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ACCORDING TO THE PRESCRIBED SYLLABUS OF
RAGIVGANDHI UNIVERSITY OF HEALTH SCIENCES
(KARNATAKA)

PHARMACOLOGY & TOXICOLOGY II

3RD PHARM D

4TH B PHARM

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IV B.Pharm
4.3: PHARMACOLOGY & TOXICOLOGY II (Theory)

50 hours

1.	Pharmacology of Autacoids and their Antagonists	
	Histamine and antihistaminics	1
	5-Hydroxytryptamine and its antagonists	1
	Lipid derived autacoids and platelet activating factor	1
2.	Pharmacology of Drugs Acting on Respiratory Tract	3
	Bronchodilators, Mucolytics, Expectorants, Antitussives, Nasal decongestants.	
3.	Pharmacology of Drugs Acting on Gastro Intestinal Tract	
	Antiulcer drugs, Antacids	1
	Laxatives and Purgatives	1
	Emetics and Antiemetics	1
	Appetizers, Digestants, Carminatives	1
4.	Pharmacology of Hormones and Hormone Antagonists	
	Thyroid and antithyroid drugs.	2
	Insulin, Insulin analogues and oral hypoglycemic agents	2
	Sex hormones and oral contraceptives	2
	Oxytocin and other uterine stimulants and relaxants	1
5.	Chemotherapy	
	a) Introduction	1
	b) Sulfonamides and Co-trimoxazole	1
	c) Penicillins and Cephalosporins	2
	d) Tetracyclins and Chloramphenicol	1
	e) Macrolides Aminoglycosides, Polyene & Polypeptide antibiotics.	2
	f) Quinolones and Fluoroquinolones	1
	g) Antifungal antibiotics	1
	h) Antiviral agents	2
	i) Chemotherapy of Tuberculosis and Leprosy	3
	j) Chemotherapy of Malaria	3
	k) Chemotherapy of Protozoal infections (amoebiasis, Giardiasis)	2
	l) Pharmacology of Anthelmintic drugs	1
	m) Chemotherapy of Cancer (Neoplasms)	2
6.	Bio Assays	
	Scope, Principles involved and General methods.	2
7.	Immunopharmacology	
	Pharmacology of immunosuppressants and stimulants	2

1. Principles of Toxicology
 - a) Acute, Subacute & Chronic toxicity
 - b) General principles of treatment of acute toxicity and acute poisoning . 1
 - c) Signs, Symptoms and treatment of acute and chronic poisoning due to.
 - i) Barbiturates ii) Alcohols iii) Benzodiazepines iv) Antidepressants 3
 - v) Neuroleptics vi) Insecticides vii) Snake bite viii) Heavy metals (iron, lead, mercury, arsenic).
2. Definitions of Drug-Drug, Drug-food interactions classification of Drug-Drug interaction. Basic concepts of mechanisms of drug – drug interactions. 2

1

-The term autacoid is derived from Greek: autos meaning self and akos meaning medicinal agent or remedy.

-They also called as local-hormones.

□ Classification:^(AIP)

1. Amine Autacoids: Histamine, 5-Hydroxy tryptamine^(Serotonin)
2. Lipid Derived A: Prostaglandins, Platelet activating factor.
3. Peptide A: Angiotensin

□ Histamine and Antihistaminics:

-Histamine is a chemical messenger present mostly within storage granules of mast cells and mediate allergic and inflammatory reactions and gastric secretion.

Location: is located in all tissues but rich amounts of histamine is present in skin, lungs and GIT.

Autacoids

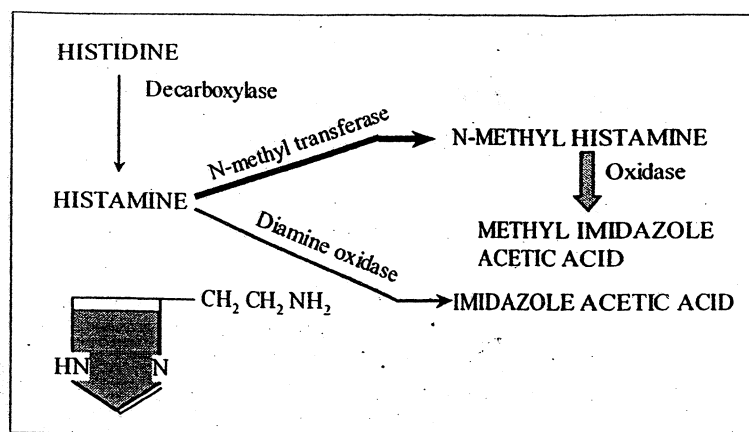


Figure Synthesis and Degradation of Histamine

- Release:

Histamine is released from mast cells by exocytosis during inflammatory or allergic reactions.

- Receptors:

- H_1

- H_2

- H_3

★ Pharmacological action of Histamine [SM, 2007]
[SM, Feb 2011]

□ Pharmacological action:

- Gastric secretion:

- Histamine stimulates the secretion of gastric acid by action on H_2 receptors.

- Smooth muscle effects:

- Histamine by acting on H_1 receptors cause contractions of the smooth muscle of the ileum,

the bronchi and the uterus.

large doses $\rightarrow$ abdominal cramps and colic

Cardiovascular effects:

- It dilates smaller blood vessels in humans by an action on H_1 receptors.

- Also increase the rate and the output of the heart by action on cardiac H_2 receptors.

CNS Effects:

- It is a transmitter in the CNS.

- The main role of histamine is as a mediator of some types of vomiting by action in the CNS.

Pathophysiological Roles:

+ triple response:

- red spot
- wheal
- Flare
- itching.

Allergic phenomena:

- is one of the mediators in hypersensitivity reactions. It is released from mast cells and cause broncho constriction and anaphylactic shock. H_1 antagonists are effective in controlling these changes.

- Triple response of Histamine [2M, Sep 2011]

pharmacol-
-Classify H_1 -receptor antagonists + Exs based on their clinical uses, Describe their
gical actions and therapeutic uses [10m, Feb 2010, Sep 2009]

As transmitter:

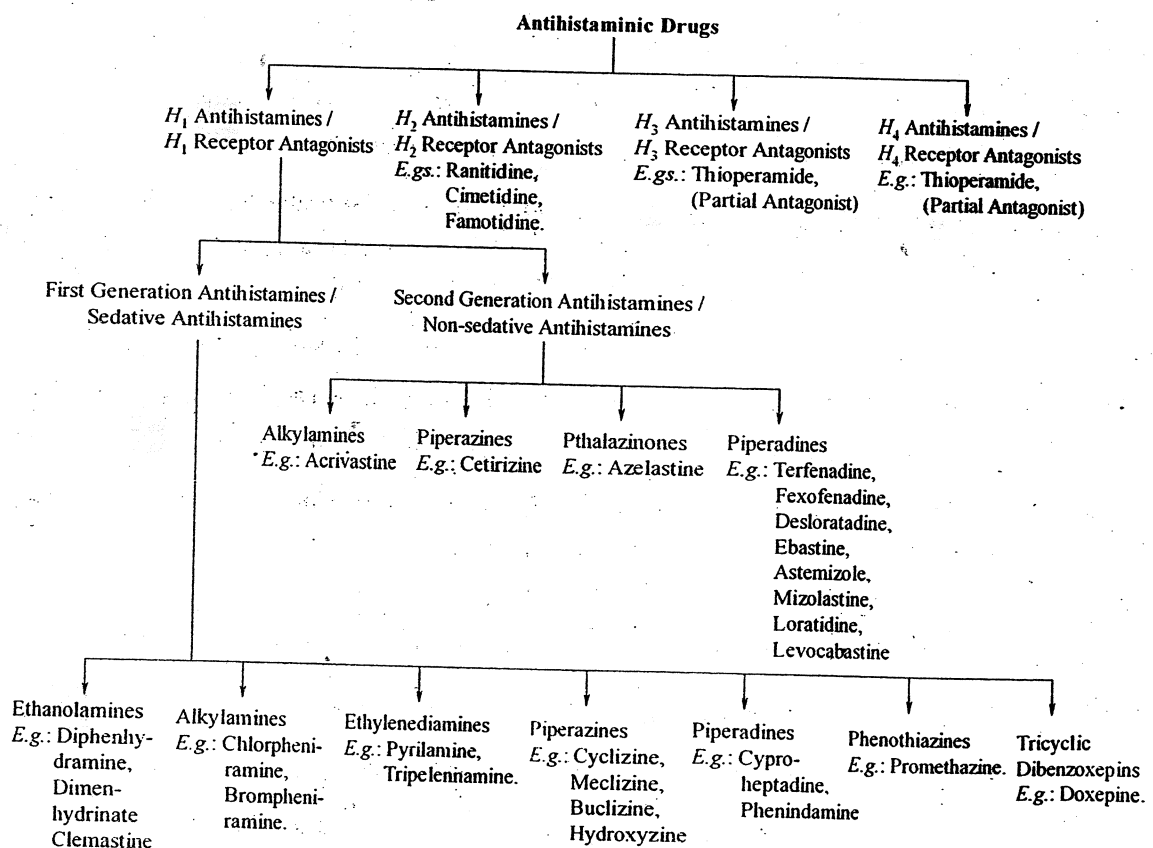
Histamine present in non mast cells of brain is involved in maintaining wakefulness.

- It also acts as transmitter in regulating body temp, cardiovascular function, etc.

□ Inflammation

- Histamine acts as a mediator of vasodilation and other changes that occur during inflammation. It promotes adhesion of leukocytes at the inflammatory site.

□ Antihistaminics:



H₁ Antagonists:

- These drugs do not influence the formation or release of histamine but, competitively antagonize the action of histamine at H₁ receptors.

1. First Generation / Sedative Antihistamines:

→ I. Highly sedative

Diphenhydramine

Promethazine

→ II. Moderately S:

Pheniramine

Meclizine

→ III. Mild S.

Chlorpheniramine

Dimethindene

Mechanism of Action:

- The antihistamines antagonize the actions of histamine by selective and competitive

binding to the histaminic receptors (H_1 and H_2). However, these drugs do not affect the formation and release of endogenous histamine.

Ex:

- diphenhydramine effectively antagonize the actions mediated through H_1 receptors.
- cimetidine, ranitidine block the H_2 receptor mediated actions.

Pharmacological Effects:

a) On Smooth muscles:

- These drugs antagonize the H_1 , mediated response of histamine such as contraction of bronchioles and contraction of smooth muscles of intestine.
- Reduce intestinal motility by relaxation.

b) ON CNS:

- May cause depression of the CNS.
- The degree of sedation depends on the lipid solubility of the drugs as it may pass through BBB.

- Toxic doses causes restlessness, excitement etc.

C- On capillary permeability:

Histamine $\longrightarrow$ dilation of capillaries $\longrightarrow$ $\uparrow$ in permeability $\longrightarrow$ oedema

Antihistamines $\longrightarrow$ block the increased capillary permeability and prevent the formation of oedema.

d- On Blood vessels:

IV Antihistamines $\longrightarrow$ a marked $\downarrow$ in BP

e- Membrane Stabilizing Property:

- The antihistamines may have varying proportion of membrane stabilizing property.

- Pharmacokinetics:

Absorption: are well absorbed orally and parenterally and easily pass through the gastrointestinal mucosa.

-Enumerate the therapeutic uses of antihistaminics [5M, May 2018]

Metabolism: $\frac{1}{2}$ go rapid first pass metabolism and may $\frac{1}{2}$ go self metabolism by inducing the cytochrome P450 enzymes.

-Excretion: through urine

Therapeutic Uses:

a-Allergic conditions:

-H₁ blockers are used in treating allergies caused by antigens acting on IgE-antibody sensitized mast cells.

b) Motion Sickness and Nausea:

-H₁ blocker such as diphenhydramine, cyclizine etc.

c) Treatment of Insomnia:

[Such as diphenhydramine] have strong sedative properties and can be used in the t of insomnia.

Adverse Effects:

- 1- Sedation ✓✓
 - 2- Fatigue
 - 3- Dizziness
- } on CNS

4- Dry mouth

5- Alteration of bowel movement.

6- Headach

2- Second Generation Antihistaminics:

Properties:

a) Higher H_1 selectivity and no anticholinergic effects.

b) Absence of CNS depressant property.

c) Additional anti-allergic mechanisms apart from histamine blockade.

Advantages than first generation:

- do not impair psychomotor performance

- produce no subjective effects

- no sedation.

- ^{do} not potentiate the actions of alcohol and benzodiazepines

Non-sedative antihistamine [2m, Ag 2010]

H_2 Antagonists:

-The H_2 receptors are mainly located on the basolateral membrane of the parietal cells of the gastrointestinal tract and are responsible for increasing the gastric $\bar{a}$ secretions, when histamine binds to them. The H_2 antihistamines antagonize the activity of H_2 receptors by blocking the binding of histamine to these receptors.

Ex:

Cimetidine

ranitidine

famotidine

-They are used in treatment of peptic ulcer diseases as they $\downarrow$ se gastric $\bar{a}$ secretion.

-Cimetidine [prototype]:

MOA:

Cimetidine results in potent inhibition of the gastric $\bar{a}$ secretion by selectively and competitively binding to the H_2 receptors

and antagonizing the actions of histamine. However it does not interfere with the formation and release of endogenous histamine.

Pharmacological Effects:

1. Reduced Gastric $\bar{a}$ secretion

2. Antihistaminic Action:

Cimetidine blocks all the actions of histamine, mediated through the H_2 receptors. It also block the histamine induced cardiac stimulation, relaxation of the uterine and bronchial smooth muscles.

Pharmacokinetics:

- is well absorbed orally
- 490 first pass metabolism [only 10 to 35%]
- reaches peak plasma concentration within 1-3 hrs of oral ad.
- in presence of food $\rightarrow$ $\uparrow$ its absorption.

Adverse Effects:

1- diarrhoea

2- constipation

3- muscular pain

4- Fatigue

5- Headache

6- delirium

7- hallucination

} IV administration.

Drug interactions:

-with antacids, proton pump inhibitors, that interfere with the rate of absorption and ultimately effect the bioavailability of cimetidine.

Uses:

1- Treatment of duodenal ulcers

2- Treatment of gastric ulcers

3- " " Stress induced ulcers

4- " " Zollinger- Ellison Syndrome

-This disease is characterized by hypersecretion of gastric H^+ due to excessive production of gastrin hormone. (firstline (proton pump inhibitor)

(2M) Feb/march 2011

Ranitidine:

- It is a more potent drug and has about 5 times more potency than cimetidine in the treatment of gastric ulcers.

Classes	Drugs	Mechanism of Action	Adverse Drug Reactions	Uses	Dosage and Route
H₁ - Antihistamines 1. First Generation / Sedative Antihistamines (a) Ethanolamines	Diphenhydramine	- Blocks the actions of histamine mediated via histaminic (H₁) and muscarinic receptors. - Inhibits serotonin reuptake.	- Sedation - Dizziness - Fatigue - Drowsiness - Disturbed Motor Incoordination	- Allergic Rhinitis - Motion Sickness - Rhinorrhoea - Antipsychotics induced Extrapyramidal side effects.	An oral dose of 25 - 50 mg t.i.d.
	Chlorpheniramine	- Competes with histamine for H₁ receptors in GIT, vasculature and respiratory tract. - Inhibits reuptake of serotonin.	- Sedation - Dizziness - Weakness	- Prophylactic measure in urticaria and rhinitis. - Motion sickness management. - Postural hypotension - Symptomatic Relief from Cough.	Oral Fixed Dose of 20 - 40 mg t.i.d or q.i.d.
	Pyrilamine	- Blocks histamine actions by competitively binding to H₁ receptors. - Its anticholinergic activity leads to moderate sedation.	- Angioedema - Dryness of Mouth, Eyes and Nose - Drowsiness - Urticaria - Blurred Vision	- Nasal Congestion - Sinusitis is associated with hay fever, flu and allergies.	An Oral Dose of 25 - 50 mg t.i.d.

Classes	Drugs	Mechanism of Action	Adverse Drug Reactions	Uses	Dosage and Route
(d) Piperazines	Cyclizine	- Exerts direct effect on labyrinthine reflexes. - Stimulates Chemoreceptor Trigger Zone (CTZ) - Possess Central Anticholinergic and Antimuscarinic Activity	- Dizziness - Drowsiness - Sedation - Dry Mouth - Urinary Retention - Hypersensitivity Reactions (Rarely)	- Motion Sickness - Relief from Cough.	An Oral Dose of 50 mg t.i.d.
(e) Piperadines	Cyproheptadine	Blocks the actions of histamine at H_1 receptors and thus reduces histamine induced vasodilatation and increased vascular permeability.	- Sedation - Anorexia - Epigastric Discomfort	Postural Hypotension	An Oral Dose of 4 mg t.i.d.
(f) Phenothiazines	Promethazine	Its active binding to H_1 receptor leads to blockade of histamine actions.	- Blurred Vision - Dizziness - Fatigue - Respiratory Depression - Neuroleptic Malignant Syndrome.	- Primary Effects of Parkinsonism - Hyper-sensitivity Reactions - Motion Sickness - During drug induced and post operative vomiting.	- An Oral Dose of 10 mg in day and 25 mg at night. - 25 – 50 mg by Deep i.m. Route.

Classes	Drugs	Mechanism of Action	Adverse Drug Reactions	Uses	Dosage and Route
2 nd Generation / Non-sedative Antihistamines	Terfenadine	Highly selective for H_1 receptors leading to blockade of actions of histamine.	Higher doses leads to polymorphic ventricular tachycardia.	- Allergic conditions such as rhinorrhoea, watery eyes. - Urticaria.	An oral dose of 60 mg b.i.d.
	Astemizole	Binds only to peripheral H_1 receptors thus antagonizing the actions of histamine	- Cardiac Arrest - Ventricular Arrhythmias - Papillaryitis - Angioedema.	- Seasonal Allergic Rhinitis - Chronic Idiopathic Urticaria.	An Oral Single Dose of 10 mg before meals.
	Cetirizine	- Highly selective towards H_1 receptors leading to blockade of histamine activities. - Inhibits the release of cytotoxic mediators like leukotrienes.	- Dizziness - Drowsiness - Headache - Gastrointestinal Distress.	Allergic conditions such as : - Rhinitis - Urticaria - Dermographism - Contact Dermatitis etc.,	A Single, Oral, daily of 10 mg.
H_2 Antihistamines	Cimetidine, Ranitidine, Famotidine.	Selectively and competitively binds to H_2 receptors, inhibiting the secretion of gastric acid. Thus they antagonize the actions of histamine.	- i.v. administration leads to slurred speech, hallucinations - Fatigue - Constipation - Blood Dyscrasias - Cimetidine leads to gynaecomastia, impotence etc., due to its antiandrogenic effects.	- Duodenal Ulcers - Gastric Ulcers - Stress-induced Ulcers - In Zollinger-Ellison Syndrome - Gastroesophageal Reflux Disease (GERD) - Adjuncts in Urticaria Treatment.	- Cimetidine : An Oral Dose of 400 mg t.i.d. or 800 mg OD. At night. - Ranitidine : 150 mg orally t.i.d or 300 mg at bed time. - Famotidine : An Oral Dose of 20 mg t.i.d or 40 mg at night.

□ 5-Hydroxytryptamine (5-HT)

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- 5-HT receptors [2M, Mar 2013]

- 5-HT antagonists [2M, Mar 2012, Sep 2009, Feb 2010, 2010]

- 5-HT Receptors:

- Four families of 5-HT receptors (5-HT_1 , 5-HT_2 , 5-HT_3 , 5-HT_{4-7}) comprising of 14 receptor subtypes have so far been recognized.

