endothelial-derived relaxing and contracting factors potentially contribute to the atypical vascular tone modulation and the pathogenesis of high blood pressure.

Hence, restoration of endothelial function must probably be a feasible approach for improving IR related to hypertension. According to a current research, improvements in IR states during hypertension after administration of ACE inhibitors or ARBs are mainly due to their protective role against endothelial dysfunction.

Varied collection of ion channels in endothelial cells modulates the cell functions significantly. It has been found that the progression of endothelial dysfunction can be facilitated by the activation of endothelial ATP -sensitive potassium channels (KATP).

Intracellular levels of Ca^{+2} ions can be regulated by the opening of KATP channels, which in turn affects the production and release of endothelial autacoids, **e.g.,** NO, endothelin -1 (ET -1), and prostaglandins. In theoretical terms, it is predicted that the **endothelial KATP channel openers** have the ability to prevent the development of IR in patients with hypertension.

The establishment and progression of IR with hypertension can b e prevented by **iptakalim** which maintains a balance between NO and ET-1 signalling within the endothelial cells. Being a highly selective KATP channel opener, it can cause relaxation of the small arteries and also efficiently decrease the blood pressure.

It was thus recommended that improvement in endothelial function could be achieved by activation of KATP channels, which in turn improves the endothelial chemerin/ChemR axis and NO production. Iptakalim has contributed widely in the area of hypertension an d IR therapy, and has gained immense popularity in cardiovascular research.

A new drug, which may be a prototype of a new class of centrally acting anti - hypertensive drugs has been synthesised. **RB150** is a prodrug which is administered orally and prevents the activity of brain, but not that of the systemic Renin-Angiotensin System (RAS). In cases of hypertension, it has been found to decrease blood pressure.

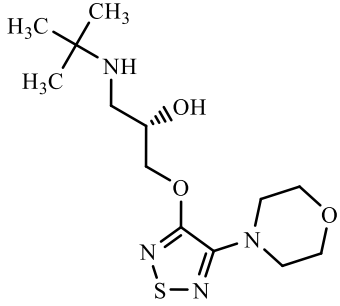
6.1.7. Study of Individual Drugs

The following anti-hypertensive agents are discussed below:

1) Timolol,
2) Captopril,
3) Lisinopril,
4) Enalapril,
5) Benazepril hydrochloride,
6) Quinapril hydrochloride,
7) Methyldopate hydrochloride,
8) Clonidine hydrochloride,
9) Guanethidine monosulphate,
10) Guanabenz acetate,
11) Sodium nitroprusside,
12) Diazoxide,
13) Minoxidil,
14) Reserpine, and
15) Hydralazine hydrochloride.

6.1.7.1. Timolol

Timolol is a β-adrenergic antagonist. It has similar actions to propranolol. Its levo-isomer is more active.



Timolol

Mechanism of Action

Timolol bind s to β_1-adrenergic receptors in the heart and vascular smooth muscles and β_2-receptors in the bronchial and vascu lar smooth muscle s by competing with adrenergic neurotransmitters (like catecholamines). The β_1-receptor blockage decreases the resting and exercise heart rate and cardiac output, decrease s the systolic and diastoli c blood pressure, and decreases the reflex orthostatic hypotension; while the β_2-receptor blockage increases peripheral vascular resistance.

The precise mechanism of t imolol (decreases ocular pressure) is still unknown, and is most likely believe to act by reducing aqueous humour secretion.

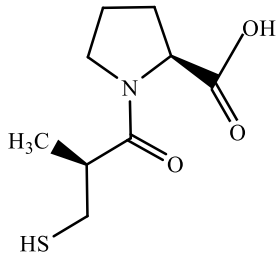
Uses

1) It is used as an anti -hypertensive, antiarrhythmic, anti -anginal, and anti -glaucoma agent.

2) It is administered orally for treating high blood pressure and preventing heart attacks.
3) It is used as an ophthalmic preparation for treating open -angle and also secondary glaucoma.
4) It is also used for treating migraine disorders and tremor.

6.1.7.2. Captopril

Captopril is a potent competitive inhibitor of Angi otensin-Converting Enzyme (ACE), which is responsible for converting Angiotensin I (ATI) to Angiotensin II (ATII). ATII controls the blood pressure and is a major component of the Renin -Angiotensin-Aldosterone System (RAAS).



Captopril

Mechanism of Action

Angiotensin II acts as a vasoconstrictor and mediates a negative feedback mechanism for renin activity. Captopril competes with angiotensin I for binding to the angiotensin -converting enzyme, and thus blocks the conversion of angiotensin I to angiotensin II. Therefore, the concentration of angiotensin II is decreased and this further decreases the bl ood pressure, increases renin activity, and stimulates the baroreceptor reflex mechanisms. **Kininase II** , an enzyme responsible for the degradation of vasodilator bradykinin, resembles the angiotensin-converting enzyme (ACE) and may also be inhibited.

Uses

1) It is used for treating essential or renovascular hypertension (generally with other drugs, especially thiazide diuretics).
2) It may be used along with other drugs (**e.g.,** cardiac glycosides, diuretics, or β-adrenergic blockers) for treating congestive heart failure.
3) It may also improve the survival of patients having left ventricular dysfunction due to myocardial infarction.
4) It may be used for treating neuropathy as well as diabetic neuropathy.

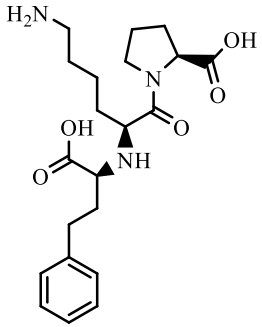
6.1.7.3. Lisinopril

Lisinopril is potent and competitive inhibitor of angio tensin-converting enzyme (ACE), which converts angiotensin I (ATI) to angiotensin II (ATII).

Mechanism of Action

Lisinopril being an ACE inhibito r inhibits the actions of angiotensin -converting enzyme (ACE) in the renin-angiotensin-aldosterone system (RAAS). As a result, the conversion of angiotensin I to angiotensin II is prevented. This also inhibits aldosterone release from the adrenal cortex, a nd aldosterone allows the kidney to

excrete sodium and water in the urine, while retaining potassium. This process occurs in the peritubular capillaries of kidneys in response to a change in Starling forces. Inhibition of the RAAS system reduces the blood pressure.



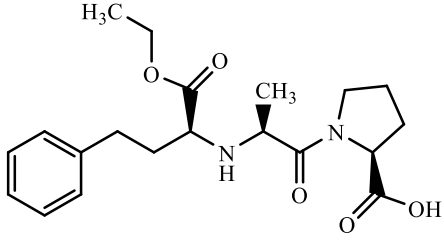
Lisinopril

Uses

1) It is used for treating hypertension and symptomatic congestive heart failure.
2) It is used with thrombolytic agents, aspirin and/or β-blockers to improve survival in haemodynamically stable individuals following myocardial infarction.
3) It is also used for slowing the progression of renal disease in hypertensive patients having diabetes mellitus and micro -albuminuria or overt nephropathy.

6.1.7.4. Enalapril

Enalapril is a prodrug of the Angiotensin-Converting Enzyme (ACE) inhibitor class. It gets quickly metabolised to enalaprilat in the liver after oral administration.



Enalapril

Mechanism of Action

Angiotensin-Converting Enzyme (ACE) converts the angiotensin I to angiotensin II, which constricts the blood vessels and increases blood pressure. Enalaprilat, the active metabolite of enalapril, inhibits the angiotensin-converting enzyme, reduces angiotensin II levels, leads to less vasoconstriction, and reduces blood pressure.

Uses

1) It is used for treating essential or renovascular hypertension and symptomatic congestive heart failure.
2) It is used either alone or in combination with thiazide diuretics.

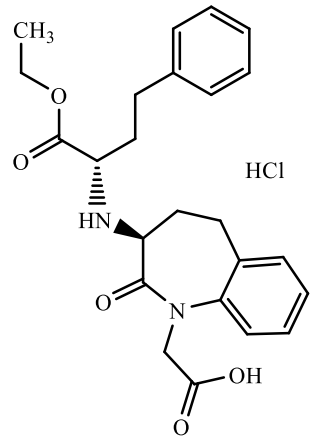
6.1.7.5. Benazepril Hydrochloride

Benazepril hydrochloride is the hydrochloride salt of benazepril, which is a carboxyl-containing ACE inhibitor having antihypertensive activity.

Mechanism of Action

Benazeprilat is the active metaboli te of benazepril. It binds with angiotensin-converting enzyme (by competing with angiotensin I), and thus prevents the conversion of angiotensin I to angiotensin II. Inhibition of ACE reduces plasma levels of angiotensin II.

Since angiotensin II is a vas oconstrictor and a negative-feedback mediator for renin activity, in lower concentrations it reduces blood pressure and stimulates baroreceptor reflex mechanisms; this leads to decreased vasopressor activity and aldosterone secretion. Benazeprilat also act on kininase II enzyme that is similar to ACE which degrades the vasodilator bradykinin.



Benazepril Hydrochloride

Uses

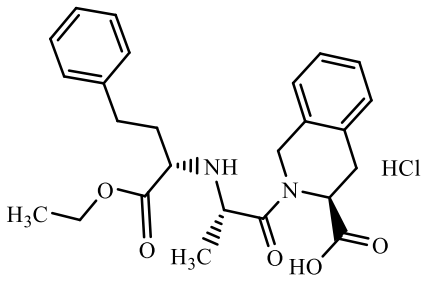
1) It is used fo r treating high blood pressure , congestive heart fail ure, and chronic renal failure.
2) It is used either alone or in combination with thiazide diuretics.

6.1.7.6. Quinapril Hydrochloride

Quinapril hydrochloride is the hydrochloride salt of quinapril. It is a prodrug and non-sulfhydryl ACE inhibitor having antihypertensive activity.

Mechanism of Action

Quinapril hydrolyses into its active form, quinaprilat that binds to and blocks the ACE. Therefore, it blocks the conversion of angiotensin I to angiotensin II. As a result, the potent vasoconstrictive actions of angiotensin II are prevented and vasodilatation occurs. Quinapril also reduces the secretion of aldosterone by the adrenal cortex induced by angiotensin II; and thus it promote s diuresis and natriuresis, and increases bradykinin levels.



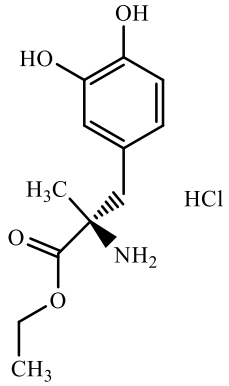
Quinapril Hydrochloride

Uses

1) It is used for treating hypertension and as an adjunct for tre ating congestive heart failure.
2) It also slows down the progression rate of renal disease in hypertensive patients having diabetes mellitus and microalbuminuria or overt nephropathy.

6.1.7.7. Methyldopate Hydrochloride

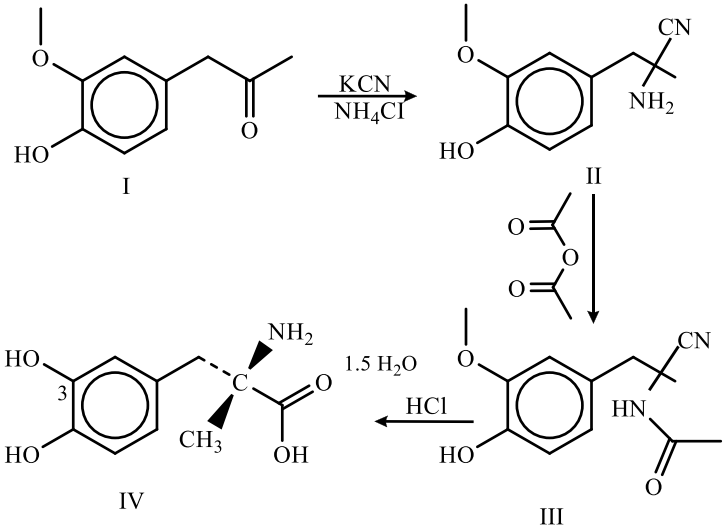
Methyldopate hydrochloride is the hydrochloride salt of methyldopa , which is a derivate of phenylalanine and inhibitor of aromatic amino acid decarboxylase. It also exhibits antihypertensive activity.



Methyldopate Hydrochloride

Synthesis

On treating 3-methoxy-4-hydroxyphenylacetone **(I)** with ammonium chloride and potassium cyanide in isopropanol, racemic α-amino-α-vanillyl propionitrile **(II)** is obtained. Acetylation of (II) forms an intermediate **(III)** whose resolution by camphorsulphonic acid salt forms the levorotatory isomer. This isomer is hydrolysed with concentrated hydrochloric acid at 130 °C temperature to form methyldopate hydrochloride **(IV)**.



Mechanism of Action

The mechanism of action of methyldopate hydrochloride is not still clear, but its hypotensive effect is believed to occur due to its action on the CNS. Methyldopa metabolises into α-methylnorepinephrine in the CNS where it stimulates the central inhibit ory α-adrenergic receptors and reduces sympathetic tone, total peripheral resistance, and blood pressure. Reduced plasma renin activity, and

inhibition of central and peripheral norepinephrine an d serotonin production is responsible for the antihypertensive effect of methyldopa; however, this is not its major mechanism of action. This is done by the inhibition of de carboxylation of dihydroxyphenylalanine (norepinephrine precursor) and 5 -hydroxytryptophan (serotonin precursor) in the CNS and in most peripheral tissues.

Uses

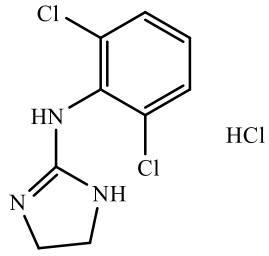
1) It is used for treating hypertension.
2) It also used for treating gestational hypertension (or p regnancy-induced hypertension) and pre-eclampsia.

6.1.7.8. Clonidine Hydrochloride

Clonidine hydrochloride is the hydrochloride salt of clonidine, which i s an imidazoline derivative and centrally-acting α-adrenergic agonist and antagonist having antihypertensive activity.

Mechanism of Action

Clonidine hydrochloride binds to and stimulates central α_2-adrenergic receptors. Thus, it decreases sympathetic outflow to the heart, kidneys, and peripheral vasculature. Reduction in sympathet ic outflow decreases peripheral vascular resistance, blood pressure, and heart rate.



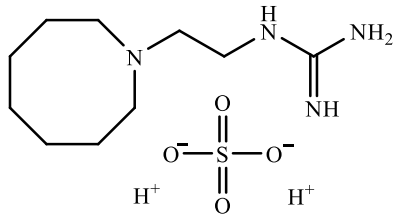
Clonidine Hydrochloride

Uses

1) It is used as an adjunct in hypertension, as an epidural infusion as an adjunct treatment in severe cancer pain (not relieved by opiate analgesics alone), a nd for differential diagnosis of pheochromocytoma in hypertensive patients.
2) It is also used in prophylaxis of vascular migraine headaches, in severe dysmenorrhea, management of vasomotor symptoms related to menopause, rapid detoxification in opiate withdra wal management, in conjunction with benzodiazepines for managing alcohol withdrawal symptoms, and management of nicotine dependence.
3) It is topically used to reduce intraocular pressure in the treatment of open - angle and secondary glaucoma and haemorrhagic glaucoma associated with hypertension.
4) It is also effective in Attention-Deficit Hyperactivity Disorder (ADHD).

6.1.7.9. Guanethidine Monosulphate

Guanethidine monosulphate is an antihypertensive agent that selectively inhibits the transmission in post-ganglionic adrenergic nerves.



Guanethidine Monosulphate

Mechanism of Action

Guanethidine acts at the sympathetic neuroeffector junction and inhibits the release and/or distribution of norepinephrine. Since guanethidine is taken up by the norepinep hrine transporters, it becomes concentrated in norepinephrine transmitter vesicles and replaces norepinephrine; thus, gradually depleting norepinephrine stores in the nerve endings. Within the terminal guanethidine blocks noradrenaline release in response to an action potential.

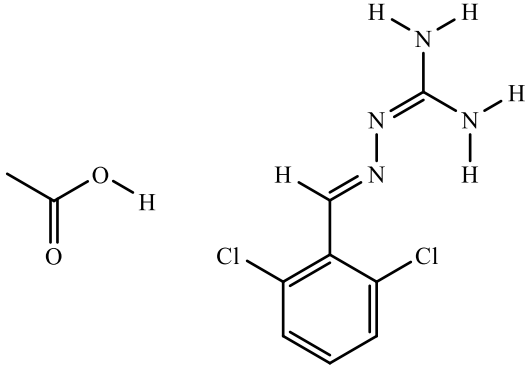
Guanethidine suppresses the responses mediated by α-and β-adrenergic receptors but does not cause parasympathetic blockade. Instead it causes sympathetic blockade, which results in decreased peripheral resistance, cardiac output, and ultimately blood pressure in the supine position.

Uses

1) It is used either alone or as an adjunct for treating moderate to severe hypertension and renal hypertension.
2) It may be used as an adjunct to anti -thyroid agents in treating hyperthyroidism and thyrotoxic crisis.
3) It is also used in eye drops for reducing intraocular pressure in glaucoma and for reducing lid retraction in thyroid disease.

6.1.7.10. Guanabenz Acetate

Guanabenz acetate is the acetate salt of guanabenz, which is a centrally-acting α_2-adrenergic receptor agonist having anti -hypertensive, potential antineoplastic, cytoprotective and bone resorption inhibitory activities.



Guanabenz Acetate

Mechanism of Action

The antihypertensive activity of guanabenz is due to central α-adrenergic stimulation that reduces the sympathetic outflow to the heart, kidneys, and peripheral vasculature, and also reduces systolic and diastolic blood pressure. The peripheral vascular resistance is also reduced on chronic administration of guanabenz.

Uses

It is used for treating high blood pressure.

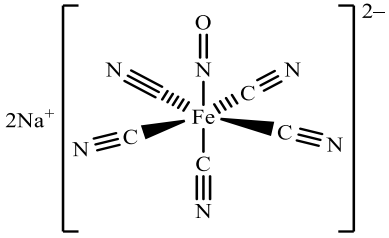
6.1.7.11. Sodium Nitroprusside

Nitroprusside is a source of nitric oxide, which is a potent peripheral vasodilator affecting the arterioles and venules. Nitroprusside is generally given intravenously to patients experiencing hypertensive emergency.

Mechanism of Action

A single molecule of sodium nitroprusside is metabolised by combination with haemoglobin to produce a cyanmethemoglobin molecule and four CN^- ions. Methemoglobin (obtained from haemoglobin) can isolate cyanide as cyanmethemoglobin. Thiosulfate and cyanide react to yield thiocyanate, which is excreted in urine. Cyanide is not excreted and binds to cytochromes. The CN^- ion is found in serum, and is derived from dietary substrates and tobacco smoke. It reversibly binds to ferric ion (Fe^{+++}), which is mostly found in erythrocyte methemoglobin (metHgb) and in mitochondrial cytochromes. When cyanide is infused or generated in the bloodstream, it binds to methemoglobin to saturate the intraerythrocytic methemoglobin.

On activation, the nitric oxide activates guanylate cyclase in vascular smooth muscles and increases intracellular production of cGMP. Calcium movement from the cytoplasm to endoplasmic reticulum is stimulated by this cGMP, thus the calcium available for binding to calmodulin is reduced. This leads to relaxation of vascular smooth muscles and dilatation of vessels.



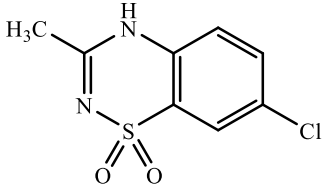
Sodium Nitroprusside

Uses

1) It is used for instant reduction of blood pressure in patients having hypertensive crises.
2) It reduces bleeding during surgery.
3) It also used for treating acute congestive heart failure.
4) It is often administered via intravenous route to patients undergoing hypertensive emergency.

6.1.7.12. Diazoxide

Diazoxide is a benzothiadiazine derivat ive. It is a peripheral vasodilator used in hypertensive emergencies. It does not have diuretic effect due to the absence of sulfonamide group.



Diazoxide

Mechanism of Action

Diazoxide inhibits reabsorption of active chloride at the early portions of distal convoluted tubule through the Na^+-Cl^- co-transporter. This increases the excretion of Na^+ and Cl^- ions, and water. Diazoxide binds to the thiazide sensitive Na^+-Cl^- transporter and inhibits the transport of Na^+ ion across the renal tubular epithelium. This increases the excretion of K^+ ions through the Na^+-K^+ exchange mechanism.

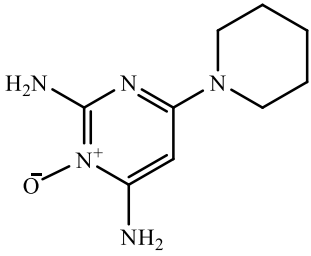
The antihypertensive mechanism of diazoxide is less well understood , but it is believed to be mediated through i ts action on carbonic anhydrase enzyme found in the smooth muscle s or through its action on the large -conductance calcium-activated potassium (KCa) channel in the smooth muscles.

Uses

1) It is used parenterally for treating hypertensive emergencies.
2) It is also used for treating hypoglycaemia secondary to insulinoma.

6.1.7.13. Minoxidil

Minoxidil is a potent direct -acting peripheral vasodilator which reduces the peripheral resistance and reduces the blood pressure.



Minoxidil

Mechanism of Action

Minoxidil as a vasodilator opens the ATP-sensitive potassium channels in vascular smooth muscle cells. Minoxidil activates extracellular signal -regulated kinase (ERK) and Akt and prevents cell death by increasing the ratio of BCl-2/Bax; thus, it stimulates the survival of human Dermal Papillary Cells (DPCs) or hair cells . Minoxidil may stimulate the growth of human hair by prolonging the anagen phase of hair growth through theproliferative and anti-apoptotic effects on DPCs.

Uses

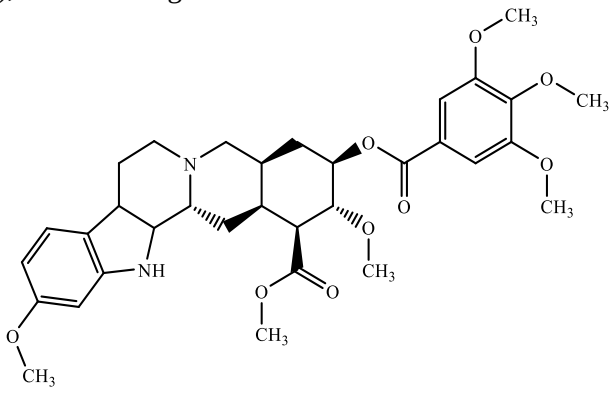
1) It is used to treat severe hypertension.
2) It is used topically in androgenic alopecia to stimulate the regrowth and stabilise hair loss in males and females.

6.1.7.14. Reserpine

Reserpine is an alkaloid obtained from the roots of *Rauwolfia serpentin a* and *Rauwolfia vomitoria*. It is an adrenergic uptake inhibitor having antihypertensive effects.

Mechanism of Action

Reserpine inh ibits the ATP -Mg^{2+} pump, which sequesters the neurotransmitters into storage vesicles found in the presynaptic neuron. The neurotransmitters that are not sequestered in the storage vesicles get rapidly metabolised by monoamine oxidase (MAO), thus reducing catecholamines.



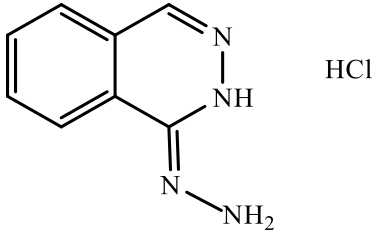
Reserpine

Uses

1) It is used as an antihypertensive for decreasing blood pressure.
2) It was used in the ancient times for treating insanity, fever and snake bites.
3) Previously, it was used for treating the symptoms of dyskinesia in patients suffering from Huntington's disease.
4) It is also used as a long-acting tranquiliser.

6.1.7.15. Hydralazine Hydrochloride

Hydralazine hydrochloride is the hydrochloride salt of hydralazine, which is a phthalazine derivative having an tihypertensive and potential antineoplastic activities.



Hydralazine Hydrochloride

Mechanism of Action

The exact mechanism of action of hydralazine is not completely understood. However, it affects the cardiovascular system in the following ways:

1) It exerts a peripheral vasodilation effect by directly relaxing the vascular smooth muscles. This effect in turn lowers the blood pressure.
2) Cyclic 3',5'-adenosine monophosphate (cAMP) is also found to be facilitating the relaxation of arterial smooth muscles by altering calcium metabolism within the cells. This altered calcium metabolism interferes with the movement of calcium within the smooth muscles (essential for initiating or sustaining the contractility of these muscles).
3) In hypertension patients, decrease in blood pressure induced by hydralazine also results in increased heart rate, cardiac output, and stroke volume, most likely due to a reflex response to decreased peripheral resistance.
4) It does not affect the heart directly.
5) It may increase the coronary, splanchnic, cerebral, and renal blood flow, and also the pulmonary arterial pressure.
6) Postural hypotension is minimised and an increase in cardiac output is stimulated by the dilation of arterioles.
7) It increases renin secretion (by the renal juxtaglomerular cells) in response to reflex sympathetic discharge, thus, increases plasma renin activity. This increased activity results in the production of angiotensin II, which in turn stimulates aldosterone and sodium reabsorption. Therefore, in case a diuretic is not administered a long with hydralazine, patients develop tolerance to its anti-hypertensive effect (especially when used for a long time period).
8) In CHF patients, it decreases the systemic vascular resistance and increases cardiac output.

Uses

1) It is used either as an adjunct or as a monotherapy to treat essential hypertension.
2) It is also used to treat severe hypertension in cases when oral administration of the drug is not possible or when an immediate decrease in blood pressure is desired.
3) It is also used in congestive heart failure (in combination with cardiac glycosides and diuretics and/or with isosorbide dinitrate), and hypertension secondary to pre-eclampsia/eclampsia.

6.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) A condition in which the blood pressure of systemic artery increases beyond the normal pressure is known as **hypertension**.
2) **Thiazide Diuretics** work initially by increasing urinary sodium excretion by inhibiting the Na^{+}-Cl^{-} pump in the early segment of the distal convoluted tubule.

3) **Loop Diuretics** act at the thick ascending loop of Henle to prevent sodium and chloride reabsorption from urine.
4) **Potassium-Sparing Diuretics** decrease the excretion of magnesium and potassium.
5) **Angiotensin-Converting Enzyme (ACE) Inhibitors** slow down the formation of angiotensin II, which reduces vascular resistance, blood volume, and blood pressure.
6) **β-Blockers** decrease the cardiac output by blocking β-adrenergic receptors in the heart, resulting in negative chronotropic (heart rate) and inotropic (contractility) effects.
7) **Calcium Channel Blockers** drugs block or alter cell membrane calcium flux.
8) **Timolol** is a β-adrenergic antagonist. It has similar actions to propranolol. Its levo-isomer is more active.
9) **Captopril** is a potent competitive inhibitor of Angiotensin -Converting Enzyme (ACE), which is responsible for converting Angiotensin I (ATI) to Angiotensin II (ATII).
10) **ATII** controls the blood pressure and is a major component of the Renin -Angiotensin-Aldosterone System (RAAS).
11) **Lisinopril** is potent and competitive inhi bitor of angiotensin -converting enzyme (ACE), which converts angiotensin I (ATI) to angiotensin II (ATII).
12) **Enalapril** is a prodrug of the Angiotensin -Converting Enzyme (ACE) inhibitor class.
13) **Benazepril hydrochloride** is the hydrochloride salt of benazepril, which is a carboxyl-containing ACE inhibitor having antihypertensive activity.
14) **Quinapril hydrochloride** is the hydrochloride salt of quinapril. It is a prodrug and non-sulfhydryl ACE inhibitor having antihypertensive activity.
15) **Methyldopate hydrochloride** is the hydrochloride salt of methyldopa, which is a derivate of phenylalanine and inhibitor of aromatic amino acid decarboxylase.
16) **Clonidine hydrochloride** is the hydrochloride salt of clonidine, which is an imidazoline derivative and centrally -acting α-adrenergic agonist and antagonist having antihypertensive activity.
17) **Guanethidine monosulphate** is an antihypertensive agent that selectively inhibits the transmission in post-ganglionic adrenergic nerves.
18) **Guanabenz acetate** is the acetate salt of guanabenz, which is a centrally -acting α_2-adrenergic receptor agonist having anti -hypertensive, potential antineoplastic, cytoprotective and bone resorption inhibitory activities.
19) **Nitroprusside** is a source of nitric oxide, which is a potent peripheral vasodilator affecting the arterioles and venules.
20) **Diazoxide** is a benzothiadiazine derivative. It is a peripheral vasodilator used in hypertensive emergencies.

21) **Minoxidil** is a potent direct -acting peripheral vasodilator which reduces the peripheral resistance and reduces the blood pressure.

22) **Reserpine** is an alkaloid obtained from the roots of *Rauwolfia serpentina* and *Rauwolfia vomitoria* . It is an adrenergic uptake inhibitor having antihypertensive effects.

23) **Hydralazine hydrochloride** is the hydrochloride salt of hydralazine, which is a phthalazine derivative having antihypertensive and potential antineoplastic activities.

6.3. EXERCISE

6.3.1. True or False

1) Reserpine is an adrenergic uptake inhibitor having antihypertensive effects.
2) Diazoxide selectively inhibits the transmission i n post -ganglionic adrenergic nerves.
3) Calcium Channel Blocker drugs block or alter cell membrane calcium flux.
4) Quinapril hydrochloride is a prodrug and non-sulfhydryl ACE inhibitor.
5) Captopril stimulates the conversion of angiotensin I to angiotensin II.
6) β-Blockers decrease the cardiac output by blocking β-adrenergic receptors in the heart.

6.3.2. Fill in the Blanks

7) _____ is an alkaloid obtained from the roots of *Rauwolfia serpentina* and *Rauwolfia vomitoria.*
8) _____ controls the blood pressure and is a maj or component of the Renin - Angiotensin-Aldosterone System (RAAS).
9) _____ drugs block or alter cell membrane calcium flux.
10) _____ act at the thick ascending loop of Henle to prevent sodium and chloride reabsorption from urine.
11) _____ is a prodrug of the Angiotensin-Converting Enzyme (ACE) inhibitor class.

Answers

1) True	2) False	3) True	4) True
5) False	6) True	7) Reserpine	8) ATII
9) Calcium Channel Blocker		10) Loop Diuretics	11) Enalapril

6.3.3. Very Short Answer Type Questions

1) What are anti-hypertensive agents?
2) Write a short note on timolol.
3) Discuss reserpine.
4) Discuss enalapril.
5) Give the SAR of β-adrenergic antagonists.

6.3.4. Short Answer Type Questions

1) Discuss SAR of angiotensin II antagonists.
2) Give the SAR of dihydropyridines (calcium channel blockers).
3) Write short notes on clonidine hydrochloride and sodium nitroprusside.
4) Write short note on hydralazine hydrochloride.

6.3.5. Long Answer Type Questions

1) What are anti-hypertensive drugs? Give their classification.
2) Give the mechanism of action of antihypertensive agents.
3) Give the uses and recent developments of anti-hypertensive agents.

CHAPTER 7

Anti-Arrhythmic Drugs

7.1. ANTI-ARRHYTHMIC DRUGS

7.1.1. Introduction

The rhythm and normal heart rate may be affected by some diseases and drugs. This condition is termed **cardiac arrhythmia** in which certain disorders affect the normal mechanical activ ity of heart. A specific sequence of electrical activation determines the normal mechanical activity of the heart; this sequential electrical activation is the same for all myocardial cells during each beat and it initially begins at the SA node and ends w ith depolarisation of the ventricle. Therefore, any alteration in conduction automaticity refractory period of the myocardial cells may result in arrhythmia.

Drugs which have the ability to revert any irregular cardiac rhythm or rate to normal are kno wn as **anti-arrhythmic** or **anti-dysrhythmic** or **anti-fibrillatory drugs**. The **properties of an ideal antiarrhythmic** drug are:

1) It should be highly efficient in controlling symptoms and improving survival in both supraventricular and ventricular arrhythmias.
2) It should have no negative effect.
3) It should produce a favourable effect on myocardial oxygen consumption.
4) It should produce both oral and intravenous activity.
5) It should have a wide therapeutic range.

7.1.2. Classification

The anti-arrhythmic drugs are classified as shown in **table 7.1**:

Table 7.1: Classification of Anti-Arrhythmic Drugs

Classes	Actions	Drugs
I	Membrane stabilising agents (Na^+ channel blockers)	
	A. Moderately decrease dv/dt of 0 phase,	Quinidine, Procainamide, Disopyramide, and Moricizine.
	B. Little decrease in dv/dt of 0 phase,	Lignocaine, Mexiletine, and Phenytoin.
	C. Marked decrease in dv/dt of 0 phase.	Propafenone, Flecainide, and Encainide.
II	Antiadrenergic agents (β-blockers)	Propranolol, Esmolol, and Sotalol (also class III).
III	Agents widening AP (prolong re-polarisation and ERP)	Amiodarone, Bretylium (also class II) , and Dofetilide.
IV	Calcium channel blockers	Verapamil and Diltiazem.

Note: Class IA agents also have Class III prop erty; Propranolol also has Class I action; Sotalol and Bretylium have Class II and Class III actions.

In Addition

Classes	Actions	Drugs
I	For PVST	Adenosine and Digitalis.
II	For A-V block	Sympathomimetics - Isoprenaline, etc. Anti-cholinergics - Atropine.
III	In AF, AFI, and PSVT to control ventricular rate.	Digitalis

7.1.3. Mechanism of Action

The mechanism of action of anti-arrhythmic drugs is as follows:

1) **Sodium Channel Blockers:** This group of anti -arrhythmic drugs is commonly used. The mechanism of action of sodium channel blockers includes blockade of myocardial Na^+ channels. The anti -arrhythmic activity of these drugs is the result of the following conditions:
   i) Decrease in inflow of sodium during phase 0 slows the maximum rate of depolarisation,
   ii) Decrease in excitability and conduction velocity,
   iii) Prolongation of effective refractory period, and
   iv) Decrease in slope of phase 4 spontaneous depolarisation (automaticity).

   Class I drugs are sub -divided into the following sub-classes **on the basis of their mechanism of action**:

Class IA	Prolongs the refractory period; moderately depresses conduction; used in supraventricular and ventricular arrhythmias.
Class IB	Shortens the refractory period; minimally depresses conduction; used in ventricular arrhythmias.
Class IC	Negligible effect on refractory pe riod; markedly depresses conduction; used in supraventricular and ventricular arrhythmias.

2) **β-Blockers:** The electrophysiological effects of β-adrenergic receptor blocking drugs pl ay a significant role. Due to β_1 blockade, phase 4 of the action potential becomes less steep. A small decrease in the level of Ca^{++} ions within the cells reduces phase 2 of the action potential. Also, the SA node automaticity decreases, con duction in AV node slows down, and ERP (Effective Refractive Period) in AV node prolongs. The catecholamine induced after depolarisations (arrhythmias) is counteracted by these agents by reduction in the accumulated cAMP and Ca^{++} ions.

   Arrhythmias mediate d by excessive catecholamines, **e.g.,** early after MI, CHF, pheochromocytoma, anxiety, exercise, anaesthesia , post-operative period, and mi tral valve prolapse are most effectively managed by β-blockers.

3) **Potassium Channel Blockers:** The mechanism of action of C lass III anti -arrhythmic drugs involves blockade of potassium channels. Therefore, the outward flow of K^+ ions is diminished during re-polarisation of cardiac cells. The duration of action potential is prolonged without any alteration in the resting membrane potential or phase 0 of depolarisation. However, the

effective refractory period is prolonged and the refractoriness is increased. All drugs belonging to this class of anti -arrhythmic agents are potent inducers of arrhythmias.

As the potassium channels are blocked during phase 3 of the action potential, the efflux of K^+ ions f rom the myocyte is slowed down. This in turn diminishes the rate of cellular repolarisation, resulting in a lengthened plateau phase of the action potential. The refractory period of atrial, ventricular and Purkinje cells is increased by these drugs, along with an increase in the QT interval, as evident on an ECG.

4) **Calcium Channel Blockers:** The mechanism of action of this group of anti - arrhythmic agents involves blockade of slow inward calcium channels. Also, conduction through the AV node is slowed down. The calcium channel blockers, **e.g.,** verapamil, diltiazem , and bepridil (blocks sodium channels also), are included in this group.

7.1.4. Uses

Therapeutic uses of anti-arrhythmic agents are:

1) **Sodium Channel Blockers:** Presently, these drugs are considered better anti-arrhythmic agents because of a broad spectrum of their anti-arrhythmic action, the improvement they show in terms of patient survival, and the ir safety compared to other anti -arrhythmic agents. When administered with several other anti-arrhythmic drugs, these agents act in synergism and further reduce their arr hythmogenic potential (a tendency to produce cardiac arrhythmia).

2) **β-Blockers:** The property of blocking β_1-receptors plays a significant role in anti-arrhythmic drugs. Though a β-blocker possessing membrane stabilising property (i.e., propranolol) is desired, yet it is not a requirement. On the other hand, an Intrinsic Sympathomimetic Activity (ISA) is not desirable. Sotalol is an anti-arrhythmic agent possessing properties of both class II and class III drugs. Esmolol is an ultra -short acting β-blocker whic h is administered intravenously.

   Drugs like **propranolol**, **metoprolol**, and **esmolol** are often used for treating the following conditions:

   i) Sinus tachycardia causing palpitations and nervousness in anxiety neurosis,
   ii) Exercise induced paroxysmal atrial tachycardia,
   iii) Tachyarrhythmia in mitral valve prolapse,
   iv) Recurrent VT (metoprolol),
   v) Amiodarone induced VT,
   vi) Tachycardia in hereditary prolonged QT syndrome,
   vii) Tachyarrhythmia in pheochromocytoma,
   viii) Atrial fibrillation (may be used with digoxin),
   ix) Frequent APBs causing palpitations, and
   x) Digitalis-induced supraventricular tachycardia.

3) **Potassium Channel Blockers:** These anti-arrhythmic drugs are employed for treating atrial fibrillation, recurrent ventricular fibrillation, and unstable ventricular tachycardia.

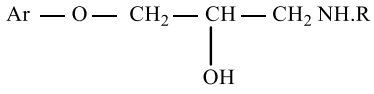
4) **Calcium Channel Blockers:** These anti-arrhythmic drugs are employed for treating prinzmetal, variant angina, unstable or chronic stable angina, hypertension, and atrial fibrillation.

7.1.5. Structure-Activity Relationship

The SAR of different anti-arrhythmic types is explained below:

1) **Sodium Channel Blockers:** The activity of sodium channel blockers can be varied by making the following changes in their structure:
   i) The activity is enhanced by substituting ethyl group at the *ortho* position.
   ii) Desirable compounds are yielded by replacing the pyridyl group with acyclic amines. A potent compound is obtained if the replacement is done with cyclohexyl group. Pentenamide showed a longer duration of action than disopyramide.
   iii) The potency of 2-pyridyl is more than that of the other isomers.
   iv) By varying the amino group using di -isopropylamine and 2,6 - dimethylpiperidine groups yields a correlation between n values and ventricular arrhythmias.

2) **β-Blockers:** The activity of β-blockers can be varied by making the following changes in their structure:



General structure

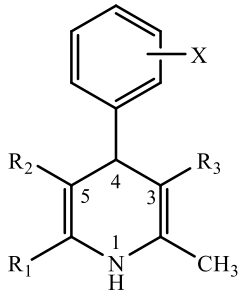
   i) The antagonistic property is due to the presence of O –CH_2 group between the aromatic ring and the ethylamino side chain.
   ii) The β-blocking activity is retained by replacing the catecho l hydroxyl group with chlorine or phenyl ring.
   iii) The β-blocking acti vity is decreased by N, N-di substitution. While the same activity is maintained by adding phenylethyl, hydroxyl phenylethyl or methoxy phenylethyl groups to amine as a part of molecule.
   iv) The β-blocking activity is also due to the presence of two carbon side chains.
   v) For the β-blocking activity to be optimum, the N atom should be of secondary amine.
   vi) For optimum affinity, the hydroxyl group of the carbon side chain should be of S-configuration (**e.g.,** Levobunolol and Timolol).
   vii) The potency of aryloxy propanolamines is more than that of the aryl ethanolamines.
   viii) The β-blocking activity decreases if the ethereal oxygen in aryloxy propanolamines is replaced with S, CH_2, or N–CH_3.
   ix) Isopropyl and tertiary b utyl group are the most effective amino group substituents.

x) The aromatic portion of the molecules can be varied with good activity.
xi) The β-blocking activity decreases if the aromatic portion is converted to phenanthrene or anthracene.
xii) Cyclic alkyl substitu ents are better than the corresponding open chain substituents at N atom of amine.
xiii) The β-blocking activity is decreased due to the presence of α-methyl group at side chain.

The general rule for aromatic substitution is ***ortho> meta> para***. This rule yields non-selective β-blockers. The β-blocking activity is decreased due to large *para* substituents, while the activity is retained due to the large *ortho* groups. The compound loses its activity on poly -substitution at C -2 and C -6, while it shows some activity on substitution at carbon C-3 and C-5.

For the highest cardio selectivity, the rule for substitution should be ***para> meta> ortho***. All the β-blockade is in one isomer, (S)-aryloxypropylamine and (R)-ethanolamine.

3) **Calcium Channel Blockers :** The activity of calcium channel blockers can be varied by making the following changes in their structure:



i) Optimum activity is attained by a phenyl ring substitution at C-4.
ii) The activity is maintained due to the presence of 1,4 -dihydropyridine ring.
iii) The activity is either decreased or eliminated by substitution at N -1 position or use of oxidised (pyridine) or reduced (piperidine) ring systems.
iv) The activity is optimised by th e electron -withdrawing effect of ester groups at C-3 and C-5 (ideal and non-identical esters).
v) All 1,4 -DHPs except amlodipine ($CH_2OCH_2CH_2NH_2$) (which shows enhanced activity compared to nifedipine) have methyl groups at C-2 and C-6.
vi) The N -1 atom is weakly b asic due to the involvement of its lone pair which is in conjugation with the double bond ring. The atom also does not ionise at physiological pH.