- All 5-HT receptors (except 5-HT₃) are G protein coupled receptors which function through ↓sing (5-HT₁) or ↑sing (5-HT₄) cAMP production or by generating IP₃/ DAG (5-HT₂) as second messengers.
- The 5-HT₃ is a ligand gated cation (Na⁺, K⁺) channel which on activation elicits fast depolarization.

- G-protein coupled receptors
- ↓sing cAMP

5-HT₁ receptors

- Five subtypes (5-HT_{1A}, B, D, E, F)
- They occur mainly in the brain.

- G-protein coupled receptors
- Generation of IP₃/ DAG

5-HT₂ receptors:

- three subtypes (5-HT_{2A}, 2B, 2C) receptors.
- act on smooth muscles and platelets.

- ligand gated cation channel
- on activation elicits fast depolarization

5-HT₃ receptors

- occur mainly in the peripheral nervous system.
- These receptors mediate indirect and reflex effects of 5-HT at:
 1. Somatic and autonomic nerve endings: Pain etc.
 2. Nerve endings in Myenteric Plexus: emetic reflex.

3. Area Postrema, a region of Medulla: Nausea, Vomiting.

5-HT₄ receptors: $\swarrow$ G-protein coupled receptors $\searrow$ $\uparrow$ cAMP production.

- Present in brain and peripheral organs [GIT, bladder and heart].

- The other receptors 5-HT₅, 5-HT₆ and 5-HT₇ are closely related to 5-HT₄ receptors. They are mainly located in brain.

Pharmacological Actions:

1. Cardiovascular system:

- Arteries are constricted by action on smooth muscle as well as dilated through release of EDRF by direct action of 5-HT.

- Also releases Adrenaline from adrenal medulla $\rightarrow$ cardiovascular reflexes.

- Not involved in the regulation of blood pressure.

2. Smooth Muscles:

- $\uparrow$ se in peristalsis in GIT $\rightarrow$ diarrhoea

- constricts bronchi

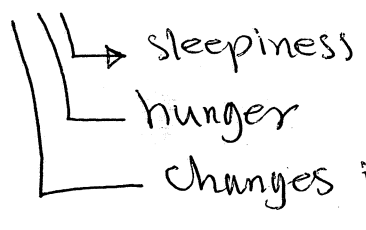
3. Glands:

inhibits gastric secretions
but ↑ mucus production

4. CNS:

- serves as an inhibitory transmitter in CNS.

direct admin into brain

- 
sleepiness
hunger
changes in body temp.

- Pathophysiological Roles of 5-HT₃

1- Neurotransmitter:

- Acts as neurotransmitter in the brain and is involved in sleep, temp regulation, vomiting, mood etc.

2- Nausea and Vomiting:

- Nausea and vomiting by cytotoxic drugs or radiotherapy is mediated by release of 5-HT by its action on 5-HT₃ receptors.

3. Migraine:

5-HT is said to initiate the vasoconstrictor phase of migraine.

4. Intestinal Motility:

□ Drugs Acting on 5-HT Receptors:

Agonists:

1. 5-HT_{1D} receptor agonists (e.g. Sumatriptan) are used in treatment of migraine.

2. 5-HT₄ receptor agonists, which stimulate the peristaltic activity are used in treating gi disorders.

Ex: Metoclopramide
Cisapride

3. LSD (is an ergot derivatives) is a non-selective 5-HT agonist, acts as a potent hallucinogen.

5-HT Antagonists:

1-Methysergide:

MoA:

-It is a potent and selective 5-HT_{2A} and 5-HT_{2C} receptor antagonist. Like Sumatriptan

(5-HT agonist), it also stimulates 5-HT receptors located in the brain. But sumatriptan is indicated for the treatment of acute migraine attacks whereas methysergide is intended for prophylaxis.

Pharmacological Effects:

a- On CNS:

- Exerts mild CNS stimulation, depression and LSD like hallucinogen reactions during therapy.

b) On Smooth Muscles:

Show vasoconstrictor and oxytocic effects.

c) In migraine: It is used only as a prophylactic agent in migrainous headaches.

Adverse Effects:

1- Nausea

2- Irritation of the GIT

3- Vertigo

4- Postural hypotension

Drug Interactions:

a-Methysergide interact with nicotine and adds to the vasoconstrictor effect, the patients should avoid tobacco smoking.

b- with ergot alkaloids → ↑ the risk of ergot toxicity

Contraindications:

- patients with:

1- Angina

2- Pulmonary disease

3- Valvular heart disease

4- During pregnancy

5- " Lactation — inhibit lactation.

6- " breast feeding → may cause symptoms of ergot poisoning in b.f → due to excreted in milk.

Clinical uses:

- It is used as a prophylactic agent in migraine.

2- 5-HT_{2A} Antagonists:

-ketanserin:

-It is the prototype for the drugs having 5-HT₂ receptor blocking activity.

-It also shows affinity towards α_1 adrenergic receptors and H₁ Histaminic receptors.

-Pharmacological Effects:

a) On Cardiovascular System:

- blocks the α_1 adr. recp $\rightarrow$ antihypertensive effects.
- In patients with normal blood pressure, effect is normal.

b- on platelets:

blocks platelet aggregation $\rightarrow$ in Raynaud's disease, it provide symptomatic relief.

c- on Bronchioles:

causes bronchoconstriction.

Adverse Effects:

- a- Nausea
- b- Dryness of mouth
- c- Dizziness

Uses:

As a prophylactic in Raynaud's disease.

3. 5-HT₃ Antagonists:

□ Ondansetron:

- It is the prototype drug for antiemetic activity.

- MOA:

- The antiemetic action of ondansetron is partly central and partly peripheral.

- It acts by blocking the depolarising action of 5-HT on the 5-HT₃ receptors located in the area postrema of the brain as well as in gut.

- Anticancer drugs and radiations induce nausea and emesis by causing cellular damage. This leads to release of 5-HT from the intestinal mucosa which activates the peripheral vagal afferent nerves in the gut. These emetogenic impulses are then carried to nucleus tractus solitarius (NTS) and chemoreceptor trigger zone (CTZ) of the brain.

- Ondansetron acts by blocking this relay of emetogenic impulses peripherally as well as centrally.

- Ondansetron [2M, Sep 2011]

- Pharmacokinetics:

- The oral bioavailability of ondansetron is 60-70%.
- It undergoes first pass metabolism.
- It is excreted through urine and faeces.

□ Adverse Effects:

- a) Headache
- b) Constipation
- c) Abdominal pain
- d) Diarrhoea

□ Contraindications: Contraindicated in patients with hypersensitivity.

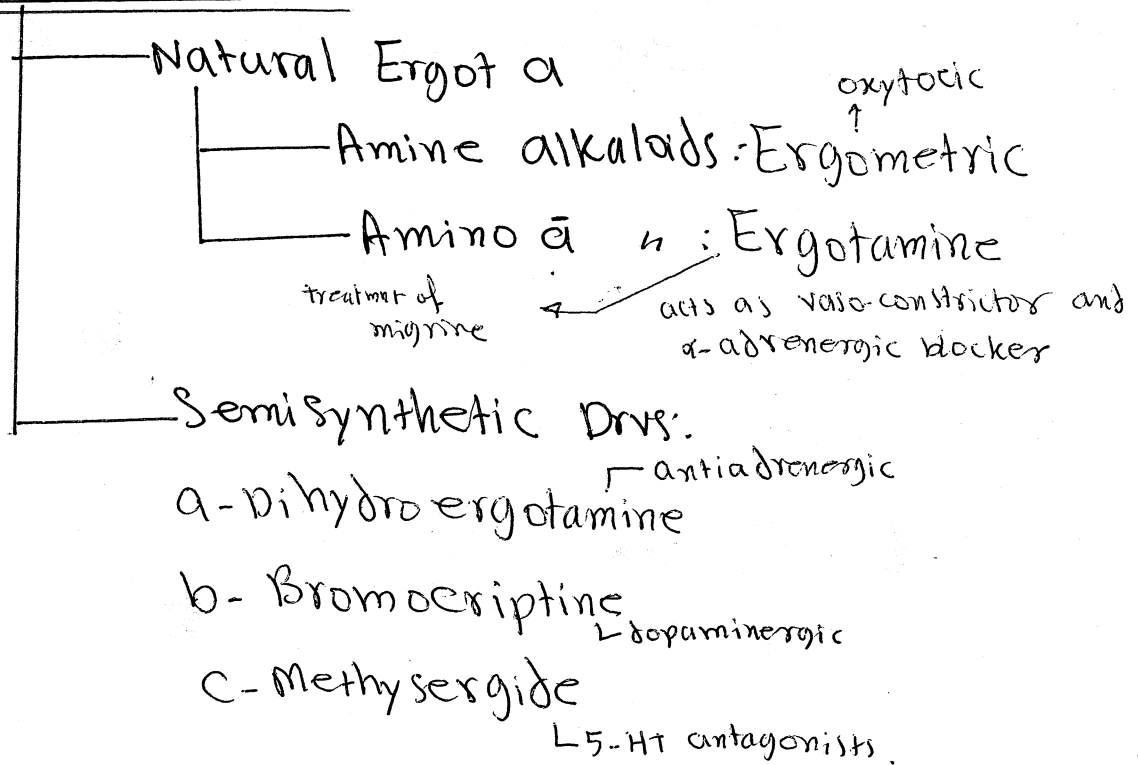
- Uses:

- Vomiting and nausea associated with cancer chemotherapy and radiotherapy, and treatment of postoperative nausea and vomiting.

□ Other Drugs affecting 5-HT System:

- Synthesis inhibitor: P-chlorophenylalanine
- uptake " : Fluoxetine
- Storage " : Reserpine

1. Ergot Alkaloids:



- Actions:

- Ergot alkaloids exert their effect through 5-HT receptors, adrenoceptors or dopamine receptors. They all cause stimulation of smooth muscle. Some of them are selective for vascular smooth muscle and others act mainly on the uterus.

- Pharmacokinetics:

- They are poorly absorbed orally due to first pass metabolism and are absorbed greatly by sublingual or rectal administration.

They are metabolized in the liver and are excreted primarily in bile.

- cross BBB.

▫ Adverse effects:

Nausea, vomiting, abdominal pain, weakness,

Lipid Derived Autacoids And Platelet Activating Factor:

Lipid Drived Autacoids:

- Prostaglandins (PGs) and Leukotrienes (LTs) are the major lipid derived autacoids. They are biologically active derivatives of 20 carbon atom polyunsaturated essential acids that are released from cell membrane phospholipids.

- The main source of prostaglandins and Leukotrienes is arachidonic acid.

- Eicosanoids are synthesized from arachidonic acid by two major pathways.

1. Cyclooxygenase pathway:

2. Lipoxygenase pathway

- Cox pathway generates eicosanoids with a ring structure (Prostaglandins, thromboxanes and prostacyclins).

cox — cox-1
 \ cox-2

- Write about the lipid derived autacoids [5M, Ag 2010]
- Platelet activating Factor (PAF) [2M, Sep 2011]

-Eicosanoids produced by COX-1 participate in physiological functions: secretion of mucus for protection of gastric mucosa, haemostasis etc while those produced by COX-2 → inflammatory and other pathological changes.

2-Lipoxygenase pathway operates mainly in lung, WBC and platelets.

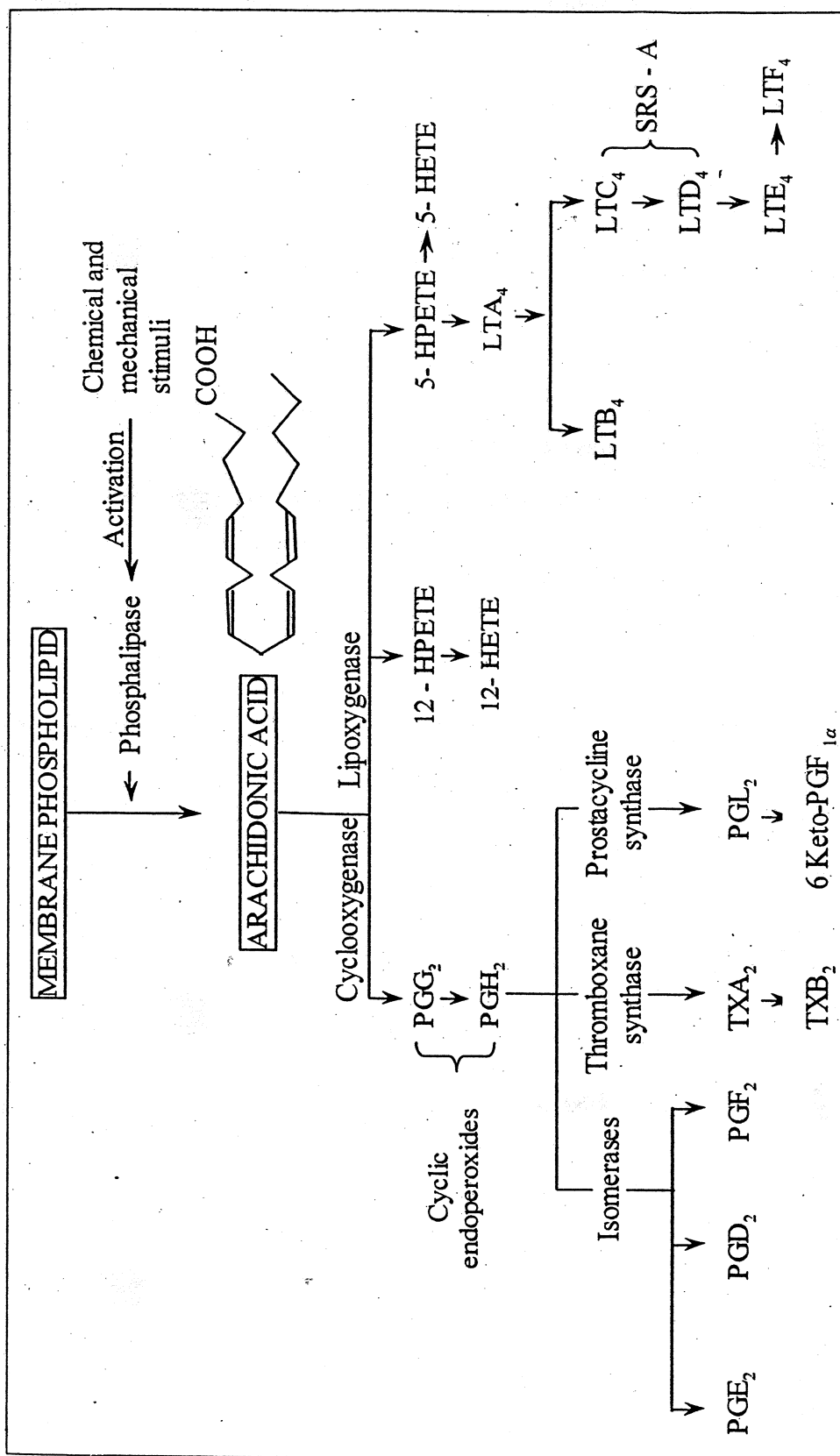
-Inhibition of synthesis:

-The substances synthesised by cyclooxygenase can be inhibited by non-steroidal anti-inflammatory drugs (NSAIDs). Ex: Aspirin.

1. Prostanoids:

-The term prostanoid includes prostaglandins and thromboxanes.

-There are mainly five classes of prostanoid receptors and all of them are typical G-protein coupled receptors.



Pharmacological Actions and Pathophysiological Roles:

- $\text{PGF}_{2\alpha}$ is a naturally occurring prostaglandin.

It is administered intra-amniotically to induce labor or abortion within the first trimester.

- PGE_1 $\rightarrow$ mainly used to maintain a patent ductus arteriosus in infants with congenital defects.

- $\text{PGE}_1 \rightarrow$ Vasodilation - Bronchodilation

- $\text{PGE}_2 \rightarrow$ Renal vasodilation, reduce secretion of stomach acid, sedation

- $\text{PGF}_2 \rightarrow$ Stimulate uterine smooth muscle contraction.

$\text{PGD}_2 \rightarrow$ weak inhibitor of platelet aggregation.

Thromboxane A is a potent inducer of platelet aggregation. And also is a potent broncho constrictor.

Role of Prostanoids in inflammation:

- Inflammatory response is always accompanied by release of prostanoids, mainly PGE_2 and PGI_2 .

- In areas of acute inflammation PGE_2 and PGI_2 are generated by local tissues and blood vessels and mast cells release PGD_2 . In inflammation prostanoids stimulate some responses while ↓ing other.

- PGE_2 , PGI_2 and PGD_2 are potent vasodilators and synergise with other inflammatory vasodilators like histamine and bradykinin, to cause inflammation and pain. The anti-inflammatory effects of NSAIDs is by prevention of these actions of prostaglandins.

2. Leukotrienes:

- Are produced in the lipoxygenase pathway.

Receptors:

LTB_4 and Cysteinyl Leukotrienes have separate receptors. All Leukotriene receptors function through the IP_3 / DAE transducer mechanism.

Actions:

a) Cardiovascular system and blood:

- Small amounts of LTC_4 and LTD_4 given intravenously cause a rapid, short-lived fall in B.P and significant constriction of small coronary resistance blood vessels.

- LTD_4 ↑ se nasal blood flow, and increases local vascular permeability. Migration of neutrophils through capillaries and their clumping at sites of inflammation in tissue is promoted by LTB_4 .

Role:

- Leukotrienes are important mediators of inflammation. They are produced locally at the site of injury.

b. Smooth muscle:

- They are potent spasmogens.

- They may also cause an increase in mucus secretion.

-Role:

The cysteinyl leukotrienes are the most important mediators in human allergic asthma.

C-Afferent Nerves:

-Like PGF_2 and PGI_2 , LTB_4 also sensitizes the afferent nerves carrying pain impulses and contributes to pain and tenderness of inflammation.

-Role of Leukotrienes in inflammation:

-They contribute to the bronchial-hyper reactivity in asthma patients.

-Cysteinyl-Leukotriene receptor antagonists zafirlukast and montelukast are used in treatment of asthma.

-Clinical uses:

GI: Misoprostol is used to prevent peptic ulcers in patients taking NSAIDs.

Ophthalmic:

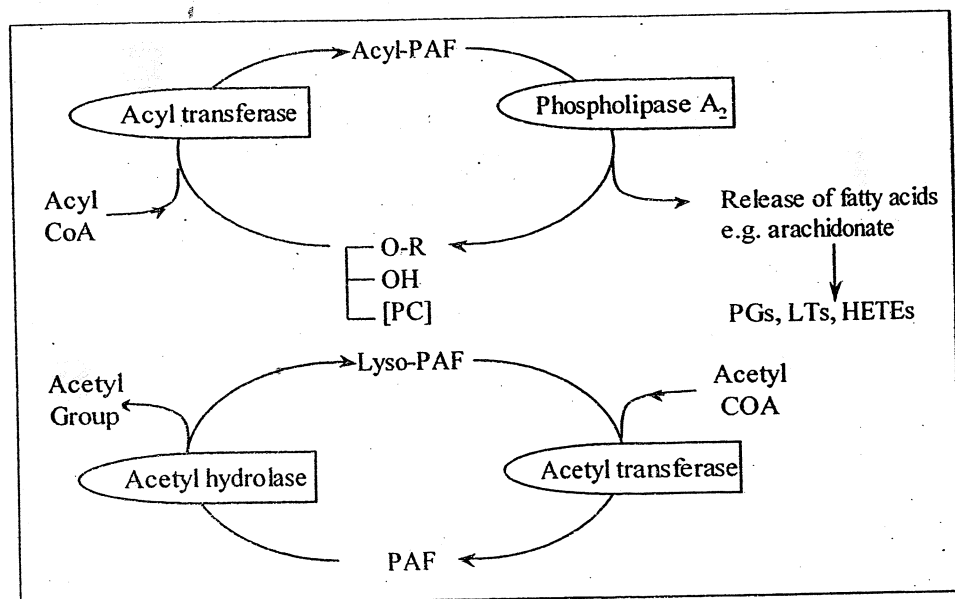
Latanoprost eye drops are used in treatment of open-angle glaucoma.

□ Platelet Activating Factor (PAF):

-It is an important mediator in both acute and persisting allergic and inflammatory phenomena.

Synthesis and Degradation:

-It is synthesised from precursor phospholipids present in cell membrane. It is derived from its precursor, acyl-PAF by phospholipase A_2 activity resulting in lyso-PAF, which is then acetylated to give PAF. This in turn can be deacetylated to lyso-PAF. PAF is generated and released from most inflammatory cells when these are stimulated and from platelets on stimulation with thrombin.



Actions:

1. Platelets:

- cause aggregation and release of granule contents in platelets. It also release thromboxane A_2 . $TXA_2 \rightarrow$ intravascular thrombosis.

2. $WBCs$: is a potent chemotaxin for neutrophils and monocytes. It induces ~~de~~degranulation of eosinophils.

3. Blood Vessels: $\uparrow$ se vascular permeability and wheal formation. also cause vasodilation.

4. Visceral smooth muscle: $\rightarrow$ contraction of smooth muscles $\rightarrow$ by direct action or by release of PGs , TXA_2 .

- a potent bronchoconstrictor.

5. Stomach:

causes ulcers in stomach.

□ Mechanism of Action:

-The PAF receptors are G-protein coupled receptors which exerts most of the actions through intracellular messengers IP_3 , $DAg-Ca^{2+}$ release. The actions of PAF are mediated or increased by PGI_2 , TXA_2 and LT_5 .

PAF Antagonists:

Competitive antagonists of PAF and specific inhibitors of Lyso-PAF acetyl transferase can be useful anti-inflammatory and/or anti-asthmatic drugs.

-Alprazolam

-triazolam.

□ Pathophysiological Roles:

1. Inflammation:

-PAF is generated at the site of inflammation by leukocytes and participate in vasodilation, exudation etc.

2. Bronchial Asthma:

PAF plays a major role in causing bronchoconstriction, mucosal edema and secretions.

3. Anaphylactic Shocks:

Are associated with high circulating PAF levels.

4. Haemostasis and Thrombosis:

PAF participates in haemostasis by promoting platelet aggregation.

Student Notes

2

→ [5M, Mar 2012, 2007, Mar 2011]

□ Drugs used for Treatment of Bronchial Asthma:

- Asthma is primarily an inflammatory disease of bronchial smooth muscle.

- Asthma is a condition where there is an increased response of bronchi to various stimuli resulting in narrowing of the airways (constriction of bronchi).

- It is a clinical syndrome characterized by difficulty in breathing, cough, wheezing accompanied by increased mucosal secretion and increased respiratory rate.

- Pathophysiology of asthma:

- Asthma may be caused due to several factors like allergens, chemical irritants which trigger the mast cells to release the inflammatory mediators like histamine, Prostaglandins (PGs), leukotrienes (LTs), cytokines etc.

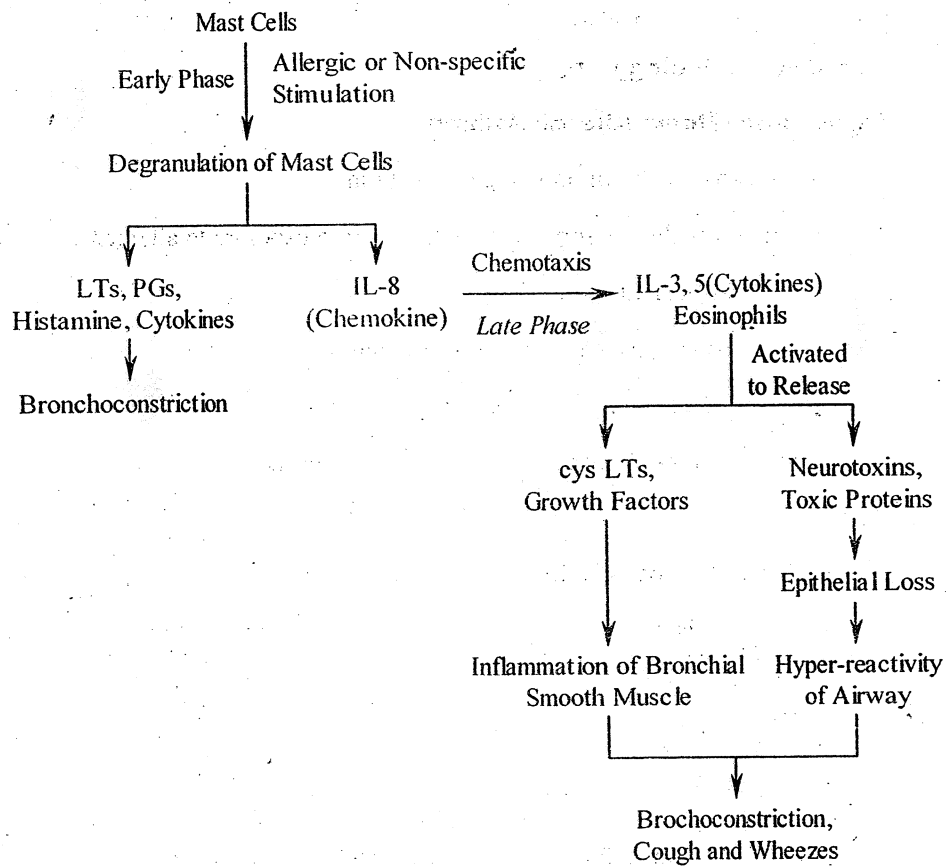
- These mediators cause bronchoconstriction, viscous mucous secretions resulting in airway obstruction.

Drugs Acting on Respiratory Tract

Phases:

Early phase or Immediate phase

Late phase



Types of asthma:

based on Etiology

- a - Extrinsic / Allergic / Atopic A.
- b - Intrinsic / non-Atopic / Idiosyncratic A.
- c - Mixed type (Both Extrinsic and Intrinsic) A:
- d - Exercise-Induced Asthma
(exercise or exposure to cold air)

a-Extrinsic:

- most common type of asthma
- due to exposure to allergens, etc.
- It is associated with:
 - Atopy
 - Family History
 - ↑ed Immunoglobulin E (IGE) levels.
- usually occurs in childhood.

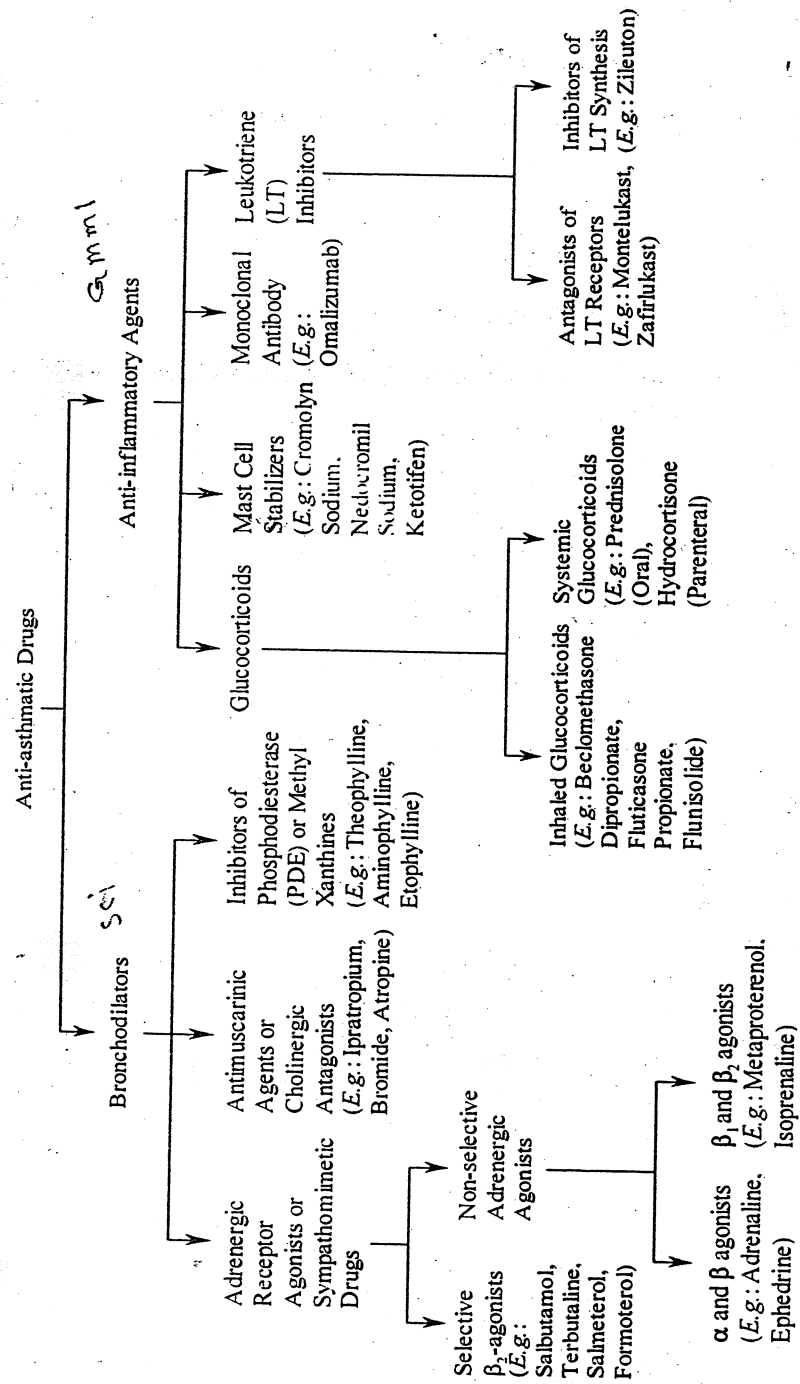
b-Intrinsic:

- occur due to some unknown cause.
- Family history is not seen.
- IgE levels are normal
- occur in the middle age.

c. In some cases asthma may be of both extrinsic and intrinsic type.

d. This may be precipitated by exercise or exposure to cold air.

Drugs used for Treatment of Asthma:



- classify bronchodilators and outline their MOA [5M, Sep 2017]

1. Broncho dilators:

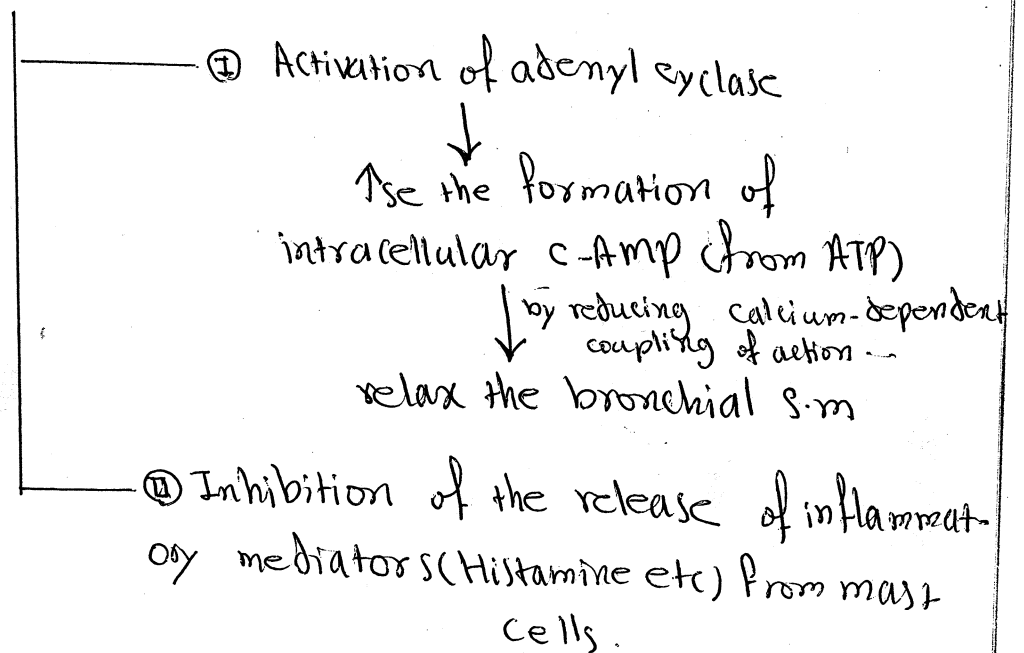
- These are the agents which cause the widening of the air passages (bronchial tubes) by the relaxation of bronchial smooth muscles.

i- Adrenergic Receptor Agonists/Sympathomimetic D:

- MOA:

- They act by directly stimulating the β_2 -adrenergic receptors present in the bronchial smooth muscle.

- This stimulation leads to the:



α- Selective β_2 - Agonists:

□ Pharmacological effects:

Stimulation of β_2 -receptors lead to:

- i- direct relaxation of bronchial S.M.
- ii- Inhibition of release of mediators from mast cells

iii- ↑ the mucociliary clearance from the airway

iv: Vasodilation.

- Salbutamol:

- Pharmacokinetics:

- absorbed from GIT.

- Only 10% of the inhaled drug reaches the bronchi.

- is excreted in urine.

- 40% first pass metabolism in the liver.

- Adverse effects:

i- Nervousness

ii - Restlessness

iii - muscle tremors

iv - Palpitation } less common

v - Tachycardia }

- Uses:

- treatment of acute asthma

- " " COPD

- Terbutaline:

- is not well absorbed from GIT.

- metabolised in the liver.

Adverse effects:

- i - Muscle tremors
- ii - Palpitation
- iii - Tachycardia

▪ Salmeterol

~~b-Non-selective Adrenergic Agonists:~~

i - α and β agonists:

- Adrenaline:

- Its weak bronchoconstriction (α action) is dominated by potent bronchodilation (β_2 action).

- But, due to its unwanted cardiac effects (β_1 action) its use in bronchial asthma is limited.

- Pharmacokinetics:

- Adrenaline is rapidly metabolized in the GIT by COMT (Catechol-O-Methyl Transferase) and MAO (Monoamine Oxidase). So, it is not given by oral route.

- It is also metabolized in the liver by MAO to metanephrine. The metabolites are excreted by the liver.

Adverse effects:

1. Tachycardia
2. Hypertension
3. Palpitation
4. arrhythmias (rarely).

-Contraindications:

- in heart diseases like angina, hypertension etc

-Uses:

1. used in the treatment of anaphylactic shock.
2. bronchial asthma.

-Ephedrine:

-Pharmacokinetics:

It is well absorbed on oral or parenteral administration. It is not inactivated by monoamine oxidase. It crosses the blood brain barrier. It is excreted unchanged in the urine.

-Adverse effects:

1. Hypertension
2. Tremors
3. sleeplessness

-Contraindications:

- Ephedrine is contraindicated in:

1. Open angle glaucoma
2. pregnant women.

-Uses:

- used in the treatment of mild chronic asthma.
- used in Hypotension
- As a nasal decongestant.

ii - β_1 and β_2 agonists:

- Metaproterenol:
- Isoprenaline

-Antimuscarinic Agents/~~cholinergic~~ Antagonists:

-MOA:

cholinergic antagonists act by binding to muscarinic receptors on bronchial smooth muscle and competitively inhibit the bronchoconstrictive action of ACh released from parasympathetic nerves. Thus they cause relaxation of bronchial smooth muscle.

a-Ipratropium Bromide:

-Pharmacokinetics:

- It is poorly absorbed from GIT on oral administration, hence it is given by aerosol inhalation or nebulized form. It is not absorbed from circulation.

-Adverse e:

- Nervousness

- dry mouth

- bad taste

-Uses:

- used in persistent asthma in combination with salbutamol.

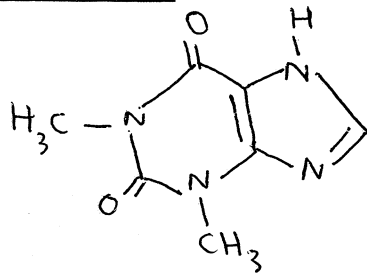
- treatment of COPD

- used in rhinorrhoea.

b-Atropine: $\swarrow$ use in mucous secretions
and reduced mucociliary clearance.

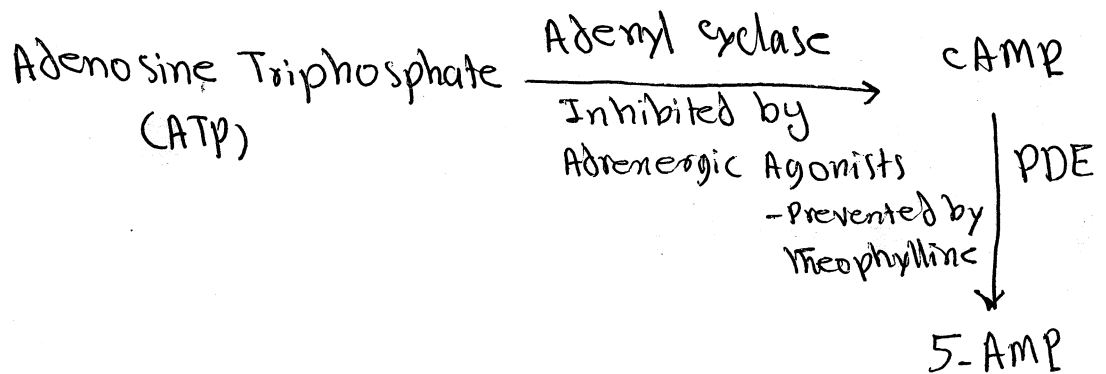
□ Inhibitors of Phosphodiesterase/Methylxanthines:

-Theophylline:



-MOA: (by one or both of the mechanism)

i - cAMP responsible for Bronchodilation: They inhibit the enzyme, phosphodiesterase (PDE) which is responsible for the degradation of cAMP and cGMP to 5-AMP and 5-GMP respectively. This inhibition of PDE leads to intracellular accumulation of cAMP which causes bronchodilation.



ii - They competitively antagonize the action of adenosine by binding to adenosine receptors. Adenosine is responsible for bronchoconstriction and release of mediators from mast cells.

Pharmacological Effects:

i) On Bronchial Smooth Muscle:

- Theophylline causes direct relaxation of bronchial smooth muscle.

- It also inhibits the release of inflammatory mediators from mast cells in bronchi.

ii) On CNS:

- is a mild CNS stimulant.

Euphoria[↓], Enhanced motor activity etc.

- Can also cause (in higher dose)

- Sleeplessness, nervousness etc

iii) On Cardiovascular System:

Heart:

- +ve inotropic action

↑ cardiac output

in high doses, → arrhythmias.

Blood vessels:

- Vasodilation. (But blood vessels in brain are constricted slightly).

iv- on Gastrointestinal Tract:

- Gastric irritation
- ↑ in gastric secretions.

v) Diuretic effect: cause mild diuresis.

v) on skeletal muscle:

- contraction of skeletal muscle.

Pharmacokinetics:

- Theophylline is well absorbed from gastrointestinal tract on oral ad.
- It is distributed to all parts of the body and crosses the placenta.
- It is metabolized in liver. A small amount of the drug is excreted unchanged in the urine.