7.1.6. Recent Developments

The current therapies for atrial fibrillation lack adequacy and hence, development of new drugs is essential. The risk of ventricular pro -arrhythmias is increased by the use of conventional anti -arrhythmic drugs. Recent drug development focuses

on the fact that the new drugs have favourable multi-channel blocking properties, atrial-specific ion-channels, and new non-channel targets (upstream therapy):

1) **Amiodarone** is a multi-channel blocker having a high efficacy. Modification of its molecular structure has been done for improving its safety and tolerability.
2) **Dronedarone** is a drug produced by modification of amiodarone; however, its efficacy is less than that of amiodarone.
3) An atrial-selective drug, **Vernakalant** has a decreased risk of pro-arrhythmia and may prove to be a useful agent for performing cardioversion during atrial fibrillation.
4) Another atrial -selective agent, **ranolazine** was initially developed for the treatment of angina. However, it has shown to be effective in treating atrial fibrillation and is under investigation in prospective clinical trials.

Upstream therapy using angiotensin-converting enzyme and angiotensin-receptor inhibitors, statins, or omega -3 fatty acids and fish oil which targets atrial remodelling may be efficient, yet, further clinical validation is required.

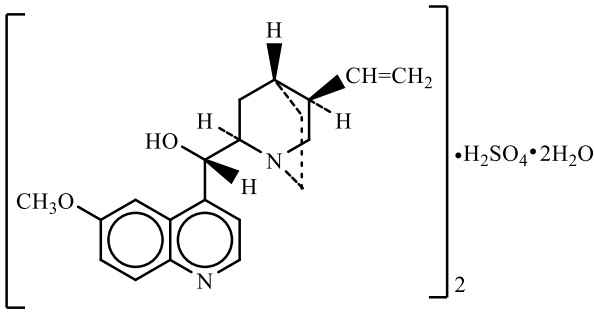
7.1.7. Study of Individual Drugs

The following anti-arrhythmic drugs are discussed below:

1) Quinidine sulphate,
2) Procainamide hydrochloride,
3) Disopyramide phosphate,
4) Phenytoin sodium,
5) Lidocaine hydrochloride,
6) Tocainide hydrochloride,
7) Mexiletine hydrochloride,
8) Lorcainide hydrochloride,
9) Amiodarone, and
10) Sotalol.

7.1.7.1. Quinidine Sulphate

Quinidine sulphate is the sulphate salt of quinidine, which is an alkaloid having antimalarial and antiarrhythmic (Class IA) properties.



Quinidine Sulphate

Mechanism of Action

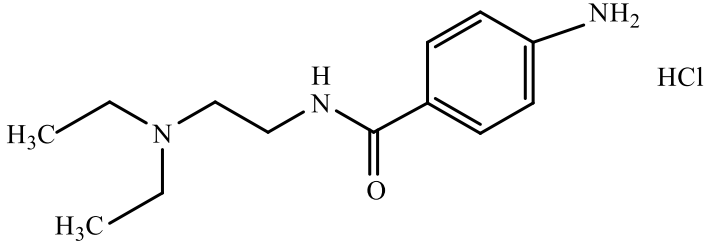
Quinidine sulphate exerts its antiarrhythmic action by depressing the flow of Na^+ ions into the cells during phase 0 of the cardiac action potential. Thus, it slow down the impulse conduction through the AV node, reduces the rate of phase 0 depolarisation, and prolongs the refractory period. Quinidine sulphate also reduces the slope of phase 4 depolarisation in Purkinje -fibres, thereby slowing down the conduction and reduced automaticity in heart.

Uses

1) It is used for treating persistent, life-threatening ventricular arrhythmias, like sustained ventricular tachycardia.
2) It is taken via intravenous route for treating *Plasmodium falciparum* malaria.

7.1.7.2. Procainamide Hydrochloride

Procainamide hydrochloride is the hydrochloride salt of procainamide, which is a procaine analogue and an amide derivative having class I A anti-arrhythmic activity.



Procainamide Hydrochloride

Mechanism of Action

Procainamide hydrochloride inhibits the activated (open) voltage -gated sodium channels by reversibly binding. This inhibits the influx of Na^+ ions into the cell, thus increases the threshold for excitation and inhibits depolarisation during phase 0 of the action potential.

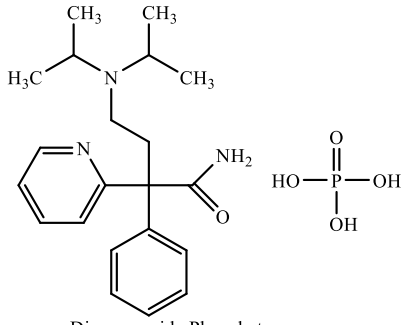
The Effective Refractory Period (ERP), Action Potential Duration (APD), and ERP/APD ratios also increase to decrease the impulse conduction velocity. The lasting action potential occurs due to blockage of outward K^+ ion currents, and decreases automaticity, increases refractory period, and slows down impulse conduction.

Uses

It is used to treat ventricular arrhythmias, ventricular ectopy, tachycardia, supraventricular arrhythmias, atrial fibrillation, re -entrant and automatic supraventricular tachycardia.

7.1.7.3. Disopyramide Phosphate

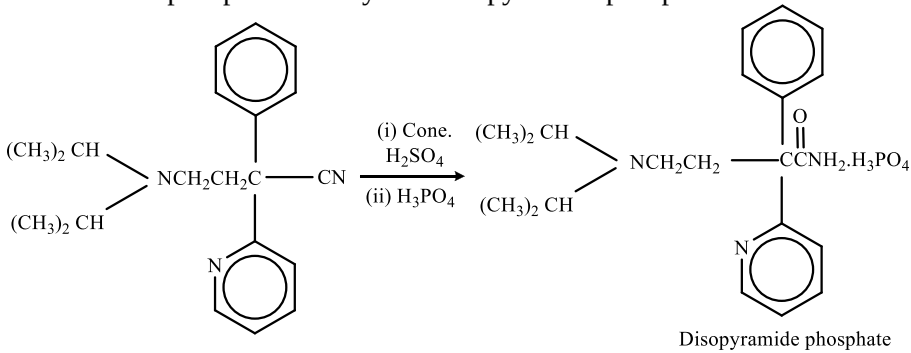
Disopyramide phosphate is a class IA antiarrhythmic agent having cardiac depressant properties. It is a sodium channel blocker.



Disopyramide Phosphate

Synthesis

On heating 4-diisopropylamino-2-phenyl-2-(2-pyridyl) butyronitrile with concentrated sulphuric acid, the corresponding amide is obtained, which on treatment with phosphoric acid yields disopyramide phosphate.



4-Diisopropylamino 2-Phenyl-2-(2-pyridyl) butyronitrile

Disopyramide phosphate

Mechanism of Action

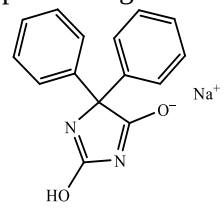
Disopyramide phosphate blocks the sodium and potassium channels in cardiac membrane in the phase 0 of action potential. This delays impulse conduction through the AV node and prolongs the duration of action potential of normal cardiac cells in atrial and ventricular tissues.

Uses

1) It is used for treating documented ventricular arrhythmias like sustained ventricular tachycardia, ventricular pre-excitation and cardiac dysrhythmias.
2) It belongs to a Class IA antiarrhythmic drug.

7.1.7.4. Phenytoin Sodium

Phenytoin sodium is the sodium salt of phenytoin, which is a hydantoin derivate and a non-sedative antiepileptic having anticonvulsant activity.



Phenytoin Sodium

Mechanism of Action

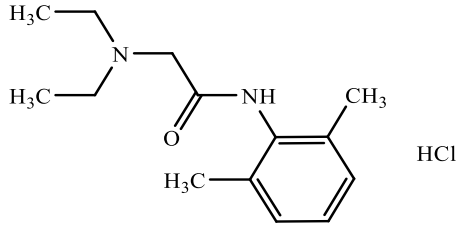
Phenytoin sodium promotes sodium efflux from the neurons present in the motor cortex, and thus stabilises the neuron and inhibits synaptic transmission. This reduces post-tetanic potentiation at synapses, inhibits repetitive firing of action potentials, and eventually inhibits the spread of seizure activity.

Uses

1) It is used in the prophylactic management of tonic -clonic seizures with complex symptomatology.
2) It provides protection against the development of focal seizures with complex symptomatology.
3) It is used for treating ventricular tachycardia and sudden episodes of atrial tachycardia when the patients do not respond to other antiarrhythmic medications or cardioversion.

7.1.7.5. Lidocaine Hydrochloride

Lidocaine hydrochloride is the hydrochloride salt of lidocaine, which is an aminoethylamide and a prototypical member of the amide class anaesthetics having anti-arrhythmia activity.



Lidocaine Hydrochloride

Mechanism of Action

Lidocaine stabilises the neuronal membrane. It does so by inhibiting the ionic fluxes required for the initiation and conduction of impulses, and affecting the local anaesthetic action. Lidocaine blocks the fast voltage gated sodium channels in the neuronal cell membrane (responsible for signal propagation), thus alters signal conduction in neurons.

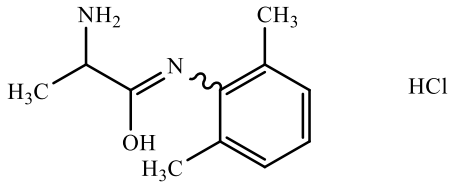
With sufficient blockage the membrane of postsynaptic neuron does not depolarises and fails to transmit an action potential. This produces the anaesthetic effect by preventing the propagation of pain signals to the brain and by terminating their production.

Uses

It is used for producing local or regional anaesthesia by penetration techniques like percutaneous injection and intravenous regional anaesthesia, by peripheral nerve block techniques like brachial plexus and intercostal, and by central neural techniques like lumbar and caudal epidural blocks.

7.1.7.6. Tocainide Hydrochloride

Tocainide hydrochloride is the hydrochloride salt of tocainide, which is a primary amine analogue of lidocaine having class IB antiarrhythmic activity.



Tocainide Hydrochloride

Mechanism of Action

Tocainide hydrochloride reversibly binds to and blocks the open and inactivated voltage-gated sodium channels to stabilise the neuronal membrane . This inhibits the inward flow of Na^+ ions (required for the initiation and conduction of impulses) and reduces the excitability of myocardial cells. Tocainide hydrochloride reduces the rate of rise and amplitude, and shortens the Action-Potential Duration (APD) in Purkinje and muscle fibres.

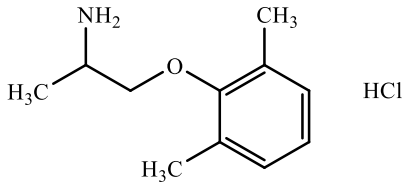
It also shortens the Effective Refractory Period (ERP) of Purkinje fibres and increases the ERP/APD ratio. These effects altogether slow down the nerve impulses and stabilise the heartbeat.

Uses

It is used for treating document ed ventricular arrhythmias , like sustained ventricular tachycardia (life-threatening).

7.1.7.7. Mexiletine Hydrochloride

Mexiletine hydrochloride is the hydrochloride salt of mexiletine, which is a local anaesthetic and Class IB antiarrhythmic.



Mexiletine Hydrochloride

Mechanism of Action

Mexiletine inhibits the sodium channels, and thus the inward flow of Na^+ ions (required for the initiation and conduction of impulses) and reduces the rate of rise of the action potential in p hase 0. Mexiletine d ecreases the Effective Refractory Period (ERP) in Purkinje fibres.

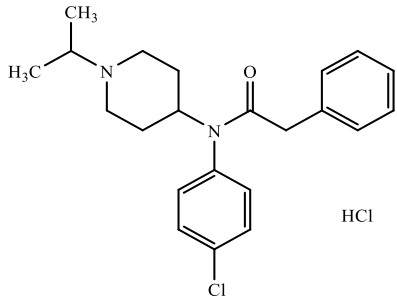
The decrease in ERP is of lesser magnitude than the decrease in Action Potential Duration (APD), and this increases ERP/APD ratio. Mexiletine does not affect the resting membrane potential or sinus node automaticity, left ventricular function, systolic arterial blood pressure, AV conduction velocity, or QRS or QT intervals.

Uses

1) It is used for treating ventricular tachycardia and symptomat ic premature ventricular beats.
2) It is also used for the prevention of ventricular fibrillation.

7.1.7.8. Lorcainide Hydrochloride

Lorcainide hydrochloride is a Class IC antiarrhythmic agent. It helps in restoring the normal heart rhythm and conduction in patients having premature ventricular contractions, ventricular tachycardiac, and Wolff-Parkinson-White syndrome.



Lorcainide Hydrochloride

Mechanism of Action

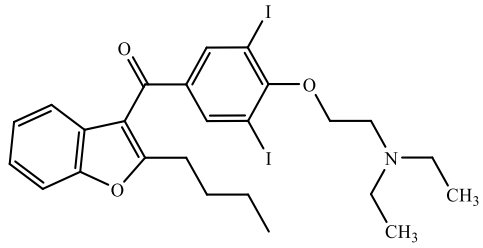
Lorcainide hydrochloride blocks the fast sodium channels , responsible for the rapid depolaris ation (phase 0) of fast -response cardiac ac tion potentials. This type of action potential is found in non -nodal, cardiomyocytes (**e.g.,** atrial and ventricular myocytes; Purkinje tissue). The slope of phase 0 depends o n the activation of fast sodium channels and rapid entry of Na^+ ions into the cell, thus blockage of these channels decreases the slope of phase 0 and also decreases the amplitude of action potential. The nodal tissue action potentials (sinoatrial and atrioventricular nodes) do es not depend on fast sodium c hannels for depolarisation; instead, phase 0 depolarisation is carried by calcium currents.

Uses

It is used for treating premature ventricular contractions, ventricular tachycardiac, and Wolff-Parkinson-White syndrome.

7.1.7.9. Amiodarone

Amiodarone is an anti -anginal and a nti-arrhythmic drug, which increases the duration of ventricular and atrial muscle action by blocking the Na -K-activated myocardial adenosine triphosphatase. This reduces the heart rate and vascular resistance.



Amiodarone

Mechanism of Action

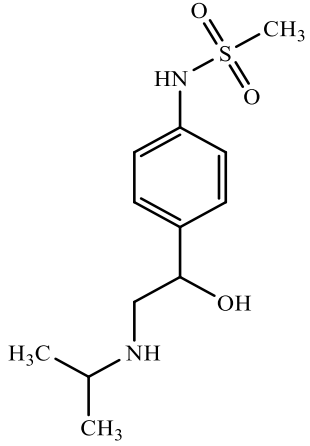
Amiodarone produc es its anti -arrhythmic action by prolonging the myocardial cell action potential (phase 3) duration and refracto ry period, and by acting as a non-competitive α- and β-adrenergic inhibitor.

Uses

1) It is used intravenously for the treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients non-compliant to other therapy.
2) It is used orally for treating the life-threatening recurrent ventricular arrhythmias, like recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia.

7.1.7.10. Sotalol

Sotalol is an ethanolamine derivative having Class III anti -arrhythmic and anti - hypertensive activities. It is a non -selective β-adrenergic receptor and potassium channel antagonist.



Sotalol

Mechanism of Action

Sotalol exhibits the anti -arrhythmic property of blocking β-adrenoreceptor (Vaughan Williams Class I) and prolonging the cardiac action potential duration (Vaughan Williams Class I). It is a racemic mixture of d - and l-sotalol. These isomers have similar Class I anti-arrhythmic activity, and the l-isomer also has β-blocking activity.

Sotalol competitively blocks the β_1-adrenergic receptors in the myocardium and β_2-adrenergic receptors in the bronchial and vascular smooth muscles, thus inhibits the response to adrenergic stimuli.

The electrophysiologic al effects of sotalol are accountable to its selective inhibition of the rapidly activating component of the potass ium channel involved in the repolaris ation of cardiac cells. Its class II electrophysiologic al effects are due to an increase in sinus cycle length (slowed heart rate), decreased AV nodal

conduction, and increased AV nodal refractoriness. Its class III electrophysiological effects include prolongation of the atrial and ventricular monophasic action potentials, and effective refractory period prolongation of atrial muscle, ventricular muscle, and atrio-ventricular accessory pathways in the anterograde and retrograde directions.

Uses

1) It is used for maintaining the normal sinus rhythm [delay in time to recurrence of Atrial Fibrillation/Atrial Flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL and sinus rhythm.
2) It also used for treating documented life-threatening ventricular arrhythmias.

7.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) Drugs which have the ability to revert any irregular cardiac rhythm or rate to normal are known as **anti-arrhythmic** or **anti-dysrhythmic** or **anti-fibrillatory drugs**.
2) The mechanism of action of **sodium channel blockers** includes blockade of myocardial Na^+ channels.
3) The mechanism of action of **calcium channel blockers** involves blockade of slow inward calcium channels.
4) **Potassium Channel Blockers** are employed for treating atrial fibrillation, recurrent ventricular fibrillation, and unstable ventricular tachycardia.
5) **Amiodarone** is a multi-channel blocker having a high efficacy.
6) **Dronedarone** is a drug produced by modification of amiodarone.
7) An atrial-selective drug, **Vernakalant** has a decreased risk of pro-arrhythmia and may prove to be a useful agent for performing cardioversion during atrial fibrillation.
8) Another atrial-selective agent, **ranolazine** was initially developed for the treatment of angina. However, it has shown to be effective in treating atrial fibrillation and is under investigation in prospective clinical trials.
9) **Quinidine sulphate** is the sulphate salt of quinidine, which is an alkaloid having antimalarial and antiarrhythmic (Class IA) properties.
10) **Procainamide hydrochloride** is the hydrochloride salt of procainamide, which is a procaine analogue and an amide derivative having class IA anti-arrhythmic activity.
11) **Disopyramide phosphate** is a class IA antiarrhythmic agent having cardiac depressant properties. It is a sodium channel blocker.
12) **Phenytoin sodium** is the sodium salt of phenytoin, which is a hydantoin derivate and a non-sedative antiepileptic having anticonvulsant activity.

13) **Lidocaine hydrochloride** is the hydrochloride salt of lidocaine, which is an aminoethylamide and a prototypical member of the amide class anaesthetics having anti-arrhythmia activity.

14) **Tocainide hydrochloride** is the hydrochloride salt of tocainide, which is a primary amine analogue of lidocaine having class IB antiarrhythmic activity.

15) **Mexiletine hydrochloride** is the hydrochloride salt of mexiletine, which is a local anaesthetic and Class IB antiarrhythmic.

16) **Lorcainide hydrochloride is** a Class IC antiarrhythmic agent. It helps in restoring the normal heart rhythm and conduc tion in patients having premature ventricular contractions, ventricular tachycardiac, and Wolff - Parkinson-White syndrome.

17) **Amiodarone** is an anti-anginal and anti-arrhythmic drug, which increases the duration of ventricular and atrial muscle action by blocki ng the Na -K-activated myocardial adenosine triphosphatase.

18) **Sotalol** is an ethanolamine derivative having Class III anti -arrhythmic and anti-hypertensive activities.

7.3. EXERCISE

7.3.1. True or False

1) Mechanism of action of sodium channel blockers includes blockade o f myocardial Na^+ channels.
2) Amiodarone is an anti -anginal and anti -arrhythmic drug, which increases the duration of ventricular and atrial muscle action.
3) Lorcainide is an ethanolamine derivative having Class III anti -arrhythmic and anti - hypertensive activities.
4) Dronedarone is a drug produced by modification of amiodarone.
5) Disopyramide phosphate is a calcium channel blocker.
6) Mexiletine hydrochloride is a local anaesthetic and Class IB antiarrhythmic.

7.3.2. Fill in the Blanks

7) _____ is an ethanolamine derivat ive having Class III anti -arrhythmic and anti - hypertensive activities.
8) _____ is a class IA antiarrhythmic agent having cardiac depressant properties.
9) _____ hydrochloride is the hydrochloride salt of tocainide.
10) _____ is a multi-channel blocker having a high efficacy.
11) Drugs which have the ability to revert any irregular cardiac rhythm or rate to normal are known as _____.

Answers

1) True 2) True 3) False 4) True
5) False 6) True 7) Sotalol
8) Disopyramide phosphate 9) Tocainide 10) Amiodarone
11) Anti-arrhythmic drugs

7.3.3. Very Short Answer Type Questions

1) Discuss anti-arrhythmic drugs.
2) Give the mechanism of action of sodium channel blockers.
3) What are the uses of sodium and potassium channel blockers?
4) Write a short note on quinine sulphate.
5) Give the mechanism of action and uses of phenytoin sodium.
6) Write a short note on amiodarone.

7.3.4. Short Answer Type Questions

1) Classify anti-arrhythmic drugs.
2) What are the recent developments in anti-arrhythmic drugs?
3) Write a short note on sotalol.
4) Discuss procainamide hydrochloride and lidocaine hydrochloride.
5) Give the uses of β-blockers.

7.3.5. Long Answer Type Questions

1) Define anti-arrhythmic drugs. Give their SAR.
2) Classify anti-arrhythmic drugs and give their recent developments.
3) Discuss any three drugs:
   i) Tocainide hydrochloride.
   ii) Mexiletine hydrochloride.
   iii) Lorcainide hydrochloride.
   iv) Amiodarone.

CHAPTER 8

Anti-Hyperlipidimic Agents

8.1. ANTI-HYPERLIPIDEMIC AGENTS

8.1.1. Introduction

Atherosclerosis is a condition characterised by damage to the arteries. During this condition, the concentration of lipids, specifically cholesterol, in plasma is increased which may put the patient at an increased risk for ischemic heart diseases, myocardial infarction, and cerebral vascular accidents. Lipids lack water solubility and are transported in plasma in the form of lipoproteins. **Hyperlipidaemia**, also referred to a s **hyperlipoproteinemia**, is a condition characterised by an increase in the lipid concentration in plasma.

Hypocholesterolemic or **anti-hyperlipidemic** or **lipid lowering agents** are the pharmacological agents decreasing the concentration of lipids in plasma.

8.1.2. Classification

The anti- hyperlipidemic agents are classified as follows:

1) **HMG-CoA Reductase Inhibitors (Statins):** Lovastatin, Simvastatin, Pravastatin, and Atorvastatin.
2) **Bile Acid Sequestrants (Resins):** Cholestyramine and Colestipol.
3) **Fibric Acid Derivatives (Fibrates):** Clofibrate, Gemfibrozil, Bezafibrate, and Fenofibrate.
4) **Triglyceride Synthesis and Lipolysis Inhibitors:** Nicotinic acid.
5) **Others:** Probucol and Omega-3 fatty acids.

8.1.3. Mechanism of Action

Anti-hyperlipidemic agents act by the following mechanism of action:

1) **HMG-CoA Reductase Inhibitors (Statins):** HMG-CoA reductase (3 - hydroxy-3methylglutaryl-coenzyme A reductase) is the enzyme responsible for the conversion of HMG -CoA to mevalonate. Statins act by inhibiting HMG-CoA reductase. Biosynthesis of cholesterol requires mevalonate as a building block. HMG -CoA binds to HMG -CoA reductase. Statins act as a competitive inhibitor of HMG-CoA resulting in a decrease in the production of mevalonate. When administered, statins are inactive and is hydrolysed to the active β-hydroxy acid form within the body.
2) **Bile Acid Sequestrants (Resins):** These are basically large polymeric compounds serving as ion exchange resins. They exchange anions like chloride ions for bile acids. These compounds sequester the bile acids by binding to them, thus, preventing their enterohepatic circulation. As the bile

acid sequestrants are larger in size, they are not absorbed well from the gut into the bloodstream. And hence, are excreted out from the body in the form of faeces (once they pass thr ough the GIT), along with any bile acids bound to them.

3) **Fibric Acid Derivatives (Fibrates):** The mechanism of action of fibrates is not clear. They act by reducing the synthesis of hepatic triglycerides and increasing their peripheral clearance. Peroxisome Proliferators Activator Receptors (PPARs) regulate gene tra nscription and three isotypes of PPAR, *viz.*α, β and γ have been identified. Fibrates act like agonists for the nuclear transcription factor Peroxisome Proliferators -Activated Receptor -alpha (PPAR-alpha) at the molecular level.

   Thus, fibrates down regulate the apo -lipoprotein C-III (apo C-III) gene and up regulate the genes for apo-lipoprotein A-I (apo A-I), fatty acid transport protein, fatty acid oxidation, and LPL by this mechanism. Increase in catabolism of triglycerides by LPL along with an increase in oxidation of fatty acids leads to decreased levels of VLDL triglycerides.

   Apoprotein I (apo A -I) and apo A -II are the main components of HDL. Increase in the synthesis of apo A-I and apo A-II increases the concentration of HDL-C. Fenofibrate increases the concentration of HDL more effectively than gemfibrozil.

   Small VLDL particles are formed as the concentration of triglycerides decreases. These small VLDL particles produce larger LDL particle s, the buoyancy of which is more and serve as better ligands for the LDL receptors. In addition, these LDL particles are also cleared easily. Therefore, the atherogenic potential of LDL is reduced by the use of fibrates.

4) **Triglyceride Synthesis and Lipolysi s Inhibitors:** The release of free fatty acids from adipose tissue is partially inhibited by nicotinic acid. It also increases the lipoprotein activity which may in turn increase the elimination rate of triglycerides from plasma. As a result, the total LDLs (bad cholesterol) and triglycerides are reduced, and thus HDLs (good cholesterol) is increased.

8.1.4. Uses

The therapeutic uses of anti-hyperlipidemic agents include:

1) **HMG-CoA Reductase Inhibitors (Statins):** These are used in the following conditions:
   i) In patie nts with symptomatic atherosclerotic disease (**e.g.,** angina, transient ischemic attacks, following acute myocardial infarction or stroke), administration of statins helps in secondary prevention of myocardial infarction and stroke.
   ii) In high risk group patien ts (due to elevated serum cholesterol concentration), statins help in primary prevention of arterial disease, particularly when other risk factors for atherosclerosis are also present.

iii) In patients with homozygous familial hypercholesterolemia, serum cholesterol can be decreased by the use of atorvastatin.

iv) Severe drug -resistant dyslipidemia (**e.g.,** heterozygous familial hypercholesterolemia) is treated by supplementing a bile acid binding resin in addition to treatment using a statin.

2) **Bile Acid Sequestrants (Resins):** Cholesterol acts as a substrate for the biosynthesis of bile acids. Therefore, any disturbance in the reabsorption of bile acids decreases the level of cholesterol, especially that of LDL (commonly known as "bad cholesterol"). Thus, resins may b e employed in the treatment of hypercholesterolemia and dyslipidemia. Bile acids may get deposited on skin in the presence of chronic liver diseases (like cirrhosis), which in turn may cause pruritus (itching). Thus, pruritus (itching) may be prevented by using bile acid sequestrants.

When bile salts enter the colon in excess amounts (instead of getting absorbed in the distal part of the small intestine), it may cause diarrhoea within a short time period after consumption of food. Removal of gall bladder m ay possibly cause bile salt diarrhoea. In such patients, bile acid sequestrants relieve diarrhoea.

3) **Fibric Acid Derivatives (Fibrates):** These are used in the following conditions:
   i) In patients with t ype III hyperlipidaemia or familial dysbetalipoproteinemia, fibrates are employed as the first-line drugs.
   ii) Moderate to severe hypertriglyceridemia and mixed hyperlipidaemia (where the predominant abnormality is hypertriglyceridemia) are treated using fibrates in combination with resins.
   iii) A fibrate can be employed along with statins for the treatment of patients with a high risk of CHD and mixed hyperlipidaemia. However, it is required to carefully monitor the safety of patient as it increases the risk for myopathy.

4) T**riglyceride Synthesis and Lipolysis Inhibitors :** For treating adults with very high levels of serum triglyceride and who are at a risk for pancreatitis, and who do not show adequate response to dietary control, niacin may be prescribed as an adjunctive to diet.

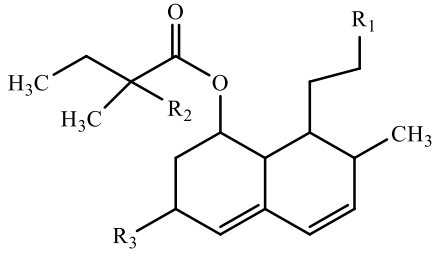
8.1.5. Structure-Activity Relationship

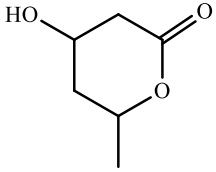
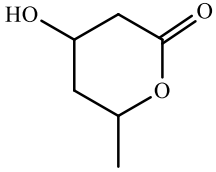
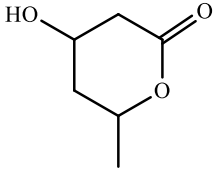
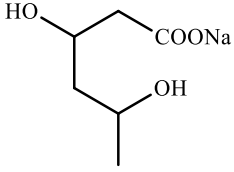
The SAR of anti-hyperlipidemics has been discussed under the following heads:
1) Structure-activity relationship of HMG CoA-reductase inhibitors, and
2) Structure-activity relationship of fibrates.

8.1.5.1. Structure-Activity Relationship of HMG CoA-Reductase Inhibitors (HMGRIs)

Mevastatin and **lovastatin** are the lead compounds in development of additional HMGRIs. The ethylene bridge present between the lactone and bicyclic rings is essential for HMGRIs' activity. It was observed that the replacement of bicyclic ring with other lipophilic rings is possible. The overall activity of the compounds is affected by the size and shape of these rings.

Simvastatin and **pravastatin** can be obtained by making minor modificatio ns to the bicyclic ring and side chain ester of lovastatin. The hydrophilicity of pravastatin (a ring-opened dihydroxyacid with a 6′-hydroxyl group) is more than that of lovastatin and simvastatin.



Drugs	R_1	R_2	R_3	Source
Mevastatin		H	H	*Penicillium sp.*
Lovastatin		H	CH_3	*Aspergillus sp.*
Simvastatin		CH_3	CH_3	Semi-synthetic
Pravastatin		H	OH	*Absidia coerulea*

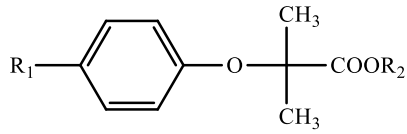
This hydrophilic nature has led to the following **advantages**:

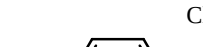
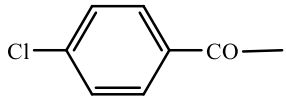
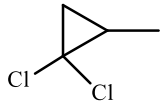
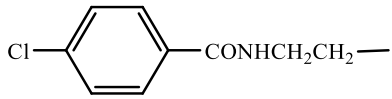
1) Minimum penetration into the lipophilic membranes of peripheral cells,
2) Better selectivity for hepatic tissues, and
3) Reduced side effects of lovastatin and simvastatin.

By replacing the bicyclic ring with various substituted, aromatic ring systems, compounds (like fluvastatin), **atorvastatin**, and **cerivastatin** can be developed. However, the potency of these compounds is less than that of mevastatin. In a research it was concluded that the activity of HMGRIs can be optimised by a variety of aromatic substitutions and heterocyclic ring systems. The activity of mevastatin can be retained by up to 30% and a number of active compounds can be produced by substituting with pyrrole (a key intermediate in substitutions and addition of spacer groups).

8.1.5.2. Structure-Activity Relationship of Fibrates

Chemically, fibrates are analogues of phenoxyisobutyric acid. All the compounds of this class are analogues of the following structure:



Drugs	R_1	R_2
Clofibrate		$—C_2H_5$
Fenofibrate		$—CH(CH_3)_2$
Ciprofibrate		H
Bezafibrate		H

The isobutyric acid group in the structure is essential for activity. **Clofibrate** and **fenofibrate** (compounds containing an ester) are pro drugs and require *in vivo* hydrolysis. Compounds with longer half-lives are yielded by substituting a chloro group or chlorine-containing isopropyl ring at the *para* position of the aromatic ring. Mostly a phenoxyisobutyric acid is present in the compounds, the addition of a *m*-propyl spacer (as in gemfibrozil) results in an active drug.

8.1.6. Recent Developments

One of the primary risk factors for atherosclerosis and other associated cardiovascular diseases and stroke is an increase in the level of lipids. Although the anti-hyperlipidemic therapy comprises of several categories of drugs, yet all of them are associated with some problems.

Probucol, **nicotinates**, **anion exchange resins**, **ethyl icosapentate**, and **dextran sodium sulphate** are some of the other drugs that can be used as anti-hyperlipidemics. Though the activity of these agents is mild, yet they show very low incidence of adverse effects and can thus appropriately be used along with fibrates or statins.

Colesevelam hydrochloride significantly decreases the reabsorption of bile acids by binding to them in the intestine. It is a non-absorbed, polymeric, lipid-lowering agent. As the bile acid pool depletes, conversion of cholesterol to bile acids increases, and thus the cholesterol concentration decreases. Colesevelam acts just like **cholestyramine** (**e.g.,** Questran) and **colestipol** (**Colestid**). Yet, the binding affinity of this drug is greater for bile acids. Therefore, a lower dose of this drug can be effectively used. The incidence of GIT adverse effects is lower with this drug. It also has a lower potential to interact with other drugs.

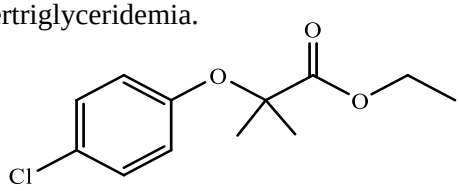
8.1.7. Study of Individual Drugs

The following anti-hyperlipidemic agents are discussed below:

1) Clofibrate,
2) Lovastatin,
3) Cholestyramine, and
4) Colestipol.

8.1.7.1. Clofibrate

Clofibrate is a fibric acid derivative used for treating hyperlipoproteinemia type III and severe hypertriglyceridemia.



Clofibrate

Mechanism of Action

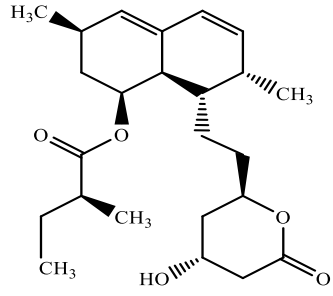
Clofibrate acts by increas ing the activity of Lipoprotein Lipase (LL) outside the liver, and thus increases the lipolysis of lipoprotein triglycerides. Degradation of chylomicrons occurs. Conversion of VLDLs into LDLs and that of LDLs into HDLs takes place. At the same time, lipid secretion into the bile (hence into the intestine) increases to some extent. Synthesis of apolipoprotein B (a carrier molecule for VLDL) is also inhibited and its clearance is increased by clofibrate.

Uses

It is used for primary dysbetalipoproteinemia (ty pe III hyperlipidemia) which does not sufficiently respond to diet. This helps in controlling high cholesterol and high triglyceride levels.

8.1.7.2. Lovastatin

Lovastatin is a hydroxymethylglutaryl coenzyme A (HMG -CoA) reductase inhibitor. It is obtained by *Aspergillus terreus* . It is a natural product derived from polyketide, and contains an oxidation susceptible hetero-annular diene ring system.



Lovastatin

Mechanism of Action

Lovastatin is a competitive inhibitor of HMG -CoA reductase enzyme and has Ki value of 1.4 nM. This inhibition restricts the biosynthesis of mevalonic acid (precursor in the production pathway of terpenes and steroids). Lovastatin acts on

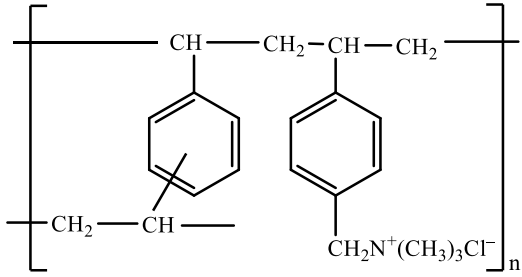
the liver, which is the major site of cholesterol biosynthesis, lipoprotein production, and LDL catabolism. However, cholesterol synthesis is also necessary for extrahepatic tissues, hence, long-term treatment with lovastatin can result in adverse reactions due to extrahepatic action.

Uses

1) It is used as an alternative in individuals having dyslipidemia at risk of atherosclerotic vascular disease.
2) It is used for reducing the risk of myocardial infarction, unstable angina, and coronary revascularisation methods in p atients having risk related to increased total cholest erol, increased LDL cho lesterol, and below average HDL cholesterol.
3) It is used to delay the progression of coronary atherosclerosis in patients having coronary heart disease.
4) It is used as an adjunct to diet for decreasing total cholesterol, LDL cholesterol and apo-lipoprotein B level in adolescents (10-17 years).

8.1.7.3. Cholestyramine

Cholestyramine (or **colestyramine**) is a bile acid sequestrant, which is a polymeric compound that acts as an ion exchange resin . Cholestyramine resin is hydrophilic, however water-insoluble.



Cholestyramine

Mechanism of Action

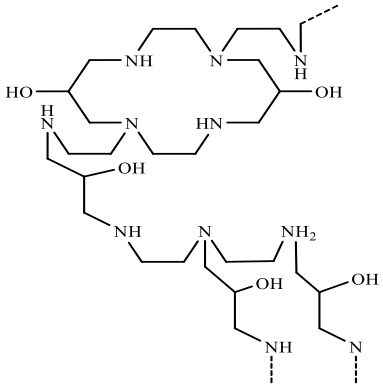
Cholestyramine binds to and prevents the reabsorption of bile in GIT . Since cholestyramine resin is a strong anion exchange resin, it can exchange its chloride anions with anionic bile acids in the GIT and bind them strongly in the resin matrix. The functional group of the anion exchange resin is a quaternary ammonium group attached to an inert styrene-divinylbenzene copolymer.

Uses

1) It is used as an adjunct to diet for decreasing the elevated serum cholesterol levels in patients having primary hypercholesterolemia (raised LDL cholesterol) and not responding to diet.
2) It is also used for treating pruritus related to partial biliary obstruction.

8.1.7.4. Colestipol

Colestipol is a highly cross-linked and insoluble basic anion exchange resin. It is used as an anti-cholesteremic. It is also used to decrease the triglyceride levels.



Colestipol

Mechanism of Action

Colestipol is a non-absorbed, lipid-lowering polymer that binds to intestinal bile acids and inhibits their reabsorption. Consequently, the bile acid pool depletes, and the upregulation of cholesterol-7α-hydroxylase (hepatic enzyme) increases cholesterol conversion into bile acids. This in turn increases the demand for cholesterol in the liver cells, and increases the transcription and activity of hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase (cholesterol biosynthetic enzyme), thereby increasing the number of hepatic LDL receptors. These effects increase the clearance of LDL cholesterol (LDL-C) from the blood, and decrease the serum levels of LDL-C. Serum triglyceride levels either increases or remains unaltered. Ultimately, the clearance of LDL-C from the blood increases, thus the serum levels of LDL-C decreases.

Uses

It is used as an adjunct to diet for decreasing the elevated serum total and LDL-C in patients having primary hypercholesterolemia (raised LDL cholesterol) and not responding to diet.

8.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Atherosclerosis** is a condition characterised by damage to the arteries.
2) **Hyperlipidaemia**, also referred to as **hyperlipoproteinemia**, is a condition characterised by an increase in the lipid concentration in plasma.
3) **Hypocholesterolemic** or **anti-hyperlipidemic** or **lipid lowering agents** are the pharmacological agents decreasing the concentration of lipids in plasma.
4) **HMG-CoA reductase** (3-hydroxy-3methylglutaryl-coenzyme A reductase) is the enzyme responsible for the conversion of HMG-CoA to mevalonate.
5) **Statins** act by inhibiting HMG-CoA reductase.
6) **Bile Acid Sequestrants (Resins)** are basically large polymeric compounds serving as ion exchange resins.
7) The release of free fatty acids from adipose tissue is partially inhibited by **nicotinic acid**.
8) **Colesevelam hydrochloride** significantly decreases the reabsorption of bile acids by binding to them in the intestine.

9) **Clofibrate** is a fibric acid derivative used for treating hyperlipoproteinemia type III and severe hypertriglyceridemia.
10) **Lovastatin** is a hydroxymethylglutaryl coenzyme A (HMG -CoA) reductase inhibitor. It is obtained by *Aspergillus terreus.*
11) **Cholestyramine** (or **colestyramine**) is a bile acid sequestrant, which is a polymeric compound that acts as an ion exchange resin.
12) **Colestipol** is a highly crosslinked and insoluble basic anion exchange resin. It is used as an anticholesteremic. It is also used to decrease the triglyceride levels.

8.3. EXERCISE

8.3.1. True or False

1) Atherosclerosis is a condition characterised by damage to the arteries.
2) Statins act by stimulating HMG-CoA reductase.
3) Lovastatin is obtained by *Aspergillus terreus.*
4) Clofibrate decreases the reabsorption of bile acids by binding to them in the intestine.
5) Hyperlipoproteinemia is a condition characterised by a decrease in the lipid concentration in plasma.

8.3.2. Fill in the Blanks

6) _____ act by inhibiting HMG-CoA reductase.
7) _____ is a condition characterised by damage to the arteries.
8) _____ significantly decreases the reabsorption of bile acids by binding to them in the intestine.
9) _____ is a bile acid sequestrant, which is a polymeric compound that acts as an ion exchange resin.
10) The release of free fatty acids from adipose tissue is partially inhibited by _____.

Answers

1) True 2) False 3) True 4) False
5) False 6) Statins 7) Atherosclerosis
8) Colesevelam hydrochloride 9) Cholestyramine 10) Nicotinic acid

8.3.3. Very Short Answer Type Questions

1) What are anti-hyperlipidemic drugs?
2) Classify anti-hyperlipidemic drugs.
3) Give the MOA of statins.
4) Give the MOA of resins.
5) Write a short note on clofibrate.

8.3.4. Short Answer Type Questions

1) Discuss lovastatin and cholestyramine.
2) Give the SAR of fibrates.
3) What are the uses of fibrates.
4) Discuss the recent developments in anti-hyperlipidemic agents.

8.3.5. Long Answer Type Questions

1) Give the mechanism of action of anti-hyperlipidemic agents.
2) What are the uses and recent developments of anti-hyperlipidemic agents?
3) Give the SAR of anti-hyperlipidemics.

CHAPTER 9

Coagulant and Anticoagulants

9.1. COAGULANTS

9.1.1. Introduction

Blood coagulation is an important biochemical reaction which ensures the cessation of blood loss from the damaged blood vessels. Coagulation is an important part of the haemostatic mechanism. Disorders of blood coagulation result to excessive haemorrhage and/or thrombosis and embolism.