- Adverse effects:

- 1- Nausea
- 2- Vomiting
- 3- Gastric irritation
- 4- Headache and insomnia

- Drug interactions:

- phenytoin ↑se the metabolism of th.
- cimetidine ↓se " " " "

- Contraindications:

- is contraindicated in peptic ulcers.

Uses:

- used in the treatment of mild to moderate asthma.
- used in management of COPD.
- " " " of apnoea in premature infants.

2- Anti-inflammatory Agents:

- Are the agents which are used in the treatment to reduce inflammation.

- Glucocorticoids:

(in asthma)

- MOA:

- Act by modulating the inflammatory response of the bronchial smooth muscle by inhibiting the release and the effects of the inflammatory mediators such as eosinophils, cytokines etc.

-Drug interactions:

-Phenobarbitone and phenytoin increase the metabolism of Glucocorticoids $\rightarrow$ $\downarrow$ bioavailability.

Contraindications:

- a) diabetes
- b) Osteoporosis

-Pharmacological Effects: Anti-inflammatory actions (Antiasthmatic effects)

- Glucocorticoids inhibit.
 - cytokine production
 - Accumulation of eosinophils and leukocytes in the bronchi.
 - Phospholipase A_2 , thereby preventing eicosanoid synthesis and PAF. They reduce mucous secretion and vascular permeability.
 - The synthesis of IL-3 which is responsible for the production of mast cells.

a) Inhaled Glucocorticoids:

- They are useful for long-term treatment.

Ex:

- Beclomethasone dipropionate
- Flunisolide
- Budesonide

Pharmacokinetics:

- They are deposited on the lungs, pharynx and a small amount is swallowed on inhalation.
- The swallowed g. are absorbed from GIT and $\frac{1}{4}$ go extensive first-pass metabolism in the liver. Only a small amount of the absorbed drug reaches the systemic circulation.
- They do not cross placental barrier and hence are safe during pregnancy.

Adverse effects:

- Dysphonia (voice changes)
- Oropharyngeal candidiasis

Uses:

- Are first line drugs for chronic persistent asthma.

b) Systemic Glucocorticoids:

- They are used only for a brief period (7-10 days) because of their severe adverse effects.

- Ex:

- Prednisolone (oral),
- Hydrocortisone (parenteral).

Pharmacokinetics

- They are bound to plasma proteins. ^(orally or par)
- They go first-pass hepatic metabolism.
- The metabolites are excreted in the urine by conjugation with glucuronic acid.

Adverse effects

- i - candidiasis
- ii - mood disturbances

Uses

- used for the treatment of severe acute asthma.

3-mast cell Stabilizers:

Cromolyn sodium and Nedocromil sodium:

MOA:

- They act by inhibiting the degranulation of mast cells and thereby preventing the release of inflammatory mediators.

Pharmacological Effects

a- They prevent the release of inflammatory mediators from mast cells in the bronchi.

b) They inhibit peripheral cough reflexes.

c) " " the accumulation of leukocytes in the airway.

Pharmacokinetics

Cromolyn and nedocromil are poorly absorbed from GIT. They are administered by inhalation.

- excrete in urine and bile.

Adverse effects

Nausea

Head ache

Throat Irritation

Hypersensitivity reactions like rashes.

Clinical Uses

a- In prophylactic treatment of asthma

b- allergic rhinitis.

4. Monoclonal Antibody:

Omalizumab:

MOA:

Inhibits IgE binding on mast cells thereby preventing allergen-induced activation of mast cells.

ADR

- reactions at injection site.

- In the treatment of moderate to severe asthma.

5. Leukotriene (LT) Inhibitors:

-Leukotrienes are the potent inflammatory mediators which cause bronchoconstriction, ↑sed mucous secretion etc.

-These effects of LTs can be inhibited either by:

- i- blocking the actions of LTs at cysLT-receptors or
 - ii- Blocking the synthesis of cysLTs. Ex: montelukast and Zafirlukast
- Ex: Zileuton

□ Treatment of Asthma:

1- Mild ^{episodic} intermittent Asthma:

Short acting selective B_2 -agonists like salbutamol is administered by inhalation during each attack. regular management therapy is not necessary.

2. ^{persistent} Chronic asthma

a- Mild chronic asthma:

- Inhaled short acting selective B_2 -agonist (salbutamol) is given during the attack.

Regular maintenance therapy involves use of inhaled glucocorticoids (low dose) or inhaled Cromolyn sodium.

b-Moderate chronic Asthma:

- Inhaled short acting selective β_2 -agonist (Salbutamol) is given during the attacks.

- Regular maintenance therapy with inhaled glucocorticoids (high dose) and long acting β_2 -agonists like Salmeterol is given by inhalation.

c-Severe Chronic Asthma:

- Inhaled short acting selective β_2 -agonists like Salbutamol.

- If the symptoms are not controlled by salbutamol, $\rightarrow$ oral glucocorticoids are given for a few days.

- Regular maintenance therapy with inhaled glucocorticoids of high doses (1600 μ g/day) and inhaled selective β_2 -agonist (Salmeterol) is given twice a day.

- In addition to this, oral theophylline / oral salbutamol may be given until the continuous symptoms are reduced.

3-Acute Asthma:

- Inhaled β_2 -agonists (short acting) during an acute attack.

- Salbutamol (inhaled) is preferred drug.

- If the acute symptoms are not controlled by salbutamol, $\rightarrow$ slow I.V. aminophylline.

4. Severe Acute Asthma:

a) Systemic glucocorticoids (parenteral) like hydrocortisone IV. (100mg three daily) [only for few days (7 to 10 days)].

b- Salbutamol and ipratropium combination should be given as inhalations at frequent intermissions.

c- Dehydration and respiratory insufficiency should be corrected with saline and oxygen inhalation respectively.

d- Salbutamol or terbutaline injection should be given to treat intense bronchospasm.

Table Overall Summary of Antiasthmatics

Classes	Drugs	Mechanism of Action	Adverse Drug Reactions	Uses	Dose
Bronchodilators 1. Adrenergic Receptor Agonists / Sympathomimetics (a) Selective β_2 Agonists	Salbutamol, Terbutaline, Salmeterol	Inhibits release of inflammatory mediators from mast cells. – Stimulates β_2 receptors in Bronchi which causes activation of adenyl cyclase leading to increased camp.	– Tremors – Palpitation – Tachycardia – Hypokalemia	– In Acute Asthma – In COPD	– Salbutamol Oral: 2 – 4 mg tid Parenteral : 0.25 – 0.5mg. Inhalation : 100 μ g. – Terbutaline Oral: 5 mg b.i.d or t.i.d. Parenteral : 0.25 mg t.i.d. Inhalation : 250 μ g.
	Adrenaline	Same as above	Same as above	– Limited use in Bronchial Asthma – In Anaphylactic Shock	
	Meta-proterenol	Same as above	-	– In Acute Asthma	Oral : 20 mg t.i.d. Parenteral : 0.5 mg.
2. Antimuscarinic Agents/Cholinergic Antagonist	Ipratropium Bromide	Inhibits Bronchoconstrictive Action of Ach by Binding to Muscarinic Receptors	– Dry Mouth – Bad Taste – Nervousness	– In the Treatment of Persistent Asthma in Combination with Salbutamol – In COPD. – In Rhinorrhoea.	40 – 80 μ g. t.i.d.
3. Inhibitors of Phosphodiesterase / Methyl Xanthines	Theophylline	It inhibits PDE which is responsible for the degradation of camp.	– Dyspepsia – Headache – Insomnia – Gastric Irritation	– In Mild to Moderate Asthma – In Apnoea. – In COPD.	100 – 300 mg. t.i.d.

Classes	Drugs	Mechanism of Action	(ADR)	Uses	Dose
Antiinflammatory Agents					
1. Glucocorticoids					
(a) Inhaled Glucocorticoids	Beclomethasone, Fluticasone	Inhibits the release of inflammatory mediators like eosinophils, cytokines and eicosanoids	- Dysphonia - Oropharyngeal Candidiasis	- In Chronic Asthma - Persistent Asthma	- Beclomethasone: 100 µg t.i.d. - Fluticasone: 100-250 µg b.i.d.
(b) Systemic Glucocorticoids	Prednisolone, Hydrocortisone	Inhibits the release of inflammatory mediators like eosinophils, cytokines and eicosanoids	- Hyperglycemia - Mood Disturbances - Candidiasis	- In severe acute asthma when it is not controlled by 2-agonists.	
2. Leukotriene (LT) Inhibitors					
(a) Antagonists of LT Receptors	Montelukast, Zafirlukast	Competitively antagonize the actions of cyst-LTs which cause bronchoconstriction.	- Dyspepsia - Headache	- In Prophylactic Treatment of Asthma	- Montelukast: 10 mg OD. - Zafirlukast: 20 mg b.i.d.
(b) Inhibitors of LT Synthesis	Zileuton	Specific inhibition of 5-lipoxygenase which catalyzes the formation of LTs from arachidonic acid.	- Dyspepsia - Hepatic Toxicity	- In Prophylactic Treatment of Asthma - To relieve Asthma induced Bronchospasm	600-800 mg 3-4 times/day.
3. Mast Cell Stabilizers					
	Cromolyn and Nedocromil Sodium	Inhibits degranulation of mast cells thereby preventing release of mediators	- Headache - Throat Irritation - Rashes - Joint Swelling	- In Prophylactic Treatment of Asthma.	Cromolyn: 1-5 mg 5 times daily.
	Ketotifen	Cromolyn like action	- Sedation - Dizziness - Dry Mouth - Rashes - Weight Gain	- In Prophylactic Treatment of Asthma - In Allergic Conjunctivitis	1-2 mg b.i.d.
4. Monoclonal Antibody					
	Omalizumab	Inhibits IgE binding on mast cells thereby preventing allergen-induced activation of mast cells.	- Reactions at injection site	- In the treatment of moderate to severe Asthma.	

Drugs Used to treat cough:

- Cough is a protective reflex mechanism that removes foreign particles and secretions from air passages.

- treatment: ^(PEAA)

1. Pharyngeal Demulcents:

- Sooth the throat and provide relief in dry cough arising from throat.

Ex:

cough drops, lozenges, glycerine and liquorice.

2- Expectorants (Mucokinetics)

a- Bronchial Secretion Enhancers:

• Sodium or potassium citrate, potassium iodide
Vasaka etc.

b- Mucolytics:

Bromhexine, Ambroxol, Acetyl cysteine etc.

3- Anti tussives (cough centre suppressants)

a- opioids: Codeine, Pholcodeine

b- Nonopioids: Noscapine, Dextromethorphan etc

c- Antihistaminics: Chlorpheniramine,
Diphenhydramine

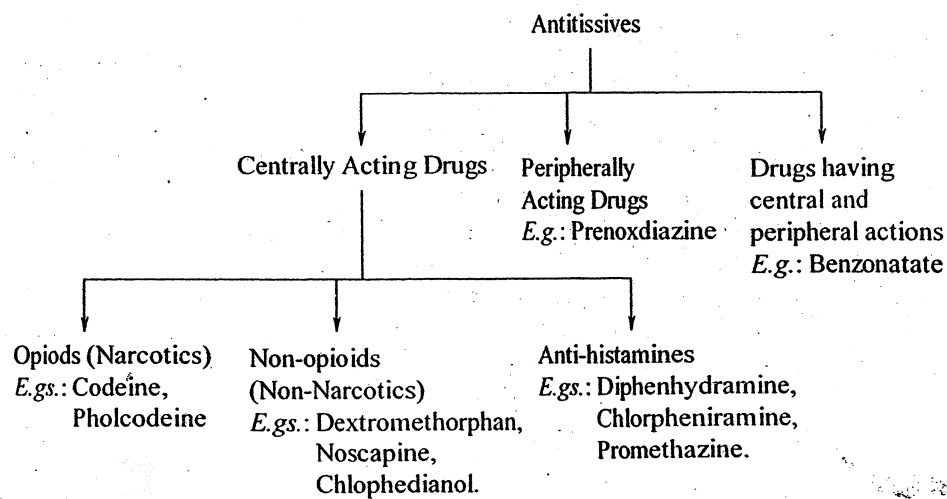
- Drugs used in the treatment of cough [5M, Feb 2010 - 2009]

4-Adjuvant Antitussives: Bronchodilators such as Salbutamol, Terbutaline

Anti-Tussives:

- Anti-tussives are the drugs used for the symptomatic relief of dry cough.

- They act by suppressing the cough centres either centrally or peripherally or both.



1. Centrally acting Drugs:

- They suppress the cough centres present in the CNS and increasing the threshold of cough.

a- Opioids (Narcotics):

- Codeine (methyl morphine).

□ Anti-tussive [2M, Nov 2013]

-MOA:

-Codeine suppress the cough centre in the medulla by binding to opioid receptors present in the CNS. Thereby, it increases the threshold of cough.

-Pharmacological Effects:

-on CNS:

-Analgesia

-Sedation

-Euphoria

- produce respiratory depression

- suppresses the cough centre

- Stimulates CTZ $\xrightarrow{\text{in low}}$ Nausea and vomiting.

suppress CTZ in large dose.

-On Cardiovascular system

- Higher dose:

1. Hypotension

2. bradycardia

3. cerebral vasodilation

iii) On GIT:

- ↓ GI secretion
- Delays gastric secretion

v) On smooth muscles:

- contraction of urinary sphincter
- mild bronchoconstriction

- Pharmacokinetics:

- codeine is well absorbed on oral ad.
- metabolism in liver
- excretion in urine.

- Adverse effects:

- i- constipation
- ii- Mild sedation
- iii- Bronchospasm
- iv- Nausea vomiting.

- Drug interactions:

- with sedatives, alcohol.

Contraindications

in

- Bronchial asthma (as it causes bronchoconstriction).
- Hypotension
- infants less than 2 years.

uses

- An antitussive
- treatment of diarrhoea
- analgesic.

- Pholcodeine:

10-15mg b.i.d orally.

b) Non-Opioids (Non-Narcotics):

- Dextromethorphan:

- It is less toxic and as effective as codeine.

- Adverse effects:

- Nausea
- Dizziness
- confusion

Dose: 10-20 mg thrice daily

Noscapine:

-Adv:

-Nausea/and Headache

-(High doses) bronchoconstriction and Hypotension.

C- Antihistaminic Agents:

-H₁ antihistamines are used in some cough formulations. They do not suppress the cough centre. But, due to their sedative action, they are useful in patients who are having sleepless nights with cough.

Drug	Dose
Chlorpheniramine	2-5 mg
Diphenhydramine	14-20 mg

- Peripherally Acting Drugs:

-They increase the threshold of cough receptors present in respiratory tract.

-Prenoxdiazine

- Drugs Having Central and Peripheral Actions:

- Benzonatate.

- It is structurally related to the local anaesthetic procaine.

- It acts on the cough centre in the medulla and also on the stretch receptors and cough receptors in the lungs.

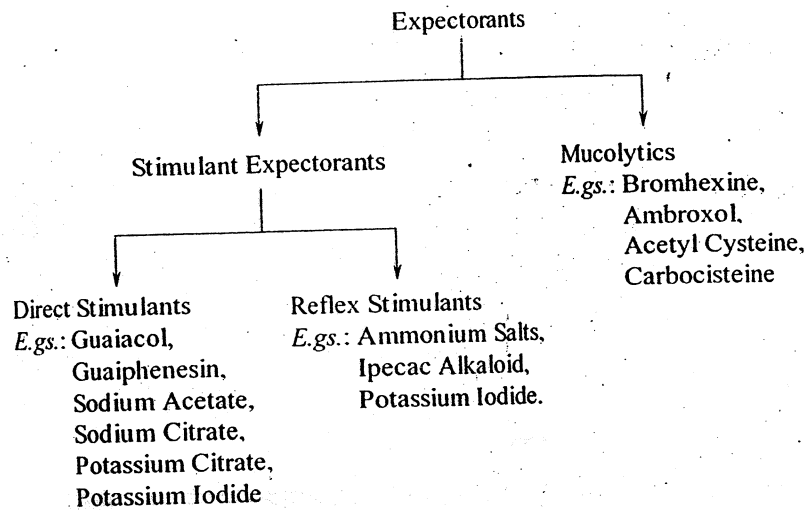
Dose: 100 mg t.i.d.

Table Overall Summary of Anti-tussives

Classes	Drugs	Mode of Action	Adverse Drug Reactions	Uses	Dose
1. Centrally Acting Drugs					
(a) Opioids (Narcotics)	Codeine	Depresses Cough Reflexes in the Medulla	- Constipation - Mild Sedation - Urticaria - Urinary Retention	- In Cough - In Diarrhoea - As an Analgesic	10 - 30 mg.
	Pholcodeine	Depresses Cough Reflexes in the Medulla	Less Constipation than Codeine	In Cough	10 - 15 mg b.i.d.
(b) Non-Opioids (Non-narcotics)	Dextro-methorphan	Depresses Cough Reflexes in the Medulla	- Nausea - Dizziness	In Dry Cough	10 - 20 mg b.i.d.
	Noscapine	Depresses Cough Reflexes in the Medulla	- Nausea - Headache	In Dry Cough	15 - 30 mg b.i.d.
2. Peripherally Acting Drugs	Prenoxdiazine	Depresses Peripheral Cough Reflexes	-	In Dry Cough	-
3. Drugs having Central and Peripheral Actions	Benzonatate	Depresses Central and Peripheral Cough Reflexes	-	In Dry Cough	100 mg t.i.d.

→ Are drugs believed to increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

□ Expectorants:



- Stimulant Expectorants:

1. Direct Stimulants:

- They ↑ the respiratory secretions by directly stimulating the glands in the bronchial mucous membrane.

- Guaicol and Guaiphenesin:

- They are the synthetic compounds.

- Guaiphenesin is a derivative of guaiacol but less irritating than guaiacol.

- Adv
↳ Gastric irritation

Dose: 100-200 mg.

2. Reflex Stimulants:

- They act by stimulating the gastric reflexes which serves as a stimulus for bronchial mucous membrane to produce respiratory secretions.

Potassium iodide:

It acts by both direct and reflex actions, ↑ sec, respiratory secretions and also liquefies the viscous sputum.

Adv:

Skin rashes, goitre etc.

Mucolytics:

- Mucolytics ↓ the viscosity of the sputum by dissolving it to thin mucus and thereby facilitating its removal from respiratory tract.

- Bromhexine:

- MOA:

- It acts by depolymerizing the mucopolysaccharides directly and by liberating the lysosomal enzymes (from bronchial glands) which dissolves the mucopolysaccharides.

Bromhexine [2M, 2011, Feb 2011]

- Mucolytic [2M, Mar 2013]
[2M, Feb 2013]

-Adverse effects:

Rhinorrhoea

lacrimation

□ Acetylcysteine and Carbocysteine:

-MOA:

-They act by breaking the disulphide bonds of mucoproteins present in sputum.

-Adverse effects:

1. Gastric irritation

2. Vomiting

3. Rhinorrhoea

Table Overall Summary of Expectorants

Classes	Drugs	Mode of Action	Adverse Drug Reactions	Uses	Dose
1. Stimulant Expectorants					
(a) Direct Stimulants	Guaiphenesin	Increases respiratory secretions by directly stimulating the glands in bronchi	Gastric irritation	In productive cough	100 – 200 mg.
(b) Reflex Stimulants	Ammonium Chloride	Increases respiratory secretions by stimulating gastric reflexes	- Nausea - Vomiting		
2. Mucolytics					
	Bromhexine	Depolymerization of Mucopolysaccharides.	- Rhinorrhoea - Lacrimiation	In productive cough	8 – 16 mg t.i.d.
	Acetylcysteine and Carbocysteine	Acts by breaking disulphide bonds of mucoproteins present in sputum.	- Gastric Irritation - Stomatitis - Rhinorrhoea	In productive cough	Carbo-cysteine 250 – 750 mg t.i.d.