Coagulants help in blood coagulation and are indicated in haemorrhagic conditions. The elements or factors required for coagulation are found in the fresh whole blood or pl asma and are therefore indicated in case of deficiency of any clotting factor.

9.1.2. Classification

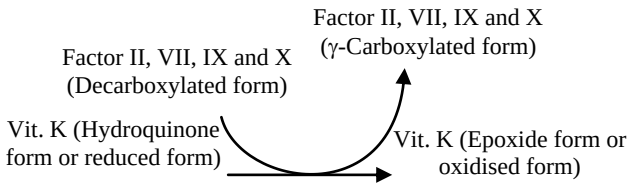
The coagulants are classified as follows:

1) **Vitamin K**
   i) K_1 (from plants, fat-soluble): Phytonadione (Phylloquinone).
   ii) K_3 (synthetic)
      a) **Fat-Soluble:** Menadione and Acetomenaphthone.
      b) **Water-Soluble:** Menadione sodium bisulfite and Menadione sodium diphosphate.
2) **Miscellaneous:** Fibrinogen (human), Anti-haemophilic factor, Desmopressin, Adrenochrome monosemicarbazone, Rutin, and Ethamsylate.

9.1.3. Mechanism of Action

The mechanism of action of coagulants is described as follows:

1) Vitamin K is required for the synthesis of clotting factors II, VII, IX, and X.
2) These factors are chemically glycoproteins with a number (10 or 11) or γ-carboxyglutamic acid at the $-NH_2$ terminal of the peptide chains.
3) Synthesis of γ-carboxyglutamic acid residues is dependent of vitamin K and the reaction occurs after peptide chain synthesis.
4) Vitamin K acts as a co-factor in the carboxylation reaction.



9.1.4. Uses

Coagulants has the following therapeutic uses:

1) **Prolonged Antimicrobial Therapy:** Antimicrobial therapy for a long period causes destruction of GIT bacteria , thus formation of vitamin K is either reduced or stopped. For the treatment of this condit ion, vitamin K preparations are given through oral route.
2) **Obstructive Jaundice:** It is caused by malabsorption of dietary or intestinal vitamin K. Vitamin K_3 can be administered orally, or vitamin K_1 or K_2 can be given through parenteral route.
3) **Overdosage of Oral Anticoagulants:** In this case, vitamin K is given as a specific antidote. Vitamin K_1 is the preparation of choice due to its rapid onset of action. Menadiol sodium diphosphate (K_3) should not be used due to its late onset of action (24 hours).
4) **Malabsorption Syndrome:** In this condition, parenteral vitamin K or oral vitamin K_3 may be used.

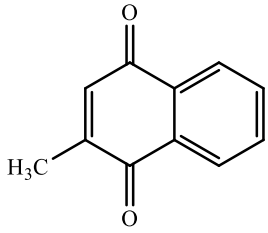
9.1.5. Study of Individual Drugs

The following coagulants are discussed below:

1) Menadione, and
2) Acetomenadione.

9.1.5.1. Menadione

Menadione is a synthetic naphtho quinone with no isoprenoid side chain and biological activity. It can be converted to pharmacologically active vitamin K_2 (menaquinone) by undergoing *in vivo* alkylation. It can act as a precursor for various forms of vitamin K, but it is not used as a nutritional supplement.



Menadione

Mechanism of Action

Menadione (vitamin K_3) serves as a cofactor in the post -translational γ-carboxylation of glutamic acid residues of certain body proteins. These proteins are the vitamin K -dependent coagulation factors II (prothrombin), VII (proconvertin), IX (Christmas factor), X (Stuart factor), p rotein C, protein S, protein Zv, and a Growth-arrest-specific factor (Gas6).

Contrary to other vitamin K-dependent proteins in the blood coagulation cascade, protein C and protein S have some anticoagulant roles to play. Two vitamin K-dependent proteins are found in bones, i.e., **osteocalcin**, also known as bone G_{1a} (γ-carboxyglutamate) protein or BGP, and the matrix G_{1a} protein or MGP.

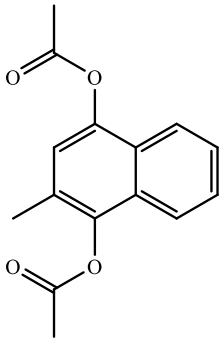
Proteins containing γ-carboxyglutamate are called G_{1a} proteins. The vitamin K - dependent γ-carboxylases catalyse the process of γ-carboxylation. The reduced form of vitamin K is vitamin K hydroquinone, which is the actual cofactor for γ-carboxylases.

Uses

1) It is used to support the normal clotting process of blood.
2) It also helps in normal bone calcification.

9.1.5.2. Acetomenadione

Acetomenadione (or menadiol diacetate) is a vitamin K analogue. It prevents hypoprothrombinemia caused by vitamin K deficiency.



Acetomenadione

Mechanism of Action

Acetomenadione serves as a cofactor for the γ-carboxylase enzymes. These enzymes catalyse the post-translational γ-carboxylation of glutamic acid residues in inactive hepatic precursors of coagulation factors II (prothrombin), VII, IX and X. In the process of γ-carboxylation, these inactive precursors are converted into active coagulation factors. These factors a re secreted into the blood by hepatocytes. Supplementing with acetomenadione relieves the symptoms of vitamin K deficiency which include easy bruisability, epistaxis, gastrointestinal bleeding, menorrhagia, and haematuria.

Uses

1) It is used for treating haemorrhagic conditions in infants.
2) It can be used as an antidote for coumarin anticoagulants in hypoprothrombinaemia.

9.2. ANTICOAGULANTS

9.2.1. Introduction

Blood coagulation is a complex process in which blood forms solid clots. It is essential part of haemostasis in w hich a damaged blood vessel wall is enclosed by a fibrin clot to prevent haemorrhage and to repair the damage d vessel. Disorders of blood coagulation increase the occurrence of haemorrhage and/or thrombosis and embolism.

Coagulation of blood occurs in the presence of coagulation factors, calcium, and phospholipids:

1) The coagulation factors are proteins obtained by the liver.
2) Ionised calcium (Ca^{++}) is present in the blood and is obtained from intracellular sources.
3) Phospholipids are the important componen ts of cellular and platelet membranes. They provide a surface for the chemical reactions of coagulation to occur.

Coagulation is initiated by any of the two pathways:

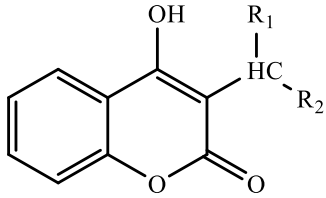
1) **Intrinsic Pathway:** This pathway starts with events taking place in the lumen of blood vessels. The intrinsic pathway utilises the elements present in or intrinsic to the vascular system. Such elements include clotting factors, Ca^{++}, platelet surface, etc.
2) **Extrinsic Pathway:** This pathway utilises tissue thromboplastin (tissue factor), which is a substance extrinsic to or not found circulating in the vessel. A ruptured vessel wall releases the tissue factor.

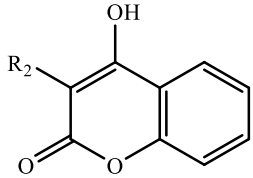
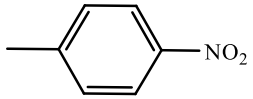
Anticoagulants decrease the coagulation ability of blood . They do not dissolve the clot that has formed but inhibit s the formation of new clots. **Examples** of these agents are **heparin** and **warfarin**. Heparin is given intravenously to patients at risk of thrombus formation and warfarin is administered orally.

9.2.2. Classification

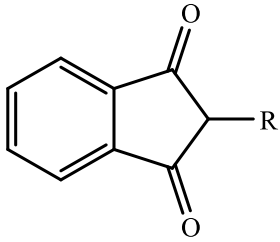
Anticoagulants are classified as follows:

1) **Coumarin Derivatives**



Drugs	R_1	R_2
Warfarin	—CH_2COCH_3	—C_6H_5
Dicoumarol	H	
Phenprocoumon	—C_6H_5	—C_6H_5
Acenocoumarol	—CH_2COCH_3	

2) **3-Indanedione Derivatives**



Drugs	R
Phenindione	—C_6H_5
Anisindione	H_3CO—
Bromindione	Br—
Diphenadione	—$COCH(C_6H_5)_2$

9.2.3. Mechanism of Action

Oral anticoagulants produce interfere with the vitamin K cycle. They interact with KO reductase enzyme so that v itamin KO does not recycle back to vitamin K. This depletes vitamin KH_2, and prevents the formation of prothrombin (factor II) from its precursor. As a result, the plasma content of prothrombin is reduced and blood coagulation is impaired.

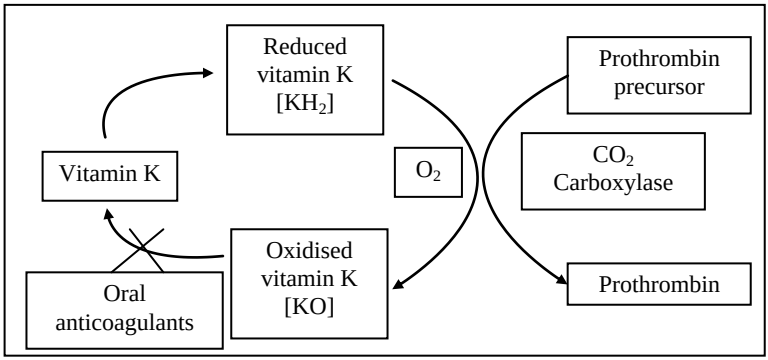


Figure 9.1: Mechanism of Action of Anticoagulants

9.2.4. Uses

Anticoagulants are used for the treatment of:

1) Retinal vascular occlusion,
2) Pulmonary embolism,
3) Cardiomyopathy,
4) Atrial fibrillation and flutter,
5) Cerebral embolism,
6) Transient cerebral ischemia,
7) Arterial embolism, and
8) Thrombosis.

9.2.5. Recent Developments

The approach to the development of new anticoagulants as alternatives to heparin and vitamin K antagonists require convenient administration with predictable pharmacokinetics, pharmacodynamics and a wide therapeutic window that would allow fixed dosing without need to monitor coagulation. Research has focused on targeting thrombin (factor IIa) and factor Xa, which are common to the intrinsic and extrinsic coagulation pathways. Direct thrombin inhibitors prevent fibrin formation, and also block thrombin-mediated activation of factors V, VIII, XI and XIII, and platelets. Direct inhibitors of factor Xa act at an earlier stage in the cascade.

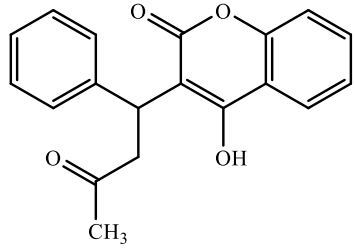
9.2.6. Study of Individual Drugs

The following anticoagulants are discussed below:

1) Warfarin,
2) Anisindione, and
3) Clopidogrel.

9.2.6.1. Warfarin

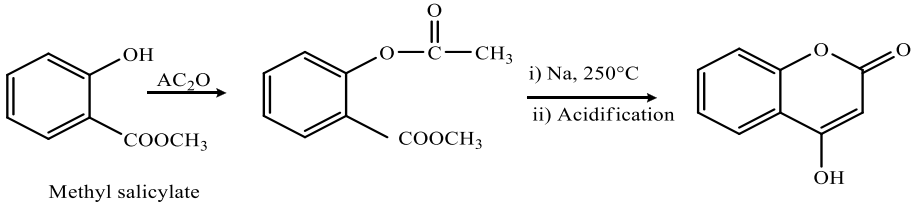
Warfarin is an anticoagulant used for preventing blood clot formation and migration.



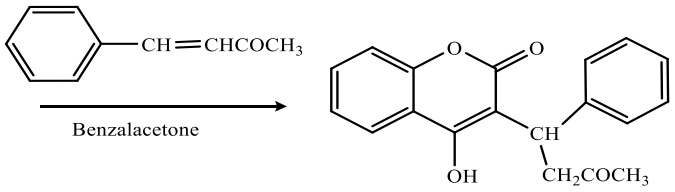
Warfarin

Synthesis

Methyl salicylate is used to obtain 4-hydroxycoumarin. The sodium derivative of 4-hydroxycoumarin is obtained by the action of sodium on methyl acetylsalicylate. Acidification yields 4-hydroxycoumarin, which undergoes Michael addition in the presence of benzalacetone to synthesise warfarin.



Methyl salicylate



Warfarin

Mechanism of Action

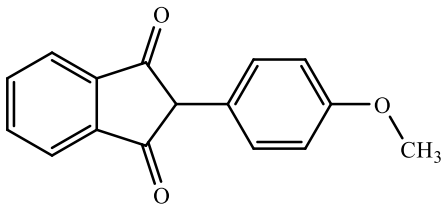
Warfarin depletes the reduced form of vitamin K (vitamin KH_2) by inhibiting the vitamin K reductase enzyme. Vitamin K serves as a cofactor for the carboxylation of glutamate residues on the N -terminal regions o f vitamin K -dependent proteins. Thus, the γ-carboxylation and subsequent activation of the vitamin K -dependent coagulant proteins is restricted . Also, the synthesis of vitamin K -dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited. Depression of vitamin K -dependent coagulation factors II, VII , and X decreases the prothrombin levels and the amount of thrombin generated and bound to fibrin. This ultimately reduces the thrombogenicity of clots.

Uses

1) It is used for prophylaxis, and for treating venous thrombosis, pulmon ary embolism and atrial fibrillation with embolisation.
2) It is also used as an aid in the prophylaxis of systemic embolism after myocardial infarction.

9.2.6.2. Anisindione

Anisindione is an indanedione derivative and a synthetic anticoagulant. It inhibits the formation of active pro -coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S in the liver. It does so by inhibiting vitamin K -mediated γ-carboxylation of precursor proteins.



Anisindione

Mechanism of Action

Anisindione acts by reducing the prothrombin activity of blood. It inhibits the formation of active pro -coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S in the liver.

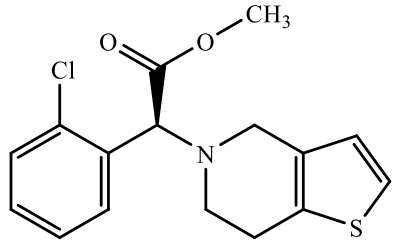
It does so by inhibiting vitamin K -mediated γ-carboxylation of precursor proteins. Anisindione exerts no direct thrombolytic effect and does not reverse ischemic tissue damage; however, it may limit extension of existing thrombi and prevent secondary thromboembolic complications.

Uses

1) It is used for prophylaxis and treatment of venous thrombosis and its extension.
2) It also treats atrial fibrillation with embolization.
3) It is used for prophylaxis and treatment of pulmonary embolism.
4) It used as an adjunct for treating coronary occlusion.

9.2.6.3. Clopidogrel

Clopidogrel is an antiplatelet agent having structure and pharmacological activity similar to ticlopidine. It is used for preventing blood clots in various conditions like peripheral vascular disease, coronary artery disease, and cerebrovascular disease.



Clopidogrel

Mechanism of Action

The active metabolite of clopido grel prevents ADP from binding to its platelet receptor, thus impairs the ADP-mediated activation of the glycoprotein $GPII_b/III_a$ complex. This inhibition involves a defect in the mobilis ation from the storage sites of platelet granules to the outer membrane. Clopidogrel specifically and irreversibly inhibits the P2Y12 sub -type of ADP receptor, which is required in platelet aggregation and cross-linking by the protein fibrin.

Since the glycoprotein $GPII_b/III_a$ complex is the major receptor for fibrinogen, its impaired activation prevents binding of fibrinogen to platelets and inhibits platelet aggregation. By hindering the am plification of platelet activation by released ADP, platelet aggregation induced by agonists other than ADP is also inhibited by the active metabolite of clopidogrel.

Uses

It is used for decreasing atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke and myocardial infarction or established peripheral arterial disease.

9.3. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Coagulation** is an important part of the haemostatic mechanism.
2) **Coagulants** help in blood coagulation and are indicated in haemorrhagic conditions.
3) **Vitamin K** is required for the synthesis of clotting factors II, VII, IX, and X.
4) **Vitamin K** acts as a co-factor in the carboxylation reaction.
5) **Obstructive Jaundice** is caused by malabsorption of dietary or intestinal vitamin K.
6) Vitamin K is given as a specific antidote for **overdosage of Oral Anticoagulants**.

7) **Menadione** can act as a precursor for various forms of vitamin K, but it is not used as a nutritional supplement.
8) **Acetomenadione** (or **menadiol diacetate**) is a vitamin K analogue. It prevents hypoprothrombinemia caused by vitamin K deficiency.
9) **Menadione** (**vitamin K_3**) serves as a cofactor in the post -translational γ-carboxylation of glutamic acid residues of certain body proteins.
10) **Menadione** helps in normal bone calcification.
11) **Acetomenadione** serves as a cofactor for the γ-carboxylase enzymes.
12) **Acetomenadione** is used for treating haemorrhagic conditions in infants.
13) **Blood coagulation** is a complex process in which blood forms solid clots.
14) **Coagulation of blood** occurs in the presence of coagulation factors, calcium, and phospholipids.
15) The **coagulation factors** are proteins obtained by the liver.
16) **Anticoagulants** decrease the coagulation ability of blood . They do not dissolve the clot that has formed but inhibits the formation of new clots.
17) **Oral anticoagulants** produce interference with the vitamin K cycle. They interact with KO reductase enzyme so that vitamin KO does not recycle back to vitamin K.
18) **Warfarin** is an anticoagulant used for preventing blood clot formation and migration.
19) Warfarin depletes the reduced form of vitamin K (vitamin KH_2) by inhibiting the vitamin K reductase enzyme.
20) **Anisindione** is an indanedione derivative and a synthetic anticoagulant. It inhibits the formation of active pro -coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S in the liver.
21) **Clopidogrel** is an antiplatelet agent having structure and pharmacological activity similar to ticlopidine. It is used for preventing blood clots in various conditions like peripheral vascular disease, coronary artery disease, and cerebrovascular disease.

9.4. EXERCISE

9.4.1. True or False

1) Coagulation is an important part of the haemostatic mechanism.
2) Menadione is used as a nutritional supplement.
3) Clopidogrel has similar pharmacological activity to ticlopidine.
4) The coagulation factors are amino acids obtained by the liver.
5) Vitamin K is required for the synthesis of clotting factors II, VII, IX, and X.

9.4.2. Fill in the Blanks

6) _____ serves as a cofactor for the γ-carboxylase enzymes.
7) The coagulation factors are _____ obtained by the liver.

8) _____ decrease the coagulation ability of blood.
9) _____ is given as a specific antidote for overdosage of oral anticoagulants.
10) _____ acts as a co-factor in the carboxylation reaction.
11) _____ helps in normal bone calcification.

Answers

1) True	2) False	3) True	4) False
5) True	6) Acetomenadione	7) Proteins	8) Anticoagulants
9) Vitamin K	10) Vitamin K	11) Menadione	

9.4.3. Very Short Answer Type Questions

1) Define coagulation and coagulants.
2) Give the classification on coagulants.
3) Give the MOA of coagulants.
4) Discuss anti-coagulants.
5) What are the uses of anti-coagulants?

9.4.4. Short Answer Type Questions

1) Write a short note on menadione.
2) Give the classification of anti-coagulants.
3) Discuss anisindione.
4) Write a short note on clopidogrel.

9.4.5. Long Answer Type Questions

1) Write a detailed note on coagulants.
2) What are anticoagulants? Discuss in detail.
3) Discuss warfarin and clopidogrel.

CHAPTER 10

Drugs Used in Congestive Heart Failure

10.1. DRUGS USED IN CONGESTIVE HEART FAILURE

10.1.1. Introduction

When a heart fails to pump blood in a quantity sufficient to fulfil the body requirements, a condition of **Congestive Heart Failure** (**CHF**) occurs, which is also known as a **Heart Failure** (**HF**). CHF is caused due to:

1) Narrowing of the arteries, supplying blood to the heart muscles,
2) The patient suffered in the past with myocardial infarction or heart attack with the injured tissue that obstructs the normal functioning of heart,
3) Any congenital heart defects,
4) Endocarditis (infection in heart valve) or myocarditis (infection of heart muscles),
5) Any heart valve disease (due to past rheumatic fever or other causes) and high blood pressure, for long-term, and
6) Cardiomyopathy (disease of the heart muscles).

10.1.2. Classification

The drugs used in CHF are classified as follows:

1) **Drugs with Positive Inotropic Effects**
   i) **Cardiac Glycosides:** Digoxin, Digitoxin, and Ouabain.
   ii) **Bipyridines/Phosphodiesterase Inhibitors:** Amrinone and Milrinone.
   iii) **β-Adrenergic Agonists:** Dobutamine and Dopamine.
2) **Drugs without Positive Inotropic Effects**
   i) **Diuretics:** Thiazides, Furosemide, and Spironolactone.
   ii) **Angiotensin Antagonists:** ACE inhibitors and Losartan.
   iii) **β-Adrenergic Antagonists:** Bisoprolol, Carvedilol, and Metoprolol.
   iv) **Vasodilators:** Nitrates and Hydralazine.

10.1.3. Cardiac Glycosides

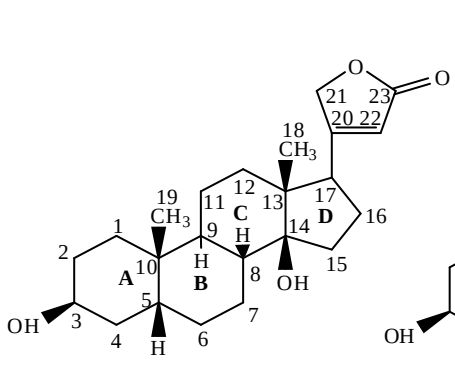
Cardiac glycosides are derived from the foxglove plant (*Digitalis purpurea*). **William Withering** described the therapeutic benefits of digitalis in **1785**. Primarily, digitalis was used for treating dropsy, an old word for oedema. Further investigations established that digitalis was most helpful for oedema caused by weakened heart (i.e., heart failure). The natural sources of cardiotonic agents are foxgloves (*Digitalis* spp.) and related plants. Foxgloves contain several cardiac glycosides with similar actions. The cardiac glycosides and their sources are given in **table 10.1**:

Table 10.1: Sources of Cardiac Glycosides

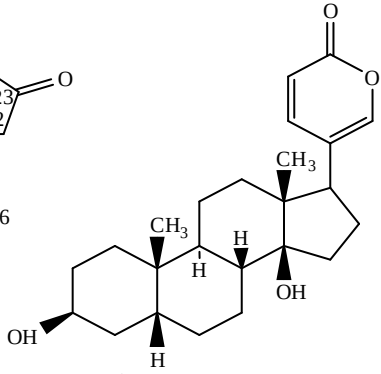
Sources	Glycosides
Digitalis purpurea (leaf)	Digitoxin, Gitoxin, and Gitalin
Digitalis lanata (leaf)	Digitoxin, Gitoxin, and Digoxin
Strophanthus gratus (seed)	Strophanthin-G (Ouabain)
Thevetia nerifolia (nut)	Thevetin
Bufo vulgaris (toad skin)	Bufotoxin
Convallaria majalis	Convallotoxin
Urginea (scilla), maritima (bulb)	Proscillaridin-A

10.1.3.1. Classification

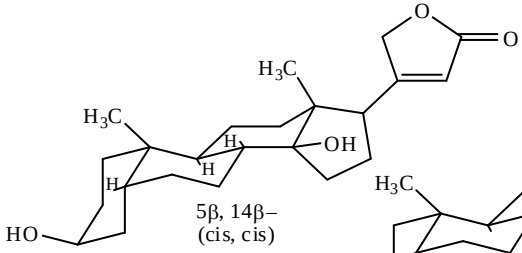
Cardiac glycosides are categorised into **cardenolides and bufadienolides**.



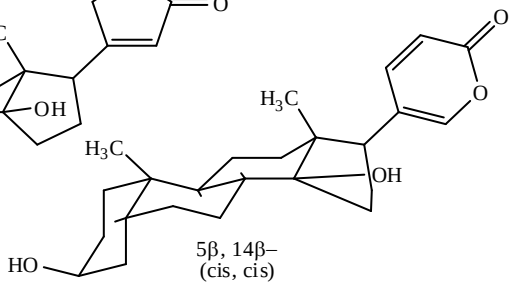
Cardenolide Prototype Digitoxigenin



Bufadienolide Prototype
(Bufalin)

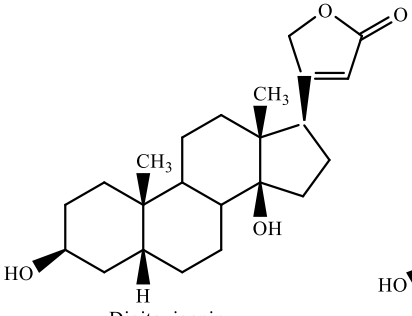


5β, 14β–
(cis, cis)

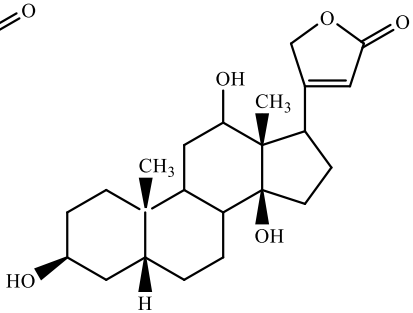


5β, 14β–
(cis, cis)

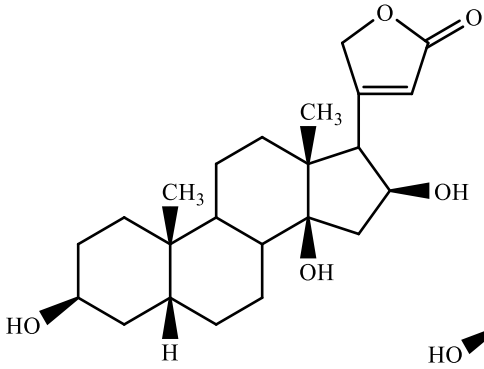
Major Cardenolide Aglycones



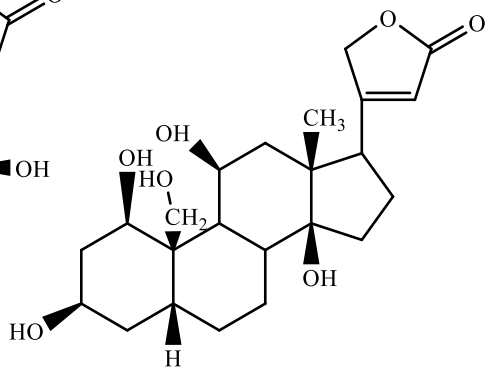
Digitoxigenin



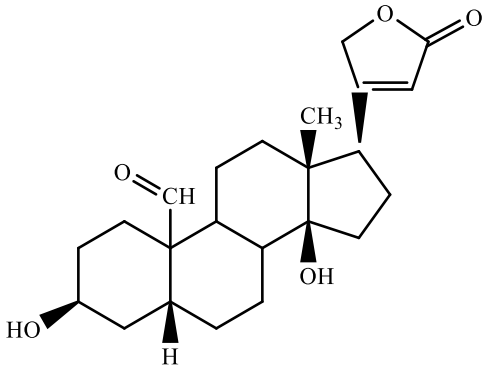
Digoxigenin



Gitoxigenin

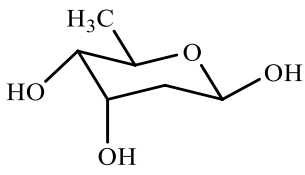


Oubagenin

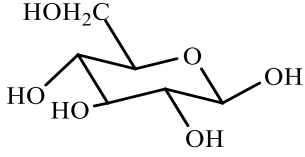


Strophanthidin

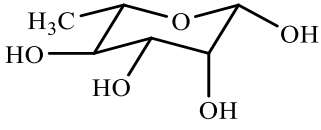
Selected Glycones of Cardiac Glycosides



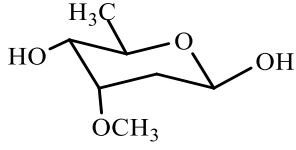
β-D-Digitoxose



β-D-Glucose



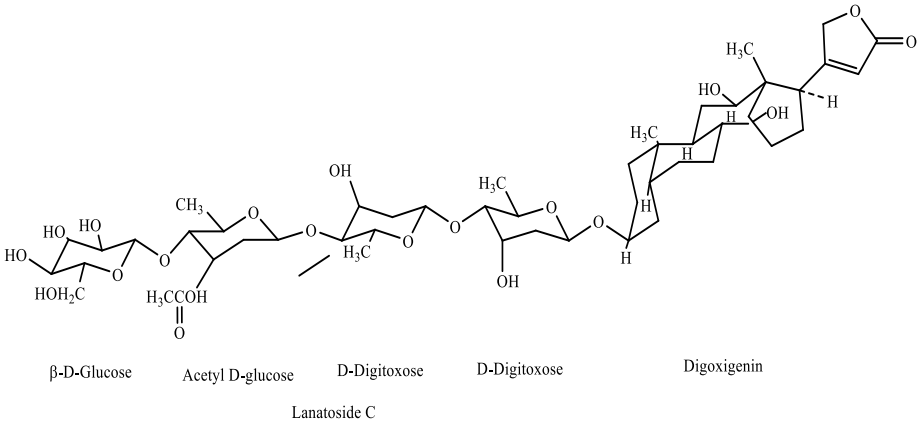
β-D-Rhamnose



β-D-Cymarose

Cardenolides (cardiac glycosides derived fr om plants) have a 5 -membered α,β-unsaturated lactone ring. On the other hand, **bufadienolides** (cardiac glycosides derived from animals) have a 6 -membered lactone ring with two conjugated double bonds (generally referred to as α-pyrone).

A number of bufadi enolides are present in the secretions from the skin of toad species, thus, are referred to as **toad poison**.

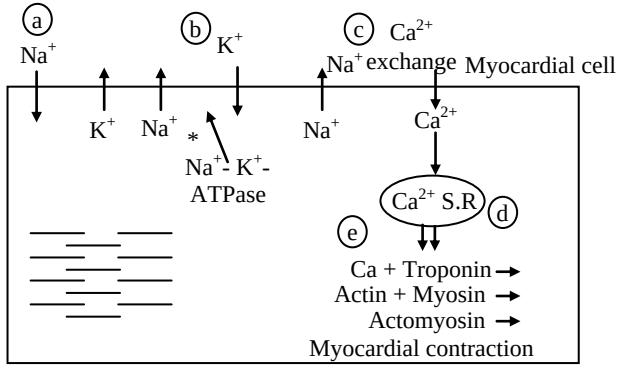


Lanatoside C

10.1.3.2. Mechanism of Action

The mechanism of action of digitalis can be explained as follows **(figure 10.1)**:

1) Digitalis exerts a positive inotropic effect due to its ability of potentiating the excitation-contraction coupling. This is possible since digitalis increases the concentration of free intracellular Ca^{2+} ions. It is independent of the adrenergic mechanism.
2) It inhibits the membrane bound Na^+-K^+-ATPase transport system (the sodium pump), resulting in increase of intracellular Na^+ ions and loss of intracellular K^+ ions.
3) As Na^+ ions accumulate inside the cell, it activates a Na^+-Ca^{2+} carrier system (which is a non -enzymatic protein carrier) within the membrane. The activation of Na^+-Ca^{2+} carrier system increases the influx of Ca^{2+} ions. Three Na^+ ions are exchanged for each Ca^{2+} ion, thereby generating an electrogenic potential by this exchanger **[figure 10.1 (c)]**.



* Digitalis acts on the enzyme N^{a+}/K^+-ATPase

Figure 10.1: Cellular Mechanism of Digitalis Action.
a) Tendency of Na^+ to flow in and K^+ to flow out along the concentration gradient; b) Na^+/K^+-ATPase pushing the Na^+ out and drawing the K^+ in; c) Na^+/Ca^{2+} exchange mechanism; d) Release of Ca^{2+} from Sarcoplasmic Reticulum (SR); e) Ca^{2+} + troponin initiating myocardial contraction.

4) Normally, the concentration of Ca^{2+} ions around the myofilaments is lowered by the calcium pump in the Sarcoplasmic Reticulum (SR). The energy for driving this pump is obtained by ATP hydrolysis carried out by Na^{+}-K^{+}-ATPase.

   However, digitalis inhibits this enzyme and hence less energy is available for driving the calcium pump. Thus, the supply of Ca^{2+} ions from SR around the myofilaments increases, which in turn activates the contractile machinery **[figure 9.1 (d and e)]**.

5) The binding of digitalis to sodium pump is inhibited by K^{+} ions present in the serum. Hence, conditions of hypokalaemia facilitate the action of digitalis. On the other hand, conditions of hyperkalaemia can decrease cardiac toxicity. Arrhythmia, induced by digitalis, is increased by conditions of hypercalcaemia or hypomagnesaemia.

10.1.3.3. Uses

Amongst digoxin and digitoxin, the former is favoured whose therapeutic uses include:

1) **Treatment of Cardiac Failure:** It modifies cardiac function and declines the frequency of hospitalisations; however, mortality is not delayed. The direct effect of digoxin on blood vessels is vasoconstriction, and when given to patients in heart failure, the systemic vascular resistance falls.

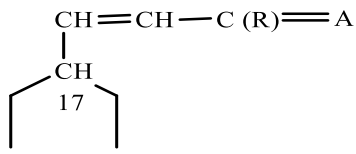
2) **Treatment of Atrial Fibrillation and Flutter:** These conditions lead to a rapid ventricular rate that can impair ventricular filling (due to decreased filling time) and reduce cardiac output. Furthermore, chronic ventricular tachycardia can lead to heart failure.

   Digoxin reduces ventricular rate by its ability to activate vagal efferent nerves to the heart (parasympathomimetic effect). Vagal activation reduces the conduction of electrical impulses within the atrioventricular node to the point where some of the impulses will be blocked. When this occurs, fewer impulses reach the ventricles and the ventricular rate falls.

10.1.3.4. Structure-Activity Relationship

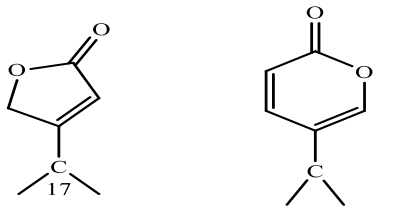
Cardiac glycosides are made up of:

1) **Genin or Aglycone Portion**
   i) **C-17 Side Chain:** At C-17 of the genin portion of cardiac glycosides, either oxygen or nitrogen can be substituted:



   Where, A = oxygen or nitrogen.

   a) In a 5- or 6-membered lactone ring, a double bond conjugated with carbonyl oxygen is present at C-17 substituent.



Butenolides Pentadienolides

b) By reducing the C-17 side chain double bond, the activity reduces.
c) The compounds show higher activity if —CH═CH—CH═NH side chain (A═N) is present at C-17.
d) The activity of a compounds is eradicated if the conjugation system in C-17 side-chain is extended, i.e., —CH═CH–CH═CH—CH═A.
e) The H-bonding between the side chain and K^+-binding site of Na^+-K^+-ATPase enzyme determines the degree of Na^+-K^+-ATPase inhibition, thus, the dipole of a molecule is an important parameter.

ii) **Steroid Nucleus**
a) The compound is efficient in activity if lactone ring is present at C-17.
b) The presence of hydroxyl group at C-14 is not essential for compound's activity because some compounds without C-14 hydroxyl group have not shown activity.

2) **Sugar Portion:** There is no direct cardiotonic role of sugars; however, their presence in the steroid at C-3 contributes to the pharmacodynamic and pharmacokinetic parameters of cardiac glycosides. The absorption and distribution of free genins is more than the corresponding glycosides. Thus, they are rapidly metabolised into less active 3-epimers, and then excreted via sulphates and glucuronides formation at free C-3 OH group. The free genins are not utilised as therapeutic agents due to their unstable nature.

Pharmacodynamically, the genins are less potent than their glycosidic forms. Their onset is also rapid and they are capable of reversing enzyme inhibitions. On the contrary, the glycosides combine with Na^+-K^+-ATPase enzyme to form complexes of high stability. By replacing the sugar moieties with side chains containing nitrogen, potent analogues of digitalis can be obtained. **For example**, the affinity of N-(4′-amino- n-butyl)-3-amino acetyl derivative of strophanthidine towards Na^+-K^+-ATPase enzyme is about 60 times greater than that of the parent genin. The sugar moieties and the enzyme interact with each other via H-bonding. The 3-OH and 5-CH_3 groups are considered the binding group in 2,6-deoxy sugars.

10.1.3.5. Recent Developments

Cardiac glycosides should fulfil the following prerequisites in order to be successfully used:

1) The inotropically active component should be separable from the toxically - active component.
2) The structure-activity relationships and/or indispensable structural features of the compounds should be known.

Inhibition of the Na^+-K^+-transport ATPase is responsible for bringing about the toxic effects of cardiac glycosides. However, ATPase inhibition does not bring about the inotropic effect.

Though several individual mechanisms are now known, the structural -activity relationships of many compounds are still unknown. However, cases like either the animal therapeutic index of this class of compounds is increased, or the frequency of arrhythmias is diminished, help in understanding cardiac glycosides to a certain extent. A series of test methods are used to explain the properties of drugs.

A systematic drug design procedure has been applied to develop a different type of cardiotonic compound. Clinical and pharmacological experience in the field of cardiotonic drugs and the biomolecular considerations have helped in the selection of a structural field (set) which possibly contains compounds showing the desired activity profile.

By systematically excluding the inappropriate portions of this structural field (sub-sets), the original set is concentrated into a small structural area (residue set). Structures (elements) of this residue set are highly potent for being new cardiotonic drugs with an activity profile superior to the compounds known till now.

10.1.4. Bipyridines

Bipyridine derivatives (such as amrinone and milrinone) show phosphodiesterase (PDE) inhibiting activity. However, these drugs are comparatively selective inhibitors of PDE -isoenzyme III which is found in the cardiac and smooth muscles.

10.1.4.1. Mechanism of Action

These drugs increase the production of cAMP in the heart and blood vessels, and thus exert a positive inotropic action along with vasodilator activities. Increased levels of intracellular cAMP enable the availability of more intracellular Ca^{2+} ions. Thus, a more positive inotropism may result.

10.1.4.2. Uses

Cardiac output is increased and the peripheral vascular resistance as well as the afterload is decreased with no significant change in heart rate and blood pressure. It is used only for the treatment of heart failure or an exacerbation of CCF.

10.1.5. β-Adrenergic Agonists

The discovery of β_1-agonists has sufficed the search for a positive inotropic β-agonist with minimal positive chronotropic and arrhythmogenic potential, with dobutamine being the most potential one amongst these agents.

10.1.5.1. Mechanism of Action

These drugs increase the cardiac output while decreasing the ventricular filling pressure and pre load. Some degree of tachycardia is seen with the use of this drug. The β-adrenergic agonists increase the consumption of oxygen.

10.1.5.2. Uses

These drugs ha ve been limited to the management of acute heart failure. They may occasionally be employed in the treatment of refractory CCF.

10.1.6. Diuretics

Diuretics are commonly used in the management of CHF. Since the last 50 years, these agents are favoured for CHF treatment.

10.1.6.1. Mechanism of Action

Diuretics increase the excretion of salt and water. This in tur n decreases the ventricular pre load and the cardiac size, improves pump function and helps relieve oedema. In patients with CHF, aldosterone promotes fibrosis in th e heart and blood vessels. This effect of aldosterone is antagonised by spironolactone (an aldosterone antagonist).

10.1.6.2. Uses

Diuretics are used in the management of all stages of CHF. Furosemide (or frusemide) is a very efficient agent in treating acute left ventricular failure (cardiac asthma).

10.1.7. Angiotensin Antagonists

The ACE inhibitors and angiotensin receptor blockers are included in this group.

10.1.7.1. Mechanism of Action

Drugs which inhibit the activity of RAS either interfere with the biosynthesis of angiotensin II [Angiotensin Converting Enzyme (ACE) inhibitors], or act as antagonists of angiotensin receptors [Angiotensin Receptor Blockers (ARBs)].

The production of angiotensin II from angiotensin I is inhibited by ACE inhibitors. These agents are known to ne utralise raised peripheral vascular resistance and retention of sodium and water that results from angiotensin II and aldosterone.

10.1.7.2. Uses

These drugs are indicated in all symptomatic and asymptomatic patients with Left Ventricular (LV) dysfunction . ACE inh ibitors (**e.g.,** enalapril, lisinopril or ramipril) have a wide diversity of actions and are considered to be better drugs for the treatment of CHF.

10.1.8. β-Adrenoceptor Antagonists

The β-blockers (most commonly propranolol and other agents having membrane-stabilising activity) were contraindicated in patients with CHF as they were found to precipitate acute decompensation. Yet, it has been found that some of these drugs may be useful in the treatment of diastolic dysfunction or cardiomyopathies in patients req uiring bradycardia and decrease the contraction velocity. It has been found in the current studies that bisoprolol, carvedilol and metoprolol may decrease mortality in patients with class II and III heart failure.

10.1.9. Vasodilators

Vasodilators have an indirect beneficial effect on the heart. Arteriolar dilatation (hydralazine and nitrates) decreases the afterload. Venodilatation (nitrates) decreases preload. These agents are useful adjunctive for the primary treatment. Use of hydralazine or isosorbide on a long -term has been shown to decrease damage to the remodelling heart.

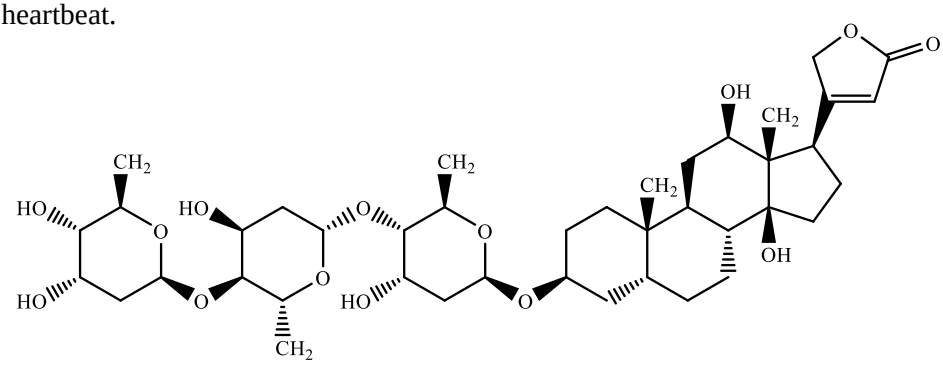
10.1.10. Study of Individual Drugs

The following drugs used in CHF are discussed below:

1) Digoxin,
2) Digitoxin,
3) Nesiritide,
4) Bosentan, and
5) Tezosentan.