□ Respiratory Stimulants

- Respiratory stimulants (analeptics) are the CNS Stimulants used to stimulate respiration and restore consciousness in comatose patients.

- They stimulate the respiration in subconvulsive doses but are not effective as they cause convulsions.

- They are used for short term management along with other supportive measures.

Ex:

Doxapram

prethcamide

- Doxapram:

MOA:

It stimulates peripheral chemoreceptors present in the carotid arteries. These chemoreceptors in turn stimulate the respiratory centre in the medulla.

- Pharmacological Effects:

1. On CNS: (in therapeutic dose)

a- ↑se in rate of respiration

b- ↑se in tidal vol.

- In higher dose, it cause convulsions.

2. On CVS:

a- ↑ stroke vol.

b- ↑ B.P.

Pharmacokinetics:

- metabolism in liver,

- Adverse effects:

1- Vomiting

2- Hypertension

3- Tachycardia

4- Convulsion (Higher dose)

- Contraindications:

1. Asthma

2. Hypertension.

Uses:

- used as an aid in COPD.

- used in premature infants with episodes of apnoea

- In acute respiratory insufficiency.

[2M,]

□ Nasal Decongestants:

- These are α agonists which produce local vasoconstriction.

Ex:

i- imidazoline compounds: (selective α_2 agonists)

Naphazoline, oxymetazoline

ii- Ephedrine, Phenylephrine, phenyl propanol amine

□ Chronic Obstructive pulmonary Disease (COPD):

- It is a syndrome consisting of chronic bronchitis and emphysema.

- Chronic bronchitis is inflammation of bronchi and bronchioles caused by air pollution but is more usually associated with cigarette smoking.

- Emphysema is distension and damage of lung tissue beyond the respiratory bronchioles it supervenes after years of coughing. The airflow limitation is partially reversible in the early stages.

- The treatment with drugs is palliative. Ipratropium bromide is mainly used. Salbutamol and

and corticosteroids can also be used in some cases.

Student Notes:

- The main function of gastrointestinal tract is the digestion and absorption of food.

- The disorders associated with the gastrointestinal system are peptic ulcers, emesis, diarrhoea and constipation.

□ Antiulcer Drugs:

- Peptic ulcer occurs in that part of the gastrointestinal tract which is exposed to gastric $\bar{a}$ and pepsin i.e., stomach and duodenum.

- Pathogenesis:

- is not fully understood.
- Infection with Gram-negative *Helicobacter pylori*
- Increased hydrochloric $\bar{a}$ secretion
- Inadequate mucosal defense against gastric $\bar{a}$.
- Peptic ulcer may occur due to imbalance b/w aggressive ($\bar{a}$, pepsin, bile and H. pylori) and the defensive (gastric mucus, bicarbonate secretion etc). factors.

- classify drugs used in the treatment of peptic ulcer with examples. Discuss the Pharmacology of Proton pump inhibitors. [Lion, Jan 2014]

- classify anti ulcer drugs + Exs + Discuss the MOA and therapeutic uses of proton pump inhibitors? [Lion, 2011]

- Prostaglandins that are synthesised in the mucosa stimulate the mucus and bicarbonate secretion, decrease $\bar{a}$ secretion and cause vasodilation all of which serves to protect the stomach against damage. Thus the ability of NSAIDs to cause gastric bleeding and erosions is explained by the inhibition of PG synthesis.

Regulation of Gastric $\bar{a}$ secretion:

- Acid secretion is controlled by ACh, histamine, PGE_2 and I_2 and gastrin. The receptor mediated binding of ACh, histamine or gastrin results in the activation of H^+/K^+ ATPase proton pump that secretes HCl into the lumen of stomach.

The receptor binding activity of PGs reduce the gastric $\bar{a}$ production. Binding of histamine cause activation of adenyl cyclase whereas binding of PGs inhibits it. Gastrin and ACh act by inducing an increase in intracellular calcium levels.

- Antiulcer agents + classification + MOA + uses [5M, 2007]

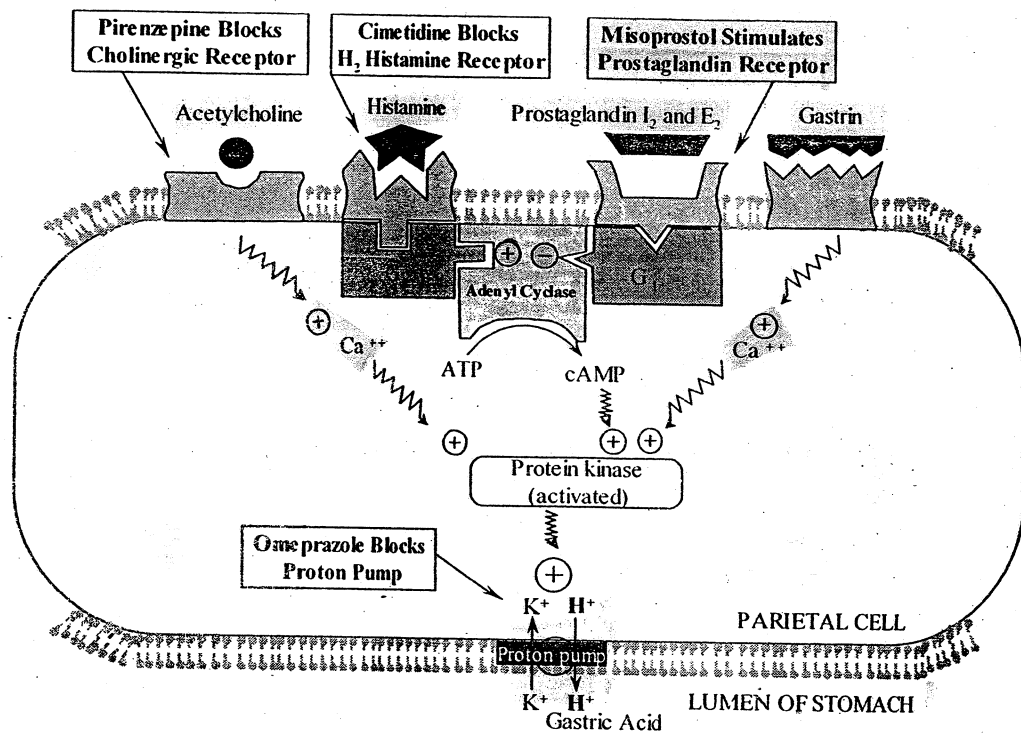


Figure Regulation of Gastric Acid Secretion

Classification:

1. Antisecretory Agents

a- Histamine H₂-receptor Antagonists

Ex: Cimetidine, Ranitidine

b- Proton-pump inhibitors

Ex: Omeprazole, Pantoprazole

c- Anticholinergic

Pirenzepine

- 2- Mucosal Protective Agents:

Misoprostol

Bismuth salts

- 3- Gastric Antacids:

- a- Non- Systemic Antacids

Aluminium Hydroxide Gel

- b- Systemic:

Sodium bicarbonate

- 4- Anti-Helicobacter Pylori Drugs:

Amoxicillin, Tetracyclines

- Histamine H_2 -receptor Antagonists:

- MOA:

H_2 -blockers competitively block the binding of Histamine to H_2 -receptors and reduce the intracellular concentrations of cAMP and thereby secretion of gastric $\bar{a}$.

-Pharmacokinetics:

- The drugs are well absorbed when given orally. Preparations of cimetidine and ranitidine for IM and IV use are also available.
- Absorption is not interfered by the presence of food in the stomach.

-Adverse effects:

- diarrhoea
- dizziness
- headache
- muscle pain

-Therapeutic Ulcer:

- a-Peptic ulcer
- b-Zollinger-Ellison Syndrome
- c-Stress Ulcers
- d-Heart burn

★★

- Proton pump inhibitors:

- It irreversibly inhibits the gastric H^+/K^+ ATPase proton pump which is final common pathway for $\bar{a}$ secretion.

- All the proton pump inhibitors are acid labile and therefore should be swallowed, unbroken etc.

- Proton pump inhibitors are prodrugs and require activation at acidic pH.

- After absorption they enter parietal cell from the blood and irreversibly inactivate the H^+-K^+ ATPase.

* Go to Note →

- Anticholinergics:

- Atropinic drugs reduce the volume of gastric juice without raising pH unless there is food in stomach to dilute the secreted $\bar{a}$. Pirenzepine which is a selective m_1 -receptor antagonist suppresses basal and stimulated gastric $\bar{a}$ secretion at doses having a min effect on salivary glands, heart and eye.

- What are antacids? classify with examples. Write the pharmacology of pantoprazole in detail.

Non-systemic Antacid [Em, Ag 2010] Systemically acting antacid (2010)
Locally acting antacid (Feb 2010)

- Prostaglandin Analogues:

- PG_2 , E_2 and I_2 which are produced by gastric mucosa inhibit the secretion of H^+ and stimulate the secretion of mucus and bicarbonate and exerts a cytoprotective effect. A deficiency in prostaglandin production (by NSAIDs) may contribute to peptic ulcers.

- Misoprostol, a stable analogue of PGE_1 , is the only agent used in prevention of gastric ulcers induced by NSAIDs. It increases the mucosal blood flow and increases the secretion of mucus and bicarbonate.

- Antacids:

- Antacids are weak bases that react with gastric H^+ and neutralises it and thus raise the gastric pH.

- Drugs that Protect Mucosa:

- These drugs are also known as "cytoprotective" agents.

- classify laxatives + Ex. - Explain the pharmacology of bulk laxative (Lom, Sep 2012)
- classify laxative - purgative + Ex. And discuss on MOA of osmotic, bulk and irritant purgative (Lom, Feb 2016)

Drugs used to treat constipation And Diarrhoea:

- many drugs in low doses act as laxative and in larger doses act as purgative.

Laxative and Purgative:

- These are drugs that promote evacuation of bowels.

- Laxatives exert a milder action.

- Bulk and osmotic laxatives:

- The bulk laxative form gels in the large intestine causing water retention and intestinal distension and thereby increasing peristaltic activity.

Ex:

- methylcellulose

- agar

① laxative or aperient: milder action, elimination of soft but formed stools.

② Purgative or cathartic: Stronger action resulting in more fluid evacuation.

- Osmotic laxative retain the water in the intestine by osmosis and distend the bowel, increasing peristalsis and producing defecation in about one hour.

Ex:

Magnesium sulfate

Magnesium hydroxide

- Faecal Softeners:

- Docusate sodium

- Acts in the gastrointestinal tract and become emulsified with the stool producing softer faeces and easy passage.

- liquid paraffin.

Adverse effects:

- Fluid and electrolyte imbalance (large dose)
- Hypokalaemia, abdominal cramps

Contraindication:

- pregnancy
- Subacute or chronic intestinal obstruction.

- Stimulant Purgatives:

- The stimulant purgatives act mainly by increasing ^① water and electrolyte secretion by the mucosa and also by increasing the peristalsis by ^② stimulating enteric nerves.

Ex:

- Castor oil

- Senna } they are hydrolysed in the colon by bacteria
- Cascara } and release the free anthracene derivatives.
- Aloe } these are absorbed and have a direct stimulant effect on the enteric nerves, resulting in peristalsis and thus defaecation.

- Write a note on Stimulant purgatives [5M, Jan 2014]
- Short a note on irritant Purgatives [5M, 2010 Feb]

Anti Diarrhoeal Agents:

- Diarrhoea is the ^{or} frequent passage of liquid faeces due to increased motility of the gastrointestinal tract and decreased absorption of fluid.

- There are numerous causes including infectious agents, toxins, anxiety etc.

treatment of diarrhoea:

- 1- maintenance of fluid and electrolyte balance ↗ by means of oral rehydration
- 2- use of anti-infective agents ↗ by erythromycin or ciprofloxacin
- 3- use of non-antimicrobial antidiarrhoeal agents.
 - ↳ Include antimotility agents: codeine
 - ↳ adsorbents: kaolin, charcoal

Antimotility Agents:

- These are mainly opiod drugs which increase small bowel tone and segmenting activity, reduce propulsive movements and diminish intestinal secretions while enhancing absorption.

Ex:

- codeine
- diphenoxylate

- Adsorbents:

- Action:

- Adsorbing microorganisms or toxins
- Altering the intestinal flora_{or}
- Coating and protecting the intestinal mucosa

- Ex:

Kaolin

charcoal

chalk

- Classification: ^(laxative) (BOS)

- ① Bulk forming: Dietary Fibre: Methylcellulose, ^{or} bran
- ② Stool softener: Docusates [BOS], liquid Paraffin
- ③ Stimulant purgative:
 - ① Diphenylmethanes:
Phenol phthalein
 - ② Anthraquinones:
Senna, Cascara sagrada
 - ③ 5-HT₄ agonists:
Tegaserod
 - ④ Fixed oil:
Castor oil
- ④ Osmotic purgative:
Magnesium sulfate
Magnesium Hydroxide

□ Drugs For Emesis And Digestive Disorders:

-Emesis:

-Vomiting is a physical event that results in forceful evacuation of gastric contents through the mouth. Vomiting is often preceded by nausea and can be accompanied by repetitive contraction of the abdominal muscles with or without actual discharge of vomit.

-Vomiting is mainly regulated by the vomiting centre and the CTZ.

-Vomiting is a valuable physiological response to the ingestion of toxic substances but it is also an unwanted effect of many clinically used drugs such as cancer chemotherapy.

[2M, Feb 2010][2M, Sep 2009]

-Emetics:

-These are drugs used to produce vomiting when an undesirable substance has been ingested.

Ex: — acts locally in the stomach.

-Ipecacuanha

-Powdered mustard suspension

↳ use in emergency

- classify anti-emetic agents and write a note on Prokinetic agents [5m, Mar 2013]

- All emetics are contraindicated in:

- 1- Corrosive Poisoning
- 2- Unconscious patients
- 3- Morphine poisoning

- Antiemetics:

- used to prevent or suppress vomiting.
- are mainly used as adjuncts to cancer chemotherapy to fight the nausea and vomiting produced by many cytotoxic drugs.
- They are also used in treatment of morning sickness during pregnancy.

- Classification of Antiemetics:

1. Receptor Antagonists:

a) Anticholinergics:

Hyoscine, Scopolamine

b) Antihistaminics:

Cyclizine
meclizine

c) 5-HT₃ receptor A.

Ondansetron

d) Anti dopaminergic agents:

Haloperidol, Droperidol

2. Miscellaneous:

- Benzodiazepines: lorazepam and alprazolam

- Corticosteroids: Dexamethasone

(in higher dose to exert antiemetic action).

- Prokinetic drugs: Metoclopramide → Note

□ Appetizers:

- A small dish of food or a drink taken before a meal or the main course of a meal to stimulate one's appetite.

Ex:

1. Alcohol:

(Alcohol (10%) in small quantities)

2. Insulin

(It increases gastric secretion by producing hypoglycaemia.

3. 5-HT antagonists:

Cyproheptadine

- amylase is an enzyme that helps digest carbohydrates.

Digestants: [2M, Feb 2012]

- The digestants are the drugs that promote the digestion of food.

1. HCl. It may be used in achlorhydria.

Very diluted $\bar{a}$ is taken during meals.

2. Pepsin: } help you digest the proteins in food.
3. Papain } Although your body produces these enzymes in the pancreas. Certain foods also contain proteolytic enzymes.

4. Pancreatin: } The primary use of proteolytic enzymes is as a digestive aid for people who have

contains the enzymes amylase, trypsin and lipase

5. Bile and Bile $\bar{a}$ s:

Bile salt preparations are employed to facilitate surgical drainage or as replacement therapy in biliary fistulae...

Carminatives: [2M, Jan 2014]

- These are drugs used to expel gas from the stomach or the intestine in the treatment of flatulence and colics.

Ex:

- Cardamom seeds
- Ginger
- Cloves
- Coriander

absorbed internally to some extent and may reduce pain and inflammation.

<< Notes >>

→ Proton Pump Inhibitors:

Omeprazole

Lansoprazole [2M, 201]

Pantoprazole

Pharmacokinetics:

- Omeprazole and lansoprazole are administered as capsules containing enteric coated granules to protect them from premature activation by gastric acid. After absorption in the duodenum, they are transported to the parietal cell canaliculus, where they are converted to active species. The metabolites of these drugs are excreted in urine and faeces.

Adverse effects:

- Headache
- Dizziness
- Diarrhoea
- impotence
- rashes

→ Omeprazole interferes with the oxidation of warfarin, phenytoin, diazepam and cyclosporine.

Therapeutic Uses:

1. Omeprazole and lansoprazole are used for

{ treatment of active duodenal ulcer
treatment of Zollinger-Ellison syndrome

2. Omeprazole is used in combination with antimicrobials to eradicate *H. pylori*.

3. Pantoprazole (IV) for stress ulcers.

Prokinetic Drugs:

- These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated ~~propulsive~~ propulsive motility.

- Metoclopramide:

- Actions:

GIT It has more prominent effect on upper g.i.t; increase gastric peristalsis while relaxing the pylorus and the first part of duodenum → speeds gastric emptying.

- It also increases intestinal peristalsis to some extent.

- CNS:

- Metoclopramide is an effective antiemetic; acting on the CTZ.

- MOA:

(D₂ antagonism)
Metoclopramide acts through both dopaminergic and serotonergic receptors.

5-HT₄ agonism

5-HT₃ antagonism

-Pharmacokinetics:

-is rapidly absorbed orally, enters brain, cross placenta and is secreted in milk etc.

interactions:

It hastens the absorption of many drugs eg. aspirin, diazepam etc by facilitating gastric emptying.

Adverse effects:

sedation, dizziness, loose stools

Uses:

① Antiemetic

② Dyspepsia

Ex₂: Cisapride, Mosapride

□ Thyroid and Antithyroid Drugs:

- Thyroid hormone:

-The thyroid gland secretes three hormones thyroxine (T_4), Triiodothyroxine (T_3) and calcitonin.

- T_3 and T_4 are produced by thyroid follicles and are important for normal growth and development and for energy metabolism.

-Calcitonin is involved in the control of plasma Ca^{2+} and regulates calcium metabolism.

- Synthesis, Storage and Secretion:

- T_3 and T_4 are iodine containing derivatives of thyronine which is a condensation product of two molecules of amino α tyrosine.

-The functional unit of thyroid is the follicle or acinus.

-Each follicle consists of a single layer of epithelial cells around a cavity, the follicle lumen, which is filled with a thick colloid containing thyroglobulin.

-The thyroid hormones are synthesized and

- Explain the biosynthesis of thyroid hormones - classify thyroid inhibitors + Ex [5M, Feb 2014]
 - Thyroid inhibitors [5M, Sep 2012]

Stored in the thyroid follicles as part of thyroglobulin.