10.1.10.1. Digoxin

Digoxin is a purified cardiac glycoside, derived from the leaves of digitalis plant. It works by affecting certain minerals (sodium and potassium) inside heart cells. This reduces strain on the heart and helps it maintain a normal, steady, and strong heartbeat.



Digoxin

Mechanism of Action

Digoxin inhibits the Na^+-K^+-ATPase membrane pump and increases the intracellular Na^+ ions. The sodium calcium exchanger tries to extrude the Na^+ ions and pumps in more Ca^{2+} ions, thereby increasing the intracellular concentrations of Ca^{2+} ions.

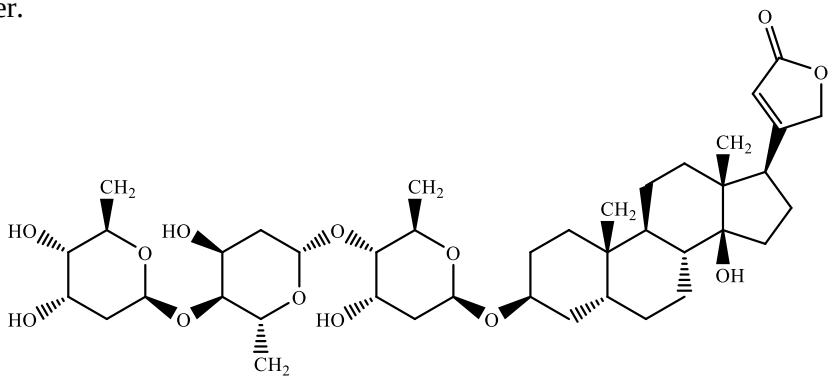
This promotes the activation of contractile proteins (**e.g.,** actin and myosin). Digoxin also acts on the electrical activity of the heart, increases the slope of phase 4 depolarisation, shortens the action po tential duration, and decreases the maximal diastolic potential.

Uses

1) It is used for treating and managing congestive cardia c insufficiency, heart failure, and arrhythmias.
2) It is also used to treat a certain type of irregular heartbeat (chronic atrial fibrillation).

10.1.10.2. Digitoxin

Digitoxin is a cardiac glycoside which is occasionally used in place of digoxin. Its half -life is longer than digoxin, and toxic effects similar to digoxin lasts longer.



Digitoxin

Mechanism of Action

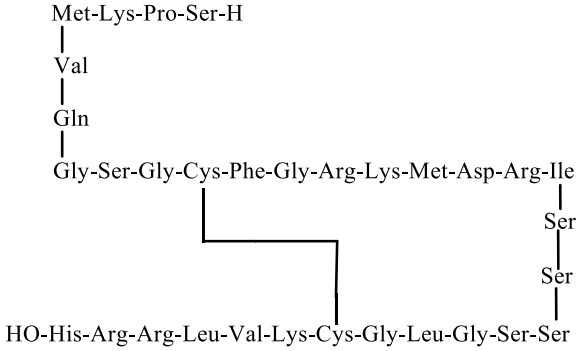
Digitoxin inhibits the Na^+-K^+-ATPase membrane pump and increases the intracellular concentration of Na^+ and Ca^{2+} ions. This i ncreased intracellular concentration of Ca^{2+} ions activate the contractile proteins (**e.g.,** actin and myosin). Digitoxin also acts on the electrical a ctivity of the heart, increases the slope of phase 4 depolarisation, shortens the action po tential duration, and decreases the maximal diastolic potential.

Uses

It is used for treating and managing congestive cardi ac insufficiency, heart failure, and arrhythmias.

10.1.10.3. Nesiritide

Nesiritide is the recombinant form of 32 amino acid human B -type natriuretic peptide. It is obtained by ventricular myocardium.



Nesiritide

Mechanism of Action

Human Brain Natriuretic Peptide (BNP) binds to the particulate guanylate cyclase receptor of vascular smooth muscles and endothelial cells. This increases the intracellular concentration of guanosine 3'5' -cyclic monophosphate (cGMP)

and smooth muscle cell rela xation. The cGMP serves as a second messenger to dilate veins and arteries. Nesiritide relax es isolated human arterial and venous tissue preparations pre -contracted with either endothelin -1 or phenylephrine (α-adrenergic agonist).

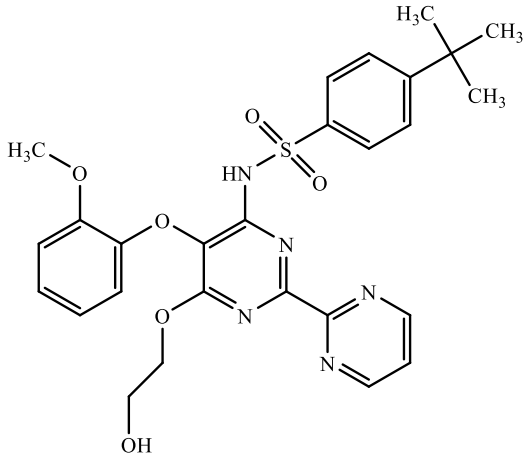
Human studies have shown that nesiritide give rise to dose-dependent reductions in Pulmonary Capillary Wedge Pressure (PCWP) and systemic arterial pressure in patients with heart failure. Animal studies have shown that nesiritide produces no effects on cardiac contractility or on measures of cardiac electrophysiology , such as atrial and ventricular effective refractory times or AV node conduction. Naturally occurring Atrial Natriuretic Peptide (ANP) increases vascular permeability in animals and humans and may reduce intravascular volume.

Uses

It is used for treating acute decompensated congestive heart failure in patients having with dyspnoea at rest or with minimum activity, such as talking, eating , and bathing.

10.1.10.4. Bosentan

Bosentan is a dual endothelin receptor a ntagonist. It is essential ly used for treating Pulmonary Artery Hypertension (PAH).



Bosentan

Mechanism of Action

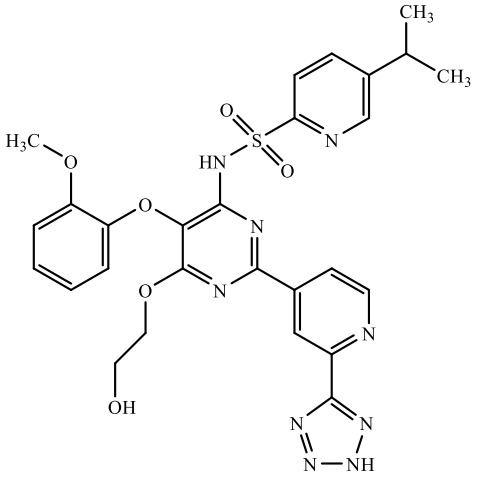
Endothelin-1 (ET -1) is a neurohormone. It produces its effects by binding to ET_A and ET_B receptors in the endothelium and vascular smo oth muscle s. The levels of ET -1 in plasma and lung tissue increase in patients having pulmonary arterial hypertension . Bosentan is a specific and competitive antagonist of endothelin ET_A and ET_B receptor, having a comparatively high affinity for ET_A receptors.

Uses

It is used for treating pulmonary arterial hypertension, for improving exercise ability, and for reducing the rate of clinical worsening in patients with WHO Class III or IV symptoms.

10.1.10.5. Tezosentan

Tezosentan is an antagonist of endothelin ET_A and ET_B receptors. It acts as a vasodilator. It is designed to be used intravenously in patients with acute heart failure.



Tezosentan

Mechanism of Action

Tezosentan relaxes the smooth muscles in blood vessels, and dilates them. This dilation of arterial (resistance) vessels reduces systemic vascular resistance, and ultimately leads to fall in arterial blood pressure. Dilation of venous (capacitance) vessels decreases venous blood pressure.

Uses

It is used for treating congestive heart failure, liver disease, and heart disease.

10.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) When a heart fails to pump blood in a quantity sufficient to fulfil the body requirements, a condition of **Congestive Heart Failure** (**CHF**) occurs, which is also known as a **Heart Failure** (**HF**).
2) **Cardiac glycosides** are derived from the foxglove plant (*Digitalis purpurea*).
3) Cardiac glycosides are categorised into **cardenolides and bufadienolides**.
4) **Cardenolides** (cardiac glycosides derived from plants) have a 5-membered α,β-unsaturated lactone ring.
5) **Bufadienolides** (cardiac glycosides derived from animals) have a 6-membered lactone ring with two conjugated double bonds (generally referred to as α-pyrone).
6) **Digitalis** exerts a positive inotropic effect due to its ability of potentiating the excitation-contraction coupling.
7) **Bipyridine derivatives** (such as amrinone and milrinone) show phosphodiesterase (PDE) inhibiting activity.

8) Bipyridines increase the production of cAMP in the heart and blood vessels, and thus exert a positive inotropic action along with vasodilator activities.
9) **β_1-agonists** have minimal positive chronotropic and arrhythmogenic potential, with dobutamine being the most potential one amongst these agents.
10) β-adrenergic agonists increase the cardiac output while decreasing the ventricular filling pressure and preload.
11) **Diuretics** are commonly used in the management of CHF.
12) **Diuretics** increase the excretion of salt and water. This in turn decreases the ventricular preload and the cardiac size, improves pump function and helps relieve oedema.
13) The production of angiotensin II from angiotensin I is inhibited by **ACE inhibitors.**
14) **Angiotensin antogonists** are indicated in all symptomatic and asymptomatic patients with Left Ventricular (LV) dysfunction.
15) **Vasodilators** have an indirect beneficial effect on the heart. Arteriolar dilatation (hydralazine and nitrates) decreases the afterload. Venodilatation (nitrates) decreases preload.
16) **Digoxin** is a purified cardiac glycoside, derived from the leaves of digitalis plant. It works by affecting certain minerals (sodium and potassium) inside heart cells.
17) **Digitoxin** is a cardiac glycoside which is occasionally used in place of digoxin. Its half-life is longer than digoxin, and toxic effects similar to digoxin lasts longer.
18) **Nesiritide** is the recombinant form of 32 amino acid human B-type natriuretic peptide. It is obtained by ventricular myocardium.
19) **Bosentan** is a dual endothelin receptor antagonist. It is essentially used for treating Pulmonary Artery Hypertension (PAH).
20) **Tezosentan** is an antagonist of endothelin ET_A and ET_B receptors. It acts as a vasodilator.

10.3. EXERCISE

10.3.1. True or False

1) Cardiac glycosides are derived from the foxglove plant.
2) Diuretics decrease the excretion of salt and water.
3) Cardenolides have a 5-membered α,β-unsaturated lactone ring.
4) β-adrenergic agonists decrease the cardiac output while increasing the ventricular filling pressure and preload.
5) Bipyridines decrease the production of cAMP in the heart and blood vessels.

10.3.2. Fill in the Blanks

6) _____ are indicated in all symptomatic and asymptomatic patients with Left Ventricular (LV) dysfunction.

7) _____ is a dual endothelin receptor antagonist.
8) _____ is the recombinant form of 32 amino acid human B -type natriuretic peptide.
9) _____ is a cardiac glycoside which is occasionally used in place of digoxin.
10) The production of angiotensin II from angiotensin I is inhibited by _____.

Answers

1)	True	2)	False	3)	True	4)	False
5)	False	6)	Angiotensin antagonists			7)	Bosentan
8)	Nesiritide	9)	Digitoxin	10)	ACE inhibitors		

10.3.3. Very Short Answer Type Questions

1) Write the causes of CHF.
2) Give the classification of drugs used in CHF.
3) Write a short note on cardiac glycosides.
4) Discuss β-adrenoceptor antagonists.
5) Write a short note on bosentan.

10.3.4. Short Answer Type Questions

1) Give the recent developments in cardiac glycosides.
2) Discuss bipyridines and diuretics.
3) Write a short note on digoxin.
4) Discuss angiotensin antagonists.

10.3.5. Long Answer Type Questions

1) Give the classification of cardiac glycosides with structures.
2) Give the MOA and uses of cardiac glycosides.
3) Discuss digitoxin, nesiritide, and tezosentan.

CHAPTER 11

Drugs Acting on Endocrine System

11.1. DRUGS ACTING ON ENDOCRINE SYSTEM

11.1.1. Introduction

The **endocrine system** consists of glands secreting hormones essential for maintenance of homeostasis throughout the body. **Hormones** are chemical messengers that act to control and coordinate different functions of tissues and organs.

Various body activities like growth and development and metabolism are also regulated by hormones. Each hormone is secreted from a particular gland and is distributed to the target tissues via blood.

Endocrine glands are **ductless glands**, thus release their products directly into the bloodstream, and are carried to their target cells. On the other hand, **exocrine glands** secrete their products (excluding hormones and other chemical messengers) into the ducts, which are then transported to the bloodstream.

The endocrine system comprises of all the endocrine glands of the body. **Pituitary**, **pineal**, **thyroid**, **adrenal**, **pancreas**, **parathyroid**, **thymus**, and **gonads** (testis in males and ovary in females) are the endocrine glands found in humans.

These glands work in conjunction with the nervous system, and therefore this complex of two systems is referred to as the **neuroendocrine system** . This system controls and coordinates various functions of the body, maintaining homeostasis (constancy of body fluids) within the body. The term **neuroendocrinology** defines the study of endocrine system in combination with the nervous system.

11.1.2. Hormones

The word **hormone** has originated from a Greek ***hormaein*** which means **to impel**. Thus, hormone is a substance which is secreted by specialised cells and transported to a distant site to exert its action upon specific tissues. Hormones are synthesised and discharged by endocrine glands directly into the blood circulation without the intervention of a duct , therefore known as **ductless glands**.

If a hormone acts on other endocrine gland or tissue, it just stimulates or inhibits its function.

11.1.3. Major Hormones Secreted by the Endocrine Glands

Table 11.1 enlists the different endocrine glands, the hormones they release, t he target tissues, and the major functions of hormones:

Table 11.1: Functions of Hormones

Endocrine Glands	Hormones Released	Chemical Classes	Target Tissues or Organs	Major Functions of Hormones
Hypothalamus	Hypothalamic releasing and inhibiting hormones	Peptide	Anterior pituitary	Regulate anterior pituitary hormones.
Posterior pituitary	i) Antidiuretic Hormone (ADH or vasopressin)	Peptide	Kidneys	Stimulates water reabsorption by kidneys.
	ii) Oxytocin	Peptide	Uterus and mammary glands	Stimulates uterine muscle contractions and release milk by mammary glands.
Anterior pituitary	i) Thyroid Stimulating Hormone (TSH)	Glycoprotein	Thyroid	Stimulates thyroid gland.
	ii) Adrenocorticotropic Hormone (ACTH)	Peptide	Adrenal cortex	Stimulates adrenal cortex.
	iii) Gonadotropins (FSH, LH)	Glycoprotein	Gonads	Produce egg, sperm, and sex hormones.
	iv) Prolactin (PRL)	Protein	Mammary glands	Produces milk.
	v) Growth Hormone (GH)	Protein	Soft tissue, and bones	Stimulates cell division, protein synthesis, and bone growth.
Thyroid	i) Thyroxine (T_4) and Triiodothyronine (T_3)	Iodinated amino acid	All tissues	Increase metabolic rate, regulate growth and development.
	ii) Calcitonin	Peptide	Bones, kidneys, and intestines	Lowers blood calcium level.
Parathyroid	Parathormone (PTH)	Peptide	Bones, kidneys, and intestines	Raises blood calcium level.
Adrenal cortex	i) Glucocorticoids (cortisol)	Steroid	All tissues	Raise blood glucose level, and stimulate protein breakdown.
	ii) Mineralocorticoids (aldosterone)	Steroid	Kidneys	Re-absorb sodium and excrete potassium.
Adrenal medulla	Epinephrine and norepinephrine	Modified amino acid	Cardiac and other muscles	Released in emergency situations, raise blood glucose level, and bring on “fight or flight’ response.
Pancreas	i) Insulin	Protein	Liver, muscles, and adipose tissues	Lowers blood glucose levels and promotes formation of glycogen.
			Liver, skeletal	

	ii) Glucagon	Peptide	muscles, and adipose tissues	Raises blood glucose and fat levels.
Testes	Androgen (testosterone)	Steroid	Gonads, skin, muscles, and bone	Stimulates male sex characteristics.
Ovaries	Oestrogen and progesterone	Steroid	Gonads, skin, muscles, and bones	Stimulate female sex characteristics.

11.2. STEROIDS

11.2.1. Introduction

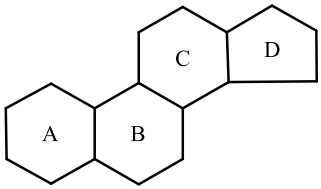
Steroids are structurally related compounds ha ving a common cyclopentanoperhydrophenanthrene nucleus. They are extensively found in plants and animals. The fused tetracyclic steroid nucleus provides the carbon framework for at least four large groups of mammalian hormones, i.e., the oestrogens, androgens, progestins, and corticosteroids.

These are of great medicinal value, and since animal sources yield them only at considerable cost, methods to manufacture them from sapogenins have been developed. Saponin is a glycoside (found in plants) consisting of a sapogenin as the aglycone moiety and a sugar. Sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Steroids are obtained from dioscin (a glycoside), and *Dioscorea floribu nda* (Mexican wild yam root).

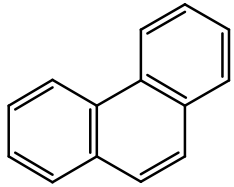
Vitamin D, cardiac glycosides, etc. are some other compounds which can be considered as steroids.

11.2.2. Nomenclature of Steroids

Steroids are made up of four fused rings, i.e., A, B, C, and D. These hydrocarbons are chemically **cyclopentanoperhydrophenanthrenes** and have a **5-membered cyclopentane ring** (D) and **three phenanthrene rings**. A perhydrophenanthrene (rings A, B, and C) is the saturated derivative of phenanthrene.

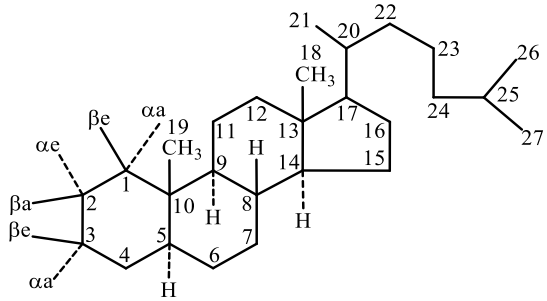


Steroid structure


Phenanthrene

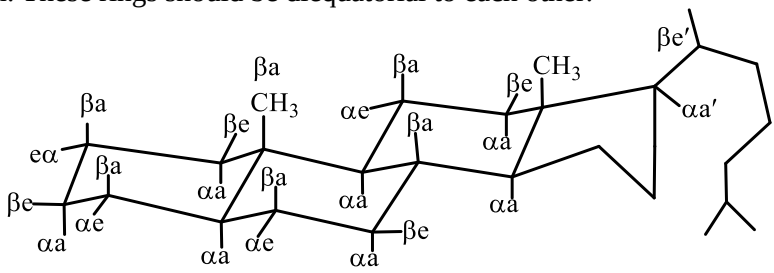
The polycyclic hydrocarbon is termed **5α-cholestane**. It is used for numbering system of a steroid. It is represented with **5α** since the hydrogen atom at position 5 is on the opposite side of the rings from the angular methyl groups at positions

18 and 19 on the β side of the molecule. The term **cholestane** is used for a steroid with 27 carbons including a side chain of 8 carbons at position 17 on the β side. Functional groups on the β side of the molecule are shown by solid lines, while the groups on α side are shown by dotted lines. Side chains at position 17 are always β unless shown by dotted lines or in the steroid nomenclature (**e.g.,** 17α).



5α-Cholestane

Cyclohexane is drawn in a chair conformation. The 3-D conformational image of 5α-cholestane is shown below. Cyclohexane can undergo a flip in conformation, but structures of steroids are rigid as they have at least one *trans* fused ring system. These rings should be diequatorial to each other.



Conformational representation of 5α-cholestane

a = axial	a′ = quasi-axial
e = equatorial	e′ = quasi-equatorial

If the angular methyl groups at 18 and 19 positions are β and are perpendicular to the plane of rings due to axial orientation (and not peripheral to the plane of rings due to equatorial orientation), the conformational orientation of the remaining bonds of a steroid is allocated easily. **For example,** in **5α-cholestane** the C-19 methyl group at position 10 is always β and have an axial orientation; the two bonds at position 1 should be either β-equatorial or α-axial as shown.

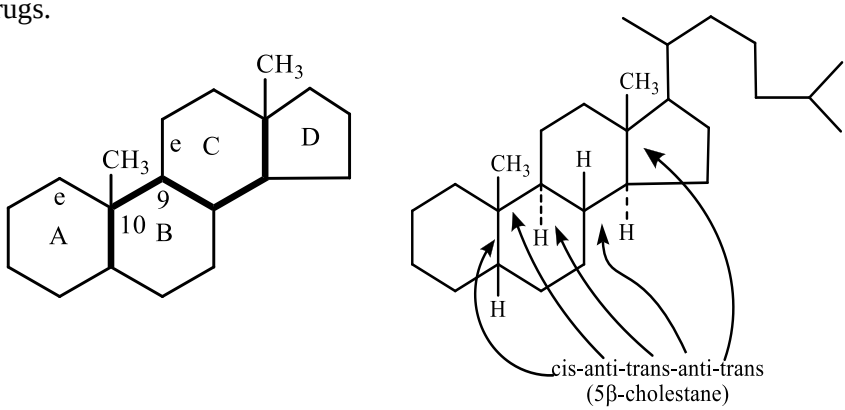
The orientation of remaining bonds on a steroid can be determined if the groups on a cyclohexane ring are positioned on adjacent carbon atoms (vicinal, $-\overset{1}{C}H-\overset{2}{C}H-$) of the ring (i.e., 1,2 to each other) and are *trans* to each other if their relationship is 1,2-diaxial or 1,2-diequatorial; while, they are *cis* if their relationship is 1,2-equatorial-axial.

The steroid chemists refer to the series of carbon-carbon bonds represented with heavy lines as the steroid backbone.

The *cis* or *trans* relationship of th e four rings is expressed in terms of the backbone. The 5α-cholestane has a ***trans*-anti-*trans*-anti-*trans* backbone** indicating that all rings are fused *trans* (diequatorial). It also indicates that the bond equatorial to ring B at position 9 that forms part of ring C, is anti (i.e., *trans*) to the bond equatorial to ring B, at position 10 that forms part of ring A, and so on.

Many stereochemical possibilities exist for the steroid backbone. **For example,** 5β-cholestane has a ***cis*-anti-*trans*-anti-*trans* backbone**.

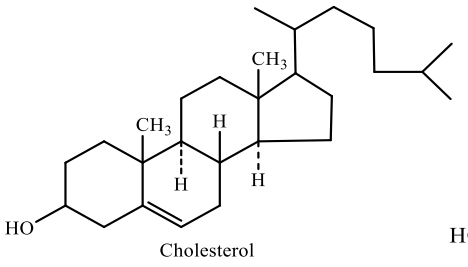
The stereochemistry of rings affects the biological activity of a specified class of drugs.



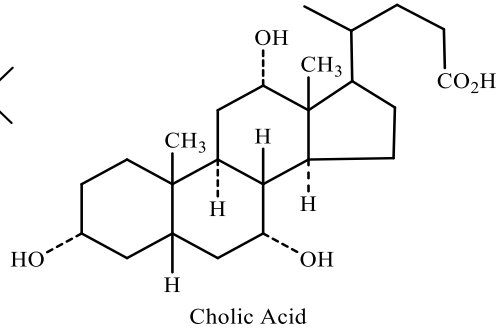
All the biologically active steroids comprise of **cholestane-type backbone**. In almost all the essential steroids, a double bond exists between positions 4 and 5 or 5 and 6. Therefore, there is no *cis* or *trans* relationship between rings A and B.

The **Δ** symbol indicates a C═C bond in a steroid. If the C═C is between 4 and 5 positions, the compound is a **Δ^4-steroid**. If the C═C is between 5 and 10 positions, the compound is a **$\Delta^{5(10)}$ steroid**.

Cholesterol (cholest-5-en-3β-ol) is a Δ^5-steroid or a Δ^5-sterol as it is an unsaturated alcohol.



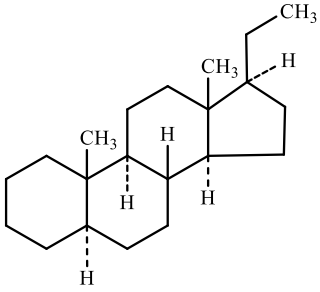
Cholesterol



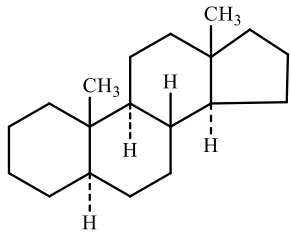
Cholic Acid

No C═C are found in the bile acids that belong to the 5β series. **For example,** cholic acid is an important cholesterol metabolite in human and animals, has 5β-cholestane backbone, and is named **3*α*,7*α*,12*α*-trihydroxy-5β-cholan-24-oic acid**.

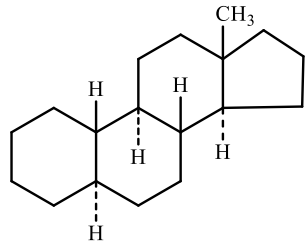
Mostly, cardiac glycosides also belong to the 5β series. The other three steroid hydrocarbons having 5α-cholestane configuration are shown below. Biologically active compounds are the members of **5α-pregnane**, **5α-androstane**, and **5α-estrane** steroid cl asses. Pregnanes a re steroids having 21 carbon atoms, androstanes have 19 carbon atoms, and estranes have 18 carbon atoms with C-19 angular methyl group at C-10 replaced by hydrogen.



5α-Pregnane



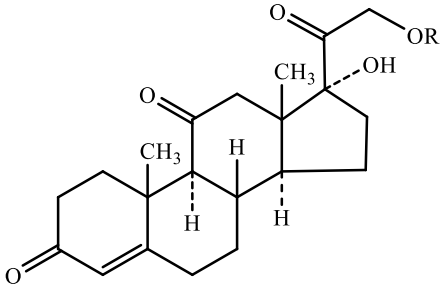
5α-Androstane



5α-Estrane

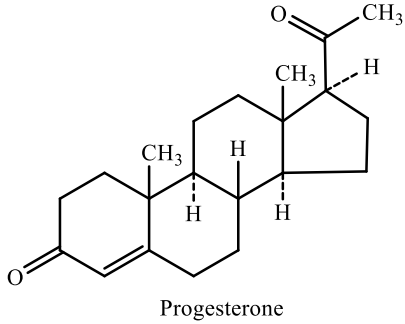
Numbering is done same as in 5α-cholestane.

Adrenocorticoids (adrenal cortex hormones) are pregnanes. **For example** , cortisone is a 17,21 -dihydroxypregn-4-ene-3,11,20-trione, and its acetate ester is named as 17,21-dihydroxypregn-4-ene-3,11,20-trione-21-acetate.



Cortisone: R = H

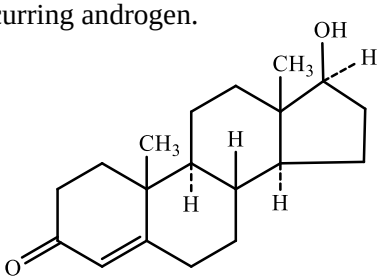
Cortisone acetate: R = $COCH_3$



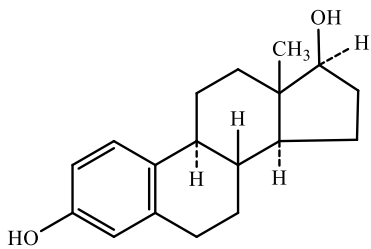
Progesterone

Progesterone (pregn-4-ene-3,20-dione) is a fem ale sex hormone. It is synthesised by the corpus luteum, which is also a pregnane analogue.

Male sex hormones (androgens) depend on the structure of 5α-androstane. Testosterone is 17β-hydroxy-4-androsten-3-one and an important naturally occurring androgen.



Testosterone



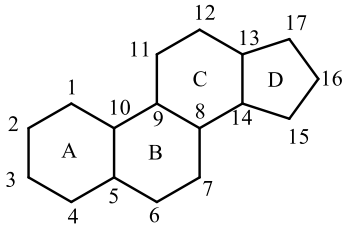
17β-Estradiol

Female sex hormones (oestrogens) are released by the Graafian follicle and are estrane analogues with an aromatic ring. This ring does not have isolated C=C groups. These analogues are named as per the position of the bonds in 17β-estradiol (shown below). Therefore, 17β-estradiol is a typical member of this class of drugs and is named as estra-1,3,5,-triene-3,17β-diol.

Aliphatic side chains at position 17 are expected to be β when using nomenclature of **cholestane** or **pregnane**. The code 17β is not required for naming these compounds. In case a pregnane has 17α chain, the final 'e' in the name of parent steroid hydrocarbon is always dropped when it comes before a vowel, not considering whether a number appears between two parts of the word.

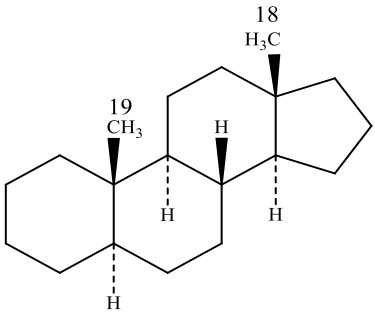
11.2.3. Stereochemistry of Steroids

All steroids have a common tetracyclic nucleus (shown below). The rings A, B, and C are 6-membered, while the ring D is 5-membered. The sequence of numbering is shown below. In the structure below, the carbons 5, 8, 9, 10, 13, and 14 are dissimilar asymmetric centres and there is a possibility of having 2^6 = 64 stereoisomers.

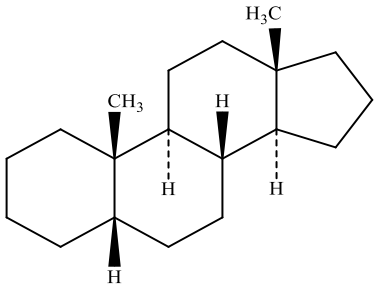


Steroid Skeleton

The situation seems slightly complex and the different functional groups present increases the steric complexity . The rings A/B in the naturally occurring saturated steroid derivatives are *cis* or *trans* fused, the rings B/C are *trans* fused, and the rings C/D are *trans* fused; however in aglycones of cardiac glycosides, the rings C/D are *cis* fused. It has been accepted that a group or hydrogen at a certain position, if shown by continuous thick line or wedge is above the nucleus plane and is indicated as beta (β); while, a group shown by dotted line is below the nucleus plane and is indicated as alpha (α). **Androstane** is a simple parent hydrocarbon with 19 carbons.



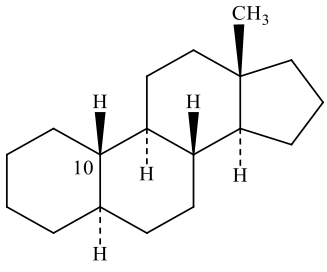
5α-Androstane



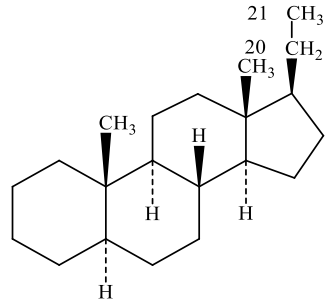
5β-Androstane

In the structures of **5α- and 5β-androstane** (shown above), rings B/C and C/D are *trans* fused, while the rings A/B are *trans* fused in 5 α-androstane and *cis* fused in 5β-androstane. **Testosterone** (male sex hormone) is the main derivative of androstane.

Estrane has 18 carbons. No angular methyl group is attached to its position 10. The 5α-estrane is also called **19-nor-5α-androstane**. The term **nor** indicates that it has one carbon less; and in this case 19-carbon (methyl group at 10) is absent. **Estradiol** (the oestrogenic hormone) is derived from estrane. The pregnane hydrocarbon has 21 carbons and position 17 has a two-carbon side chain. **Progesterone** (the progestational hormone) and the **adrenocortical hormones** are pregnane derivatives.

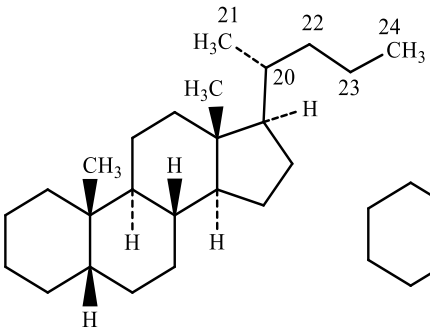


5α-Estrane

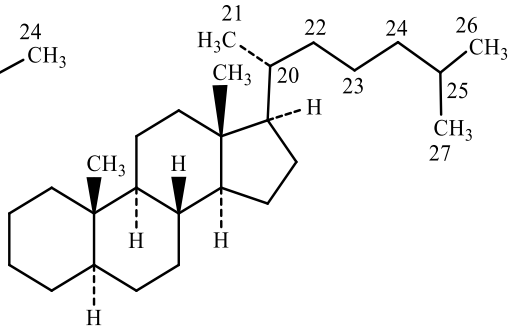


5β-Pregnane

The hydrocarbon **5β-cholane** and **5α-cholestane** are shown below. Cholane has 24 carbons and 5-carbon branched chain at position 17. Cholestane comprises of 27 carbons, and has a 8-carbon branched chain at position 17. The branching and stereochemistry of the side chains at position 20 and 17 β-disposition of attachment are to be noted. The bile acids are structurally related to cholane and cholesterol (derivative of hydrocarbon cholestane).

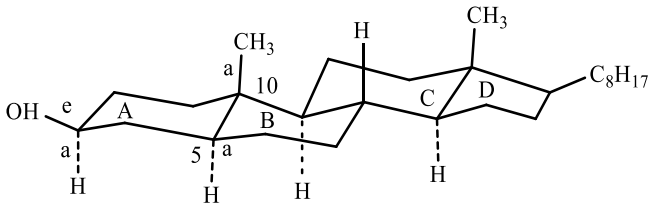


5β-Cholane

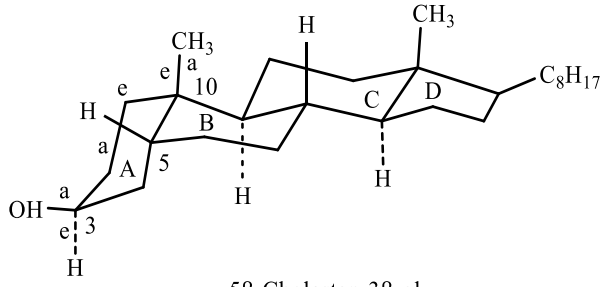


5α-Cholestane

Arrangement of various atoms or groups in space is without regard to arrangements that differ after rotation around one or more single bonds. The conformational perspectives of the steroid nucleus can be indicated as the arrangements of molecular atoms in space that is interconverted by rotations about single bonds. The conformational aspects are explained by examining the shapes of **5α-cholestan-3β-ol** and **5β-cholestan-3β-ol**, in which the rings B and C are locked and both have chair conformations.



5α-Cholestan-3β-ol



5β-Cholestan-3β-ol

The ring A has the flexibility to take boat conformation; however it also has chair conformation. The r ing D is slightly puckered. The conformations of C—H, C—CH_3 and C—OH bonds are observed. A bond may be axial (a), parallel to the axis of symmetry of the ring, or equatorial (e), radiating in the plane of the ring. The 5α- and 5 β-cholestan-3β-ol vary with respect to the ir configurations at position 5. In the former, the rings A/B are *trans* fused and in the latter the rings A/B are *cis* fused.

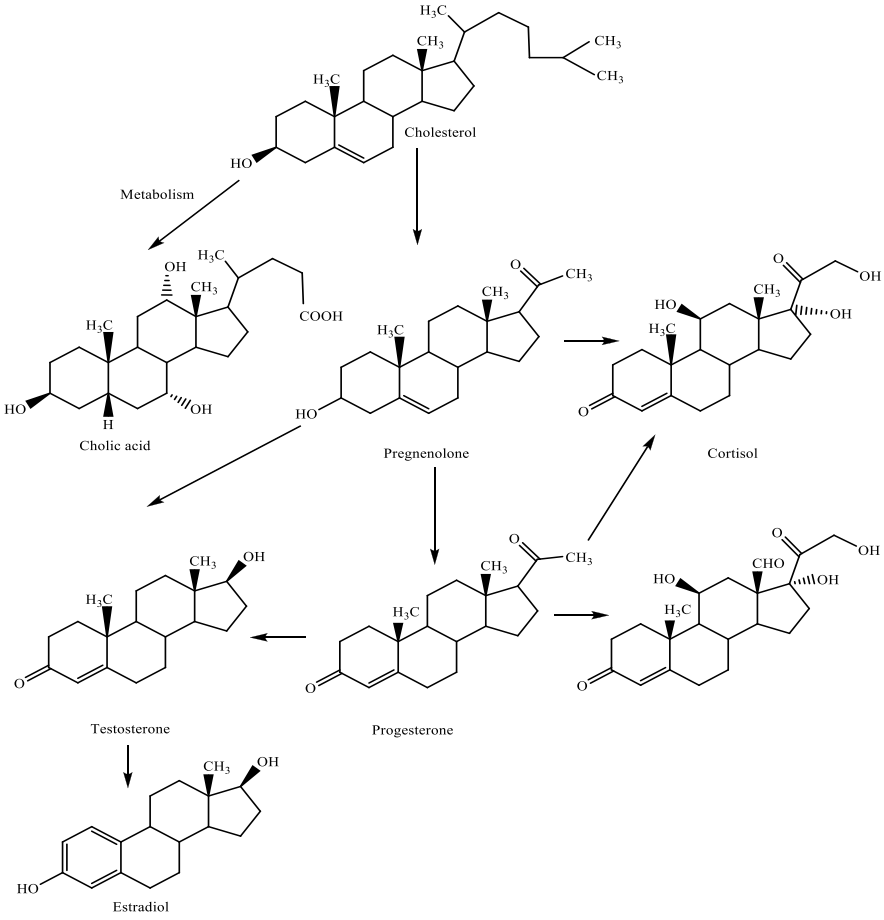
Due to this difference the conformationsget disturbed at different ring A positions, and this can be seen at positions 3, 5, and 10. The hydroxyl groups at position 3 in both have the same configuration (β), but conformationally the 3β-OH are equatorial and 3α-H are axial in 5α-cholestan-3β-ol, while the condition is just the reverse in 5β-cholestan-3β-ol. In 5α-cholestan-3β-ol, 5α-H and 10β-CH_3 are axial in relation torings A and B; whilein 5β-cholestan-3β-ol, 5β-H is axial with respect to ring A and equatorial with respect to ring B; in the same molecule, 10β-CH_3 is equatorial with respect to ring A and axial with respect to ring B. Conformational analysis provides a description of3-D forms of the steroids.

11.2.4. Biosynthesis of Steroids

The steroids secreted by the endocrine glands (such as ovaries, testes and adrenal glands) are released directly in the blood circulation, and are termed **steroidal hormones**. These hormones have many activities and their absence may prove to be fatal. The major classes of steroidal hormones are given below:

1) **Female Sex Hormones :** The major hormones are oestrogens and progesterones.
2) **Male Sex Hormones:** The major hormone is androgens.
3) **Adrenocorticoids:** The major hormones are glucocorticoids and mineralocorticoids.

These steroids are biosynthesised within the body as follows:



It is clea r from the above figure that the inter -conversion occurs between male and female sex hormones. Females have more oestrogens and progesterones, whereas males have more androgens.

For example, females release around 20mg progesterone per day and males have only 2-5mg progesterone.

11.2.5. Metabolism of Steroids

The metabolic conversion of a biologically active compound into an inactive one is termed **inactivation**, which occurs at many stages of hormone action.
Peripheral inactivation (**e.g.**, by liver enzymes) is needed to confirm steady-state levels of plasma hormones as steroids are continuously released into the blood circulation.

When a hormone acts as a chemical signal , its half -life in the bloodstream is limited so that any alteration in secretion rate is reflected by altered plasma concentration (when secretion rates are reduced) . Hormone inactivation also occurs in target tissues, particularly after the hormone has triggered significant biological effects to make sure that the hormone action is terminated.

Liver is the major site of peripheral steroid inactivation and catabolism. However, certain cat abolic activities occur in the kidney s also . Generally, the inactive hormones are eliminated in urinary as conjugated metabolites. Steroids after inactivation are not recycled, but are eliminated from the human body.

This elimination (**e.g.**, as urinary excretion products) needs conversion to hydrophilic compounds for confirming their solubility in biological fluids at high concentrations.

The following reactions are involved depending on the structure of the starting steroid:

1) Reduction of a double bond at C-4 and reduction of an oxo (keto) group at C-3 to yield a secondary alcoholic group.
2) Reduction of an oxo group at C-20 to yield a secondary alcoholic group.
3) Oxidation of a 17β-hydroxyl group.
4) Hydroxylation at various positions of the steroid nucleus (**e.g.,** 7-hydroxylation of 5α-reduced androgens).
5) Sulphate and/or glucuronide conjugation.

11.2.6. Classification

Steroids are classified as follows:

1) **Sex Hormones:** Androgens, oestrogens, and Progesterone.
2) **Glucocorticoids (GCs):** These are a class of steroid hormones which bind to the Glucocorticoid Receptor (GR found in most of the vertebrate animal cells. The name **glucocorticoid** (glucose + cortex + steroid) has been derived from its role in regulating glucose metabolism, its synthesis in the adrenal cortex, and its steroidal structure. **Examples** of glucocorticoids are **hydrocortisone**, **11-dehydrocorticosterone**, and **corticosterone**.
3) **Mineralocorticoids (MCs):** The essential natural mineralocorticoids are **aldosterone** and **desoxycorticosterone**. Their effects on electrolyte and water metabolism and on cardiovascular system are identical; however, aldosterone is 30 times more potent than desoxycorticosterone. **Examples** of mineralocorticoids are **aldeosterone**, **11-deoxycorticosterone**, and **11-deoxy-17-oxycorticosterone**.
4) **Cardiac Glycosides:** Digitoxin and Digoxin.

11.2.7. Mechanism of Action

Regulation of gene expression is the major mechanism of action of steroid hormone. The lipophilic steroid hormones along with the majority of hormone reversibly bound to carrier proteins and a low quantity of free steroids are passed into the bloodstream.

The free steroid enters the cells by passing through the cell membrane. In the cytosol or in the nucleus of the sensitive cells , a high affinity steroid hormone receptor is present **(figure 11.1**).

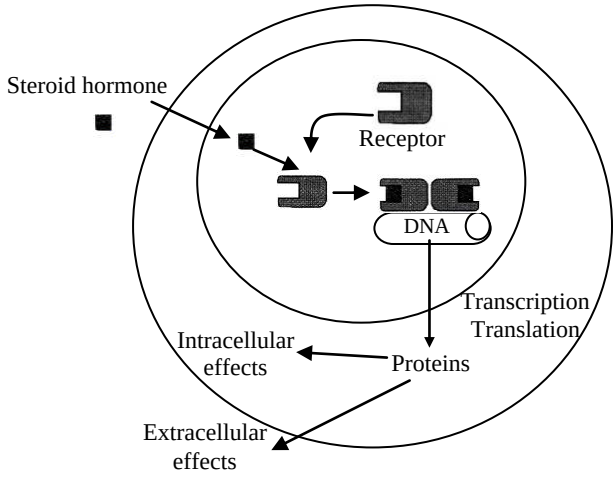


Figure 11.1: Mode of Action of Steroids

The steroid -receptor complex enters the nucleus and brings about a conformational change, i.e., dimerization. This activates the complex and allows it to interact with specific regions on cellular DNA ; these regions are stated as **Hormone Responsive Elements** (HRE).

This interaction starts the transcription process to form mRNA and translation process to form proteins that control the function of cell, growth differentiation, etc. Hence, the process of protein expression is regulated by these hormones, and the proteins perform their normal functions.

11.2.8. Recent Developments

Testosterone is approved by the FDA to be used as replacement therapy in men having low testosterone levels due to disorders of testicles, pituitary gland, or brain that causes hypogonadism. However, the benefits and safety of this use is not yet clear.

According to the FDA, the health care professionals should prescribe **testosterone therapy** to men having low testosterone levels due to some medical conditions and diagnosed by laboratory tests. Patients should be informed by the health care professionals about increased cardiovascular risk associated with testosterone therapy. Immediate medical attention should be given to patients who are taking testosterone and experience symptoms of a heart attack or stroke, like chest pain, breathlessness, weakness in one part or one side of the body, or slurred speech.

The most common female pelvic malignancy is endometrial carcinoma. The uterine endometrial cell proliferation is controlled by oestrogen and progesterone. According to recent studies on biosynthesis and action of oestrogen and progesterone in normal endometrium and their disorder with new aspects of hormonal therapies in patients with endometrial carcinoma involve various methods.

The enzymes responsible for intra-tumoral oestrogen metabolism and biosynthesis are different between human breast and endometrial carcinoma; however, both of them are said to be **oestrogen-dependent malignancies**. The biological importance of Progesterone Receptor (PR) isoforms differ between endometrial and breast carcinomas. According to clinical data on Hormone Replacement Therapy (HRT) and oestrogen-dependent cancer risk also support these findings.

11.3. SEX HORMONES

11.3.1. Introduction

Sex hormones are synthesised by the gonads. These hormones are required for conception, embryonic maturation, and development of primary and secondary sexual characteristics at the time of puberty. The activity of sex hormones on target cells is regulated by the receptors.

Testosterone is a male sex hormone. It is essential for sexual and reproductive development. It belongs to a class of male hormones known as **androgens**; this class is also referred to as **steroids** and **anabolic steroids**. Testosterone is involved in the development of male sex organs before birth and in the development of secondary sex characteristics (deepening of voice, increased penis and testes size, and growth of facial and body hair) at puberty.

The major three types of female sex hormones are given below:

1) **Oestrogen:** It is a female sex hormone formed by the ovaries, adrenal gland, and body fat (in low quantities). It helps in retaining calcium in bones and regulating the balance of High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) cholesterol in the bloodstream. It also helps in maintaining the blood levels of sugar, memory functions, emotional balance, etc.
2) **Progesterone:** It is a female sex hormone formed in high quantities during and after ovulation. It prepares the uterus for implantation of a fertilised egg. It also decreases body fat, helps in relaxation and reduction of anxiety, and stimulates hair growth.
3) **Testosterone:** It is a male sex hormone; however, it is also formed in females in low quantities by the ovaries and adrenal glands. It has an essential role in the health and well-being. It affects libido, mood, energy, and body fat. It also provides protection against osteoporosis.

11.3.2. Classification

The sex hormones are classified as follows:

1) **Androgens:** This group of hormones affect the growth and development of the male reproductive system. Androgens are divided into:
   i) **Naturally Occurring Androgens :** Testosterone, Dihydrotestosterone, Dehydroepiandrosterone, and Androsterone.
   ii) **Synthetic Androgens :** Methyl testosterone, Fluoxymesterone, Testosterone undecanoate, and Mesterolone.

2) **Oestrogens:** These are the main female sex hormone s. Oestrogens are divided into:
   i) **Natural Oestrogens**
      a) Oestradiol (the most common type in women of child bearing age),
      b) Oestrone (the only oestrogen body makes after menopause), and
      c) Oestriol (the main oestrogen during pregnancy).
   ii) **Synthetic Oestrogens**
      a) **Steroidal:** Ethinylestradiol, Mestranol, and Tibolone.
      b) **Non-Steroidal:** Diethylstilbestrol (stilbestrol), Hexestrol, and Dienestrol.

3) **Progesterone:** It is one of the hormones in the bodies which stimulates and regulates many functions. Progesterone is divided into:
   i) **Natural Progestin:** Progesterone
   ii) **Synthetic Progestins**
      a) **Progesterone Derivatives**
         - **Older Compounds:** Medroxyprogesterone acetate (weak androgenic), Megestrol acetate, Dydrogesterone, and Hydroxyprogesterone caproate (long acting injection).
         - **Newer Compound:** Nomegestrol acetate.
      b) **19-Nortestosterone Derivatives**
         - **Older Compounds:** Norethindrone (Norethisterone), Norethynodrel, Ethynodiol diacetate, Lynestrenol (Ethinylestrenol), Allylestrenol, Norgestrel (Gonane), and Levonorgestrel.
         - **Newer Compounds:** Desogestrel, Norgestimate, and Gestodene.

11.3.3. Study of Individual Steroidal Drugs

The following steroids are discussed below:
1) Testosterone,
2) Nandrolone,
3) Progesterone,
4) Oestriol,
5) Oestradiol,
6) Oestrone, and
7) Diethylstilbestrol.

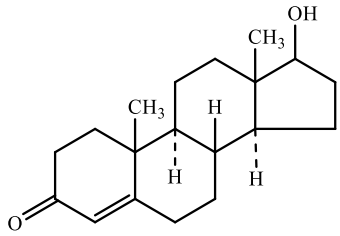
11.3.3.1. Testosterone

Testosterone is a steroid sex hormone present in males as well as in females. It is produced by the Leydig (interstitial) cells of the testes in males, if stimulated by Luteinizing Hormone (LH).

Mechanism of Action

Testosterone acts by the following two mechanisms:
1) It activates the androgen receptor (directly or as DHT), and
2) It converts to estradiol and activates certain oestrogen receptors.

Free testosterone (T) is transported into the c ytoplasm of target tissue cells, and binds to the androgen receptor or reduces to 5α-Dihydrotestosterone (DHT) by the cytoplasmic enzyme 5α-reductase. DHT binds to the same androgen receptor more strongly than the free testosterone; thus, its androgenic potency is 2.5 times more than that of testosterone. The structure of T-receptor or DHT -receptor complex changes, and then they move into the cell nucleus and bind to specific nucleotide sequences of the chromosomal DNA. The binding areas, called **Hormone Response Elements** (HREs), influence transcripti onal activity of certain genes to produce androgen effects.



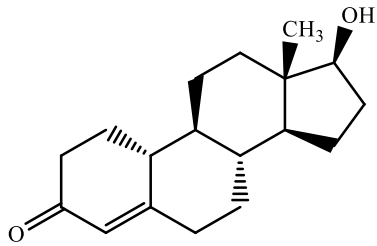
Testosterone

Uses

1) It is used as a replacement of reduced or absent endogenous testosterone.
2) It is used in males for management of congenital or acquired hypogonadism, hypogonadism related to HIV infection, and male climacteric (andropause).
3) It is used in females for palliative treatment of androgen -responsive, advanced, inoperable, metastatis (skeletal) carcinoma of the breast in women after 1-5 years of their menopause.
4) Its esters are used in combination with oestrogens in the manage ment of moderate to simple vasomotor symptoms related with menopause in women not responding suitably to oestrogen therapy.

11.3.3.2. Nandrolone

Nandrolone (or 19 -nortestosterone or 19 -norandrostenolone) is a synthetic Anabolic-Androgenic Steroid (AAS) obtained from testosterone.



Nandrolone

Mechanism of Action

Nandrolone binds to testosterone receptors present in the cytoplasm of cells in androgen responsive organs and tissues. The resultant hormone-receptor complex binds with DNA to enhance transcription of DNA and formation of mRNA. This modifies the protein synthesis.

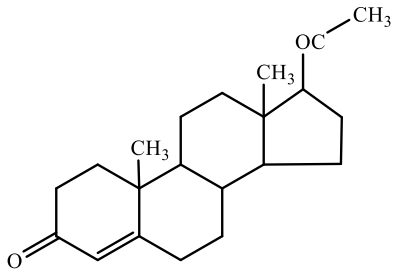
Nandrolone produces anabolic effects on skeleton and skeletal muscles . It also stimulates erythropoiesis by increasing the levels of erythropoietin hormone that is involved in RBC production. Nandrolone maintains positive nitrogen balance. It reverses catabolism induced by corticosteroid and stimulates development of tissues. Due to its androgenic action, it produces inhibitory effects on hormone responsive breast tumours and metastases.

Uses

It is used for the treatment of chronic wasting diseases and for the management of anaemia and osteoporosis in postmenopausal women.

11.3.3.3. Progesterone

Progesterone is the main progestational steroid which is released by the co rpus luteum and placenta. It works on the uterus, mammary glands, and brain.



Progesterone

Mechanism of Action

Progesterone binds to and activates the Progesterone Receptor (PR) expressed in the female reproductive tissue and in the CNS. The resultant complex helps in the signaling of stimuli to prepare the endometrium for pregnancy.

When progesterone binds to PR, it modulates the expression of genes governing the development, differentiation, and proliferation of target tissues. In humans, PR is highly expr essed in the stromal (connective tissue) cells during the secretory phase and during pregnancy.

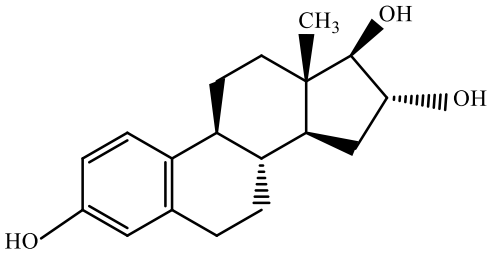
Progesterone may even prevent pregnancy by changing the consistency of cervical mucus, thus making it hostile to sperm penetration. It can also do so by inhibiting the Follicle-Stimulating Hormone (FSH) that causes ovulation.

Uses

1) It is used as a supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment of infertile wome n with progesterone deficiency.
2) It is also used for the treatment of secondary amenorrhea, and for reducing endometrial hyperplasia and risk of endometrial carcinoma in postmenopausal women receiving oestrogen replacement therapy.
3) It is used in abnormal uterine bleeding because of hormonal imbalance in the absence of organic pathology like fibroids or uterine cancer.

11.3.3.4. Oestriol

Oestriol is a hydroxylated metabolite of oestradiol or oestrone having a hydroxyl group at C3-β, 16-α, and 17-βposition. It is the principal urinary oestrogen. It is formed in large quantities by the placenta during pregnancy.



Oestriol

Mechanism of Action

The levels of oestriol are measured to determine a foetus's general health. The adrenal cortex of foetus produces Dehydroepiandrosterone Sulphate (DHEA-S), which is converted to oestriol by the placenta. If a pregnant woman has abnormally low levels of unconjugated oestriol, there might be a problem in child development. Oestriol interacts with the target cell receptor.

When the oestrogen receptor has bound its ligand, it can enter the target cell nucleus, and regulate gene transcription to stimulate mRNA formation. The mRNA and ribosomes interact to produce specific proteins that express the effect of oestriol on the target cell.

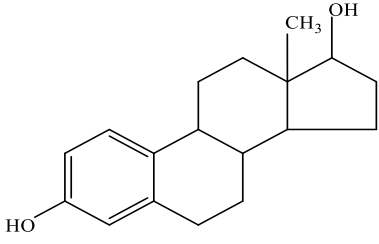
Oestrogens increase the hepatic synthesis of Sex Hormone Binding Globulin (SHBG), Thyroid-Binding Globulin (TBG), and other serum proteins and suppress the release of Follicle-Stimulating Hormone (FSH) from the anterior pituitary.

Uses

It is used for testing the general health of an unborn foetus.

11.3.3.5. Oestradiol

Oestradiol (or E2 or 17β-oestradiol) is a naturally occurring hormone which circulates endogenously in the human body. It is the most potent form of mammalian oestrogenic steroids. It is the major female sex hormone.



Oestradiol

Mechanism of Action

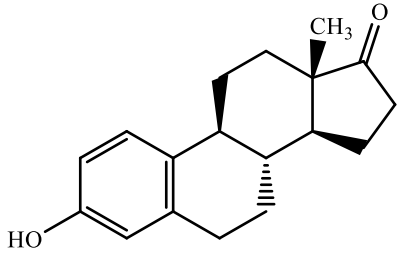
Oestrogen mediates its effects through potent agonism of the Oestrogen Receptor (ER), found in the tissues of breasts, uterus, ovaries, skin, prostate, bone, fat, and brain. Oestradiol binds to the sub-types of ER, i.e., Oestrogen Receptor Alpha (ERα) and Oestrogen Receptor Beta (ERβ). It also acts as a potent agonist of G Protein-coupled Oestrogen Receptor (GPER), which is a major mediator of the cellular effects of oestradiol.

Uses

1) It is used in moderate to high vasomotor symptoms, and vulvar and vagina l atrophy because of menopause.
2) It is also used for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.
3) It is indicated for the prevention of post-menopausal osteoarthritis.
4) It is also given in the treatment of breast cance r in selected women and men with metastatic disease.
5) Advanced androgen-dependent carcinoma of the prostate is also treated with oestradiol.

11.3.3.6. Oestrone

Oestrone is a mammalian oestrogen. It is an aromatis ed C-18 steroid with a 3 -hydroxyl gr oup and a 17 -ketone. It is produced from androstenedione or testosterone by oestradiol *in vivo*. Mainly, it is formed in the ovaries, placenta, and peripheral tissues (mainly adipose tissue) by the conversion of androstenedione.



Oestrone

Mechanism of Action

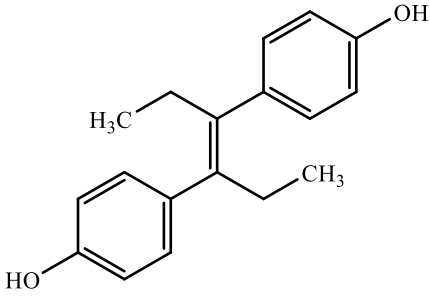
Oestrone enters the cells of responsive tissues (**e.g.,** female organs, breasts, hypothalamus, and pituitary) to interact with the oestrogen receptors. Hormone-bound oestrogen receptors translocate to the nucleus of cells and bind to Oestrogen Response E lements (ERE) of genes. This b inding alters the transcription rate of affected genes. Oestrone also increase the hepatic synthesis of sex hormone binding globulin, thyroid -binding globulin, and other serum proteins. It suppresses the release of follicle -stimulating hormone from anterior pituitary.

Uses

It is used for treating pre-menopausal and post-menopausal symptoms.

11.3.3.7. Diethylstilbestrol

Diethylstilbestrol is a non -steroidal oestrogen. It is used for treating menopausal and post-menopausal disorders.



Diethyl Stilbestrol

Mechanism of Action

Diethylstilbestrol is a synthetic, non -steroidal form of oestrogen. It is a well -known teratogen and carcinogen. It inhibits the hypothalamic -pituitary-gonadal axis, thus blocks the testicular synthesis of testosterone, lowers the plasma levels of testosterone, and induces a chemical castration.

Uses

1) It is used for treating prostate cancer.
2) It was used formerly for preventing miscarriage or premature delivery in pregnant women prone to miscarriage or premature delivery.

11.4. SUMMARY

The details given in the chapter can be summarised as follows:

1) The **endocrine system** consists of glands secreting hormones essential for maintenance of homeostasis throughout the body.
2) **Hormones** are chemical messengers that act to control and coordinate different functions of tissues and organs.
3) **Endocrine glands** are **ductless glands.**
4) Endocrine glands work in conjunction with the nervous system, and therefore this complex of two systems is referred to as the **neuroendocrine system**.
5) **Hormone** is a substance which is secreted by specialised cells and transported to a distant site to exert its action upon specific tissues.
6) **Steroids** are structurally related compounds having a common cyclopentanoperhydrophenanthrene nucleus.
7) All **steroids** have a common tetracyclic nucleus.
8) The steroids secreted by the endocrine glands (such as ovaries, testes and adrenal glands) are released dire ctly in the blood circulation, and are termed **steroidal hormones**.
9) **Liver** is the major site of peripheral steroid inactivation and catabolism.

10) **Testosterone** is approved by the FDA to be used as replacement therapy in men having low testosterone levels due to disorders of testicles, pituitary gland, or brain that causes hypogonadism.
11) The most common female pelvic malignancy is **endometrial carcinoma**.
12) **Sex hormones** are synthesised by the gonads.
13) **Testosterone** is essential for sexual and reproductive development.
14) **Oestrogen** is a female sex hormone formed by the ovaries, adrenal gland, and body fat (in low quantities).
15) **Progesterone** is a female sex hormone formed in high quantities during and after ovulation.
16) **Nandrolone** (or 19-nortestosterone or 19-norandrostenolone) is a synthetic Anabolic-Androgenic Steroid (AAS) obtained from testosterone.
17) **Oestriol** is a hydroxylated metabolite of oestradiol or oestrone having a hydroxyl group at C3-β, 16-α, and 17-βposition.
18) **Oestradiol** (or E2 or 17β-oestradiol) is a naturally occurring hormone which circulates endogenously in the human body.
19) **Oestrone** is a mammalian oestrogen. It is an aromatised C-18 steroid with a 3-hydroxyl group and a 17-ketone.
20) **Diethylstilbestrol** is a non-steroidal oestrogen.

11.5. EXERCISES

11.5.1. True or False

1) The endocrine system consists of glands secreting hormones.
2) Endocrine glands work in conjunction with the circulatory system.
3) Endocrine glands are ductless glands**.**
4) Hormone is a substance which is secreted by specialised cells and transported to a distant site to exert its action upon specific tissues.
5) Hormones are structurally related compounds having a common cyclopentanoperhydrophenanthrene nucleus.
6) All steroids have a different nucleus.
7) The steroids secreted by the endocrine glands are released directly in the blood circulation.
8) Kidney is the major site of peripheral steroid inactivation and catabolism.
9) Testosterone is not approved by the FDA to be used as replacement therapy.

11.5.2. Fill in the Blanks

10) _____ are chemical messengers that act to control and coordinate different functions of tissues and organs.
11) Endocrine glands are _____**.**
12) _____ are structurally related compounds having a common cyclopentanoperhydrophenanthrene nucleus.
13) The most common female pelvic malignancy is _____.

14) _____ is a female sex hormone formed by the ovaries, adrenal gland, and body fat.
15) Progesterone i s a female sex hormone formed in high quantities during and after _____.
16) _____ is a synthetic Anabolic -Androgenic Steroid (AAS) obtained from testosterone.
17) _____ is a non-steroidal oestrogen.
18) _____ is a naturally occurring hormone which circulates endogenously in the human body.
19) _____ is a mammalian oestrogen.

Answers

1) True	2) False	3) True	4) True
5) False	6) False	7) True	8) False
9) False	10) Hormones	11) Ductless glands	12) Steroids
13) Endometrial carcinoma		14) Oestrogen	15) Ovulation
16) Nandrolone	17) Diethlystilbestrol	18) Oestradiol	19) Oestrone

11.5.3. Very Short Answer Type Questions

1) Define hormone.
2) What are ductless glands?
3) What are the parts of endocrine system?
4) Define neuroendocrine system.
5) Define steroids.
6) What are sex hormones?
7) Define testosterone.
8) Define oestrogen.

11.5.4. Short Answer Type Questions

1) Give the biosynthesis of steroids.
2) Classify steroids.
3) What is the mechanism of action of steroids?
4) Give the classification of sex hormones.
5) Write the mechanism of action of testosterone.

11.5.5. Long Answer Type Questions

1) Define steroids and give its nomenclature and stereochemistry.
2) Explain sex hormone in details and write notes on testosterone, nandrolone, progesterone and oestradiol.

CHAPTER 12

Drugs for Erectile Dysfunction

12.1. DRUGS FOR ERECTILE DYSFUNCTION

12.1.1. Introduction

The National Institutes of Health defined Erectile Dysfunction (ED) as the inability to attain or maintain an erection sufficient for satisfactory sexual performance. There is no ideal first-line diagnostic test for ED, and routine screening is also not suggested. Mostly, the patient history and physical examination are enough for diagnosing ED.

Erectile dysfunction is caused due to organic causes (**e.g.,** vascular, neurogenic, hormonal, anatomic, and drug-induced), psychological causes, or both. Sexual erectile response is caused by the interaction between neurotransmitter, biochemical, and vascular smooth muscle responses stimulated by parasympathetic and sympathetic neuronal triggers that integrate physiologic stimuli of the penis with sexual sensitivity and desire. Nitric oxide produced from the endothelial cells after parasympathetic stimuli triggers a molecular cascade which causes smooth muscle relaxation and arterial influx of blood into the corpus cavernosum. This causes compression of venous return that results in erection.

12.1.2. Drugs Used

Phosphodiesterase type 5 (PDE5) inhibitors are the most effective oral drugs used for treating ED. It is considered as first-line therapy. **Sildenafil** is an effective and safe drug for ED related to diabetes mellitus and spinal cord injury, and in men with sexual dysfunction secondary to antidepressant therapy. About 1/3rd of men having ED do not respond to PDE5 inhibitors. These agents are also not effective for treating libido.

Table 12.1: Phosphodiesterase Type 5 Inhibitors for Erectile Dysfunction

Drugs	Standard Dose(*)	Recommended Time Between Dosing and Intercourse	Onset of Action	Duration(†)
Sildenafil (Viagra)	50-100mg	One hour	14-60 minutes	Up to 4 hours
Tadalafil (Cialis)	10-20mg	One to 12 hours	16-45 minutes	Up to 36 hours
Vardenafil (Levitra)	10-20mg	One hour	25 minutes	Up to 4 hours
* – Maximum recommended dose per 24 hours is the maximum strength dose for each drug.				
† – Duration in which successful erections may be achieved after a dose.				

The above mentioned PDE5 inhibitors (**table 12.1**) have relatively the same efficiency; however, there dosing, onset of action, and duration of therapeutic effect are different. PDE5 inhibitors are well-tolerated, and produce mild

transient adverse effects like headache, flushing, dyspepsia, rhinitis, and abnormal vision. The most common side effect is headache that occurs in around 10% of patients. PDE5 inhibitors and nitrates should not be taken at the same time as this may produce a synergistic effect causing a serious or even fatal reduction in blood pressure. These inhibitors are metabolised by the cP450 3A4 and affect the metabolism of protease inhibitors and antifungal drugs.

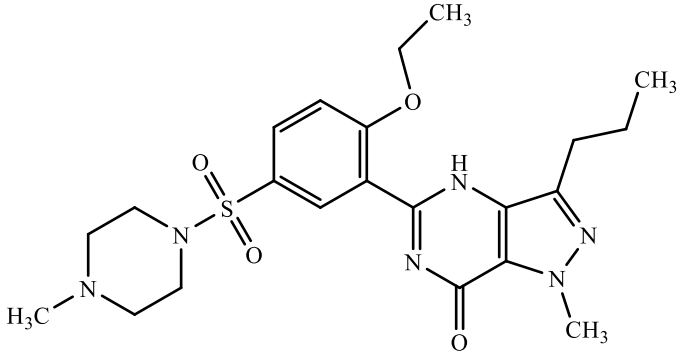
12.1.3. Study of Individual Drugs

The following drugs for erectile dysfunction are discussed below:

1) Sildenafil, and
2) Tadalafil.

12.1.3.1. Sildenafil

Sildenafil is a vasoactive agent. It is used for treating e rectile dysfunction and reducing the symptoms of Pulmonary Arterial Hypertension (PAH).



Sildenafil

Mechanism of Action

Sildenafil is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), which causes cGMP degradation in the corpus cavernosum of penis. Sildenafil does not produce any direct relaxant effec t on isolated human corpus cavernosum. Rather, it enhances the relaxant effect of Nitric Oxide (NO) on this tissue. When sexual stimulation the NO/cGMP pathway is activated, sildenafil causes inhibition of PDE5, thus increasing cGMP levels in corpus cavernosum. Therefore, sexual stimulation is required so that sildenafil can exert its pharmacological effects.

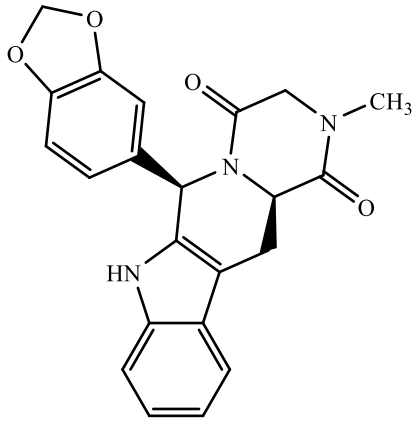
PDE5 is not only present in the corpus cavernosum, but also in the pu lmonary vasculature. Thus, sildenafil increases cGMP in pulmonary vascular smoot h muscle cells and causes relaxation. In cases of pulmonary arterial hypertension, vasodilation of the pulmonary vascular bed and vasodilatation in the systemic circulation (to a lesser extent) occurs.

Uses

It is a phosphodiesterase -5 inhibitor, and is ma inly used in the treatment of erectile dysfunction and pulmonary hypertension.

12.1.3.2. Tadalafil

Tadalafil is an orally administered drug. It is used for treating erectile dysfunction.



Tadalafil

Mechanism of Action

Tadalafil inhibits the cGMP specific PDE5 that causes cGMP degradation in the corpus cavernosum of penis. Relaxation of penile arteries and corpus cavernosal smooth muscle increases the penile blood flow, thus causing penile erection during sexual stimulation. This effect is stimulated by the release of Nitric Oxide (NO) from nerve terminals and endothelial cells, which further stimulates cGMP synthesis in smooth muscle cells. The cGMP relaxes the smooth muscles and increases the blood flow in corpus cavernosum. Inhibition of PDE5 by tadalafil enhances the erectile function by increasing the amount of cGMP.

Uses

1) It is used for treating erectile dysfunction.
2) It raises the blood flow to penis, thus resulting in sexual stimulation.
3) It is also used for treating the signs and symptoms of Benign Prostatic Hyperplasia (BPH).

12.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) The National Institutes of Health defined **Erectile Dysfunction** (ED) as the inability to attain or maintain an erection sufficient for satisfactory sexual performance.
2) Mostly, the patient history and physical examination are enough for **diagnosing ED**.
3) Erectile dysfunction is caused due to organic causes (**e.g.,** vascular, neurogenic, hormonal, anatomic, and drug-induced), psychological causes, or both.
4) **Phosphodiesterase type 5 (PDE5) inhibitors** are the most effective oral drugs used for treating ED.

5) **Sildenafil** is an effective and safe drug for ED related to diabetes mellitus and spinal cord injury, and in men with sexual dysfunction secondary to antidepressant therapy.
6) **Sildenafil** is a vasoactive agent.
7) **Sildenafil** is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), which causes cGMP degradation in the corpus cavernosum of penis.
8) **Tadalafil** is an orally administered drug. It is used for treating erectile dysfunction.

12.3. EXERCISE

12.3.1. True or False

1) The National Institutes of Health defined Erectile Dysfunction (ED) as the inability to attain or maintain an erection sufficient for satisfactory sexual performance.
2) The patient history and physical examination are not enough for diagnosing ED.
3) Erectile dysfunction is caused due to inorganic causes.
4) Phosphodiesterase type 5 (PDE5) inhibitors are the most effective oral drugs used for treating ED.
5) Sildenafil is a vasoactive agent.

12.3.2. Fill in the Blanks

6) Erectile dysfunction is caused due to _____, _____, or both.
7) _____ inhibitors are the most effective oral drugs used for treating ED.
8) _____ is a potent and selective inhibitor of cGMP specific phosphodiestera se type 5 (PDE5).
9) Sildenafil is a _____.
10) _____ is an orally administered drug. It is used for treating erectile dysfunction.

Answers

1) True 2) False 3) False 4) True
5) True 6) organic causes, psychological causes
7) Phosphodiesterase type 5 (PDE5) 8) Sildenafil 9) Vasoactive agent
10) Tadalafil

12.3.3. Very Short Answer Type Questions

1) What is erectile dysfunction?
2) What are the causes of erectile dysfunction?
3) What are drug used in erectile dysfunction?
4) Enlist the uses of sildenafil.
5) Enlist the uses of tadalafil.

12.3.4. Short Answer Type Questions

1) Write a short note on erectile dysfunction.
2) Give mechanism of action of sildenafil.
3) Give mechanism of action of tadalafil.

12.3.5. Long Answer Type Question

1) Briefly explain erectile dysfunction and drugs used in it with their mechanism of action and uses.

CHAPTER 13

Oral Contraceptives

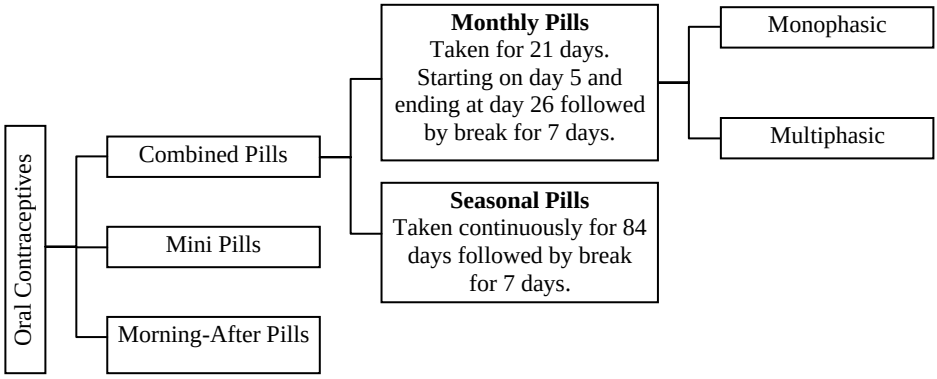
13.1. ORAL CONTRACEPTIVES

13.1.1. Introduction

Oral contraceptives (or **birth-control pills**) are used for preventing pregnancy. The combination of oestrogen and progestin (female sex hormones) is used to prevent ovulation, i.e., relea se of eggs from the ovaries. These hormones also change the uterus lining for inhibiting pregnancy. These hormones prevent the development and change occurring at the mucus lining of the cervix (opening of the uterus), thus prevent the entry of sperms. Oral contraceptives are highly effective methods of birth control. However, t hey do not inhibit the Human Immunodeficiency Virus (HIV, the virus that causes AIDS) and other sexually transmitted diseases.

13.1.2. Classification

The oral contraceptives are classified as follows:



Combined Oral Contraceptives (COCs) are found in either monophasic or multiphasic packaging:

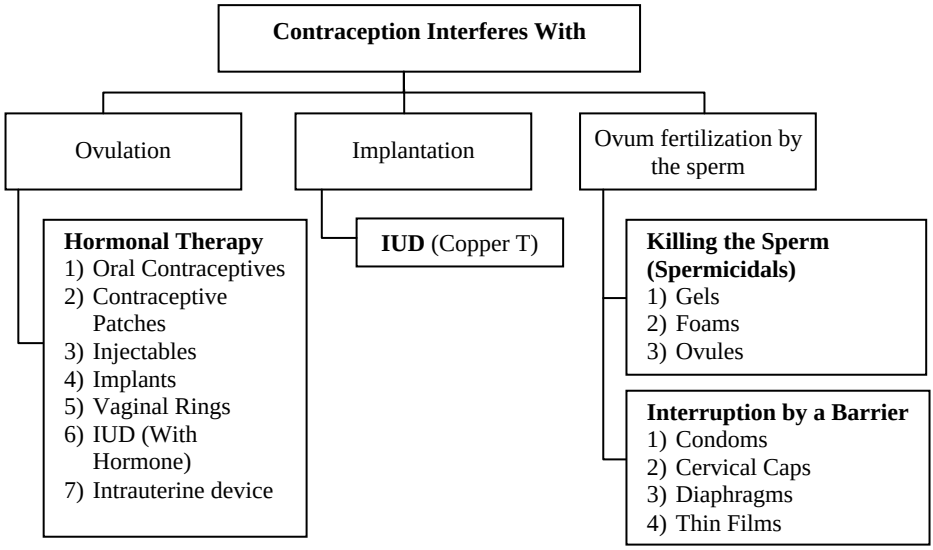
1) **Monophasic Formulations:** Each hormone-containing pill has similar doses of the oestrogen and progestin as other active pills.
2) **Multiphasic Formulations:** The quantity of hormones changes in the active pills.
   i) **Biphasic Formulations:** These have two different combinations of oestrogen and progestin in the packet of pills.
   ii) **Triphasic Formulations:** These have three different combinations. Sometimes, in stepwise progression of the cycle, the progestin content increases. However, some other formulations also change the quantity of oestrogen given during the cycle. One formulation has constant progestin dose, whereas the amount of oestrogen is increased later in the cycle.

13.1.3. Mechanism of Action

Birth contro l pills work as contraceptives and prevent fertil isation. The progestins in all COCs provide most of the contraceptive effect, although the oestrogens also contribute to ovulation suppression. Cycle control is enhanced by oestrogen.

The mechanisms of action for birth control pills that have been repeatedly proven include:

1) Thickening of cervical mucus to pre vent sperm entry into the upper genital tract.
2) Suppression of ovulation by providing negative feedback to the hypothalamic-pituitary system:
   i) Decreased GnRH pulsatility,
   ii) Decreased pituitary responsiveness to GnRH stimulation,
   iii) Suppression of LH and FSH production, and
   iv) Inhibition of mid-cycle LH surge.



13.1.4. Uses

Oral contraceptives have the following uses other than the prevention of unwanted pregnancy:

1) They reduce the rate of dysmenorrhea and menorrhagia.
2) They decrease menstrual irregularities and pre-menstrual tension.
3) They are used for treating inter-menstrual bleeding.
4) They decrease the chances of benign breast disease such as endometriosis , ovarian cancer, and ectopic pregnancy.
5) They decrease the risk of thyroid disease and also rheumatoid arthritis.
6) They are used to inhibit the pregnancy or to control the menstrual cycle.
7) Some brands are used in the treatment of acne or as a “morning after” pill for emergency contraception.

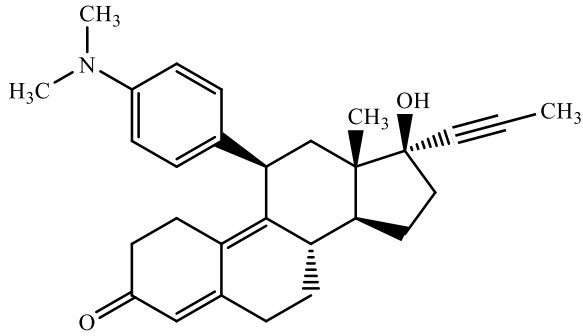
13.1.5. Study of Individual Drugs

The following oral contraceptives are discussed below:

1) Mifepristone,
2) Norgestrel, and
3) Levonorgestrel.

13.1.5.1. Mifepristone

Mifepristone is a progestational and glucoc orticoid hormone antagonist. It inhibits progesterone, and this releases endogenous prostaglandins from the endometrium or decidua. As a result, b leeding occurs in the luteal phase and in early pregnancy.



Mifepristone

Mechanism of Action

Mifepristone exhibits anti-progestational activity as it competitively interacts with progesterone at the progesterone-receptor sites. Several studies have been conducted in mouse, rats, rabbits, and monkeys using oral doses of mifepristone. The results have revealed that it inhibits the activity of endogenous or exogenous progesterone, thus terminating the pregnancy.

In the treatment of Cushing's syndrome, m ifepristone prevents the cortisol from binding to its receptor. It does not reduces cortisol production, but reduces the effects of excess cortisol, such as high blood sugar levels.

Uses

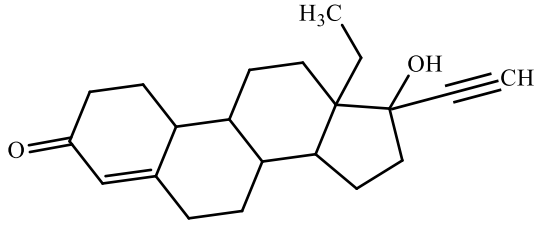
1) It is used for the medical termination of intrauterine pregnancy (49 days' pregnancy).
2) It is also used for controlling hyperglycaemia secondary to hypercortisolism in adults having endogenous Cushing's syndrome, type 2 diabetes mel litus, glucose intolerance , on whom surgery cannot be conducted, or who had unsuccessful surgery.

13.1.5.2. Norgestrel

Norgestrel is a synthetic steroidal progestin. It is used with ethinyl estradiol for oral contraception. It is made up of a rac emic mixture of two stereoisomers, i.e., dextronorgestrel and levonorgestrel; of which only the levorotary enantiomer (levonorgestrel) is biologically active.

Mechanism of Action

Norgestrel binds to the progesterone and estrogen receptors found in the female reproductive tract, mammary gland, hypothalamus, and pituitary gland. After binding, the progestins (like levonorgestrel) delay the release of Gonadotropin Releasing Hormone (GnRH) from hypothalamus and block the pre-ovulatory flow of Luteinizing Hormone (LH). This in turn inhibits ovulation and prevents pregnancy.



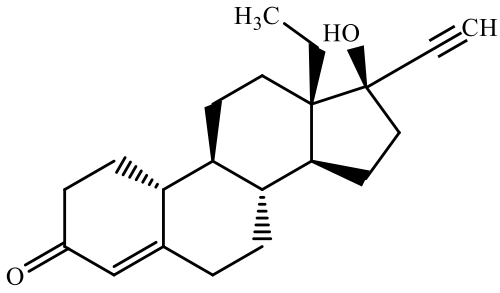
Norgestrel

Uses

It is used with ethinyl estradiol for preventing pregnancy in women who use this product as a contraception method.

13.1.5.3. Levonorgestrel

Levonorgestrel is a synthetic progestational hormone. It s actions are similar to those of progesterone, and its potency is twice as that of its racemic (+)-isomer (norgestrel). It is used for contraception and control menstrual disorders. It is also used for treating endometriosis.



Levonorgestrel

Mechanism of Action

Levonorgestrel binds to the progesterone and estrogen receptors. The female reproductive tract, mammary gland, hypothalamus, and pituitary gland are the target organs for this drug. After binding to the receptor s, pro gestins like levonorgestrel delay the release of Gonadotropin Releasing Hormone (GnRH) from hypothalamus and block the pre-ovulatory flow of Luteinizing Hormone (LH).

Uses

1) It is used for treating menopausal and post-menopausal disorders.
2) It is used either alone or with other hormones as an oral contraceptive.

13.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Oral contraceptives** (or birth-control pills) are used for preventing pregnancy.
2) The combination of **oestrogen** and **progestin** is used to prevent ovulation.
3) **Birth control pills** work as contraceptives and prevent fertilisation.
4) **Combined Oral Contraceptives** (COCs) are found in either monophasic or multiphasic packaging.
5) The **progestins** in all COCs provide most of the contraceptive effec t, although the oestrogens also contribute to ovulation suppression.
6) **Mifepristone** is a progestational and glucocorticoid hormone antagonist. It inhibits progesterone, and this releases endogenous prostaglandins from the endometrium or decidua. As a result, bleeding occurs in the luteal phase and in early pregnancy.
7) **Mifepristone** exhibits **anti-progestational activity** as it competitively interacts with progesterone at the progesterone-receptor sites
8) In the treatment of Cushing's syndrome, **mifepristone** prevents the cortisol from binding to its receptor.
9) **Norgestrel** is a synthetic steroidal progestin. It is used with ethinyl estradiol for oral contraception.
10) **Levonorgestrel** is a synthetic progestational hormone. Its actions are similar to those of progesterone, and its potency is twice as that of its racemic (+) - isomer (norgestrel).

13.3. EXERCISE

13.3.1. True of False

1) Oral contraceptives (or birth-control pills) are used for preventing pregnancy.
2) The combination of oestrogen and progestin is used to prevent ovulation.
3) Combined Oral Contraceptives (COCs) are not found in either monophasic or multiphasic packaging.
4) Mifepristone does not exhibit anti-progestational activity.
5) Mifepristone is a progestational and glucocorticoid hormone antagonist.

13.3.2. Fill in the Blanks

6) The _____ in all COCs provide most of the contraceptive effect.
7) Mifepristone exhibits _____ activity.
8) In the treatment of Cushing's syndrome, mifepristone prevents the cortisol from binding to its receptor.
9) _____ is a synthetic steroidal progestin. I t is used with ethinyl estradiol for oral contraception.
10) _____ is a synthetic progestational hormone.

Answers

1) True	2) True	3) False	4) False
5) True	6) Progestins	7) Anti- progestational	8) Mifeprisotne
9) Norgestrel	10) Levonorgestrel		

13.3.3. Very Short Answer Type Questions

1) What are oral contraceptives?
2) What is monophasic packing?
3) Enlist the uses of oral contraceptives.
4) Give the structure of mifepristone.
5) Write the uses of levonorgestrel.

13.3.4. Short Answer Type Questions

1) Classify oral contraceptive.
2) Give the mechanism of action of oral contraceptive.
3) Write structure and uses of mifepristone.

13.3.5. Long Answer Type Question

1) Explain oral contraceptives in detail and its drugs.