660 Tortora

Steps:

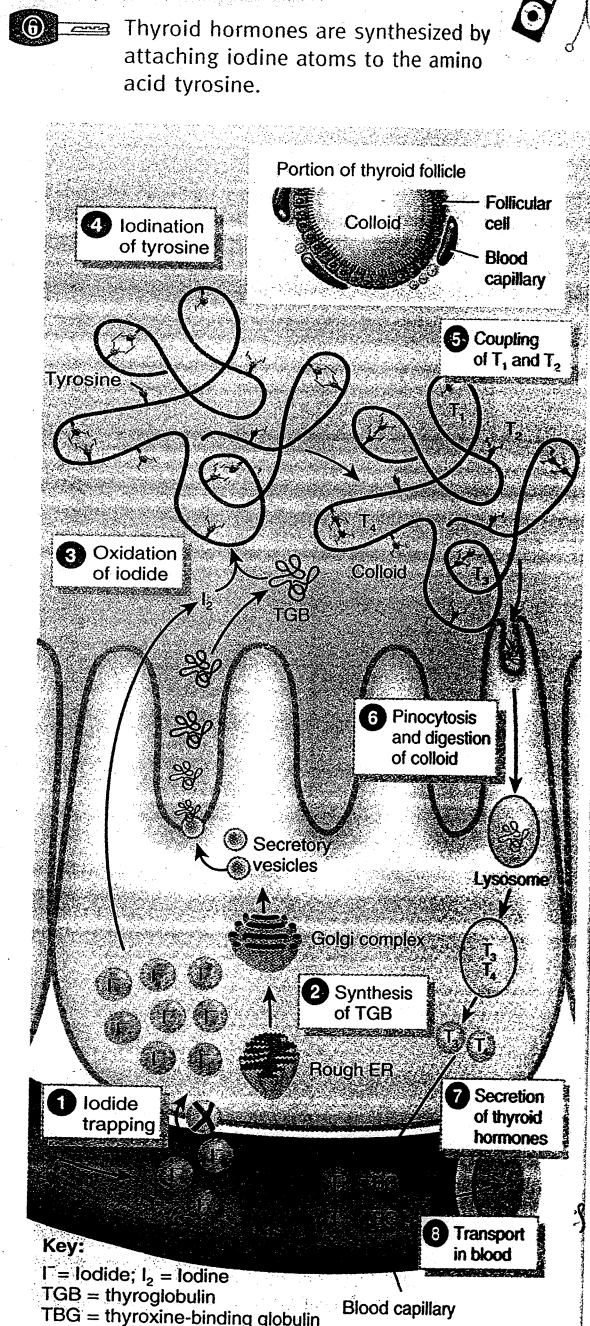
- Iodide trapping.** Thyroid follicular cells trap iodide ions (I^-) by actively transporting them from the blood into the cytosol. As a result, the thyroid gland normally contains most of the iodide in the body.
- Synthesis of thyroglobulin.** While the follicular cells are trapping I^- , they are also synthesizing **thyroglobulin (TGB)**, a large glycoprotein that is produced in the rough endoplasmic reticulum, modified in the Golgi complex, and packaged into secretory vesicles. The vesicles then undergo exocytosis, which releases TGB into the lumen of the follicle.
- Oxidation of iodide.** Some of the amino acids in TGB are tyrosines that will become iodinated. However, negatively charged iodide ions cannot bind to tyrosine until they undergo oxidation (removal of electrons) to iodine: $2 I^- \rightarrow I_2$. As the iodide ions are being oxidized, they pass through the membrane into the lumen of the follicle.
- Iodination of tyrosine.** As iodine molecules (I_2) form, they react with tyrosines that are part of thyroglobulin molecules. Binding of one iodine atom yields moniodotyrosine (T_1), and a second iodination produces diiodotyrosine (T_2). The TGB with attached iodine atoms, a sticky material that accumulates and is stored in the lumen of the thyroid follicle, is termed **colloid**.
- Coupling of T_1 and T_2 .** During the last step in the synthesis of thyroid hormone, two T_2 molecules join to form T_4 or one T_1 and one T_2 join to form T_3 .
- Pinocytosis and digestion of colloid.** Droplets of colloid reenter follicular cells by pinocytosis and merge with lysosomes. Digestive enzymes in the lysosomes break down TGB, cleaving off molecules of T_3 and T_4 .
- Secretion of thyroid hormones.** Because T_3 and T_4 are lipid-soluble, they diffuse through the plasma membrane into interstitial fluid and then into the blood. T_4 normally is secreted in greater quantity than T_3 , but T_3 is several times more potent. Moreover, after T_4 enters a body cell, most of it is converted to T_3 by removal of one iodine.
- Transport in the blood.** More than 99% of both the T_3 and the T_4 combine with transport proteins in the blood, mainly **thyroxine-binding globulin (TBG)**.

Actions of Thyroid Hormones

Because most body cells have receptors for thyroid hormones, T_3 and T_4 exert their effects throughout the body.

- Thyroid hormones increase **basal metabolic rate (BMR)**, the rate of oxygen consumption under standard or basal conditions (awake, at rest, and fasting), by stimulating the use of cellular oxygen to produce ATP. When the basal metabolic rate increases, cellular metabolism of carbohydrates, lipids, and proteins increases.

Figure 18.11 Steps in the synthesis and secretion of thyroid hormones.



- What is the storage form of thyroid hormones?

cyclic AMP.

-Thyroid function is also influenced by plasma iodide concentration.

-A reduced iodine intake ↓ses plasma iodine concentration will result in a ↓se of hormone production and an increase in TSH secretion.

An increased plasma iodide has the opposite effect.

-Transport, Metabolism and Excretion:

-Thyroid hormones are mainly bound to TBG.

-The thyroid hormones are degraded by deiodination, deamination and conjugation with glucuronic and sulfuric acids.

-Liver is the primary site and the conjugates are excreted in bile... and to be finally excreted in urine.

plasma half-life of T_4 = 6 to 7 days

" " T_3 = 1-2 days

-Actions: T_4 and T_3

1- Effects on Metabolism

2- Effects on Growth and Development.

-Anti thyroid agents [2M, Mar 2012]

- classify antithyroid drugs and add a note on thiouracils [5M, Feb 2010] [5M, 2009]

1- Effects on Metabolism:

They ↑se Basal Metabolic Rate (BMR). This is important for maintaining body temp.

2- T_4 and T_3 are essential for normal growth and development.

▢ Abnormalities of Thyroid Function:

1. Hyperthyroidism (Thyrotoxicosis):

- is due to excessive secretion of thyroid hormones → high metabolic rate
↑se in skin temp
sweating
Nervousness
tachycardia
loss of weight

Types:

└─ diffuse Toxic Goitre
└─ Toxic Nodular Goitre

2. Hypothyroidism:

- The decrease in activity of thyroid results in hypothyroidism and in severe cases may lead to myxoedema.

- low metabolic rate
- brady cardia
- sensitivity to cold
- slow speech

3. Simple/Non-Toxic Goitre:

-The prolonged dietary deficiency of iodine can cause a rise in plasma TRH and eventually an increase in size of the gland.

-This condition is known as simple or non-toxic goitre.

-Ingestion of goitrogens may also cause simple or non-toxic goitre.

-Treatment of Hypothyroidism:

-is treated with levothyroxine (T_4) Thyroxine is the drug of choice and liothyronine (T_3) is reserved for rare condition of myxoedema coma.

-Treatment of Hyperthyroidism:

→ 1-removal of part or all of the Thyroid surgically or with radioactive iodine

2-Inhibition of Thyroid Hormone Synthesis:

- Thioureylenes ↓ the synthesis of hormones from the gland. and cause

- Propylthiouracil also inhibits peripheral conversion of T_4 to T_3 .

3. Blockade of Hormone Release:

- A pharmacologic dose of iodide inhibits the iodination of tyrosines, thus using the supply of stored thyroglobulin. Iodide is not useful for long-term therapy, because the thyroid ceases to respond to drug after a few weeks.

- Other:

- B-adrenoceptor Antagonists:

- Propranolol is used to decrease the signs and symptoms of hyperthyroidism such as tachycardia etc. They are used along with iodide for preoperative preparation, initial treatment of hyper-

...!

Describe the conventional and newer insulin preparations [10M, March 2013]
Briefly on Insulin preparations [5M, Feb 2010]
Insulin preparations [2M, Sep 2012]

□ Insulin:

- Insulin hormone is a small protein consisting of two polypeptide chains that are connected by disulfide bonds.

- It is synthesized in the B cells of Islets of Langerhans in Pancreas.

- The other hormones secreted in the islets are glucagon, somatostatin and pancreatic polypeptide.

- Glucagon opposes insulin by ^{stimulating} raising blood glucose and ^{stimulating} protein breakdown in muscle.

- Somatostatin inhibits secretion of insulin and glucagon.

Synthesis and Secretion:

- Insulin is synthesized as a precursor (preproinsulin) in the rough endoplasmic reticulum. Preproinsulin is transported to Golgi apparatus where it undergoes proteolytic cleavage first into proinsulin and then to insulin and a fragment of peptide-C.

- Insulin secretion is regulated by.

- blood glucose level
- other hormones
- autonomic mediators.

- Rise in ATP levels blocks K^+ channels, leading to membrane depolarization and influx of Ca^{++} which cause insulin exocytosis.

- Insulin secretion is also stimulated by many GI hormones (Gastrin, secretin etc). They are released on intake of diet. These hormones provide a signal from GIT to the islets.

Other stimuli include the parasympathetic nervous system and drugs that act on sulfonylurea receptors.

- Insulin release is inhibited by the Sympathetic nervous system.

- Adrenaline increases blood glucose by inhibiting insulin release through α_2 -adrenoceptors.

- Explain the various pharmacological actions of insulin [5m, Sep 2011]
- Explain the physiological role of insulin and its therapeutic applications [5m/2011]

□ Action of Insulin:

- The overall effect of insulin is to ^{conserves} conserve fuel by facilitating the uptake and storage of glucose, amino acids and fats. Having function on liver, muscle and fats.

□ Effect on carbohydrate Metabolism:

- Insulin inhibits glycogenolysis and gluconeogenesis while stimulating glycogen synthesis.

- The main end-product of glucose metabolism in adipose tissue is glycerol.

- The uptake of glucose is slow in muscles.

□ Effect of Insulin on Fat metabolism:

- ↑ synthesis of fatty acid and triglycerides in adipose tissue and liver.

- inhibit lipolysis partly

- inhibits the lipolytic actions of adr, growth hormone.

□ Effects on protein metabolism:

↑ protein synthesis

↓ protein catabolism

inhibit oxidation of amino acid in liver.

- Explain various pharmacological actions of insulin. Mention different preparations of insulin [10m, Oct 2007]

- Other:

Include transport of K^+ , Ca^{2+} , nucleosides and inorganic phosphate into cells.

- MOA:

- Insulin acts on specific receptors located on the cell membrane.

- The insulin receptor consisting of two α and two β subunits.

- The α subunits are extracellular and each carries an insulin binding site, where the β subunits are transmembrane proteins with tyrosine kinase activity. This activity is suppressed by the α -subunit but insulin binding causes a conformational change that activates the tyrosine kinase activity of the β subunits which act on each other and on other target proteins. (★) $\Rightarrow$ next page

- The receptors occupied by insulin ^{insulin} aggregate into ^{insulin bound} clusters, which are subsequently internalised in vesicle resulting in down regulation. Internalised insulin is degraded in

lysosomes, but the receptors are recycled to the plasma membrane.

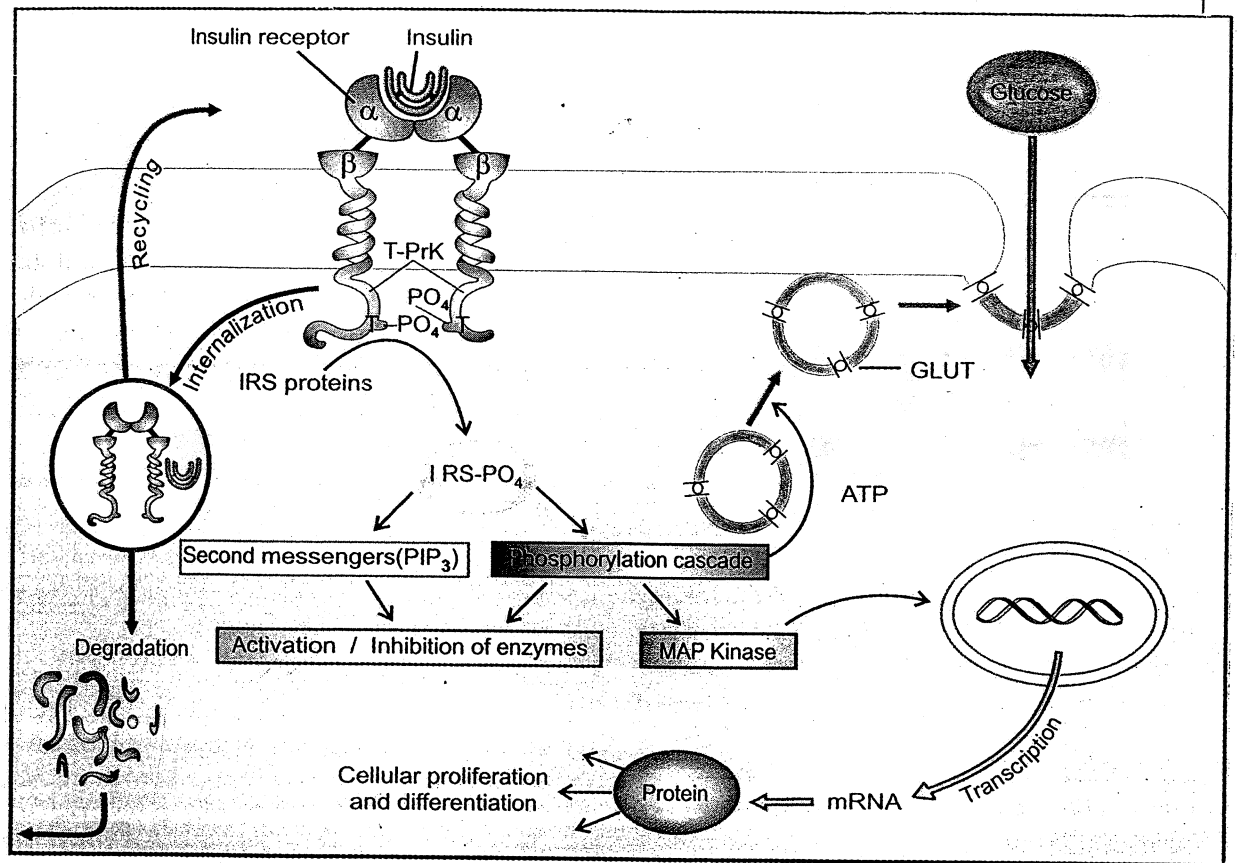


Fig. 19.3: A model of insulin receptor and mediation of its metabolic and cellular actions; T—Tyrosine residue; GLUT—Glucose transporter; IRS—Insulin receptor substrate proteins; PIP_3 —Phosphatidylinositol trisphosphate; MAP-kinase—Mitogen activated protein kinase; T-PrK—Tyrosine protein kinase

-Diabetes Mellitus:

- is a metabolic disorder characterized by an elevation of blood glucose, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced.

★ Insulin stimulates glucose transport across cell membrane by GLUT4 and GLUT1 to the plasma membrane as well as by increasing its activity.... Activation of transcription factors also promotes proliferation and differentiation of specific cells.

- This high blood glucose produces the classical symptoms of polyuria, polydipsia and polyphagia.

- Types:

- Type 1
- Type 2

1. Type 1-Diabetes:

Also known as insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes.

- The disease is characterised by absolute deficiency of insulin resulting from auto-immune destruction of β -cells. The pancreas fail to respond to ingestion of glucose.

Treatment:

- It mainly treated by exogenous (injected) insulin.

2. Type - 2 Diabetes:

- is caused by both insulin resistance and by impaired insulin secretion by β -cells.

Treatment: Treatment is initially dietary.

Although oral hypoglycaemic drugs are usually

used, weight reduction, exercise and dietary modification ↓ insulin resistance and correct the hyperglycaemia of type 2 diabetes in some patients.

Insulin Treatment:

- Insulin for clinical use can be obtained from beef and pork pancrease.

- However human insulin obtained by recombinant DNA technology in which it is produced by special strain of E. coli.

-Pharmacokinetic:

- Because insulin is a protein, it is destroyed in the GIT and must be given parenterally, usually subcutaneously.

- Insulin is inactivated by the reducing enzyme, insulinase, found mainly in the liver and kidney.

-Adverse effects:

- Hypoglycaemia ✓✓
- lipo-dystrophy
- allergic reactions.

-Insulin preparations:

1- Rapid Action

a-regular or soluble Insulin
suitable for IV

2-Intermediate Action:

a-Semilente insulin suspension
not suitable for IV

b- Lente Insulin:

-It is given only subcutaneously.

c- Isophane Insulin suspension:
only SC.

3-Prolonged Action:

Ultra Lente Insulin

255

256

- classify oral hypoglycaemic agents + Explain the pharmacological actions of insulin in detail. [10M, Feb 2019]
 - Biguanides [2M, Feb 2010]

actions of sulfonylurea derivatives
 10M, Feb 2019

- Oral Hypoglycaemic Drugs:

- These agents are useful in treatment of patients with non-insulin-dependent diabetic mellitus (NIDDM) but cannot be managed by diet alone.

- These drugs lower blood glucose levels and are effective orally.

All have similar pharmacological profile.
 Sole significant action being lowering of blood glucose level in normal subjects and in type 2 diabetics, but not in type 1 diabetics.

- Sulfonylureas:

- Tolbutamide

- Glibenclamide

(more potent)

} cause hypoglycaemia

- MOA:

1. Stimulation of insulin release from the B-cells of the pancreas.

2. Reduction of serum glucagon levels
3. Increased binding of insulin to target tissues and receptors.

- Pharmacokinetics:

- well absorbed orally
- Strongly bind to plasma albumin
- mainly excreted in urine
(most of them)
- Cross the placenta $\rightarrow$ severe hypoglycaemia at birth $\rightarrow$ contra-indicated in pregnancy

- Unwanted Effects:

- hypoglycaemia
 - may stimulate appetite $\rightarrow$ weight gain.
 - Hypersensitivity: rashes etc.
 - Non-specific side effects: Nausea, vomiting, diarrhoea or constipation, Headache etc.
- Clinical uses:

they are useful in early stages of type 2 diabetes.

- They can also be combined with metformin or with thiazolidinediones.

Drug interactions:

- $\rightarrow$ effect $\uparrow$ with: NSAIDs, coumarins
- $\rightarrow$ effect $\downarrow$ with:
 - oral contraceptive
 - corticosteroids

2-Biguanides: ^(2M)

Metformin

-MOA:

- 1- ↓ ^{تقليل} hepatic glucose output,
- 2- retarding intestinal absorption of glucose
- 3- Enhancing insulin-mediated glucose disposal in muscle and fat. ^{التخلص}
- 4- Enhance anaerobic glycolysis.

Unwanted effects:

diarrhoea

nausea

Clinical use:

Metformin is the drug of choice in newly diagnosed Type 2 diabetes patients who are obese and who fail treatment with diet alone.

-It does not cause hypoglycaemia and can be combined with sulfonylureas.

3-Thiazolidinediones:

Pioglitazone

- stimulates nuclear PPAR-gamma receptor
- reduces insulin resistance

-MOA:

- They bind and change the PPAR_γ-RXR complex so that it binds DNA and promotes transcription of several genes with products that are important in insulin signalling.

Unwanted effect:

edema

weight gain

headache

Gastrointestinal disturbances.

- Thiazolidinediones are contraindicated in pregnant or breast feeding women.

Clinical use:

Thiazolidinediones are indicated in type-2 diabetes mellitus.

4-α-Glucosidase Inhibitors:

Acarbose

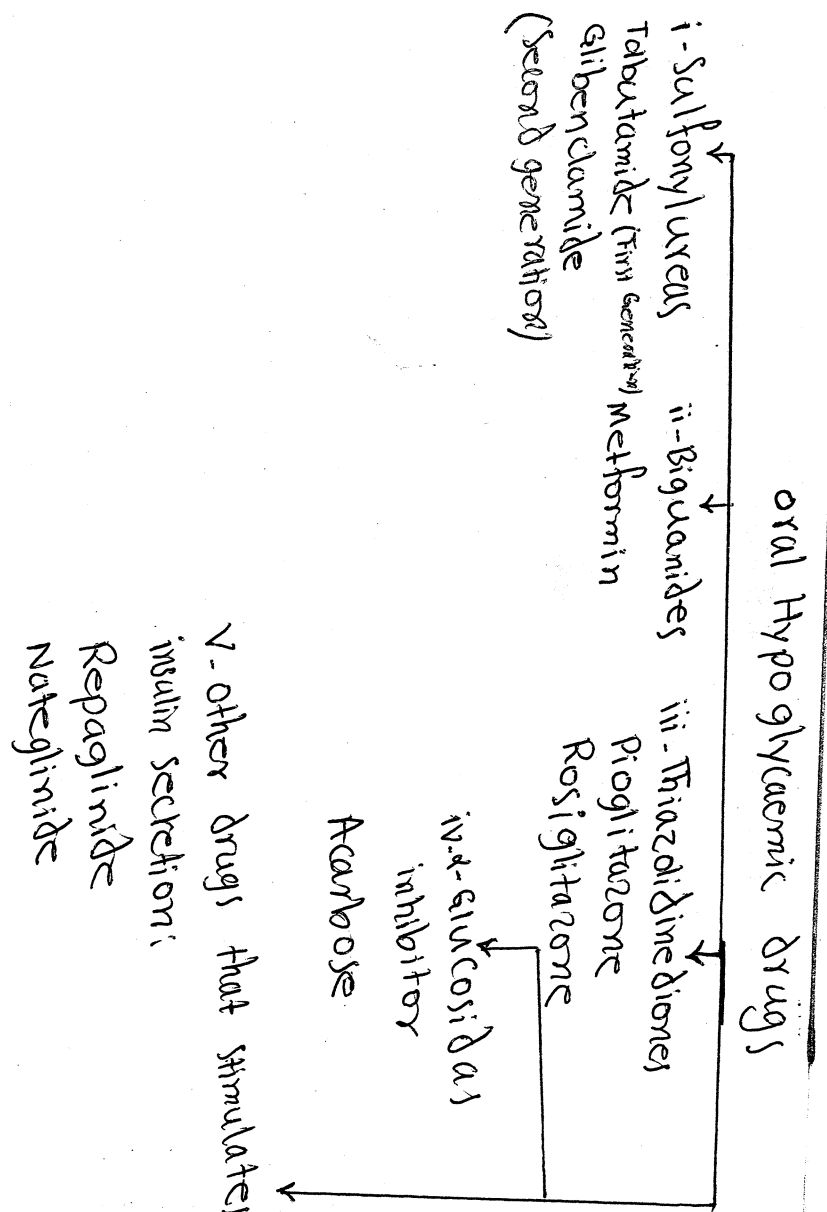
- Used in Type-2 diabetic mellitus
- delays carbohydrate absorption
- diarrhoea, abdominal pain

5- Other drugs that stimulate Insulin Secretion

Repaglinide

Nateglinide

-These drugs are administered shortly before a meal to reduce the glucose rise in Type-2 diabetic patients inadequately controlled with diet and exercise.



-- Pharmacology of female sex hormone [5M, Mar 2012]
-- Pharmacological actions of estrogen and progestins [5M, Oct 2007]

□ Sex Hormones And Oral Contraceptives:

- Sex hormones include androgens, progestins and estrogens.
- Sex hormones produced by the gonads.
- The gonadal hormones are used therapeutically in replacement therapy and in the case of estrogen for contraception and osteoporosis. The sex hormones are mainly involved in the hormonal control of the reproductive systems in men and women.

- Hormonal Control of Female Reproductive System:

- The secretion of estrogenic sex steroids is stimulated at puberty by an increased output of the hormones of the hypothalamus and anterior pituitary. These are responsible for the maturation of the reproductive organs and the development of secondary sexual characters.
- Sex hormones are also involved in the regulation of the cyclic changes expressed in the menstrual cycle and are important in pregnancy.

-During the menstrual cycle, the GnRH from the hypothalamus stimulates the anterior pituitary to release FSH and LH. These hormones act on the ovaries to promote the development of small group of follicles, each of which contains an ovum.

-Estrogens are responsible for the proliferative phase of endometrial regeneration in the mid cycle of menstrum. Estrogen has a -ve feedback action on the anterior pituitary, ↓ing gonadotrophin release during chronic administration of estrogen as oral contraception.

-Progesterone acts on estrogen-primed endometrium, stimulating the secretory phase of the cycle.

-If implantation of ovum does not occur, progesterone secretion stops, triggering menstruation.

-If implantation occurs, the corpus luteum continues to secrete progesterone, which exerts effect the hypothalamus anterior pituitary to prevent further ovulation.

-As pregnancy proceeds, the placenta develops further hormonal functions and secret gonadotrophins, progesterone and estrogen.

- During pregnancy
- Progesterone controls the development of the secretory alveoli in the mammary gland
 - Estrogen stimulates the lactiferous ducts.

- After parturition, estrogens along with prolactin are responsible for stimulating and maintaining lactation, whereas high doses of exogenous estrogen suppress this.

- Hormonal control of Male Reproductive System:

- The male reproductive system is controlled by endocrine secretions from the hypo-thalamus, anterior pituitary and gonads.

- FSH is responsible for the integrity of the seminiferous tubules and after puberty is important in gametogenesis.

- LH stimulates the secretion of androgens, in particular testosterone.

- At puberty, testosterone secretion causes maturation of the reproductive organs and

development of secondary sexual characteristics.

- The primary function of testosterone is the maintenance of spermatogenesis.

- Testosterone causes development of the musculature and increase bone growth, resulting in a rapid increase in height at puberty.

- The secretion of testosterone is mainly controlled by LH and FSH.

-Estrogen:

- Estrogens are mainly synthesised by the ovary and placenta and in small amounts by the testes and adrenal cortex.

- The starting substance for the synthesis of estrogen is cholesterol.

-Action:

(in female)

: growth of uterus, fallopian tubes and vagina.

- they produce secondary sexual characters such as Growth of breast etc.

-Effects of exogenous estrogen:

✓1- In primary hypogonadism, estrogen stimulates the development of secondary sexual characteristics and accelerates growth.

✓2- In adults with primary ^{فقدان یا توقف غیرطبیعی قاعدگی} amenorrhoea, estrogen given cyclically with a progestin induces an artificial cycle.

✓3. At or after the menopause, estrogen replacement prevents menopause symptoms and bone loss.

- They increase the plasma concentrations of high density lipoproteins which contribute to low risk of atheromatous disease in premenopausal women.

- They also increase the coagulability of blood.

-MOA:

- Estrogens bind to specific nuclear receptors in the target cells and produce effects by regulating protein synthesis which mediate a no. of

physiological functions.

-Types of receptors:

$\begin{cases} \text{ER}_\alpha \\ \text{ER}_\beta \end{cases}$

present in female sex organ,
breast, bone etc.

-Preparations:

1. Steroidal: Mestranol

2. Non steroidal: Dienestrol

□ Pharmacokinetics:

- are well absorbed orally / administration into vagina as creams or pessaries for local effect.
- metabolism in liver
- excret in urine

Unwanted effects:

- tenderness in the breasts
- nausea
- vomiting
- increased risk of thromboembolism.

-Uses:

- 1- Replacement therapy such as
 - a- Primary ovarian failure
 - b- Secondary " "

2- Contraception

3- Prostate Cancer

Anti-Estrogens:

- modify or oppose the actions of estrogens.

Ex:

- Clomiphene: To induce ovulation in treating infertility
- Tamoxifen: To treat estrogen-sensitive breast cancer

Progestins:

- Progesterone is the natural progestin which is produced in response to LH, by both females and males. This is secreted by the corpus luteum in the second part of the menstrual cycle, and by the placenta during pregnancy. Small amounts are also secreted by testes and adrenal cortex.

MOA: Progestins act on intracellular receptors like other steroid hormones. Unlike other steroid receptors, the progesterone receptor (PR) has a limited distribution in the body.

-The density of the progesterone receptors is controlled by estrogens.

Actions:

-The main functions of progesterone is to promote the development of a secretory endometrium that can accommodate implantation of a newly forming embryo and maintenance of pregnancy.

advers effects:

- Weight change^{*}
- depression^{*}
- change in libido^{*}
- irregular menstrual cycle^{*}
- breast discomfort

Clinical uses:

-The major clinical use of progestins is in contraception, in which they are generally used with estrogens either in combination or in a sequential manner.

233 - Therapy consisting of a combination of estrogen and progestin designed to replace the loss of these hormones in menopause. Hormone therapy is used to combat the effects of hormone deficit.

- control of dysfunctional uterine bleeding
- suppression of postpartum lactation

Anti progestins:

- Mifepristone is used as a medical alternative to surgical termination of pregnancy.

Postmenopausal Hormone Replacement Therapy:

② - Due to decrease of ovarian function at menopause women suffer a no. of physical, psychological and emotional consequences [osteoporosis, urethral changes] and these problems can be overcome by hormone replacement therapy (HRT).

③ - Estrogen replacement therapy (HRT) has some benefits:

1. Improvement of symptoms caused by reduced estrogen such as vasomotor symptoms (hot flashes) and vaginitis.
2. Prevention and treatment of osteoporosis.
3. A reduced or delayed onset of Alzheimer's disease.

4.5

- Tibolone is marketed for the treatment of postmenopausal symptoms and prevention of osteoporosis. It has estrogenic, progestogenic and weak androgenic activity.

⑥
□ Adverse effects:

- increases the risk of heart attack, breast cancer, blood clots and strokes in older postmenopausal women.

⑦
□ Who should avoid hormones:

- Current or past history of breast cancer
- Coronary heart disease
- A previous blood clot, heart attack, or stroke

Androgens:

- Testosterone is the main natural androgen.

Actions:

- The effects of exogenous androgens are the same as those of testosterone and depend on the age and sex of the recipient.

- Administration to boys at the age of puberty, there is a rapid development of the secondary sexual characteristics, maturation of the reproductive organs and a marked increase in muscular strength.

- If it is given to prepubertal males, the individuals do not reach their full predicted height because of premature closure of the epiphyses of the long bones.

- Administration to women results in masculinisation.



Adverse effects:

1. In male: impotence, decreased spermatogenesis etc.
2. In female: masculinisation, Growth of facial hair, deepening the voice. etc
3. In children: Androgens can cause growth disturbances.

Clinical uses:

- Androgens are used in conjunction with other hormones to promote skeletal growth in prepubertal boys with pituitary dwarfism.

- They are also used to increase lean body mass, muscle strength and aggressiveness in athletes and body builders.

Anabolic Steroids

- Synthetic androgens

Ex:

Nandrolone

Oxymetholone

- These anabolic steroids increase protein synthesis and enhance muscle development, resulting in weight gain.

- They are used in the therapy of some aplastic anaemias.

- Anabolic steroids are used by some athletes to increase strength and athletic performance.

Q → Androgen: MoA: Androgens also bind to a specific nuclear receptor in the target cell. They modify gene transcription and stimulates the synthesis of specific RNA's and proteins.

Pharmacokinetics:

- IM
- is bound to plasma protein
- excreted in urine

-Anti-Androgens:

-Both estrogens and progestogens have anti androgen activity. Estrogens mainly inhibit gonadotrophin secretion and progestogens by competing with androgens in target organs.

-Gonadotrophin-Releasing Hormone (GnRH):

-GnRH controls the secretion of FSH and LH by the anterior pituitary. GnRH secretion is controlled by neural input or through -ve feedback by the sex steroids. Exogenous androgens, estrogens and progestins all inhibit GnRH secretion.

-Danazol inhibits the release of GnRH

-Clomiphene stimulates gonadotrophine release.

-Synthetic GnRH is termed as gonadorelin.

-GnRH agonists: Goserelin etc.

-Uses:

-GnRH agonists stimulates gonadotrophin release and induce ovulation.

-GnRH analogues are given to cause gonadal suppression in various sex-hormone dependent conditions including prostate and breast cancer.

-Also be useful as contraceptives.

-Anti

- Adverse Effects:

- Menopausal symptoms } in women.
- bone loss

Oral Contraceptives: α

- Contraceptives are hormonal preparations used for reversible suppression of fertility.

- Types:

- 1. Combinations of an estrogen with a progestin (The combined Pill)
- 2. Progestin alone (The progestin-only pill).

1. The combined Pill:

- It contains an estrogen and a progestin.
- Combined pills contain a constant low dose of estrogen given over 21 days plus a current low but increasing dose of progestin given over 3 successive 7-day periods. The pills are taken for 21 days followed by a 7-day withdrawal period to induce menses.

- MoA:

- 1. Estrogen inhibits secretion of FSH through -ve feedback mechanism on the anterior pituitary and thus suppresses development of the ovarian follicle.

2. Progesterin inhibits secretion of LH and this prevents ovulation. It also makes the cervical mucus much less suitable for the passage of sperm.

Adverse effects:

1. Weight gain
2. Mild nausea
3. Depression
4. Skin changes

Clinical uses:

- markedly decreases menstrual symptoms such as intermenstrual bleeding etc.
- Iron deficiency anaemia and premenstrual tension are reduced, as are benign breast disease, etc.

2. The progesterin - Only Pill

- contains progestins
- They are taken daily on a continuous schedule.
- The mode of action is primarily on the cervical

mucus, which is made inhospitable to sperm. The progestin probably also hinders implantation through its effect on the endometrium and on the motility and secretions of the fallopian tubes.

Unwanted effects:

- Disturbances of menstruation
- Missing dose may result in conception.

Uses:

-Progestin-only pill is an alternative to the combined pill for some women in whom estrogen is contraindicated and are also suitable for women whose blood pressure increases unacceptably during treatment with estrogen.

Other Drug Regimens Used For Contraception:

1. Postcoital (Emergency) Contraception:

-Oral administration of levonorgestrel alone or combined with estrogen is effective if taken within 72 hours of unprotected intercourse and repeated after 12 hours.

2. long-Acting Progestogen-Only Contraception:

- Subdermal capsules containing only levonorgestrel offer long-term conception.

3. Contraceptives For Male

- It is done by drugs is to inhibit spermatogenesis, But the methods are not acceptable and they are also not satisfactory.

Erection: ^{دواء}

□ Drugs For Erectile dysfunction:

- Erectile dysfunction refers to the inability of men to attain and maintain an erect ^{مستقيم و ثابت} penis with sufficient rigidity to allow sexual intercourse.

- Drugs:

1. Androgens:

- Parenteral testosterone esters or transdermal testosterone therapy is effective only when androgen deficiency is demonstrated to be responsible for the loss of libido and erectile dysfunction.

2. Phosphodiesterase-5 inhibitors:

Ex: Sildenafil

Tadalafil

- MOA:

- Nitric oxide cause smooth muscle relaxation by generating cGMP intracellularly. The increase in GMP mediates vasodilation through action on protein kinase G. Inhibition of PDE-5 results in increased cGMP, potentiates the vasodilation effect on penile vascular smooth muscle.

- Adverse:

- Hypotension
- headache

- Flushing

Uterine Stimulants:

- Oxytocin
- Ergometrine
- PGE / PGF

1. Oxytocin:

- is secreted by the posterior pituitary along with Vasopressin (ADH).

- It regulates the myometrial activity.

- Oxytocin is either extracted from animal posterior pituitaries or is chemically synthesised.

Actions:

a- Uterus:

- ↑ the force and frequency of uterine contractions.

Estrogen sensitizes the uterus to oxytocin by inducing oxytocin receptor synthesis.

b- Breast:

↳ causes the expression of milk from the alveoli and ducts.

c- Cardiovascular System:

↳ Higher doses → vasodilation resulting in but fall in B.P, reflex tachycardia and flushing.

- Uterine Stimulants [2m, Aug 2010] [5m, March 2013]
- Oxytocin [3m, 2014 2m] write the pharmacology of oxytocin + uses [5m, Mar 2012]

→ - oxytocin.

□ Pharmacokinetics:

- Since oxytocin is a peptide it is inactive orally and can be given by IV or IM.

- It is inactivated in the liver and kidneys.

□ Adverse effects: abdominal pain,

confusion,

fast or irregular heartbeat

↓ kidney:

↳ In high doses produces antidiuretic action.

- Uses:

- is used to induce or increase labour when the uterine muscle is not functioning adequately.

- It can also be used to treat post partum haemorrhage.

2. Ergometrine

↳ increases the force, frequency and duration of uterine contractions.

- The mechanism of action is believed to result from partial agonist action on 5-HT₂ and α -adrenergic receptors.

- Uses:

- to control and prevent post partum haemorrhage

Adverse effects:

- Vomiting

- nausea

- Vasoconstriction → ↑ in B.P.

oxytocin
+
ergometrine

For the management of the third stage of labor

Prior to surgery to control bleeding owing to incomplete abortion.

3. Prostaglandins:

- Endogenous PGs:

- PGE_2 , $\text{PGF}_{2\alpha}$ are potent uterine stimulants, especially in the later part of the pregnancy and cause ripening of cervix.

- Exogenous PGs:

- used in obstetrics are dinoprostone, carboprost etc.

Unwanted effects:

- uterine pain

- nausea

- vomiting

- Clinical use:

- Dinoprostone

□ Uterine Relaxants (or) Tocolytics:

- These are drugs which ↓ se uterine motility.
- They have been used to delay or postpone labour, arrest threatened abortion and in dysmenorrhoea.

Drugs: coca

1-Adrenergic Agonists:

- Selective β_2 -adrenoceptor agonists (Ex: salbutamol) inhibit spontaneous or oxytocin-induced contractions of the pregnant uterus.

- These uterine relaxants are used in selected patients to prevent premature labour...!

2-Oxytocin Antagonists:

Ex: Atosiban

- It is used to inhibit uncomplicated premature labour, and it provides an alternative to β_2 -adrenoceptor agonists.

- Adverse effects:

- Vasodilation

- Nausea

- Vomiting

- rash.

3. Cyclo Oxygenase Inhibitors:

- Cox inhibitors such as indomethacin can inhibit labour,

Adverse effects (in baby):

- renal dysfunction
- delayed closure of ductus arteriosus

4. Calcium channel blockers:

- Because influx of calcium ions plays an imp't role in uterine contractions, calcium channel blockers, especially nifedipine can be used to reduce tone of myometrium and oppose contractions.

«Notes»

□ Thyroid Inhibitors:

- These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

- Thyrotoxicosis is due to excessive secretion of thyroid hormones. The two main causes are Graves' disease and toxic nodular goiter.

□ Classification:

1. Inhibit hormone synthesis (Antithyroid drugs)
Methimazole, Carbimazole, Propylthiouracil
2. Inhibit iodide trapping (Ionic inhibitors)
Thiocyanates, Perchlorates, Nitrates.
3. Inhibit hormone release:
Iodine, Iodides of Na and K
4. Destroy thyroid tissue
Radioactive iodide (^{131}I , ^{125}I , ^{123}I)

□ Compounds in groups 1 and 2 may be collectively called goitrogens.

□ Antithyroid drugs:

- Antithyroid drugs bind to thyroid peroxidase and prevent oxidation of iodide/iodotyrosyl residues, thereby;

- i - inhibit iodination of tyrosine residues in thyroglobulin
- ii - Inhibit coupling of iodotyrosine residues to form T_3 and T_4 .

iii - Thyroid colloid is depleted over time and blood levels of T_3/T_4 are reduced.