CHAPTER 14

Corticosteroids

14.1. CORTICOSTEROIDS

14.1.1. Introduction

Corticosteroids are the class of steroid hormones that include the hormones synthesised in the adrenal cortex of vertebrates, and the synthetic analogues of these hormones. They have a large ran ge of physiological processes such as stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behaviour. **Examples** of some common natural hormones include corticosterone ($C_{21}H_{30}O_4$), cortisone ($C_{21}H_{28}O_5$, 17-hydroxy-11-ehydrocorticosterone), and aldosterone.

14.1.2. Classification

Two types of corticosteroids are given below:

1) **Glucocorticoids:** They control carbohydrate, fat and protein metabolism. They show anti-inflammatory actions by inhibiting the phospholipid release, reducing the eosinophil action, and some other mechanisms.
2) **Mineralocorticoids:** They regulate the electrolyte and water levels by stimulating sodium retention in the kidneys.

14.1.3. Mechanism of Action

Glucocorticoids bind to cytosolic glucocortic oid receptor s, which activates on binding to ligands . After binding, the resultant receptor-ligand complex translocates itself into the cell nucleus and binds to various Glucocorticoid Response Elements (GRE) , present in the promoter region of the target genes. Then, the DNA bound receptor interacts and the basic transcription factors interact and increase the expression of certain target genes. This process is termed **transactivation** and most of the chief metabolic and cardiovascular side effects of glucocorticoids are mediated by this process.

The opposite mechanism of transactivation is termed **transrepression** in which the ac tivated hormone receptor interacts with certain transcription factors. This interaction prevents the transcription of targeted genes. Glucocorticoids prevent the transcription of any immune gene, including the IL-2 gene.

Glucocorticoids do not differentiate between transactivation and transrepression and influence the ‘wanted’ immune and the ‘unwanted’ genes controlling the metabolic and cardiovascular functions . Recently, research es are being carried out to discover the selectively acting glucocorticoids that would repress only the immune system.

Aldosterone receptors are only found in the tissues of kidney, colon, and urinary bladder. The steroid-receptor complex helps in the synthesis of Na^+-K^+ ATPase, which promotes sodium-potassium exchanges in distal tubular epithelium. Increase in sodium reabsorption is promoted in the colonic epithelium and urinary bladder. The aldosterone-receptor complex acts same as the glucocorticoids.

14.1.4. Uses

Glucocorticoids are used in the treatment of the diseased conditions mentioned in **table 14.1**:

Table 14.1: Therapeutic Uses of Glucocorticoids in Non-Adrenal Disorders

Disorders	Examples
Allergy	Asthma, drug allergy, contact dermatitis, urticaria, allergic rhinitis, serum sickness, and angioneurotic oedema.
Skin diseases	Atopic dermatitis, dermatoses, chronic lichen simplex, pemphigus, mycosis fungoides, xerosis, and seborrheic dermatitis.
Eye diseases	Acute uveitis, allergic conjunctivitis, optic neuritis, and choroiditis.
Haematological disorders	Leukaemia, acquired haemolytic anaemia, autoimmune haemolytic anaemia, acute allergic purpura, idiopathic thrombocytopenic purpura, and multiple myeloma.
Collagen-vascular disorders	Lupus erythematosus, rheumatoid arthritis, polymyositis, and mixed connective tissue syndromes.
Neurological disorders	Cerebral oedema (large doses of dexamethasone) and multiple sclerosis.
Gastrointestinal disorders	Inflammatory bowel disease and non-tropical sprue.
Organ transplants	To prevent and treat graft/transplant rejection.
Pulmonary disorders	Bronchial asthma, prevention of infant respiratory distress syndrome, aspiration pneumonia, and sarcoidosis.
Renal disorders	Nephrotic syndrome.
Thyroid disorders	Malignant exophthalmos and sub-acute thyroiditis.
Bones and joints	Arthritis, bursitis, and tenosynovitis.
Infections	Gram-negative septicaemia.
Miscellaneous	Mountain sickness and hypocalcaemia.

Aldosterone and its synthetic derivatives (**e.g.,** fludrocortisone) are used for treating:

1) Addison's disease,
2) Salt losing congenital adrenal hyperplasia,
3) Hyporeninemic, hypoaldosteronism as in chronic kidney disease due to diabetes mellitus and other causes.
4) Severe postural hypotension from autonomic neuropathy of any etiology, and
5) Hyperaldosteronism.

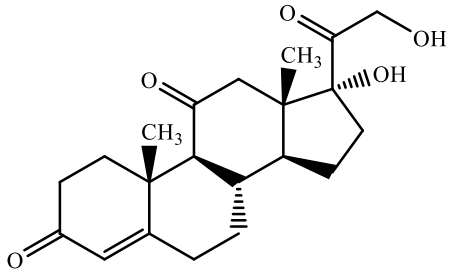
14.1.5. Study of Individual Drugs

The following corticosteroids are discussed below:

1) Cortisone,
2) Hydrocortisone,
3) Prednisolone,
4) Betamethasone, and
5) Dexamethasone.

14.1.5.1. Cortisone

Cortisone is a naturally occurring glucocorticoid. It is used in replacement therapy for adrenal insufficiency. It is also used as an anti -inflammatory agent. It is an inactive compound, and converts in the liver to hydrocortisone (its active metabolite).



Cortisone

Mechanism of Action

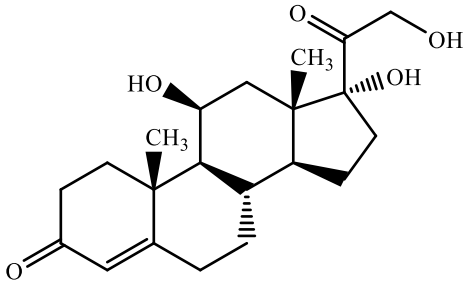
Cortisone is an adrenocortical steroid. It inhibits the accumulation of inflammatory cells at inflammation sites . It also inhibits phagocytosis, synthesis and release of lysosomal enzyme, and release of inflammation mediators.

Uses

Cortisone is used in replacement therapy for adrenal insufficiency and as an anti - inflammatory agent. It is also used in rheumatoid arthritis, severe shock, allergic conditions, and chronic lymphatic leukaemia.

14.1.5.2. Hydrocortisone

Hydrocortisone is a synthetic or semi -synthetic analogue of natural hydrocortisone hormone. It is formed by the adrenal glands and exhibits primary glucocorticoid and minor mineralocorticoid effects.



Hydrocortisone

Mechanism of Action

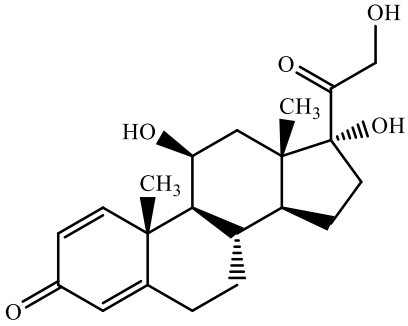
Hydrocortisone binds to the cytosolic glucocorticoid receptor. The resultant receptor-ligand complex translocates into the cell nucleus and binds to Glucocorticoid Response Elements (GRE), present in the promoter region of the target genes. Then, the DNA bound recepto r interacts and the basic transcription factors interact and increase the expression of certain target genes. The anti - inflammatory actions of corticosteroids involve lipocortins and phospholipase A2 inhibitory proteins, which inhibit arachidonic acid and control prostaglandins and leukotrienes biosynthesis.

Uses

1) Its synthetic counterpart is used either as injectable or topically for treating inflammation, allergy, arthritis, lupus, severe psoriasis, ulcerative colitis, collagen diseases, Crohn's disease, asthma, adrenocortical deficiency, shock, and some neoplastic conditions.
2) It is also used for the treatment of adrenal insufficiency and Addison's disease.

14.1.5.3. Prednisolone

Prednisolone is a glucocorticoid having the general properties of corticosteroids. It is the drug of choice in conditions where routine systemic corticosteroid therapy is indicated, except in adrenal deficiency states.



Prednisolone

Mechanism of Action

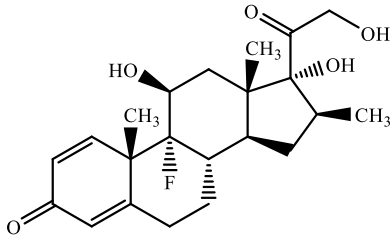
Prednisolone inhibits leukocyte infiltration at the inflammation sites, interferes with inflammation mediators, and suppresses humoral immune responses. It reduces inflammatory reaction by preventing capillary dilatation and permeability of vascular structures. It prevents the accumulation of polymorphonuclear leukocytes and macrophages, and reduces the release of vasoactive kinins. Prednisolone is a glucocorticoid receptor agonist. After binding, a corticoreceptor-ligand complex is formed that translocates itself into the cell nucleus and binds to the Glucocorticoid Response Elements (GRE) present in the promoter region of the target genes. Then, the DNA bound receptor interacts and the basic transcription factors interact and increase the expression of certain target genes, including suppression of IL2 (interleukin 2) expression.

Uses

1) It is used in the treatment of primary or secondary adrenocortical insufficiency (like congenital adrenal hyperplasia and thyroiditis).
2) It is also used in psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, acute gouty arthritis, and epicondylitis.
3) It is also given in systemic lupus erythematosus, pemphigus and acute rheumatic carditis.
4) It can be used for the treatment of leukaemia, lymphomas, thrombocytopenia purpura, and autoimmune haemolytic anaemia.
5) It is also used in the treatment of celiac disease, insulin resistance, ulcerative colitis, and liver disorders.

14.1.5.4. Betamethasone

Betamethasone is a glucocorticoid. It is administered orally, parenterally, by local injection, inhalation, or used topically for treating many disorders in which corticosteroids are used.



Betamethasone

Mechanism of Action

Betamethasone is a glucocorticoid receptor agonist. It binds to GRE and the resultant complex changes the genetic expression. The anti-inflammatory activities of corticosteroids involve lipocortins (phospholipase A2 inhibitory proteins) which inhibit arachidonic acid and control the biosynthesis of prostaglandins and leukotrienes. Corticosteroids decrease the function of lymphatic system, reduce the concentration of immunoglobulin and precipitation of lymphocytopenia, and interfere with antigen-antibody binding. As a result, the immune system is suppressed.

Uses

1) It is used topically in many creams, foams lotions, and ointments for relieving inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
2) It is systemically used in endocrine disorders, rheumatic disorders, collagen diseases, dermatological diseases, allergic states, ophthalmic diseases, respiratory diseases, hematologic disorders, neoplastic diseases, oedematous states, gastrointestinal diseases, tuberculosis, meningitis, and trichinosis.

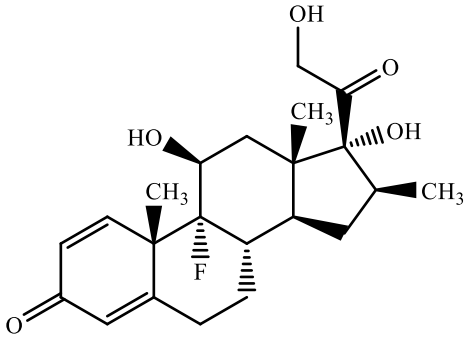
14.1.5.5. Dexamethasone

Dexamethasone is a potent synthetic glucocorticoid. It is used as an anti-inflammatory and immunosuppressant.

Mechanism of Action

Dexamethasone is a glucocorticoid agonist. In free form, it crosses the cell membranes and binds to specific cytoplasmic glucocorticoid receptors. The resultant complex binds to DNA elements (glucocorticoid response elements) and modifies the transcription process and thus protein synthesis. As a result, leukocyte infiltration at the inflammation site is inhibited, the function of inflammatory mediators is restricted, humoral immune responses are suppressed, and oedema or scarosis reduced.

The anti-inflammatory actions of dexamethasone involve lipocortins (phospholipase A_2 inhibitory proteins) which control the biosynthesis of prostaglandins and leukotrienes (potent inflammatory mediators).



Dexamethasone

Uses

1) **Injection:** It i s used for treating endocrine di sorders, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, h aematologic disorders, neoplastic diseases, oedematous states, and cerebral oedema.
2) **Ophthalmic Ointment and Solution:** It is used for treating the steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.
3) **Ophthalmic Solution:** It is used for treating steroid responsive inflammatory situations of the external auditory meatus.
4) **Topical Cream:** It is used in the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.
5) **Oral Aerosol:** It is used for treating bronchial asth ma and associated corticosteroid responsive bronchospastic states intractable to suitable trial of conventional therapy.
6) **Intranasal Aerosol:** It is used for treating allergic or inflammatory nasal conditions, and nasal polyps.

14.2. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Corticosteroids** are the class of steroid hormones that include the hormones synthesised in the adrenal cortex of vertebrates, and the synthetic analogues of these hormones.
2) **Glucocorticoids** control carbohydrate, fat and protein metabolism.
3) **Mineralocorticoids** regulate the electrolyte and water levels by stimulating sodium retention in the kidneys.
4) **Aldosterone** receptors are only found in the tissues of kidney, colon, and urinary bladder.
5) **Cortisone** is a naturally occurring glucocorticoid.
6) **Hydrocortisone** is a synthetic or semi -synthetic analogue of natural hydrocortisone hormone.

7) **Prednisolone** is a glucocorticoid having the general properties of corticosteroids.
8) **Betamethasone** is a glucocorticoid.
9) **Dexamethasone** is a potent synthetic glucocorticoid.

14.3. EXERCISE

14.3.1. True of False

1) Corticosteroids are the class of steroid hormones that include the hormones synthesised in the adrenal cortex of vertebrates, and the synthetic analogues of these hormones.
2) Glucocorticoids do not control carbohydrate, fat and protein metabolism.
3) Mineralocorticoids regulate the electrolyte and water levels by stimulating sodium retention in the kidneys.
4) Aldosterone receptors are only found in the tissues of kidney, colon, and urinary bladder.
5) Cortisone is a synthetic glucocorticoid.

14.3.2. Fill in the Blanks

6) _____ control carbohydrate, fat and protein metabolism.
7) Hydrocortisone is a synthetic or semi-synthetic analogue of _____ hormone.
8) _____ is a glucocorticoid having the general properties of corticosteroids.
9) Betamethasone is a _____.
10) Dexamethasone is a _____ glucocorticoid.

Answers

1)	True	2)	False	3)	True	4)	True
5)	False	6)	Glucocorticoids	7)	Natural hydrocortisone		
8)	Prednisolone	9)	Glucocorticoids	10)	Potent synthetic		

14.3.3. Very Short Answer Type Questions

1) Define corticosteroids.
2) Classify corticosteroids.
3) Give the mechanism of action of cortisone.
4) Give the structure of hydrocortisone.
5) Enlist the uses of hydrocortisone.

14.3.4. Short Answer Type Questions

1) Give the mechanism of action of corticosteroids.
2) Enlist few uses of corticosteroids.
3) Write the mechanism of action and uses of dexamethasone.

14.3.5. Long Answer Type Question

1) Write a note on corticosteroids and give the mechanism of action structure and uses of following drugs:
   i) Cortisone
   ii) Hydrocortisone
   iii) Prednisolone
   iv) Betamethasone
   v) Dexamethasone

CHAPTER 15

Thyroid and Anti-Thyroid Drugs

15.1. THYROID HORMONES

15.1.1. Introduction

Thyroxine (T_4) and **tri-iodothyronine (T_3)** are the two hormones synthesised by thyroid gland. The similar feature of these two thyroid hormones is their high iodine concentration. Both the hormones are tyrosine derivatives.

Thyroxine (T_4) is the **major form of thyroid hormone** in blood. Its half-life is longer than that of T_3. The ratio of T_4 to T_3 released in the blood lies between 14:1 to 20:1. The T_4 converts into T_3 (active and 3-4 times more potent than T_4) in the cells by deiodinases (5'-iodinase enzyme). Further, they undergo decarboxylation and deiodination to form iodothyronamine (T_{1a}) and thyronamine (T_{0a}). All the three isoforms of deiodinases are enzymes containing selenium. Therefore, selenium is required in the diet for production of T_3.

The receptors for thyroid hormones are intracellular DNA-binding proteins, which work as hormone-responsive transcription factor. These receptors are almost conceptually same as the steroid hormone receptors.

15.1.2. Synthesis, Storage, Release, and Metabolism

Thyroid follicle is the functional unit of thyroid gland. It comprises of a cavity lined with a single epithelial cell layer. The cavity lumen is filled with thyroglobulin, which is a large glycoprotein (6,00,000MW) produced in the thyroid gland. Each molecule of this glycoprotein has about 115 tyrosine residues. The synthesis, storage, release, transport, and metabolism of thyroid hormones are discussed below:

1) **Synthesis of Thyroid Hormones (Figure 15.1)**:
   i) An energy-dependent active process allows the follicle cells to take up the circulating iodide. The TSH stimulates this uptake, which also depends on thyroid iodine concentration. The uptake is stimulated in iodine deficient state and is delayed in the presence of high amounts of thyroid iodine.
   ii) The iodide oxidises into iodine atom or free radical (I^0) in the follicle cells by thyroperoxidase enzyme that needs H_2O_2 (oxidising agent).
   iii) Tyrosine residues of thyroglobulin undergo iodination in the presence of thyroperoxidase enzyme and form iodotyrosine and then monoidotyrosine (MIT) and diiodotyrosine (DIT).
   iv) Iodotyrosine molecules undergo coupling to produce T_3 (MIT+DIT) or T_4 (2 molecules of DIT) in the presence of thyroperoxidase enzyme. The iodinated thyroglobulin is released and stored in the follicular lumen.

2) **Release:** The iodinated thyroglobulin is taken back by the follicle cells by endocytosis in the presence of thyrotropin. In the process of endocytosis, the follicle cells engulf some amount of the thyroglobulin colloid, which is acted upon by proteolytic enzymes to release thyroid hormones in the bloodstream. Mostly T_4 hormone is released, about 80% of which is deiodinated into the active T_3 in the peripheral tissues.

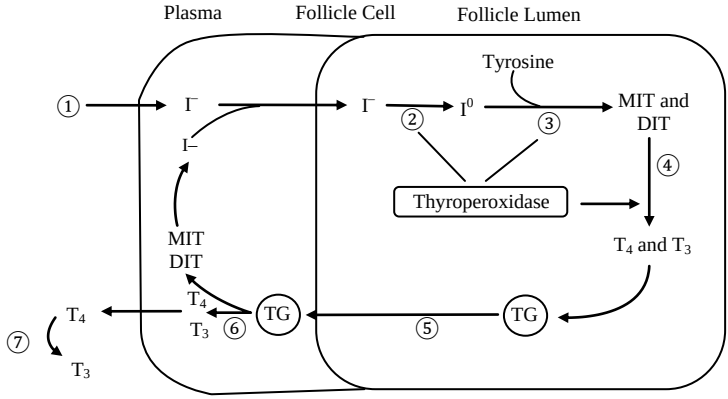


Figure 1 5.1: Thyroid Hormones Synthesis and the Effect of Drugs. 1) Trapping of iodide – inhibited by thiocyanates and perchlorates; stimulated by TSH. 2) Oxidation of iodide – inhibited by anti-thyroid agents, iodide; stimulated by TSH. 3) Iodination of tyrosine into monoiodotyrosine (MIT) and diiodotyrosine (DIT) – inhibited by anti-thyroid agents; stimulated by TSH. 4) Coupling of MIT and DIT for T_3 and T_4 synthesis – inhibited by anti-thyroid agents; stimulated by TSH. 5) Endocytosis of thyroglobulin (TG) into follicle cell – stimulated by TSH. 6) Proteolytic release of T_4 and T_3 – inhibited by iodides; stimulated by TSH. 7) Peripheral deiodination of T_4 into T_3 – inhibited by propylthiouracial and propranolol

3) **Transport:** The T_4 and T_3 hormones are largely bound to plasma proteins, primarily to Thyroxine-Binding Globulin (TBG) and to a lesser extent to thyroxine-binding albumin. The oestrogens, oral contraceptives, clofibrate, neuroleptics, and during pregnancy the concentration of thyroxine-binding proteins is increased; while its concentration is decreased by corticosteroids, androgens, and anabolic steroids. Phenytoin and salicylates displace thyroid hormones from plasma protein binding sites.

4) **Metabolism:** A part of T_4 is deiodinated into active T_3 or reverse T_3 (rT_3). Thyroid hormones are deiodinated in the liver, deaminated, and partially conjugated. Free and conjugated metabolites are excreted in bile and urine.

15.1.3. Mechanism of Action

Thyroid hormones enter the cells via membrane transporter proteins. Out of many recognised plasma membrane transporters, some of them need ATP hydrolysis. The comparative significance of various carrier systems is not yet known and may change between tissues.

The hormone binds to its receptor after entering the nucleus and the hormone-receptor complex acts on the specific DNA sequences in the promoters of responsive genes. The binding of **hormone-receptor complex with DNA modulates gene expression** either by stimulation or inhibition of transcription of specific genes.

Cardiac contractility partially depends on the relative ratio of various myosin proteins in cardiac muscles. Thyroid hormones stimulate the transcription of some myosin genes, while inhi bit the transcription of others. The overall effect alters the ratio towards increased contractility.

15.1.4. Uses

Thyroid hormones have the following uses:

1) **Hypothyroidism (Myxoedema):** They are used for lifetime to treat t his condition.
2) **Hypothyroid Coma:** It is an emergency condition in which the thyroid activity needs to be restored rapidly. L-thyroxine (500 μg) is administered intravenously followed by a daily maintenance dose after a week. Then again, liothyronine (5-10μg) is administered via orogastric tube after every 8 hours, followed by maintenance therapy after recovery. Many patients are administered with hydrocortisone through intravenous route due to related hypoadrenal state.
3) **Cretinism:** The symptoms can be subdued if thyroid therapy is started as soon as the hypothyroid infant is born. L-thyroxine is given in 25μg dose to infants below one year of age, and after every 6 months the dose is increased by 12.5 -25μg followed by maintenance dose of 6 -8μg/kg/day. A higher initial dose of 50μg is given to children above one year of age.
4) **Goitre:** Thyroid hormones are required in simple and nodular goitre with thyroxine deficiency. Carcinoma has to be ruled out. Usual maintenance doses are used.

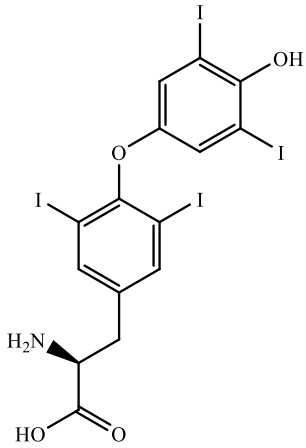
15.1.5. Study of Individual Thyroid Hormone

The following thyroid hormones are discussed below:

1) L- Thyroxine, and
2) L-Thyronine

15.1.5.1. L- Thyroxine

L-Thyroxine (or levothyroxine) is the major hormone produced by the th yroid gland. It is synthesised in the thyroglobulin by the iodination of tyrosine (monoiodotyrosine) an d coupling of iodotyrosine (diiodotyrosine). After synthesis, it is released into the blood from the thyroglobulin by proteolysis. Thyroxine is peripherally deiodinated to form triiodothyronine that produces a broad spectrum stimulatory effects on cell metabolism.



L-Thyroxine

Mechanism of Action

L-Thyroxine acts like the endogenous thyroid hormone, thyroxine (T_4, a tetra -iodinated tyrosine derivative). In liver and kidneys, T_4 converts into its

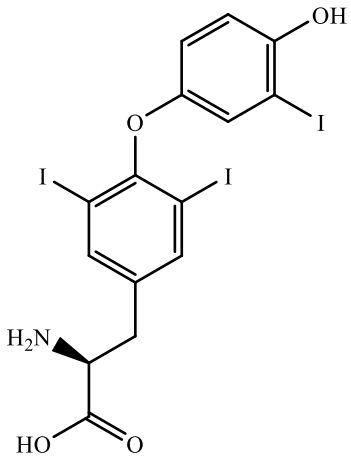
active metabolite, T_3. The solubility of thyroid hormones increases when t hey attach to thyroid hormone binding proteins, thyroxin e-binding globulin, and thyroxine-binding prealbumin (transthyretin). T hen the thyroid hormone receptors t ransport and bind in the cytoplasm and nucleus. In this way, L - thyroxine acts as a rep lacement for natural thyroxine and relieves thyroxine deficiency symptoms.

Uses

It is used either alone or with anti -thyroid drugs for treating hypothyroidism, goitre, chronic lymphocytic thyroiditis, myxoedema, coma, and stupor.

15.1.5.2. L-Thyronine

L-Thyronine (or l iothyronine or T_3) is a thyroidal hormone. It is synthesised by the thyroid gland in a ratio of 4:1 as compared with T_4:T_3. L-Thyronine is the active form of thyroxine, and has tyrosine bound with iodine in its basic chemical structure.



L-Thyronine

Mechanism of Action

L-Thyronine replaces the endogenous thyroid hormone and produces its physiological effects by controlling DNA transcription and protein synthesis. This effect is the result of binding of liothyronine to the thyroid recepto rs attached to DNA. Exogenous liothyronine can produce all the normal effects of T_3 hormone. Hence, it increases energy expenditure, accelerates the rate of cellular oxidation stimulating growth, maturation, and metabolism of body tissues, aids in myelinat ion of nerves and development of synaptic processes in the nervous system, and enhances carbohydrate and protein metabolism.

Uses

1) It is used as a replacement therapy in primary (thyroidal), secondary (pituitary), and tertiary (hypothalamic) congenital or acquired hypothyroidism.
2) It is used as an adjunct to surgery and radioiodine in thyroid cancer.
3) It is used as a diagnostic agent in suppression tests for mild hyperthyroidism or thyroid gland autonomy.

15.2. ANTI-THYROID DRUGS

15.2.1. Introduction

Anti-thyroid drugs are the hormone antagonists that act on thyroid hormones. Carbimazole, methimazole, and propylthiouracil are the examples of common anti-thyroid drugs. Potassium perchlorate is a rarely used anti-thyroid agent.

15.2.2. Classification

The anti-thyroid drugs are classified as follows:

1) **Inhibit Hormone Synthesis (Anti-Thyroid Drugs) :** Propylthiouracil, Methimazole, and Carbimazole.
2) **Inhibit Iodide Trapping (Ionic Inhibitors) :** Thiocyanates (–SCN), Perchlorates ($–ClO_4$), and Nitrates ($–NO_3$).
3) **Inhibit Hormone Release:** Iodine, Iodides of Na and K, and Organic iodide.
4) **Destroy Thyroid Tissue:** Radioactive iodine (^{131}I, ^{125}I, ^{123}I).

15.2.3. Mechanism of Action

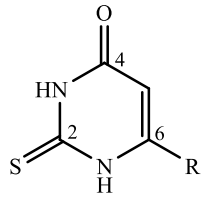
Anti-thyroid drugs act by either inhibiting the release or biosynthesis of thyroid hormones. Iodine and its salts prevent the release of thyroid hormones into the bloodstream; hence, cause rapidly reduces the symptoms of hyperthyroidism. **Thioureylenes** prevent the peroxidase enzymes which catalyse the biosynthesis of thyroid hormones. Thioureylenes do so by inhibiting the introduction of iodide into the tyrosine residues of thyroglobulin and coupling of iodotyrosine residues to produce iodothyronines.

Radioactive iodine isotopes are used for treating hyperthyroidism and thyroid carcinoma which causes localised damage or destroys the thyroid cells without damaging the neighbouring tissues or organs. In sodium ^{131}I, the β-radiation produces this effect as γ-radiation is not absorbed adequately.

15.2.4. Structure-Activity Relationship

Addition of enolic hydroxyl group at C-4 in **propylthiouracil** (PTU) and alkyl group at C-5 and C-6 enhances the inhibitory potency. The thyroid peroxidase inhibitory activity of **methimazole** is more than PTU and it is also longer-acting. However, it does not inhibit the peripheral de-iodination of T_4 because of the presence of methyl group at N-1 position.

Efforts to improve the taste and decrease the release rate of methimazole led to the development of **carbimazole**, which is the prodrug derivative of methimazole and is used in the same dosage.



Thiouracil; R = H
Methylthiouracil; R = CH_3
Propylthiouracil (PTU); R = n-C_3H_7

15.2.5. Uses

Anti-thyroids drugs are used in toxic adenoma or toxic multi-nodular goitre. They are able to induce remission of hyperthyroidism in Graves' disease if taken for a time period of 12 months, or they can bridge the time till spontaneous remission of the u nderlying autoimmune process occurs.It means that the euthyroid state is restored successfully and maintained after the withdrawal of drug in some patients. In autonomous thyroid disease, anti-thyroid drugs do not induce remission, and spontaneous remission is alsoimprobable and not worth waiting for.

Mainly, the anti-thyroid drugs are used for treating toxic adenoma and toxic multi-nodular goitre to achieve a euthyroid state before the patients undergo any other ways of therapy. It is also used for blocking iodine uptake before exposing to radiographic contrast agents in patients at risk of iod ine-induced hyperthyroidism.

Radioiodine treatment or surgery is a def initive cure of hyperthyroidism . Thionamide drugs are used for a long -term in severely ill and multi -morbid patients only who cannot undergo one of these treatments.

Generally, anti-thyroid drugs are used:
1) For treating hyperthyroidism, or
2) As preparative therapy before radiotherapy or surgery.

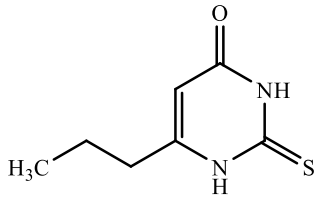
Mostly, the a nti-thyroid drugs are considered the main treatment for patients of Graves' disease, in whom remission (the remaining biochemically euthyroid for one year after cessation of drug) is possible.

15.2.6. Study of Individual Drugs

The following anti-thyroid drugs are discussed below:
1) Propylthiouracil, and
2) Methimazole.

15.2.6.1. Propylthiouracil

Propylthiouracil is a thiourea anti -thyroid agent. It inhibits the peripheral conversion of thyroxine to tri-iodothyronine, and inhibits thyroxine synthesis.



Propylthiouracil

Mechanism of Action

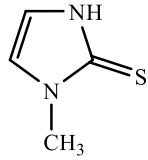
Propylthiouracil inhibits iodide conversion to iodine by binding to thyroid peroxidase. This enzyme converts iodide to iodine (via hydrogen peroxide as a cofactor) and also catalys es the attachment of the resulting iodi de molecule at 3

and/or 5 positions of the phenol rings of tyrosine in thyroglobulin. T_4 and T_3 (the major hormones of the thyroid gland) are released by the degradation of thyroglobulin. Thus, propylthiouracil inhibits the production of new thyroid hormones.

Uses
It is used for treating hyperthyroidism.

15.2.6.2. Methimazole

Methimazole is a thioureylene anti-thyroid agent which inhibits thyroid hormone production by interrupting the integration of iodine into tyrosyl residues of thyroglobulin.



Methimazole

Mechanism of Action
Methimazole inhibits iodide conversion to iodine by binding to thyroid peroxidase. This enzyme converts iodide to iodine (via hydrogen peroxide as a cofactor) and also catalyses the attachment of the resulting iodide molecule at 3 and/or 5 positions of the phenol rings of tyrosine in thyroglobulin. T_4 and T_3 (the major hormones of the thyroid gland) are released by the degradation of thyroglobulin. Thus, methimazole inhibits the production of new thyroid hormones.

Uses
Methimazole is used for treating hyperthyroidism, goitre, psoriasis, and Grave's disease.

15.3. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Thyroxine (T_4)** and **tri-iodothyronine (T_3)** are the two hormones synthesised by thyroid gland.
2) **Thyroxine** (T_4) is the **major form of thyroid hormone** in blood.
3) The **T_4** converts into **T_3** (active and 3-4 times more potent than T_4) in the cells by **deiodinases** (5'-iodinase enzyme).
4) The **receptors** for **thyroid hormones** are intracellular DNA-binding proteins, which work as hormone-responsive transcription factor.
5) **Thyroid follicle** is the functional unit of thyroid gland.
6) **L-Thyroxine** (or levothyroxine) is the major hormone produced by the thyroid gland.
7) **L-Thyroxine** is synthesised in the thyroglobulin by the iodination of tyrosine (monoiodotyrosine) and coupling of iodotyrosine (diiodotyrosine).

8) **L-Thyronine** (or liothyronine or T_3) is a thyroidal hormone.
9) **L-Thyronine** is synthesised by the thyroid gland in a ratio of 4:1 as compared with T_4:T_3.
10) **Anti-thyroid drugs** are the hormone antagonists that act on thyro id hormones.
11) **Propylthiouracil** is a thiourea anti-thyroid agent.
12) **Methimazole** is a thioureylene anti -thyroid agent which inhibits thyroid hormone production by interrupting the integration of iodine into tyrosyl residues of thyroglobulin.

15.4. EXERCISES

15.4.1. True or False

1) Thyroxine and tri-iodothyronine are the two hormones synthesised by thyroid gland.
2) Thyronine is the major form of thyroid hormone in blood.
3) The T_3 converts into T_4 in the cells by deiodinases.
4) Thyroid follicle is the functional unit of thyroid gland.
5) L-Thyroxine is the major hormone produced by the thyroid gland.

15.4.2. Fill in the Blanks

6) _____ is synthesised in the thyroglobulin.
7) _____ is a thyroidal hormone.
8) _____ is synthesised by the thyroid gland in a ratio of 4:1 as compared with T_4:T_3.
9) _____ is a thiourea anti-thyroid agent.
10) _____ is a thioureylene anti-thyroid agent.

Answers

1) True	2) False	3) False	4) True
5) True	6) L-thyroxine	7) L-thyronine	8) L-thyronine
9) Proplythiouracil	10) Methimazole		

15.4.3. Very Short Answer Type Questions

1) What are the hormones synthesised by the thyroid glands?
2) Enlist some uses of thyroid hormones.
3) Give the structure of L-thyroxine.
4) Give classification of anti-thyroid drugs.
5) Give the mechanism of proplythiouracil.

15.4.4. Short Answer Type Questions

1) Give the synthesis of thyroid hormones.
2) Write the mechanism of action of L-thyronine.
3) Write a short note on anti-thyroid drugs.

15.4.5. Long Answer Type Questions

1) Briefly explain thyroid hormones with its hormones.
2) Explain anti-thyroids drugs in detail.

CHAPTER 16

Antidiabetic Agents

16.1. ANTIDIABETIC AGENTS

16.1.1. Introduction

Diabetes mellitus is a group of metabolic diseases in which an individual has high blood sugar level because the body either does not produce insulin in sufficient amount , or the body cells do not respond to the in sulin formed. Polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) are some typical symptoms caused by high blood sugar.

Diabetes may be of the following two types:

1) **Diabetes Mellitus Type 1:** It is caused due to the lack of insulin, thus insulin should be injected to treat this condition.
2) **Diabetes Mellitus Type 2:** It is caused due to insulin resistance by cells. It is the most common type of diabetes and can be treated using:
   i) Agents increasing insulin secretion by the pancreas,
   ii) Agents increasing the sensitivity of target organs to insulin, and
   iii) Agents decreasing the rate at which glucose is absorbed from the GIT.

Anti-diabetic agents are used for treating diabetes mellitus by decreasing the blood glucose levels. Some of these drugs are administered orally and termed **oral h ypoglycaemic** or **oral anti -hyperglycaemic agents** ; however, insulin, exenatide, and pramlinti de are the only anti-diabetic drugs that are injected. Different classes of anti -diabetic drugs exist, and they are selected based on the nature of diabetes, individual's age and situation, and other factors.

16.1.2. Insulin

Paul Langerhans (a German medical student) in **1869** studied that the pancreas has two different groups of cells, i.e., the **acimer cells** that secrete digestive enzymes, and **islets** (cells clustered in islands) that serve a second function. **Banting**, **Macleod**, **Bert**, and **Collip** isolated insulin from bovine pancreas and used it for treating diabetes mellitus.

Insulin is a hormone produced in pancreas and permits the body to utilise sugar (glucose) from carbohydrates in the food. Insulin restricts the blood sugar level s from getting too high (hyperglycaemia) or too low (hypoglycaemia). Insulin occurs as a white or almost white coloured crystalline powder. It is faintly soluble in water; soluble in dilute solution of mineral acids and with degradation in solutions of alkali hydroxide; and almost insoluble in alcohol, chloroform, and ether.

16.1.2.1. Synthesis

Significant quantity of insulin is synthesised in the pancreatic beta cells. The insulin mRNA is translated as a single chain precursor known as **pre-pro-insulin**, and removal of its signal peptide during insertion into the endoplasmic reticulum produces **pro-insulin**.

Pro-insulin contains three domains, i.e., an **amino-terminal B chain**, a **carboxy-terminal A chain** , and a **C peptide** (connecting peptide in the middle). Pro - insulin, in the endoplasmic reticulum, is exposed to some specific endopeptidases that excise the C peptide and generates the mature form of insulin. Insulin and free C peptide are packaged in the Golgi into secretory granules accumulating collect in the cytoplasm.

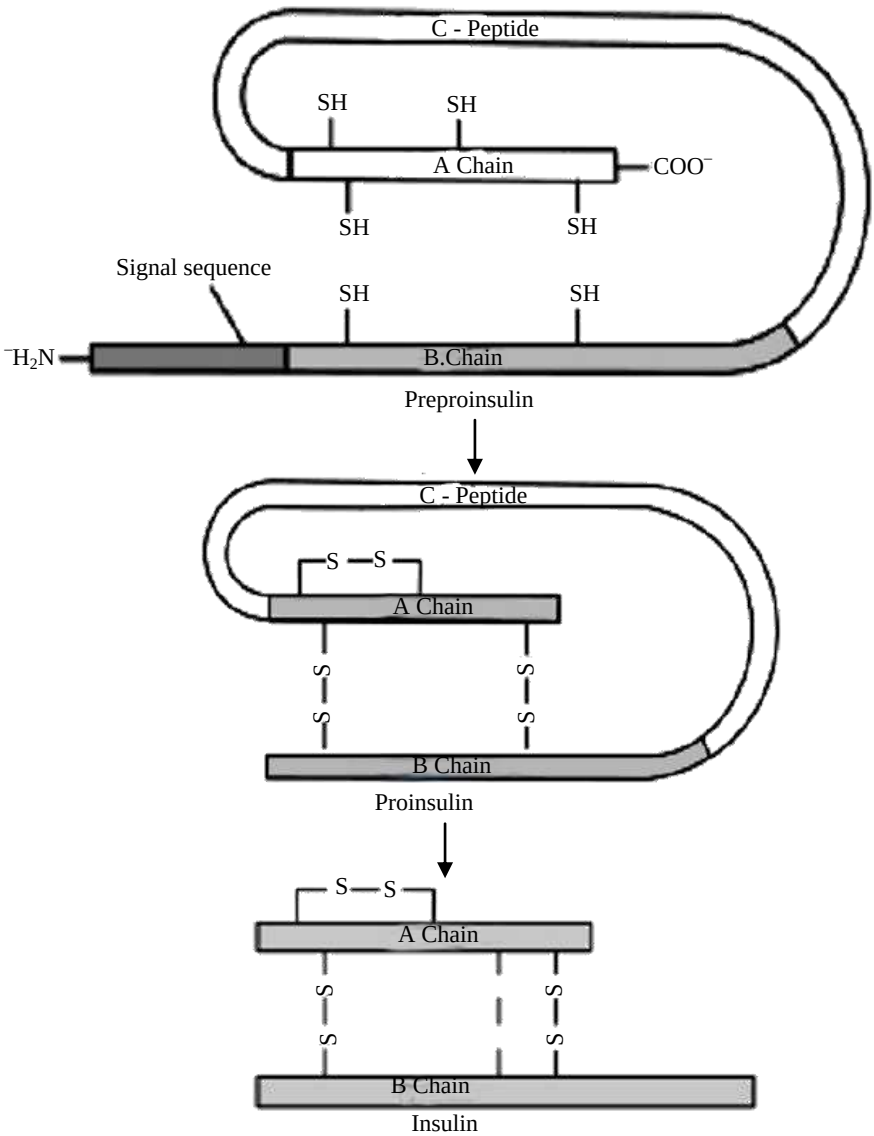


Figure 16.1: Biosynthesis of Insulin

Insulin is secrete d from the pancreatic β-cells by exocytosis when these cells are stimulated. After its release, the insulin diffuses into islet capillary blood. C peptide is also secreted into bloodstream; however it is not biologically active.

16.1.2.2. Mechanism of Action

Insulin produces its action throughout specific insulin receptors present on cell membranes. Insulin binds to these receptors with high specificity and affinity. The resultant insulin-receptor complex enters the cell and releases insulin.

The receptors inversely vary with the plasma insulin concentrations. When insulin concentration is high, these receptors are down-regulated (number reduced), whereas in the presence of low insulin concentrations, these receptors are up-regulated (numbers increase). This leads to reduced and increased responsiveness to insulin, respectively.

Apart from receptor numbers, reduced affinity of these receptors for insulin may also contribute to insulin resistance. Thus in Type II diabetes, reduction in body weight can restore responsiveness to endogenous insulin by up-regulation and increased affinity for insulin by these receptors.

The insulin receptor contains an extracellular α sub-unit (recognition site) and a β sub-unit, spanning the cell membrane, and containing tyrosine kinase that constitutes the second messenger system, which through a complex series of phosphorylation leads to glucose transporter protein activation and entry of glucose into the cell.

Internalisation of insulin receptor units inside the cell may help action of insulin or result in lysosomal degradation of these receptors.

16.1.2.3. Uses

Insulin has the following uses:

1) It is used for controlling diabetes mellitus (uncontrollable by diet alone) or for treating insulin dependent diabetes mellitus.
2) It is used for regulating carbohydrate metabolism.
3) It is used for treating hyperkalemia.
4) It is used for treating severe ketoacidosis or diabetic coma.

16.1.2.4. Insulin Preparations

Some common insulin preparations are given in the **table 1**:

Table 16.1: Insulin Preparations, Onset of Action, Peak Time, and Duration of Action

Preparations		Onset of Action	Peak Time	Effective Duration of Action	Comme
ric Names	Trade Names				
Aspart	NovoLog	5-10 minutes	1-3 hours	3-5 hours	Eat within 5-10 minutes c
Lispro	Humalog	< 15 minutes	$\frac{1}{2}-1\frac{1}{2}$ hours	2-4 hours	Eat within 5-10 minutes c
Glulisine	Apidra	< 15 minutes	$\frac{1}{2}-1\frac{1}{2}$ hours	$1-2\frac{1}{2}$ hours	Take from 15 ″ before to meal. May only be mixed
r	Humulin R Novolin R	$\frac{1}{2}-1$ hours	2-3 hours	3-6 hours	Humulin R is also made i The onset is slower than U is up to 24 hrs.
	Humulin N Novolin N	2-4 hours	4-10 hours	10-16 hours	Roll vigorously to mix. G daily.
Glargine	Lantus	1 hour	No peak	24 hours	Do not put in the same sy other insulin. Usually giv
r	Levemir	1-2 hours	No peak	6-23 hours, depending on dose	Do not put in the same sy insulin. May be given onc
PH+ 30% r	Humulin 70/30 Novolin 70/30	$\frac{1}{2}-1$ hour	There are 2 peaks: 2-3 hours and 4-10 hours	10-16 hours	Roll vigorously to mix. D same syringe with any oth
spart ine + 30%	Novolog Mix 70/30	5-10 minutes	There are 2 peaks: 1-3 hours and 4-10 hours	10-16 hours	Eat within 5-10 minutes c Roll vigorously to mix. D same syringe with any oth
spro ine + 50%	Humalog 50/50	< 15 minutes	There are 2 peaks: $\frac{1}{2}-1\frac{1}{2}$ hours and 4-10 hours	10-16 hours	Eat within 5-10 minutes c Roll vigorously to mix. D same syringe with any oth
spro ine + 25%	Humalog® Mix 75/25	< 15 minutes	There are 2 peaks: $\frac{1}{2}-1\frac{1}{2}$ hours and 4-10 hours	10-16 hours	Eat within 5-10 minutes c Roll vigorously to mix. D same syringe with any oth

n may vary depending on the insulin dose, physical activity, site of injection, and temperature.

16.2. ORAL HYPOGLYCAEMIC DRUGS

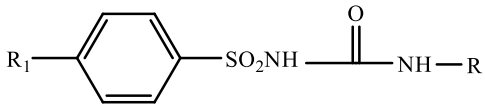
16.2.1. Introduction

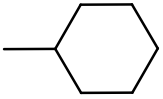
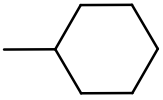
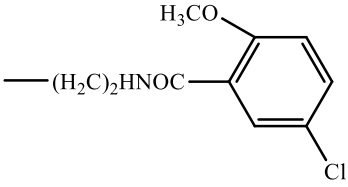
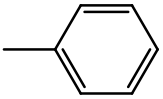
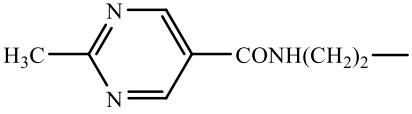
Hypoglycaemic agents are used in the treatment of diabetes mellitus by lowering the blood glucose levels. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all the other hypoglycaemic agents are administered orally and are therefore known as **oral hypoglycaemic agents** or **oral anti-hyperglycaemic agents**.

16.2.2. Classification

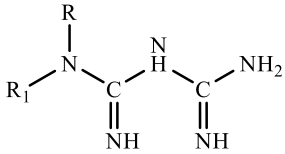
Hypoglycaemic agents are classified as follows:

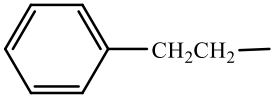
1) **Sulphonylureas:**



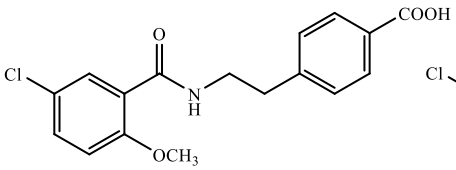
Drugs	R	R_1
Carbutamide	$-CH_2CH_2CH_2CH_3$	$-NH_2$
Tolbutamide	$-CH_2CH_2CH_2CH_3$	$-CH_3$
Chlorpropamide	$-CH_2CH_2CH_3$	$-Cl$
Acetohexamide		$-COCH_3$
Glibenclamide		
Glipizide		

2) **Biguanides**

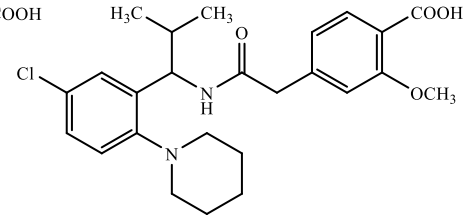


Drugs	R	R_1
Phenformin		H
Metformin	$-CH_3$	$-CH_3$
Buformin	$-CH_3CH_2CH_2CH_2$	H

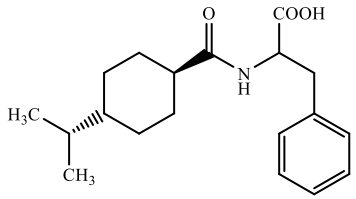
3) **Substituted Benzoic Acid Derivatives (Meglitinides)**



Meglitinide

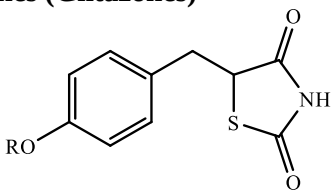


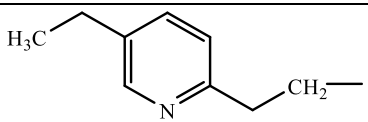
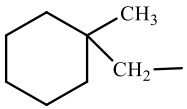
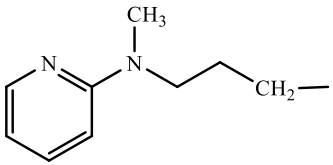
Repaglinide



Nateglinide

4) **Thiazolidindiones (Glitazones)**



Drugs	R
Pioglitazone	
Ciglitazone	
Rosiglitazone	

5) **Miscellaneous:** Linogliride and Palmoxirate sodium

16.2.3. Sulphonylureas

Janbon and colleagues in **1942** accidentally observed that some sulphonamides initiated hyperglycaemia in the experimental animals. **Carbutamide** was the first sulphonylurea that was clinically used for treating the diabetes. Generally, sulphonylureas are grouped into two generations or groups:

1) **First Generation:** Tolbutamide
2) **Second Generation:** Glibenclamide, Glimepiride, Glipizide, Gliclazide, and Gliquidone.

All the sulphonylureas have similar actions, i.e., t hey decrease blood glucose levels in type 2 diabetes.

16.2.3.1. Mechanism of Action

Sulphonylureas stimulate the secretion of insulin from the β-cells of pancreas without entering the cell (**figure 16.2**). This occurs when glucose is not present. Intact pancreatic β-cells are required for the hypoglycaemic action of sulphonylureas.

The β-cells have sulphonylurea receptors linked to an AT Pase-sensitive K^+ ion channel. As given in **figure 16.2**, inhibition of K^+ ion efflux causes depolarisation of β-cell membrane and opens the voltage-dependent Ca^{++} ion channels.

The kinases involved in exocytosis of secretory granules are activated by the increased influx of Ca^{++} ions and their intracellular binding to calmodulin. Hence, more insulin is released with increase in blood glucose level.

The potency order of sulphonylurea in binding to β-cells approximates its potency for stimulating insulin release and blocking the effect of K^+ ions. Sulphonylureas also act synergistically with insulin by raising insulin sensitivity at a post-receptor level.

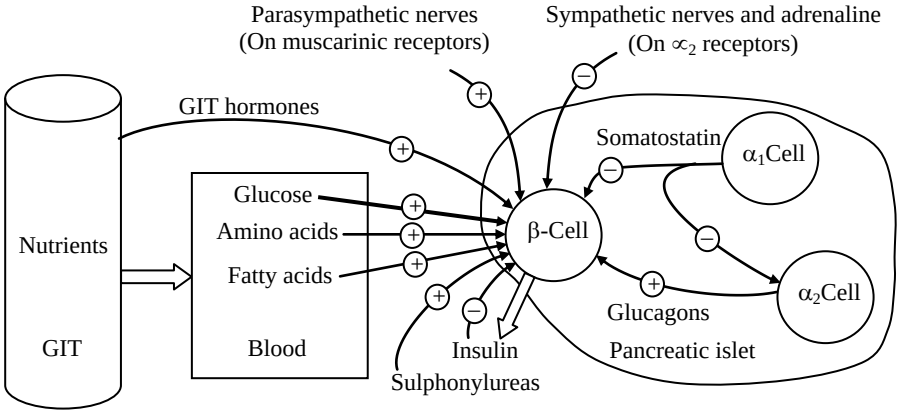
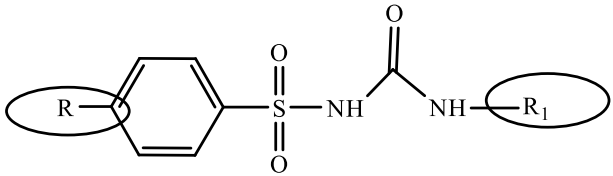


Figure 16.2: Endogenous Factors Regulating the Secretion of Insulin by the β-Cells of the Islets of Langerhans in the Pancreas

16.2.3.2. Structure-Activity Relationship

The benzene ring should contain a substituent in the *para* position. Substituents like methyl, acetyl, amino, chloro, bromo, trifluoromethyl and thiomethyl enhance the anti-hyperglycaemic activity.



Sulphonylureas

On substituting the *para* position of benzene with arylcarboxamidoalkyl group (second generation sulphonylurea,such as glibenclamide), the anti-hyperglycaemic is more enhanced. This happensbecause of a specific distance between the nitrogen atom of the substituent and the sulphonamide nitrogen atom

Size of the group attached to the terminal nitrogen is essential for activity, and should impart lipophilicity to the compound. N -Methyl and ethyl substituents do not produce any activity, while N-propyl and higher homologues are active; however, their activity is lost when the number of carbons in N-substituent is 12 or more.

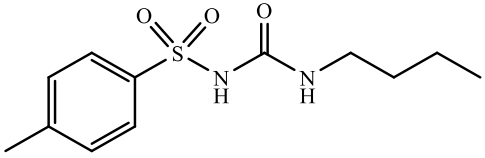
16.2.3.3. Study of Individual Drugs

The following oral hypoglycaemic drugs are discussed below:

1) Tolbutamide,
2) Chlorpropamide,
3) Glipizide, and
4) Glimepiride.

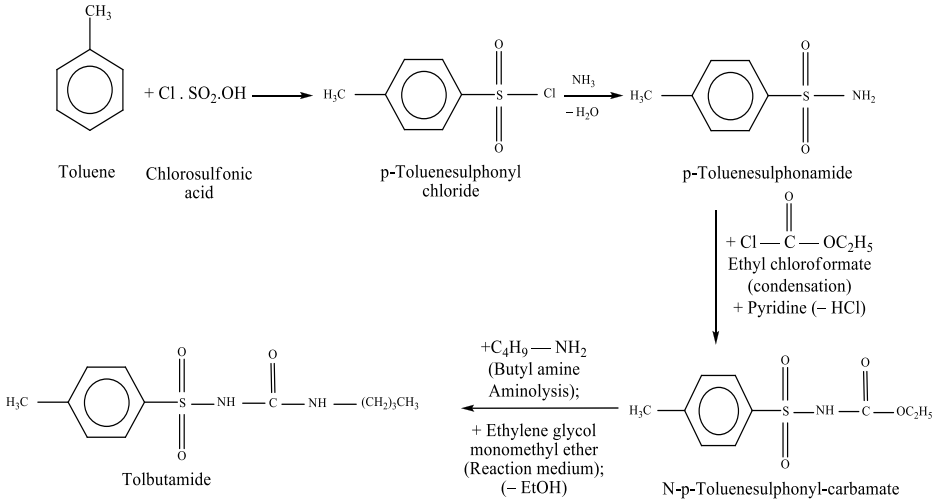
16.2.3.4. Tolbutamide

Tolbutamide belongs to the class of sulph onylureas. It decreases the blood sugar levels by affecting the pancreas to produce insulin and help the body to use insulin effectively.



Tolbutamide

Synthesis



Mechanism of Action

Tolbutamide lowers the blood glucose level in individuals having Non-Insulin Dependent Diabetes Mellitus (NIDDM) by directly stimulating insulin release from the functioning pancreatic β-cells by a process that involves a sulphonylurea receptor (receptor 1) on the beta cell.

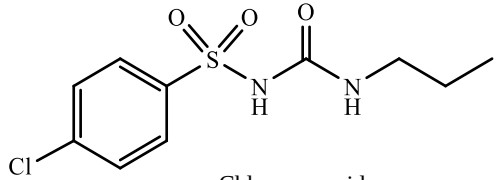
Tolbutamide also inhibits the ATP-potassium channels on the β-cell membrane and efflux of K^+ ions. This results in depolarisation, influx of Ca^{++} ions and their binding to calmodulin, activation of kinase, and release of insulin-containing granules by exocytosis.

Uses

1) It is used for controlling blood glucose in previously untreated NIDDM.
2) It is used in the treatment of diabetes which remains uncontrolled even after proper diet.
3) It is used with metformin to control blood glucose level.
4) It is used as a substitute for other oral hypoglycemic agents.

16.2.3.5. Chlorpropamide

Chlorpropamide is an oral anti-hyperglycaemic agent used for treating NIDDM. It comes under the sulphonylurea class of insulin secretagogues, which stimulate the pancreatic β-cells to release insulin.



Chlorpropamide

Mechanism of Action

Chlorpropamide binds to ATP-sensitive potassium channels present on the pancreatic cell surface, thus depolarises the membrane and reduces potassium conductance.

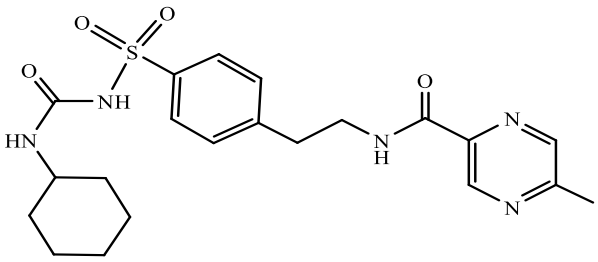
This depolarisation stimulates the influx of Ca^{++} ions through voltage-sensitive calcium channels. As a result, the intracellular concentration of Ca^{++} ions increases, thus inducing the secretion or exocytosis of insulin.

Uses

1) It is taken with a proper diet and exercise program for controlling high blood sugar in type 2 diabetic patients.
2) It can also be used as an adjunct to other diabetes drugs.

16.2.3.6. Glipizide

Glipizide is an oral medium-to-long acting anti-diabetic drug belonging to the class of sulphonylurea. It is an oral hypoglycaemic agent that undergoes rapid absorption and complete metabolism.



Glipizide

Mechanism of Action

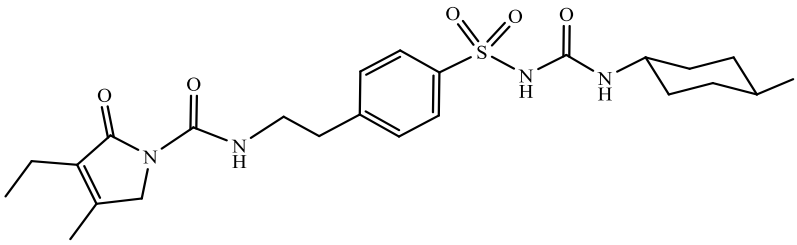
Glipizide binds to ATP -sensitive potassium channels presen t on the pancreatic cell surface, thus depolarises the membrane and reduces potassium conductance. This depolarisation stimulates the influx of Ca^{++} ions through voltage -sensitive calcium channels. As a result, the intracellular concentration of Ca^{++} ions increases, thus inducing the secretion or exocytosis of insulin.

Uses

It is use d as an adjunct to diet for controlling hyperglycaemia and its related symptoms in patients having NIDDM (earlier NIDDM was known as maturity-onset diabetes).

16.2.3.7. Glimepiride

Glimepiride is the first III generation sulphonyl urea. It is a highly potent sulphonylurea having a long duration of action.



Glimepiride

Mechanism of Action

Glimepiride decreases blood glucose levels by stimulating insulin release from the functioning pancreatic β-cells, and by increasing the sensitivity of peripheral tissues to insulin. Glimepiride binds to ATP-sensitive potassium channels present on the pancreatic cell surface, thus depolarises the membrane and reduces potassium conductance.

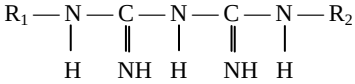
This depolarisation stimulates the influx of Ca^{++} ions through voltage -sensitive calcium channels. As a result, the intracellular concentration of Ca^{++} ions increases, thus inducing the secretion or exocytosis of insulin.

Uses

It is used with insulin for treating the non -insulin-dependent (type 2) diabetes mellitus.

16.2.4. Biguanides

The generic formula of biguanides is:



Two commonly used biguanides are **phenformin** and **metformin**. They decrease the blood glucose level in diabetic patien ts by potentiating the hyperglycaemic action of insulin. They also increase the utilisation of glucose by muscles and decrease the deflation of insulin.

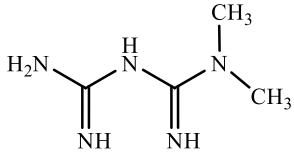
16.2.4.1. Mechanism of Action

Biguanides act by:

1) Directly stimulating glycolysis in tissues,
2) Reducing hepatic and renal gluconeogenesis,
3) Delaying glucose absorption from the GIT by increasing the conversion of glucose to lactate by enterocytes, and
4) Reducing the plasma levels of glucagon.

16.2.4.2. Study of Individual Drug - Metformin

Metformin is a biguanid e antihypertensive agent. It improves glycaemic control by decreasing hepatic glucose production and glucose absorption, and also by increasing insulin-mediated glucose uptake.



Metformin

Mechanism of Action

Metformin reduces the blood glucose levels by decre asing hepatic glucose production (gluconeogenesis), decreasing the intestinal absorption of glucose, and increasing insulin sensitivity by increasing the glucose uptake and utilis ation by the peripheral tissues.

Uses

1) It is used as an adjunct to diet and e xercise in NIDDM patients older than 18 years.
2) It can also be used for managing metabolic and reproductive abnormalities related to polycystic ovary syndrome.
3) It can also be used with a sulphonylurea or insulin to improve glycaemic control in adults.

16.2.5. Thiazolidinediones

Thiazolidinediones (TZDs or glitazones) act by reducing the insulin resistance, which is a common problem in many individuals having type 2 diabetes.

Thiazolidinediones allow insulin to effectively improve the blood glucose levels by decreasing the body's resistance to it. They also reduce the blood pressure and improve lipid metabolism by increasing the levels of HDL (or good) cholesterol.

16.2.5.1. Mechanism of Action

Thiazolidinediones are selective agonists for nuclear Peroxisome Proliferator-Activated Receptor-γ (PPARγ) that enhances the transcription of several insulin responsive genes. Thiazolidinediones reverse insulin resistance by stimulating GLUT4 expression and translocation, and also improve the entry of glucose into muscles and fat. They also suppress hepatic gluconeogenesis. The insulin sensitizing action of thiazolidinediones is due to the activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue.

16.2.5.2. Uses

Thiazolidinediones are used in individuals having type 2 diabetes mellitus. They decrease blood glucose levels and HbA_{1c} without increasing the circulating insulin. Some patients with low baseline insulin levels are non-responders. Generally, they are used to supplement sulphonylureas/metformin in case of insulin resistance. Thiazolidinediones are also used as monotherapy along with diet and exercise in mild cases. They are also used to supplement insulin in advanced cases.

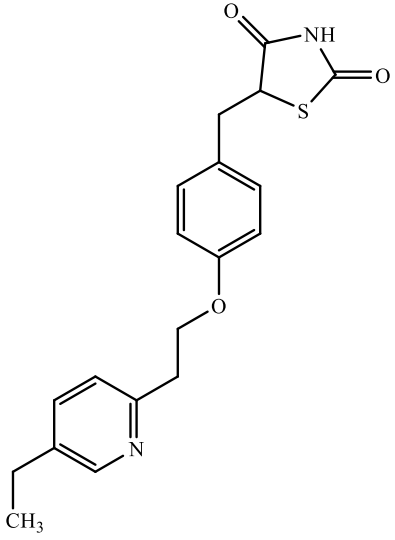
16.2.5.3. Study of Individual Drugs

The following thiazolidinediones are discussed below:

1) Pioglitazone, and
2) Rosiglitazone.

16.2.5.4. Pioglitazone

Pioglitazone is used as an adjunct to diet, exercise, and other anti-diabetic drugs to control type 2 diabetes mellitus.



Pioglitazone

Mechanism of Action

Pioglitazone is a selective agonist of Peroxisome Proliferator Activat ed Receptor-γ (PPARγ) present in the target tissues (adipose tissue, skeletal muscle, and liver) for insulin action. The PPAR-γ receptors on activation increase the transcription of insulin -responsive genes that are involved in control ling production, transport, and utilisation of glucose.

Thus, pioglitazone enhances tissue sensitivity to insulin and also reduces glucose production via hepatic gluconeogenesis. In this way insulin resistance related to type 2 diabetes mellitus is improved without increase in insulin secretion by the pancreatic β cells.

Uses

It is used as an adjunct to diet and exercise for improving glycaemic control in individuals having type 2 diabetes mellitus.

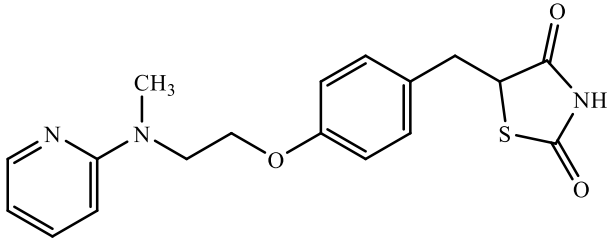
16.2.5.5. Rosiglitazone

Rosiglitazone is an anti -diabetic drug which not only acts on insulin resistance, but also has anti-inflammatory effect; nuclear factor kappa-B (NFκB) levels fall and inhibitor (IκB) levels increase in patients taking rosiglitazone.

Mechanism of Action

Rosiglitazone is a selective agonist of Peroxisome Proliferator Act ivated Receptor-γ (PPARγ) present in the target tissues (adipose tissue, skeletal muscle, and liver) for insulin action.

The PPAR -γ receptors on activation increase the transcription of insulin-responsive genes that are involved in controlling production , transport, and utilisation of glucose. Thus, rosiglitazone enhances tissue sensitivity to insulin.



Rosiglitazone

Uses

It is used as an adjunct to diet and exercise for improving the glycaemic control in individuals having type 2 diabetes mellitus.

16.2.6. Meglitinides

The structure of meglitinides is similar to that of sulphonylureas. The sulphonylurea and meglitinide classes of oral hypoglycaemic drugs are termed as **endogenous insulin secretagogues** as they induce the pancreatic release of endogenous insulin.

Repaglinide is a new non -sulphonylurea insulin secretagogue, and the first available. **Nateglinide** is another newest available meglitinide. Unl ike the sulphonylureas, the meglitinides have a very short onset of action and a short half-life. Some **advantages** of meglitinides are a greater decrease in post - prandial glucose and a decreased risk of hypoglycaemia.

16.2.6.1. Mechanism of Action

The mechanism of action of meglitinides is also somewhat similar to that of sulphonylureas. Meglitinides stimulate insulin release from the pancreatic β-cells, and this action is mediated by a different binding site on the sulphonylurea receptor of the β-cell. Meglitinides also act on potassium conductance. They do not produce any direct effect on the circulating levels of plasma lipids.

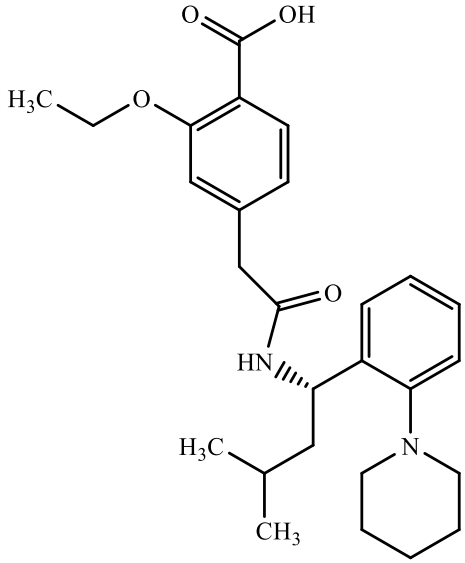
16.2.6.2. Study of Individual Drugs

The following meglitinides are discussed below:

1) Repaglinide, and
2) Nateglinide.

16.2.6.3. Repaglinide

Repaglinide is used for treating NIDDM. It is an oral anti-hyperglycaemic drug of meglitinide clas s having short-acting insulin secretagogues that bind to pancreatic β-cells for stimulating insulin release.



Repaglinide

Mechanism of Action

Repaglinide depends on the presence of functioning pancreatic β-cells and glucose. It does not produce any effect on insulin re lease in the absence of glucose; instead it potentiates the effect of extracellular glucose on ATP-sensitive potassium channel and produces little effect on insulin levels between meals and overnight.

Repaglinide more effectively reduces post-prandial blood glucose levels than fasting b lood glucose levels and requires a longer duration of therapy (one month) before decreasing fasting blood glucose levels. The insulinotropic effects of repaglinide are highest at intermediate g lucose levels (3 -10mmol/L) and it does not increase insulin rel ease that is already stimulated by high glucose concentrations (<15mmol/L). Repaglinide is selective for pancreatic β-cells and does not affect skeletal or cardiac muscles or thyroid tissues.

Uses

It is used as an adjunct to diet and exercise for improving glycaemic regulation in individuals having type 2 diabetes mellitus.

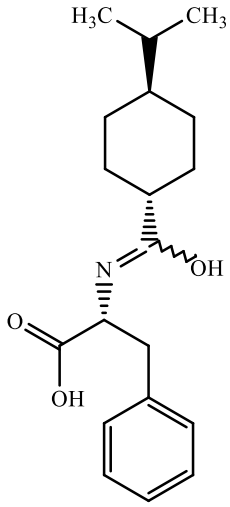
16.2.6.4. Nateglinide

Nateglinide is used for treating NIDDM. It is an oral anti-hyperglycaemic drug of meglitinide class of short-acting insulin secretagogues that binds to pancreatic β-cells of to stimulate insulin release.

Mechanism of Action

Nateglinide is an amino -acid derivative that lowers the blood glucose levels by stimulating the release of insulin from pancreas. This action depends on the functioning pancreatic β-cells. Nateglinide interacts with the ATP -sensitive potassium channel present on pancreatic β-cells cell surface, thus depolarises the membrane and reduces potassium conductance.

This depolarisation stimulates the influx of Ca^{++} ions through voltage -sensitive calcium channels. As a result, the intracellular concentration of Ca^{++} ions increases, thus inducing the secretion or exocytosis of insulin.



Nateglinide

Uses

It is used in conjunction with diet and exercise for treating non -insulin dependent-diabetes mellitus.

16.2.7. α-Glucosidase Inhibitors

The α-glucosidase inhibitors are oral anti-diabetic drugs. They are used for treating type 2 diabetes mellitus by inhibiting the digestion of carbohydrates starch and table sugar).

Generally, the carbohydrates are converted into simple sugars (monosaccharides) that can be absorbed in the intestines. Therefore, α-glucosidase inhibitor drugs are used to decrease the effect of carbohydrates on blood sugar.

16.2.7.1. Mechanism of Action

The α-glucosidase enzyme is found in the brush border of small intestine . This enzyme is responsible for cleaving the dietary carbohydrates and hence enhancing their rapid absorption in the body.

Hence, any way which can inhibit this enzyme will leave less-dietary carbohydrate available for absorption and thus, less available in the blood stream after having a normal meal.

It is observed th at the usual inhibitory characteristic features of α-glucosidase inhibitors are maximum for glycoamylase followed by sucrose, maltase , and dextranase respectively.

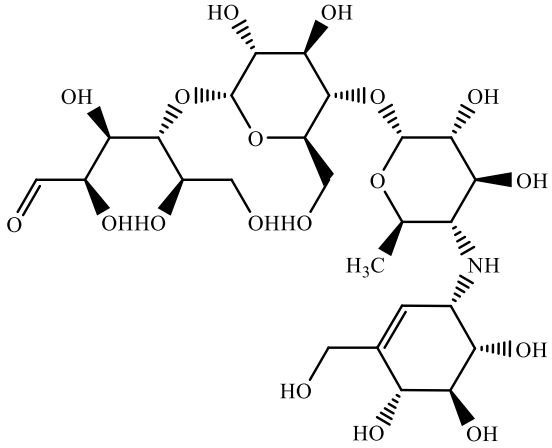
16.2.7.2. Study of Individual Drugs

The following α-glucosidase inhibitors are discussed below:

1) Acarbose, and
2) Voglibose.

16.2.8. Acarbose

Acarbose is an inhibitor of α-glucosidase, which delays digestion and absorption of carbohydrates in small intestine , and thus decreases the increase in blood - glucose concentrations after a carbohydrate load.



Acarbose

Mechanism of Action

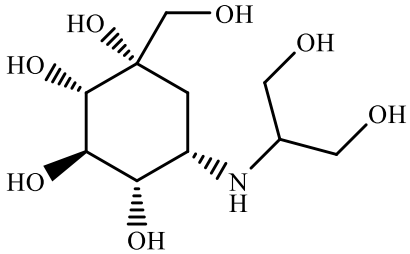
Acarbose reversibly binds to pancreatic α-amylase and membrane-bound intestinal α-glucoside hydrolases enzymes. The former enzyme inhibits the hydrolysis of complex starches into oligosaccharides in the lumen of small intestine; while the latter inhibits the hydrolysis of oligosaccharides, trisaccharides, and disaccharides into glucose and other monosaccharides in the brush border of small intestine.

Uses

It is used for treating type II diabetes in combination therapy as a second or third line agent.

16.2.9. Voglibose

Voglibose is an α-glucosidase inhibitor. It is used for reducing post-prandial blood glucose levels in individuals having diabetes mellitus.



Voglibose

Mechanism of Action

Voglibose is a competitive inhibitor of enzymes required for digestion of carbohydrates. The most common enzyme is α-glucosidase present in the brush border of small intestines. The membrane-bound intestinal α-glucosidase enzyme causes hydrolysis of oligosaccharides, trisaccharides, and disaccharides, and produces glucose and other monosaccharides in the small intestine. Pancreatic α-amylase causes hydrolysis of complex starches and produces oligosaccharides in the lumen of small intestine.

When these enzymes are inhibited, the digestion rate of complex carbohydrates is reduced. The carbohydrates are not broken down into glucose molecules, thus less glucose is absorbed.

In diabetic patients, the short-term effect of voglibose decreases the blood glucose levels, and the long-term effect is a small reduction in haemoglobin-A1c level.

Uses

1) It is used for treating diabetes.
2) Mainly, it is used for decreasing post-prandial blood glucose levels, hence decreases the risk of macrovascular complications.

16.3. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Diabetes mellitus** is a group of meta bolic diseases in which an individual has high blood sugar level because the body either does not produce insulin in sufficient amount, or the body cells do not respond to the insulin formed.
2) **Anti-diabetic agents** are used for treating diabetes mellitus by decreasing the blood glucose levels.
3) **Banting**, **Macleod**, **Bert**, and **Collip** isolated insulin from bovine pancreas and used it for treating diabetes mellitus.
4) **Insulin** is a hormone produced in pancreas and permits the body to utilise sugar (glucose) from carbohydrates in the food.
5) **Hypoglycaemic agents** are used in the treatment of diabetes mellitus by lowering the blood glucose levels.
6) **Carbutamide** was the first sulphonylurea that was clinically used for treating the diabetes.
7) All the **sulphonylureas** have similar actions, i.e., they decrease blood glucose levels in type 2 diabetes.
8) **Tolbutamide** belongs to the class of sulphonylureas.
9) **Chlorpropamide** is an oral anti -hyperglycaemic agent used for treating NIDDM.
10) **Glipizide** is an oral medium -to-long a cting anti -diabetic drug belonging to the class of sulphonylurea.
11) **Glimepiride** is the first III generation sulphonylurea.
12) **Metformin** is a biguanide antihypertensive agent.
13) **Pioglitazone** is used as an adjunct to diet, exercise, and other anti -diabetic drugs to control type 2 diabetes mellitus.
14) **Rosiglitazone** is an anti -diabetic drug which not only acts on insulin resistance, but also has anti -inflammatory effect; nuclear factor kappa -B (NFκB) levels fall and inhibitor (IκB) levels increase in patients taking rosiglitazone.
15) The **sulphonylurea** and **meglitinide** classes of oral hypoglycaemic drugs are termed as **endogenous insulin secretagogues** as they induce the pancreatic release of endogenous insulin.
16) **Repaglinide** is used for treating NIDDM. It is an oral anti -hyperglycaemic drug of meglitinide class having short -acting insulin secretagogues that bind to pancreatic β-cells for stimulating insulin release.
17) **Acarbose** is an inhibitor of α-glucosidase, which delays digestion and absorption of carbohydrates in small intes tine, and thus decreases the increase in blood-glucose concentrations after a carbohydrate load.
18) **Voglibose** is an α-glucosidase inhibitor.

16.4. EXERCISES

16.4.1. True or False

1) Diabetes mellitus is a group of metabolic diseases in which an individual has low blood sugar level.
2) Anti-diabetic agents are used for treating diabetes mellitus by decreasing the blood glucose levels.
3) Insulin is a hormone produced in pancreas and permits the body to utilise sugar (glucose) from carbohydrates in the food.
4) Hypoglycaemic agents are used in the treatment of diabetes insipidus by lowering the blood glucose levels.
5) Carbutamide was the first sulphonylurea that was clinically used for treating the diabetes.
6) All the sulphonylureas have similar actions.
7) Chlorpropamide is an oral anti -hyperglycaemic agent used for treating type 1 diabetes.
8) Glimepiride is the first II generation sulphonylurea.

16.4.2. Fill in the Blanks

9) Tolbutamide belongs to the class of _____.
10) _____ is an oral medium-to-long acting anti-diabetic drug belonging to the class of sulphonylurea.
11) Metformin is a _____ antihypertensive agent.
12) _____ is used as an adjunct to diet, exercise, and other anti -diabetic drugs to control type 2 diabetes mellitus.
13) _____ is an anti-diabetic drug which not only acts on insulin resistance, but also has anti-inflammatory effect.
14) The sulphonylurea and meglitinide classes of oral hypoglycaemic drugs are termed as _____ as they induce the pancreatic release of endogenous insulin.
15) _____- is used for treating NIDDM. It is an oral anti -hyperglycaemic drug of meglitinide class having short -acting insulin secretagogues that bind to pancreatic β-cells for stimulating insulin release.
16) _____ is an inhibitor of α-glucosidase, which delays digestion and absorption of carbohydrates in small intestine, and thus decreases the increase in blood -glucose concentrations after a carbohydrate load.
17) _____ is an α-glucosidase inhibitor.

Answers

1) False	2) True	3) True	4) False
5) True	6) True	7) False	8) False
9) Sulphonylurea	10) Glipizide	11) Biguanide	12) Pioglitazone
13) Rosiglitazone	14) Endogenous insulin secretagogues		
15) Repaglinide	16) Acarbose	17) Voglibose	

16.4.3. Very Short Answer Type Questions

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

16.4.4. 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.

16.4.5. 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 α-glucosidase inhibitors.

CHAPTER 17

Local Anaesthetics

17.1. LOCAL ANAESTHETICS

17.1.1. Introduction

Local anaesthetic agents act locally to **abolish the sensory perception over a local area**. They vary in their pharmacological properties and are used in the following local anaesthesia techniques:

1) Topical anaesthesia (surface),
2) Infiltration,
3) Plexus block,
4) Epidural (extradural block), and
5) Spinal anaesthesia (subarachnoid block).

Local anaesthetics bind to cell membrane sodium channels and inhibit sodium ion passage, thus prevent the membrane depolarisation of nerve cells. Sodium channel is liable to local anaesthetic binding in the open state; therefore the frequently stimulated nerves are blocked easily. The ability of local anaesthetics to block a nerve depends on the length of the nerve ex posed, nerve diameter, myelination, and the anaesthetic used.

17.1.2. Classification

Local anaesthetics are classified as follows:

1) **Natural Agents:** Cocaine.
2) **Synthetic Nitrogenous Compounds**
   i) Derivatives of benzoic acid.
   ii) Derivatives of *para*-amino benzoic acid
      a) **Freely Soluble:** Procaine and Amethocaine.
      b) **Poorly Soluble:** Benzocaine and Orthocaine.
   iii) **Derivatives of Acetanilide:** Lignocaine, Mepivacaine, Bupivacaine, Prilocaine, and Etidocaine.
   iv) **Derivatives of Quinoline:** Cinchocaine and Dimethisoquin.
3) **Synthetic Non-Nitrogenous Agents:** Benzyl alcohol and Propanediol.
4) **Miscellaneous Drugs with Local Action:** Clove oil, Phenol, Chlorpromazine and Diphenhydramine.

Based on Duration of Action

1) **Injectable Anaesthetics**
   i) **Low Potency and Short Duration:** Procaine and Chloroprocaine.

ii) **Intermediate Potency and Duration:** Lignocaine and Prilocaine.

iii) **High Potency and Long Duration:** Tetracaine, Bupivacaine, Ropivacaine, and Dibucaine.

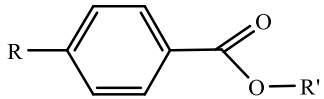
2) **Surface Anaesthetics**

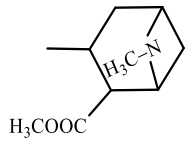
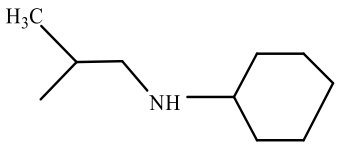
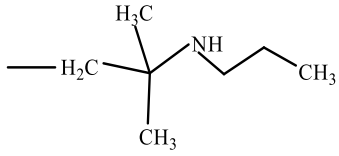
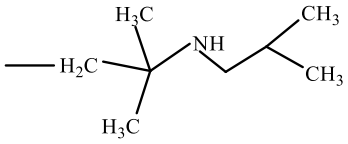
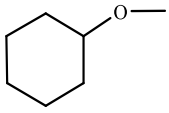
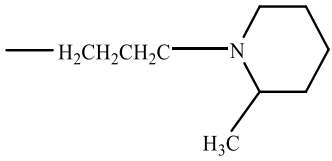
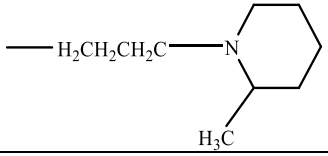
i) **Soluble:** Cocaine, Lignocaine, Tetracaine, and Benoxinate.

ii) **Insoluble:** Benzocaine, Butyl aminobenzoate, and Oxethazaine.

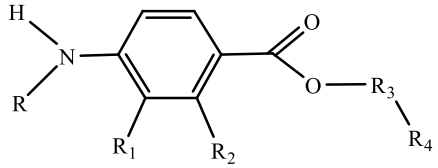
Based on Chemical Structure

1) **Benzoic Acid Derivatives**



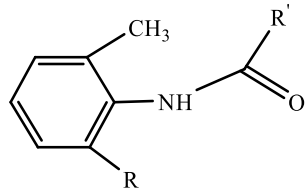
Drugs	R	R′
Cocaine	H	
Hexylcaine	H	
Meprylcaine	H	
Isobucaine	H	
Cyclomethycaine		
Piperocaine	H	

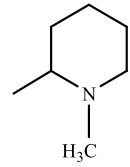
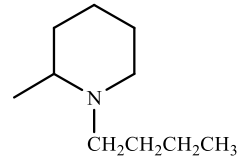
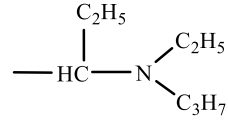
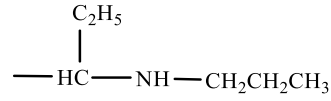
2) *p*-Aminobenzoic Acid Derivatives



Drugs	R	R_1	R_2	R_3	R_4
Benzocaine	H	H	H	—CH_2CH_3	—
Butamben	H	H	H	— $(CH_2)_3CH_3$	—
Procaine	H	H	H	—CH_2CH_2—	—$N(C_2H_5)_2$
Chloroprocaine	H	H	CI	—CH_2CH_2—	—$N(C_2H_5)_2$
Tetracaine	Butyl	H	H	—CH_2CH_2—	—$N(C_2H_5)_2$
Butacaine	H	H	H	—CH_2CH_2—	—$N(C_4H_{9(n)})_2$
Benoxinate	H	H	Butoxy	—CH_2CH_2—	—$N(C_2H_5)_2$
Propoxycaine	H	H	Propoxy	—CH_2CH_2—	—$N(C_2H_5)_2$

3) Anilide Derivatives



Drugs	R	R′
Lignocaine	CH_3	— $CH_2N(C_2H_5)_2$
Mepivacaine	CH_3	
Bupivacaine	CH_3	
Etidocaine	CH_3	
Prilocaine	H	

4) **Miscellaneous:** Phenacaine, Diperodon, Dimethisoquin, Pramoxine, Dyclonine, and Dibucaine.

5) **Newer Drugs:** Ropivacaine and Levobupivacaine.

17.1.3. Mechanism of Action

Local anaesthetics prevent the voltage-dependent increase in Na^+ ion conduction, thus block the **initiation propagation of nerve impulse**. Entry of Na^+ ions through voltage-gated channels is either reduced by a similar effect on the membrane as that induced by inhalation general anaesthetics, or by specifically plugging Na^+ ion channels. The nerve conduction blocking activity of local anaesthetics is ordered as small and large myelinated axons (motor). Thus, initially nociceptive and sympathetic transmission is blocked, and motor nerves are blocked last.

17.1.4. Uses

Local anaesthesia is the loss of sensation in a body part without the loss of consciousness or impairment of central regulation of vital functions. It is used during minor surgical methods. Local anaesthetics are used for surface application, infiltration, nerve blocks, epidural, spinal and intravenous regional block anaesthesia. Local anaesthetics are classified as follows according to their administration method:

1) **Topical Anaesthesia:** The mucous membranes of nose, throat, tracheobronchial tree, oesophagus, and genito-urinary tract can be anaesthetised by direct application of aqueous solutions of salts of various local anaesthetics or by suspension of the poorly soluble local anaesthetics. Vasoconstriction is achieved for prolonged duration of action by adding a low concentration of a vasoconstrictor, **e.g.,** phenylephrine (0.005%), lignocaine (2-10%), cocaine (1-4%), and tetracaine (2%).

2) **Infiltration Anaesthesia:** Local anaesthetics are injected directly into the superficial tissue of the skin or deeper structures including intra-abdominal organs. The duration of infiltration anaesthesia is doubled by adding epinephrine (5 µg/ml) to the injection solution, **e.g.,** lignocaine (0.5-1.0%), procaine (0.5-1.0%), and bupivacaine (0.125-0.25%).

3) **Field Block Anaesthesia** This is produced by subcutaneous injection of a local anaesthetic solution to anaesthetise the region distal to the injection. The advantage of field block anaesthesia is that less drug is used for providing a greater area of anaesthesia in comparison to infiltration anaesthesia, **e.g.,** lignocaine (0.5-1.0%), procaine (0.5-1.0%), and bupivacaine (0.125-0.25%).

4) **Nerve Block Anaesthesia :** This involves injecting a solution of local anaesthetic into or around individual peripheral nerves or nerve plexus, **e.g.,** lignocaine (1.0-1.5%), mepivacaine (up to 7mg/kg of 1.0-2.0%), and bupivacaine (2-3mg/kg of 0.25-0.375%). Duration is prolonged by adding 5µg/ml of epinephrine.

5) **Intravenous Regional Anaesthesia :** This technique relies on using the vasculature to bring the local anaesthetic solution to the nerve trunks and endings. Mostly, it is used for the forearm and hand, and also for foot and distal leg, **e.g.,** lignocaine (0.5%) and procaine (0.5%).

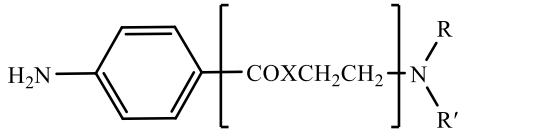
6) **Spinal Anaesthesia:** This local anaesthetic is injected into the cerebrospinal fluid in the lumbar space, **e.g.,** lignocaine, tetracaine, and bupivacaine.

7) **Epidural Anaesthesia:** This local anaesthetic is injected into the epidural space (the space bounded by the ligamentum flavum posteriorly, the spina periosteum laterally, and the dura anteriorly), **e.g.,** bupivacaine (0.5-0.75%), etidocaine (1.0-1.5%), lignocaine (2%), and chloroprocaine (2-3%).

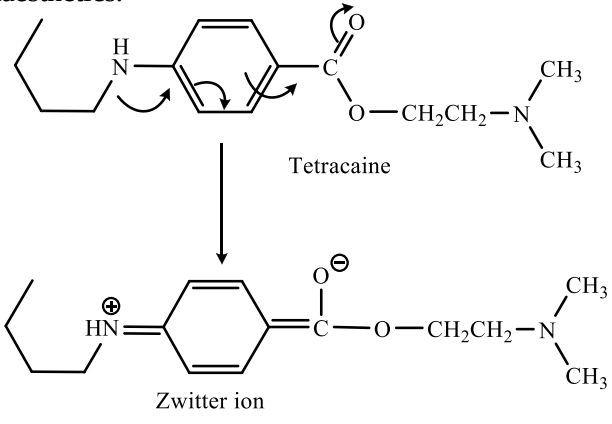
17.1.5. SAR of Local Anaesthetics

SAR of Benzoic Acid Derivatives

Mostly, the benzoic acid derivatives are tertiary amines found as HCl salts having pKa in the range of 7.5 -9.0. Any structural modificati on in these local anaesthetics that may alter the pKa will have a pronounced effect to reach hypothetical receptor or the binding sites.



1) **Lipophilic Portion**
   i) A local anaesthetic of this class that is clinically useful is highly lipophilic and has an aryl radical directly attached to the carbonyl group. This plays an important role in the binding of local anaesthetics to the channel receptor protein.
   ii) Placing the aryl group with substituents that increases the electron density of carbonyl oxygen enhances the activity of local anaesthetics.
   iii) Structural modification changes the physical and chemical properties of local anaesthetics . Placement of electron withdrawing substituents at *ortho* or *para* or both the positions increases the activity of local anaesthetics.
   iv) Amino (procaine, butacaine) , alkyl amino (tetracaine) , and alkoxyl (cyclomethycaine) groups contribute to electron density in the aromatic ring by resonance and inductive effects. This increases the activity of local anaesthetics.



v) Any substitution that enhances the formation of Zwitter ion will be more potent. Hence substitution at *m*-position decreases the activity of local anaesthetics.

vi) The potency of tetracaine is 40 -50 times more than that of procaine. Although the butyl group present in it increases lipid solubility, the potentiation is partially due to ele ctron releasing property of the n -butyl group via inductive effect, which increases the formation of Zwitter ion.

vii) Electron withdrawing group (Cl^-) if present *ortho* to carbonyl pulls the electron density away from carbonyl group, and makes it more susceptible to nucleophilic attack by the esterase.

2) **Intermediate Portion**

i) In procaine series, the anaesthetic potency decreases in the following order: sulphur > oxygen > carbon > nitrogen.

ii) Modifications affect the duration of action and toxicity. Amides (X = N) are more resistant to metabolic hydrolysis than esters (X = O). Thioesters (X = S) may cause dermatitis.

iii) Substitution of small alkyl groups (branching) around ester group (hexylcaine/meprylcaine) or amide function delays hydrolysis and increases the duration of action.

3) **Hydrophilic Portion**

i) The amino alkyl group is not necessary for local anaesthetic activity, but for forming water-soluble salts such as HCl salts.

ii) Tertiary amines are more useful. Secondary amines have a longer duration of action, but are more ir ritating. Primary amines are inactive and cause irritation.

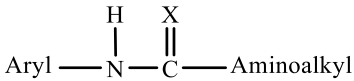
iii) Placement of tertiary amino group (diethyl amino, piperidine, or pyrrolidino) forms a product with same degree of activity.

iv) Placement of a more hydrophilic morpholino group reduces the potency.

v) The local anaesthetic drug should have increased lipid solubility and lower pKa values to increase the onset of action and decrease toxicity.

SAR of Anilides

Given below is the general structure of anilides:

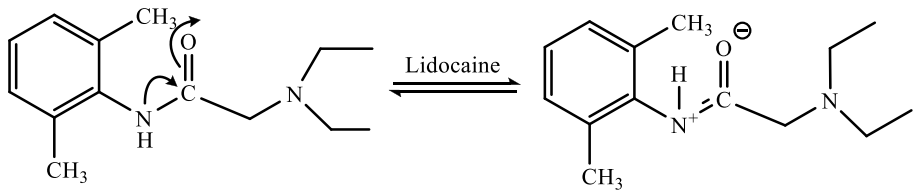


1) **Aryl Group**

i) The clinically useful local anaesthetic belonging to class of anilides has a phenyl group attached via nitrogen bridge to the sp^2 carbon atom.

ii) Placement of substituents on the phenyl ring with a methyl group at 2 (or) 2 and 6 -position increases the local anaesthetic activity. The methyl substituent also provides steric hindrance to hydrolysis of the amide bond and enhances the coefficient of distribution.

iii) A substituent on the aryl ring that enhances the formation of Zwitter ion will be more potent.



Lidocaine Zwitterion

2) **Substituent X:** This substituent may be a carbon, oxygen, or nitrogen . Lidocaine series (X = O) has proved to be more clinically useful.

3) **Amino Alkyl Group**
   i) The amino group can lead to salt formation and is the hydrophilic portion of the local anaesthetic molecule.
   ii) Tertiary amines (diethyl amine or piperidine) are more useful than the primary and secondary amines, as they are more irritating to tissues.

17.1.6. Recent Developments

The cardiovascular system in comparison to the central nervous system is more resistant to the toxic effects of local a naesthetics. However, if sufficient doses and blood levels of local anaesthetics are achieved, signs of cardiovascular depression may be observed. Different local anaesthetics have different potential for cardiotoxicity.

Cardiotoxicity of local anaestheti cs can be compared using the **CC/CNS dose ratio**, which is the ratio of the dose causing Cardiac Collapse (CC) to the dose causing seizure or convulsions. The CC/CNS ratio for lidocaine is more than that for bupivacaine and eti docaine. **Bupivacaine** may also precipitate ventricular arrhythmias and ventricular fibrillation.

Local tissue toxicity can also occur on administering local anaesthetics. The neural tissue is relatively resistant to the irritant effects of local anaesthetic s. However, large doses of **chloroprocaine** solutions administered intrathecally may cause prolonged sensory-motor deficits in some patients due to low pH and presence of sodium bisulfite in the chloroprocaine solutions. The occurrence of toxic reactions to local anaesthetic agents is generally very low. However, as with any class of pharmacological agents, local anaesthetics may cause severe toxic reactions, due to improper use.

17.2. BENZOIC ACID DERIVATIVES

17.2.1. Introduction

Benzoic acid is an aromatic carboxylic acid found naturally in plant and animal tissues. It can also be produced by microorganisms. Benzoic acid and derivatives, and related benzene compounds, such as salts, alkyl esters, parabens, benzyl alcohol, benzaldehyde, and benzoyl peroxide, are used as antibacterial and antifungal preservatives and as flavouring agents in food, cosmetic, hygiene, and

pharmaceutical products. These compounds due to their extensive occurrence, production, and use, are widely distributed in the environment and in water, soil, and air. Consequently, hum an exposure to them can be high, common, and lengthy.

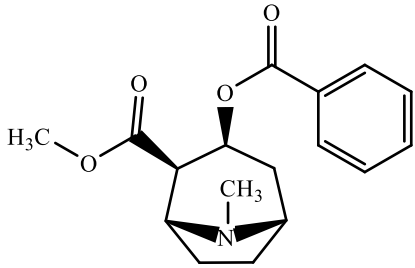
17.2.2. Study of Individual Drugs

The following benzoic acid derivatives are discussed below:

1) Cocaine,
2) Hexylcaine,
3) Meprylcaine,
4) Cyclomethycaine, and
5) Piperocaine.

17.2.2.1. Cocaine

Cocaine is a **benzoyl methylecgonine hydrochloride** (a benzoic acid ester). It is an alkaloid and is extracted from the leaves of coca tree (*Erythroxylum coca*).



Cocaine

Mechanism of Action

Cocaine produces anaesthetic effect by blocking excitation of nerve endings or by blocking conduction in peripheral nerves. It is achieved by reversibly binding to and inactivating sodium channels. Sodium influx by these channels is required for the depolarization of nerve cell membranes and subsequent propagation of impulses along the cours e of the nerve. Cocaine is the only local anesthetic wi th vasoconstrictive properties.

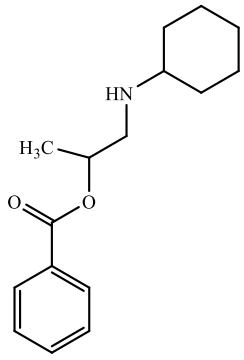
It causes anaesthesia due to the blockade of norepinephrine reuptake in the autonomic nervous system. It binds differentially to the dopamine, serotonin, and norepinephrine transport proteins and directly blocks the re-uptake of dopamine, serotonin, and norepinephrine into pre -synaptic neurons. Its effect on dopamine levels is most responsible for the addictive property of cocaine.

Uses

It is used for introduction of lo cal (topical) anesthesia in the accessible mucous membranes of the oral, laryngeal and nasal cavities.

17.2.2.2. Hexylcaine

Hexylcaine (or cyclaine or osmocaine) is a short-acting local anaesthetic. It acts by blocking the sodium channel conduction.



Hexylcaine

Mechanism of Action

Hexylcaine blocks the influx of Na^+ ions through voltage gated sodium channels present in the neuronal cell membrane of peripheral nerves. When the influx of Na^+ ions is interrupted, an action potential does not arise and signal conduction is inhibited. The receptor site is situated at the cytoplasmic (inner) portion of the sodium channel.

Uses

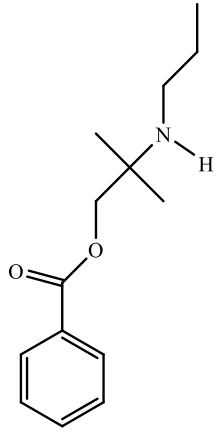
It is used as a local anaesthetic for surface application, infiltration , or nerve block.

17.2.2.3. Meprylcaine

Meprylcaine (or epirocaine or oracaine) is a local anaesthetic having stimulant properties. Its structure is related to dimethocaine.

Mechanism of Action

Meprylcaine has a relatively potent inhibitory action on the monoamine transporter. It blocks the reuptake of dopamine, norepinephrine, and serotonin.



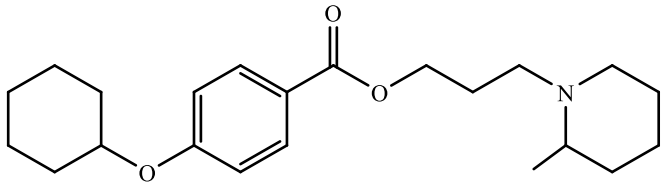
Meprylcaine

Uses

It is used as a local anaesthetic for surface application, infiltration , or nerve block.

17.2.2.4. Cyclomethycaine

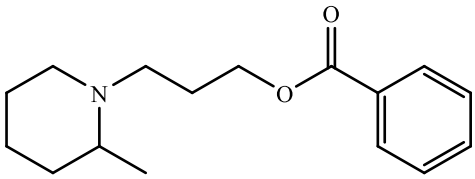
Cyclomethycaine is a benzoate ester. It is used as a loca l anaesthetic for surface application, and infiltration or nerve block.



Cyclomethycaine

17.2.2.5. Piperocaine

Piperocaine is a benzoate ester. It is a local anaesthetic developed in the 1920s. Its hydrochloride salt was used for infiltration and nerve block . It is a white coloured crystalline powder that is soluble in water and chloroform. It is used as a surface anesthesia for eyes, throat, and caudal analgesia.



Piperocaine

17.3. AMINO BENZOIC ACID DERIVATIVES

17.3.1. Introduction

Aminobenzoic acid is an organic acid with UV absorption and anti -fibrotic properties. On exposure to light, aminobenzoic acid (*para*-aminobenzoic acid or PABA) absorbs UV light and releases excessive energy by a photochemical reaction that damages DNA. Since the DNA defects contribute to skin cancer, aminobenzoic acid is no more used in sunscreen formulations. Aminobenzoic acid also increase s oxygen uptake by the tissue s and increases the activity of Monoamine Oxidase (MAO) to promote serotonin degradation, which in excess leads to fibrotic changes.

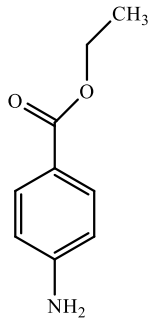
17.3.2. Study of Individual Drugs

The following aminobenzoic acid derivatives are discussed below:

1) Benzocaine,
2) Butamben,
3) Procaine,
4) Butacaine,
5) Proxycaine,
6) Tetracaine, and
7) Benoxinate.

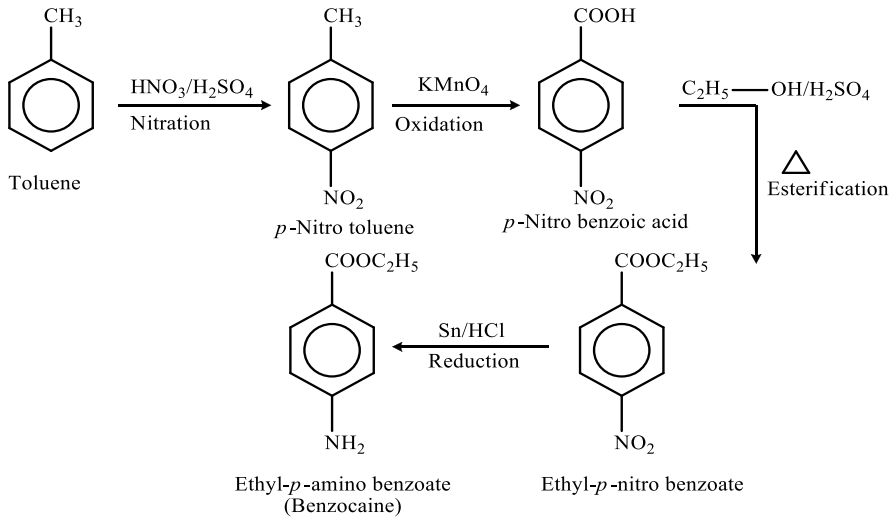
17.3.2.1. Benzocaine

Benzocaine is a surface anaesthetic which prevents the transmission of impulses on nerve fibres and at nerve endings.



Benzocaine

Synthesis



Mechanism of Action

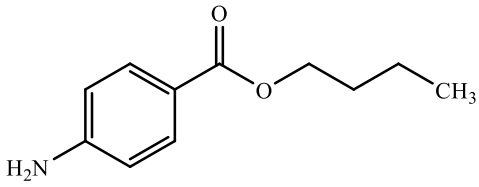
Benzocaine binds to sodium channel and reversibly stabilis es the neuronal membrane. This reduces the permeability of sodium channel to Na^+ ions. Depolarisation of the neuronal membrane is blocked, and hence the initiation and conduction of nerve impulses is blocked.

Uses

It is used for suppressing gag reflex, as a lubricant and topical anaesthetic on oesophagus, mouth, larynx, nasal cavity, rectum, urinary tract, vagina, and respiratory tract or trachea.

17.3.2.2. Butamben

Butamben is a local anaesthetic that occurs in the form of n -butyl-*p*-aminobenzoate. Its structure corresponds to the standard molecule of a hydrophilic and hydrophobic domain separated by an intermediate ester present in most of the local anaesthetics.



Butamben

Mechanism of Action

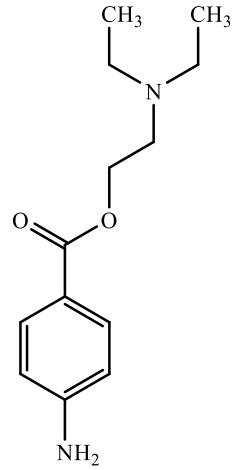
Butamben blocks the voltage-gated calcium channels present in the dorsal root ganglion neurons. Modification of these channels disturbs the channel kinetics acceleration. Butamben is an inhibitor of sodium channels and a delayed rectifier of potassium currents. All its effects are produced in the root ganglion neurons and the related anaesthetic effect is caused by the reduced electrical excitability.

Uses

1) It is used for treating chronic pain because of its long duration effect.
2) It is also used as a surface anaesthetic for skin and mucous membrane.
3) It is used for relieving pain and pruritus related to anorectal disorders

17.3.2.3. Procaine

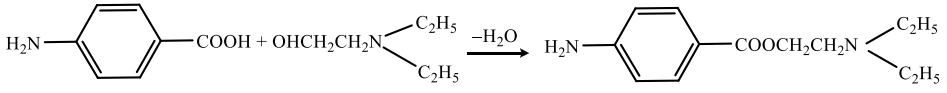
Procaine is an ester type local anaesthetic. It has a slow onset and a short duration of action. It is a benzoic acid derivative with antiarrhythmic and local anaesthetic properties.



Procaine

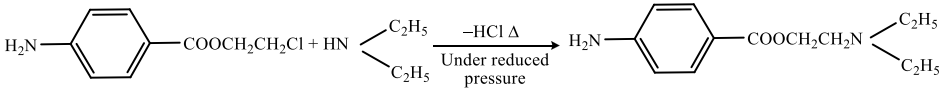
Synthesis

Route I: From: *p*-Aminobenzoic acid



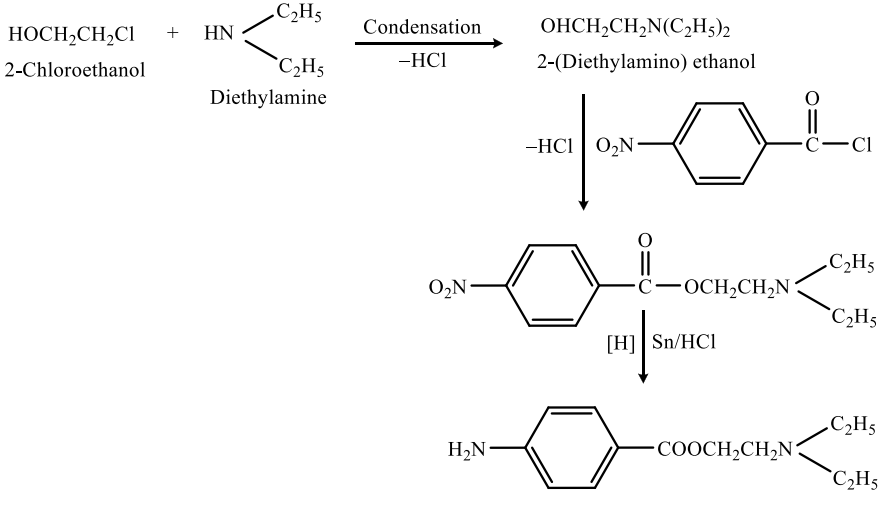
4-Aminobenzoic acid 2-(N,N-diethylamino) ethanol Procaine

Route II: From: 2-Chloro ethyl 4-amino benzoate



2-Chloroethyl 4-amino benzoate Diethylamine Procaine

Route III: From: 2-Chloro ethanol



Procaine

Mechanism of Action

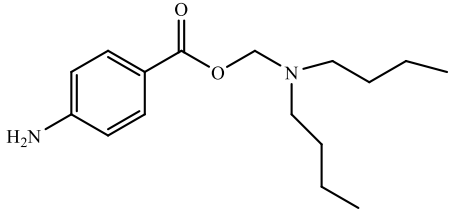
Procaine blocks the influx of Na^+ ions through voltage gated sodium channels in the neuronal cell membrane of peripheral nerves. Inhibition of Na^+ ion influx cannot arise an action potential cannot arise, and thus blocks signal conduction. The receptor site is situated at the cytoplasmic (inner) portion of the sodium channel. Procaine binds to or antagonises the function of N-Methyl-D-Aspartate (NMDA) receptors, nicotinic acetylcholine receptors, and serotonin receptor-ion channel complex.

Uses

1) It is used for penetration anaesthesia, spinal block , and peripheral nerve block.
2) It is used as a local anaesthetic, mainly in oral surgery.

17.3.2.4. Butacaine

Butacaine is a white crystalline benzoate ester used as a local anaesthetic.



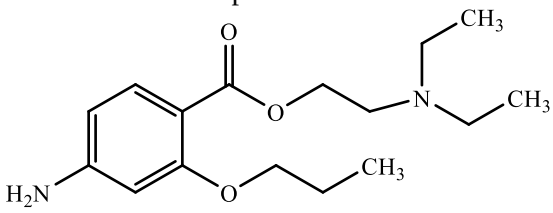
Butacaine

Mechanism of Action
Butacaine accumulates in the nerve cell membrane, thus making it to expand and lose its ability to depolarise.

Uses
It is used as a local anaesthetic.

17.3.2.5. Propoxycaine

Propoxycaine is a local anaesthetic of the ester type. It has a rapid onset of action and a longer duration of action than procaine.



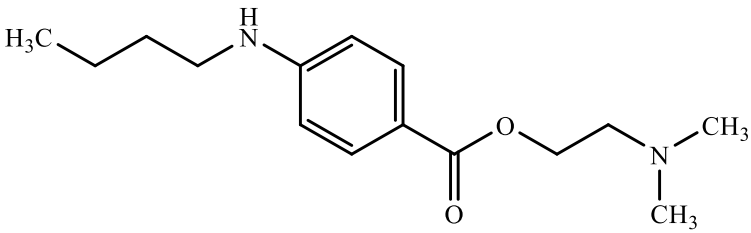
Propoxycaine

Mechanism of Action
Propoxycaine is a *para*-aminobenzoic acid ester having local anaesthetic activity. It binds to and inhibits voltage-gated sodium channels, thus blocks the ionic flux that is essential for nerve impulse conduction. This causes loss of sensation.

Uses
1) It is a local anaesthetic medication.
2) It was used in dental procedures in the 1950s.
3) It is combined with procaine to accelerate its onset of action and provide a long-lasting anaesthetic effect.
4) It i s used in patients who are allergic to amide local anaesthetics or are unresponsive to amide anaesthetics.

17.3.2.6. Tetracaine

Tetracaine is an ester-type local anaesthetic. Currently, it is available as a cream and patch in combination with lidocaine.



Tetracaine

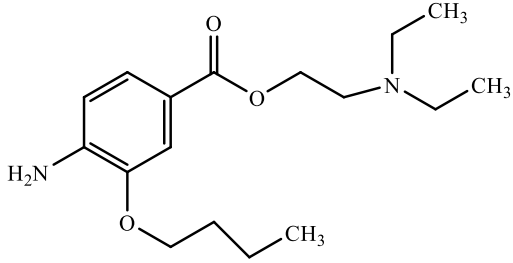
Mechanism of Action
Tetracaine produces local anesthesia by inhibiting the sodium ion channels involved in initiation and conduction of neuronal impulses.

Uses

1) It is used in combination with lidocaine as a local dermal analgesia patch for superficial dermatological procedures and superficial venous access.
2) It is also used in combination with lidocaine as a topical local analgesia cream for superficial dermatological methods.

17.3.2.7. Benoxinate

Benoxinate (or oxybuprocaine) is a local anaesthetic. It is used in ophthalmology and otolaryngology. It binds to sodium channe ls and reversibly stabilis es the neuronal membrane that reduces its permeability to sodium ions.



Benoxinate

Mechanism of Action

Benoxinate binds to sodium channel and reversibly stabilis es the neuronal membrane that reduces its permeability to Na^+ ions. Depolaris ation of the neuronal membrane is blocked, and hence the initiation and conduction of nerve impulses is blocked.

Uses

It is used to temporarily numb the f ront surface of the eye, while measuring the eye pressure or removing a foreign body.

17.4. LIDOCAINE/ANILIDE DERIVATIVES

17.4.1. Introduction

Lidocaine is a local anaesthetic and cardiac depressant. It is used as an anti - arrhythmic agent. Its actions are more intense and its effects are more prolonged than those of procaine. However, its duration of action is shorter than that of bupivacaine or prilocaine. Aniline, phenylamine, or aminobenzene is an organic compound consisting of phenyl group attached to an amino grou p, and aniline is the prototypical aromatic amine.

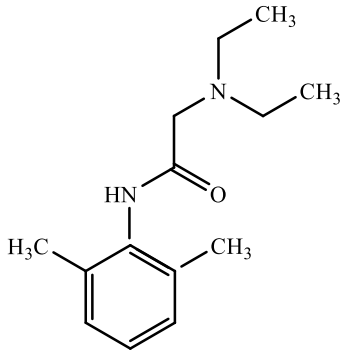
17.4.2. Study of Individual Drugs

The following anilide derivatives are discussed below:

1) Lignocaine,
2) Mepivacaine,
3) Prilocaine, and
4) Etidocaine.

17.4.2.1. Lignocaine

Lignocaine (or lidocaine and xylocaine) produces temporary loss of sensory, motor, and autonomic function when injected or applied close to neural tissue.



Lignocaine

Mechanism of Action

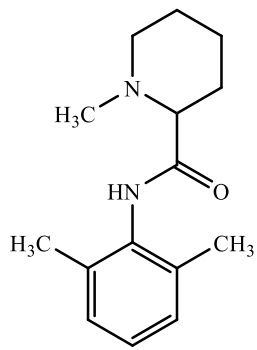
Lignocaine stabilises the neuronal membrane by blocking the ionic fluxes that is essential for the initiat ion and conduction of impulses , thus it affects the local anaesthetic action. It inhibits the fast voltage gated sodium channels in the neuronal cell membrane which are responsible for signal propagation, and thus disturbs signal conduction in neurons. Wit h sufficient blockage the postsynaptic neuron membrane will not depolarise and thus will not give rise to an action potential. This produces an anaesthetic eff ect by inh ibiting the propagation of pain signals to the brain and also by preventing their generation.

Uses

It is used for producing local or regional anaesthesia by penetration techniques such as percutaneous injection and intravenous regional anaesthesia, by peripheral nerve block techniques like brachial plexus and intercostal, and by central neural techniques like lumbar and caudal epidural blocks.

17.4.2.2. Mepivacaine

Mepivacaine is local anaesthetic. Chemically, it is related to bupivacaine , however pharmacologically it is related to lidocaine. It is used for infiltration, nerve block, and epidural anesthesia.



Mepivacaine

Mechanism of Action

Mepivacaine inhibits the generation and conduction of nerve impulses by increasing the threshold for electrical excitation in the nerve , by delaying nerve impulse propagation, and by decreasing the rate of rise of action potential.

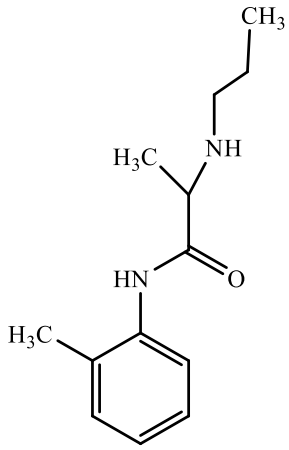
Generally, anesthesia progression is associated with the diameter, myelination, and conduction velocity of affected nerve fibres. The order of loss of nerve function first occurs with pain, followed by temperature, touch, proprioception, and finally the skeletal muscle tone.

Uses

It is used for the production of local or regional analgesia and anesthesia by local infiltration, peripheral nerves block techniques, and central neural techniques including epidural and caudal blocks.

17.4.2.3. Prilocaine

Prilocaine is a local anaesthetic and is pharmacologically similar to lidocaine. It is used for infiltration anesthesia in dentistry.



Prilocaine

Mechanism of Action

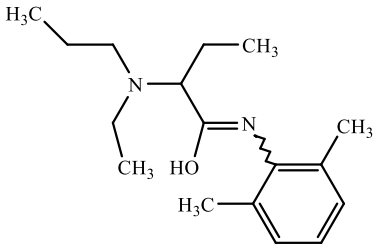
Prilocaine acts on the sodium channels in neuronal cell membrane, limits the spread of seizure activity, and decreases seizure propagation. The anti-arrhythmic actions of prilocaine are mediated through its effects on sodium channels in Purkinje fibres.

Uses

It is used as a local anaesthetic in dentistry.

17.4.2.4. Etidocaine

Etidocaine is a local anaesthetic. It is injected during surgical procedures and labour and delivery. It has a long duration of action. Its main disadvantage is increased in bleeding during oral surgery.



Etidocaine

Mechanism of Action

Etidocaine stabilises the neuronal membrane by blocking the ionic fluxes that is eesential for the initiation and conduct ion of impulses. Therefore, it a ffects the local anaesthetic action.

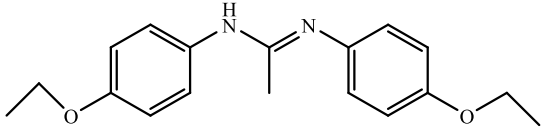
Uses

1) It is used as a local anaesthetic.
2) It is injected during surgical procedures and labour and delivery.
3) Clinically, it is used in epidural, infiltrative, and regional anaesthesia.

17.5. MISCELLANEOUS

17.5.1. Phenacaine

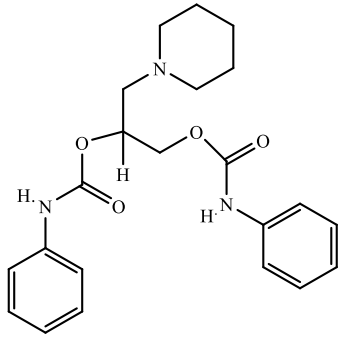
Phenacaine is an aromatic ether. It exists as white coloured, odourless and crystalline powder. It is structurally related to anilides, in which the aromatic ring is attached to a sp^2 carbon via nitrogen bridge. It is one among the oldest synthetic local anaesthetics. It is used for producing local anaesthesia of the eye.



Phenacaine

17.5.2. Diperodon

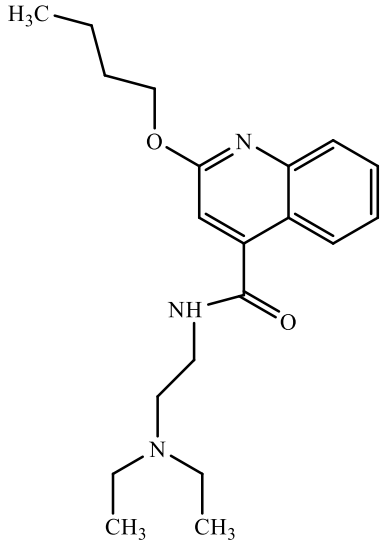
Diperodon is a carbamate ester. It is structurally similar to anilides, in which the aromatic ring is attached to sp^2 carbon via nitrogen bridge. It exists as white crystals that are soluble in water and are potent surface anaesthetic. It is used for anaesthetising anus, and is highly toxic in nature.



Diperodon

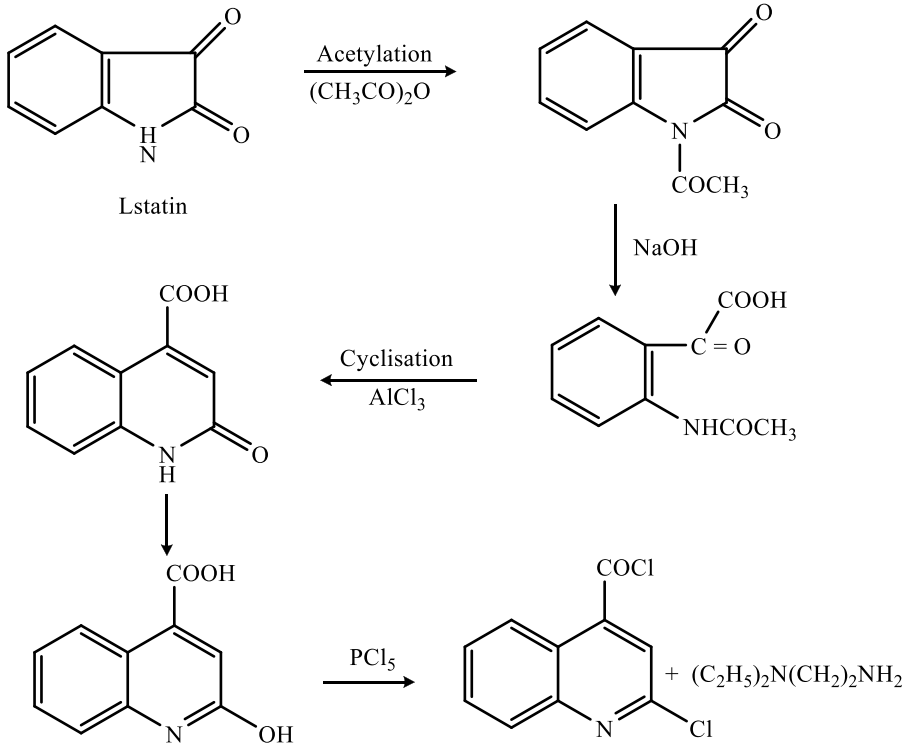
17.5.3. Dibucaine

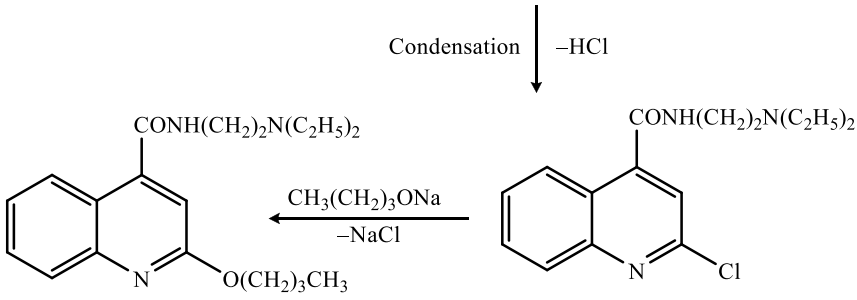
Dibucaine is a local anaesthetic of amide type . It is used for surface anaesthesia. It is one among the most potent and toxic long-acting local anaesthetics. I ts parenteral use is limited to spinal anaesthesia.



Dibucaine

Synthesis





Dibucaine

Mechanism of Action

Dibucaine inhibits the initiation and conduction of nerve impulses as it reduces the permeability of neuronal membrane to Na^+ ions by inhibiting the sodium channels. This reversibly stabilises the membrane and blocks depolarisation, thus does not give rise to a propagated action potential blocking the conduction.

Uses

It is used for producing local or regional anaesthesia by infiltration techniques like percutaneous injection and intravenous regional anaesthesia by peripheral nerve block techniques like brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks.

17.6. SUMMARY

The details given in the chapter can be summarised as follows:

1) **Local anaesthetic** agents act locally **to abolish the sensory perception over a local area**.
2) **Benzoic acid** is an aromatic carboxylic acid found naturally in plant and animal tissues.
3) **Cocaine** is a **benzoyl methylecgonine hydrochloride** (a benzoic acid ester). It is an alkaloid and is extracted from the leaves of coca tree (*Erythroxylum coca*).
4) **Hexylcaine** (or cyclaine or osmocaine) is a short -acting local anaesthetic. It acts by blocking the sodium channel conduction.
5) **Meprylcaine** (or epirocaine or oracaine) is a local anaesthetic having stimulant properties. Its structure is related to dimethocaine.
6) **Cyclomethycaine** is a benzoate ester. It is used as a local anaesthetic for surface application, and infiltration or nerve block.
7) **Piperocaine** is a benzoate ester. It is a local anaesthetic developed in the 1920s.
8) **Aminobenzoic** acid is an organic acid with UV absorption and anti -fibrotic properties.

9) **Benzocaine** is a surface anaesthetic which prevents the transmission of impulses on nerve fibres and at nerve endings.

10) **Butamben** is a local anaesthetic that occurs in the form of n -butyl-*p*-aminobenzoate.

11) **Procaine** is an ester type local anaesthetic.

12) **Butacaine** is a white crystalline benzoate ester used as a local anaesthetic.

13) **Propoxycaine** is a local anaesthetic of the ester type. It has a rapid onset of action and a longer duration of action than procaine.

14) **Tetracaine** is an ester -type local anaesthetic. Currently, it is available as a cream and patch in combination with lidocaine.

15) **Benoxinate** (or oxybuprocaine) is a local anaesthetic.

16) **Lidocaine** is a local anaesthetic and cardiac depressant.

17) **Lignocaine** (or lidocaine and xylocaine) produces temporary loss of sensory, motor, and autonomic function wh en injected or applied close to neural tissue.

18) **Mepivacaine** is local anaesthetic. Chemically, it is related to bupivacaine, however pharmacologically it is related to lidocaine.

19) **Prilocaine** is a local anaesthetic and is pharmacologically similar to lidocaine.

20) **Etidocaine** is a local anaesthetic. It is injected during surgical procedures and labour and delivery.

21) **Phenacaine** is an aromatic ether. It exists as white coloured, odourless and crystalline powder.

22) **Diperodon** is a carbamate ester. It is structurally similar to anilides, in which the aromatic ring is attached to sp^2 carbon via nitrogen bridge.

23) **Dibucaine** is a local anaesthetic of amide type. It is used for surface anaesthesia.

17.7. EXERCISES

17.7.1. True or False

1) Local anaesthetic agents act locally to abolish the sensory perception over a local area.
2) Benzoic acid is an aromatic carboxylic acid found naturally in plant and animal tissues.
3) Cocaine is a benzoyl methylecgonine hydrochloride. It is an alkaloid and is extracted from the roots of coca tree.
4) Hexylcaine is a intermediate-acting local.
5) Meprylcaine (or epirocaine or oracaine) is a local anaesthetic having stimulant properties.

6) Piperocaine is a benzoate ester. It is a local anaesthetic developed in the 1920s.
7) Benzocaine is a local anaesthetic which prevents the transmission of impulses on nerve fibres and at nerve endings.
8) Butamben is a local anaesthetic that occurs in the form of n -butyl-*p*-aminobenzoate.
9) Mepivacaine is topical anaesthetic.
10) Phenacaine is an aromatic ether.

17.7.2. Fill in the Blanks

11) _____ is a short-acting local anaesthetic.
12) _____ is a local anaesthetic having stimulant properties. Its structure is related to dimethocaine.
13) _____ acid is an organic acid with UV absorption and anti -fibrotic properties.
14) _____ is a surface anaesthetic which prevents the transmission of impulses on nerve fibres and at nerve endings.
15) _____ is a local anaesthetic and cardiac depressant.
16) _____ is local anaesthetic. Chemically, it is related to bupivacaine, however pharmacologically it is related to lidocaine.
17) _____ is a local anaesthetic and is pharmacologically similar to lidocaine.
18) _____ is an aromatic ether. It exists as white coloured, odourless and crystalline powder.
19) _____ is a carbamate ester. It is structurally similar to anilides.
20) _____ is a local anaesthetic of amide type.

Answers

1) True	2) True	3) False	4) False
5) True	6) True	7) False	8) True
9) False	10) True	11) Hexylcaine	12) Meprylcaine
13) Aminobenzoic	14) Benzocaine	15) Lidocaine	16) Mepivacaine
17) Prilocaine	18) Phenacaine	19) Diperodon	20) Dibucaine

17.7.3. Very Short Answer Type Questions

1) Define local anaesthetics.
2) What are benzoic acid derivative.
3) Give the structure of cocaine.
4) What is the mechanism of action of butaben?
5) Give the structure of propoxycaine
6) Write the uses of benoxinate
7) Write the mechanism of action of lignocaine
8) What are the uses of diperodon?

17.7.4. Short Answer Type Questions

1) Classify local anaesthetics.
2) Give the mechanism of action of local anaesthetics.
3) Write short note on benzoic acid derivative.
4) Give the synthesis of benzocaine.
5) Write the mechanism of action and uses of lignocaine.
6) Give the synthesis of dibucaine.

17.7.5. Long Answer Type Questions

1) Give the SAR and write about recent developments of local anaesthetics.
2) Write a detailed note on benzoic acid derivatives.
3) give the mechanism of action structure and uses of following drugs:
   i) Benzocaine
   ii) Butamben
   iii) Procaine
   iv) Tetracaine
   v) Lignocaine
   vi) Prilocaine
   vii) Phenacaine
   viii) Dibucaine

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About the Book

This textbook introduces details of Medicinal Chemistry with exercises after every chapter. Chapter 1, 2 and 3 introduces antihistaminic agents, gastric PPIs and antineoplastic agents. Chapter 4, 5, and 6 details on anti-anginal agents, diuretics, and anti-hypertensives. Chapter 7 to 10 illustrates anti-arrhythmics, anti-hyperlipidemics, coagulants, anticoagulants, and drugs of CHF. Chapter 11 to 15 details on hormonal drugs. Chapter 16 and 17 illustrates anti-diabetics and local anaesthetics.

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