- Pharmacokinetics:

- Are quickly absorbed orally.
- Widely distributed in the body, milk and cross placenta.
- Metabolised in liver
- excreted in urine

□ Adverse effects:

- i - Hypothyroidism and goiter can occur due to overtreatment, but is reversible on stopping the drug
- ii - skin rashes
- iii - Joint Pain
- iv - loss or graying of Hair

□ Use:

- Control thyrotoxicosis in both Graves' disease and toxic nodular goiter.

2- Ionic inhibitors:

- Certain monovalent anions inhibit iodide trapping by the thyroid probably because of similar hydrated ionic size - T_3 and T_4 cannot be synthesized.

- They are toxic and not used now.

Thiocyanates: can cause liver, kidney, bone marrow and brain toxicity

Perchlorates: rashes, fever etc.

3. Iodine and iodides:

- It appears to be a direct action on thyroid cells - !
Excess iodide inhibits its own transport in thyroid cells and may alter the redox potential of cells, thus interfering with iodination → reduced T_3/T_4 synthesis (Wolff-Chaikoff effect).

-uses:

1. Preoperative preparation: for thyroidectomy. The aim is to make the gland firm, less vascular and easier to operate on.

2. Antiseptic

Adverse effects:

① Acute reaction ② Chronic overdose (iodism)

4. Radioactive iodide:

- They ^{تتسلل}traverse the tissues and can be monitored by a counter, while the latter are utilized for their destructive effect on thyroid cells.

- Diagnostic: 25-100 μ curies is given.

- Therapeutic: 3-6 m curie

-Advantages:

- treatment with ^{131}I is simple, inexpensive

- No surgical risk

Disadvantages:

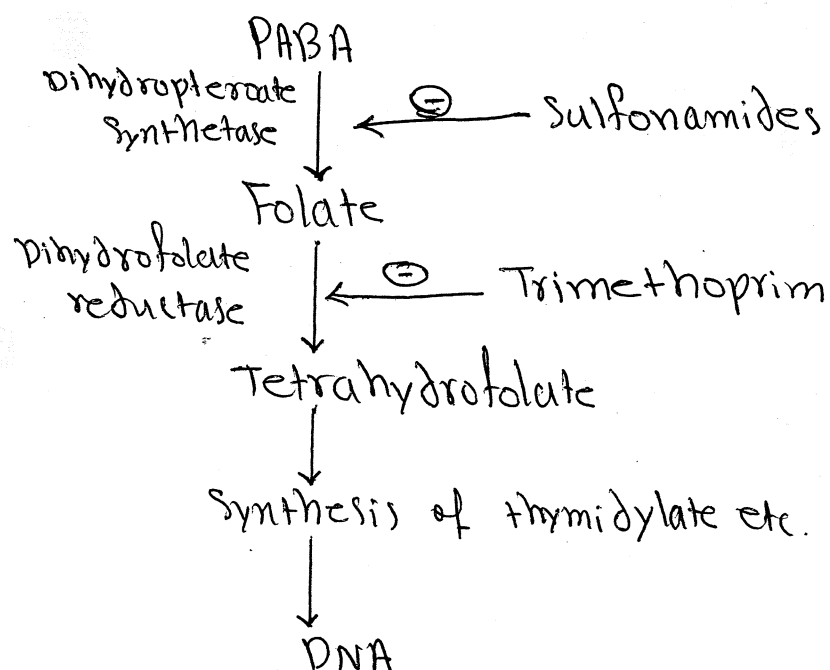
Hypothyroidism.

□ Contraindicated during pregnancy.

Sulfonamides:

MOA:

Many bacteria synthesize their own folic acid (FA) of which para amino benzoic acid (PABA) is a constituent. Folate is required for the synthesis of the precursor of DNA and RNA both in bacteria and mammals. But mammals can obtain their folic acid in their diet whereas bacteria need to synthesize it. Sulfonamides being structural analogues of PABA compete with PABA for the enzyme dihydropteroate synthetase and interfere with the synthesis of folate. Since sulfonamides are chemically similar to PABA, they may get incorporated to form an altered folate which is metabolically injurious.



CHEMOTHERAPY

Resistance To sulfonamides:

- Bacterial resistance to sulfonamides can arise from plasmid transfers or random mutations.

Ex:

Staphylococci, Streptococci, E. coli etc.

- Resistance is generally irreversible and may be due to any of the following reasons:

i. Altered Enzyme:

- Bacterial dihydropteroate synthase can undergo mutation or be transferred via a plasmid to result in a decreased affinity for sulfas. The drugs therefore become less effective competitors of PABA.

ii - Production of increased amount of PABA.

iii - low affinity of folate synthase for sulfonamides

Contraindication:

1 - pregnant women

2 - Avoided in newborns and infants less than 2 months old.

Pharmacokinetics:

1. Administration:

- can be administered orally, parentally and topically.

2. Distribution:

- Distributed throughout the body water and penetrate well into CSF and they can also pass the placental Barrier and into milk.

3. Metabolism:

- They are metabolised mainly by liver into acetylated derivatives which are inactive.

4. Excretion:

by kidney.

Adverse effects:

- 1- Nausea, vomiting, headache
2. Hypersensitivity reactions
3. Crystalluria
4. Hemopoietic disturbance

Therapeutic Uses:

1- Topical use:

Prevention of colonization of burns and wounds.

Ex: Sulfonamide

2. Antimicrobial

3. Certain sulfonamides are used in combination with pyrimethamine for treating malaria and toxoplasmosis.

Classifications:

1. Short acting (4-8 hr) Sulfadiazine

2. Intermediate acting (8-12 hr) Sulfamethoxazole

3. Long acting (~7 days) Sulfadoxine

4. Special purpose sulfonamides:

Silver sulfadiazine, Mafenide etc.

Antibacterial spectrum:

- Sulfonamides are mainly bacteriostatic agents and acts against many Gram +ve and Gram -ve bacteria.

- These are active against selected Enterobacteria, Nocardia etc.

Cotrimoxazole:

- The fixed dose combination of trimethoprim and sulfamethoxazole is called co-trimoxazole.
- The resulting combination shows greater antimicrobial activity than equivalent quantities of either drug used alone.

-MOA:

- The synergistic antimicrobial activity of co-trimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.

1. Sulfamethoxazole inhibits the incorporation of PABA into folic acid.
2. Trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.

- Resistance: Resistance to co-trimoxazole has been slow to develop compared to either of the drugs alone because it requires simultaneous resistance to both drugs.

Pharmacokinetics:

- It is generally administered orally.
- Trimethoprim is more lipid soluble than sulfamethoxazole and has a greater volume of distribution.
- Trimethoprim is partly metabolised in liver and excreted in urine.

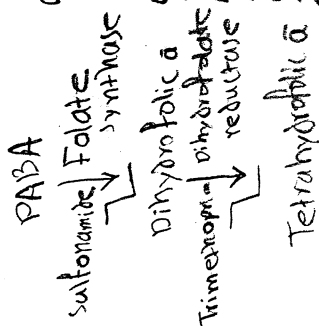
Adverse effects:

1. nausea, vomiting
2. Skin rashes
3. Megaloblastic anemia
4. leukopenia.

URDTC

Therapeutic uses:

1. treatment of urinary tract infections (*H. influenzae*)
2. " " respiratory tract infections ↗
3. Typhoid *Salmonella typhi*
4. Co-trimoxazole is also used for severe and invasive infections of *E. coli*, *Shigella* etc.
5. Bacterial diarrhoeas and dysentery [*E. coli*, *Shigella*]
6. Chancroid.



□ Explain why Nephrotoxicity develops with sulfonamides. How you can prevent it? ^{is dose related}

- Nephrotoxicity develops as a result of crystalluria.

- In the presence of acid urine, the acetylated form of the drug may be precipitated, mainly in the collecting tubule and the calyces.

- Minimize:

a- adequate fluid intake to maintain urine output of 1200 ml/day.

b- Making the urine alkaline to increase the solubility of the conjugation products.

c- Use of sulfonamides with acetylated metabolites soluble in a urine. eg: sulfisoxazole.

Sulfamethoxazole

Penicillins

- Penicillin was the first antibiotic used clinically.
- It was originally obtained from the fungus Penicillium notatum. Commercially penicillin is now obtained from mutant of Penicillium chrysogenum.
- Penicillins belong to a group of antibiotics called as beta-lactam antibiotics.
- The other members of this group include Cephalosporine, Monobactams and Carbapenems.
- MOA:
 - All B-lactam antibiotics interfere with the synthesis of the bacterial cell wall peptidoglycan. They inhibit the transpeptidation enzyme that cross-links the peptide chains attached to the backbone of the peptidoglycan. This weakens the bacterial cell wall and makes the organisms vulnerable to rupture by solutes in the surrounding medium. As cell wall synthesis occurs during the growth phase, the antibiotic is most effective against actively multiplying organisms.
 - The cell wall of gram +ve bacteria is almost entirely made of peptidoglycan. In gram -ve

bacteria the cell wall is complex consisting of alternative layers of lipoprotein and peptidoglycan. Hence high concentrations of drugs are required to achieve effect in Gram -ve organisms.

- Bacterial Resistance:

1- Natural or

2- Acquired

- Natural resistance to the penicillins occurs in organisms that either lack a peptidoglycan cell wall or that have cell walls that are impermeable to the drugs. The primary mechanism of acquired resistance is production of penicillinase.

- Penicillinase: hydrolyzes the cyclic amide bond of the β -lactam ring and inactivates penicillin and some closely related congeners.

Ex:

Majority of staphylococci and some strains of E. coli etc produce penicillinase.

- Some of the resistant bacteria are penicillin tolerant but not penicillin destroying. Their target

Enzymes are altered to have low affinity for penicillins.

- The gram -ve bacteria have some porin channels formed by specific proteins located in their outer membrane. Permeability of various β -lactam antibiotics through these channels differ. Some gram -ve bacteria become resistant by loss or alteration of porin channels.

Classification:

1- Natural Penicillins

Penicillin G

2- Semi-Synthetic Penicillins

i- Acid resistant alternative to penicillin G

- Phenoxyethyl penicillin (Pen V)

ii- Penicillinase-resistant penicillins

Methicillin, Cloxacillin

iii- Extended spectrum penicillins:

a- Aminopenicillins: Ampicillin, Amoxicillin

b- Carboxypenicillins: Carbenicillin

c- Ureidopenicillins: Piperacillin

Pharmacokinetics:

i-route of administration:

- Penicillin $\rightarrow$ IV or IM
- Pen V, Amoxicillin $\rightarrow$ orally

ii-Absorption:

- Incompletely absorbed after oral administration except Pen V, Amoxicillin.
- Absorption of Pen G is decreased by food in the stomach since gastric emptying time is reduced and the drugs are destroyed in the acidic environment.

iii-distribution:

- Distribution free drug through out the body good.
- All the penicillin cross placental barrier $\rightarrow$ no teratogenic effect

iv-Metabolism:

- The metabolism of these drug by the host usually insignificant.

5. Excretion:

- through the kidney as well as GI

Adverse Effects:

1. Hypersensitivity ^{***}

- Are caused by the degradation products of penicillin, mainly penicilloic acid, which combine with host protein and become antigenic.

Ex:

- Skin rashes and fever
- Acute anaphylactic shock, which may in some cases be fatal.

2. Diarrhoea:

- is caused by disruption of the normal balance of intestinal microorganisms.

3. Superinfections

4. Platelet dysfunction

- involves decreased agglutination.

Uses: ^{ASAD}

These are the drugs of choice for many infections such as:

1. Streptococcal infections like pharyngitis etc.

Treponema pallidum

2. Sexually transmitted diseases such as Syphilis and Gonorrhoea
3. Anthrax → *Corynebacterium diphtheriae*
4. Diphtheria
5. tetanus → *Clostridium tetani* *Neisseria gonorrhoeae*
6. Actinomycosis

□ Cephalosporins:

- Cephalosporins are β -lactam antibiotics that are closely related both structurally and functionally to the penicillins.

-MOA:

-The moa of these agents is similar to that of penicillins i.e. inhibition of bacterial cell wall synthesis.

- All the cephalosporines are bactericidal.

-Antibacterial Spectrum:

-Cephalosporins are classified into four generations on the basis of bacterial susceptibility, potency and resistance to β -lactamases.

→ These cephalosporins act as substitutes for penicillin and are resistant to staphylococcal penicillinase.

1. First Generation Drugs: - They are highly active against Gram +ve but weaker against Gram -ve bacteria.
no effective against 1. Salmonella Typhi
2. Shigella

i. Gram +ve cocci 1. Staphylococcus aureus
2. Streptococcus pneumoniae

ii. Gram -ve rods: 1. E. coli
2. Proteus

2. Second Generation:

- Are more active against Gram -ve organisms.
They have less activity than first generation compounds against Gram +ve organisms.

i. Gram +ve cocci 1. Staphylococcus aureus
2. Streptococcus pneumoniae

ii. Gram -ve 1. Neisseria gonorrhoeae
E. coli
Proteus

Acquired resistance to cephalosporins could have the same basis as for penicillins, i.e.:

3. Third generation:

- More active against the Gram -ve bacilli than 1st and 2nd generation.

- poor activity against Gram +ve cocci.

1-Gram +ve cocci: Streptococci pneumoniae

2- Gram -Ve cocci *Neisseria gonorrhoeae*

Gram -ve rods E-coli

4- Fourth generation:

- Fourth generation:

Active against: Gram +ve Cocci

- Streptococcus pneumoniae
- Staphylococcus aureus

Gram -ve Bacilli

Gram -ve cocci *Neisseria gonorrhoea*

Gramme -ve rod E. coli

Proteus

□ Resistance:

- Resistance to cephalosporins develops slowly and is mediated either by bacterial β -lactamases or by lack of bacterial permeability to the drug.

- i - alteration in target proteins reducing affinity for the antibiotics.
- ii - impermeability to the antibiotics or its efflux so that it does not reach its site of action.
- iii - elaboration of β -lactamases which destroy specific cephalosporins.

Adverse Effects:

1. Allergy (skin rash, fever)
2. Nephrotoxicity
3. CNS Toxicity
4. Hematological toxicity
5. A disulfiram-like ^{inter} reaction with alcohol
6. Superinfections
7. Intramuscular injections are painful and intravenous injections can cause thrombophlebitis.

Clinical uses: URGIT

1. Respiratory and urinary tract infections caused by gram -ve bacteria especially Klebsiella, Proteus etc.
2. They also used in treatment of:
 - Ceftriaxone + ampicillin → meningitis
 - Ceftriaxone → Gonorrhoea caused by penicillinase producing organisms
3. Typhoid caused by Salmonella Typhi
 - Ceftriaxone and Cefoperazone injected i.v.

Pharmacokinetic: orally, parentally widely distributed (some drugs bind)

- urine/bile

Therapeutic application of Ampicillin:

1- Urinary tract infection:

caused by E.coli, proteus etc.

2- Respiratory tract infections

caused by: Haemophilus influenza

3- Meningitis:

Caused by: Staphylococcus aureus etc.

4- Biliary tract and intestinal infections

Caused by: i-E.coli

Shigella

5- Gonorrhoea

caused by Neisseria gonorrhoea

□ Explain why clavulanic acid is given with Amoxicillin.

- β -lactamase inhibitors, such as clavulanic acid, sulbactam and tazobactam contain β -lactam ring, but they do not have significant antibacterial activity.

- They bind to β -lactamase and inactivate it, thereby protecting the antibiotics that are normally substrates for these enzymes.

- Clavulanic acid:

- is produced by *Streptomyces clavuligerus*. It is a potent and irreversible inhibitor of many β -lactamases and protects β -lactam antibiotics from inactivation, when combined with them.

- Clavulanic acid is usually used in combination with amoxycillin. When combined with amoxycillin, it widens the antibacterial spectrum of amoxycillin to include β -lactamase producing strains of *S. aureus*, *H. influenza*, *N. gonorrhoea*, *E. coli*, *Proteus* species. It is also used in combination with ticarcillin.

Tetracyclines:

- Belongs to class of protein synthesis inhibitors effects by targeting the bacterial ribosome.

[bacterial ribosome 70s $\rightarrow$ subunit 50s and 30s]

- Tetracyclines consists of 4 fused rings with a system of conjugated double bonds. Variation in their individual pharmacokinetics due to substitution on these rings.

MOA:

- The accumulation of these antibiotics in susceptible bacteria is mediated by an active transport system which is absent in the mammalian cells. Tetracyclines bind to 30s ribosomes and interfere with protein synthesis by blocking the attachment of aminoacyl transfer RNA to the acceptor site on mRNA-ribosome complex. Thus tetracyclines are bacteriostatic, not bactericidal.

-Resistance:

due to

1- the bacteria acquire capacity to pump tetracyclines out.

2- possible modification of the tetracycline binding site

Ex:

E. coli, H. influenzae etc.

-Pharmacokinetics:

1- Tetracyclines are usually administered orally but can also be given parenterally. [they form insoluble complexes by chelation with calcium, magnesium etc and hence substances like milk that contain calcium, and anta reduce their absorption.

2- Tetracyclines are widely distributed in the body.

All tetracyclines cross the placental barrier.

3- Tetracyclines are metabolised in the liver and metabolites are excreted mainly in the urine (Generally).

-Adverse effects:

- 1- Gastric discomfort
- 2- hepatic dysfunction (large dose)
- 3- nausea, vomiting, diarrhoea
- 4- Phototoxicity
- 5- Vestibular toxicity
- 6- Superinfection
- 7- Administration of tetracyclines during pregnancy may cause temporary suppression of bone growth and yellow staining of the teeth of infant.

Includes: {
Tetracycline
oxytetracycline
doxycycline
minocycline

Clinical uses:

- 1- Tetracyclines are first choice for rickettsial, mycoplasma and chlamydial infections; cholera, plague and Lyme disease.
caused by  
Vibrio cholerae
Spirochetes
- 2- They are useful in mixed infections of the respiratory tract and in acne.

□ Chloramphenicol:

- MOA:

- Chloramphenicol penetrates into bacterial cell and acts by interfering with the protein synthesis by inhibiting 50s ribosome. Because of the similarity of mammalian mitochondrial ribosomes to those of bacteria, protein synthesis in these organelles may be inhibited at high circulating chloramphenicol levels, producing bone marrow toxicity.

Resistance:

Chloramphenicol resistant *S. typhi* have emerged due to transfer of R-factor by conjugation. etc.

- Pharmacokinetics:

- Chloramphenicol is rapidly and completely absorbed by oral administration.

- It is widely distributed throughout the body and freely penetrates serous cavities and B.B.B. It crosses placenta and is secreted in bile and milk.

- It is largely inactivated by hepatic conjugation to glucuronide and is excreted in the urine.

Adverse reaction:

- 1- Allergy (skin rashes, drug fever)
- 2- Bone marrow toxicity
- 3- liver toxicity
- 4- CNS toxicity
- 5- Gray-baby syndrome.

- This adverse effects in neonates if the dosage regimen of chloramphenicol is not properly adjusted. Neonates have a low capacity to glucuronylated the antibiotic and they have under developed renal function. Inadequate inactivation and excretion of drug can result in 'gray baby syndrome'.

- The drug which accumulates to levels that interfere with the function of mitochondrial ribosomes.

- Toxic levels of chloramphenicol after 2-9 days:

- 1- Vomiting
- 2- ^{or} Ashen gray colour of the skin
- 3- Hypotension
- 4- Hypothermia
- 5- Cyanosis

- Adults who have received very high doses of the drug can also exhibit this toxicity.

□ Clinical uses: ^{out}

1. Typhoid fever caused by salmonella Typhi
2. Ophthalmic infections
3. plague
4. It is used for urinary tract infections.

- Contraindications of chloramphenicol:

- Pregnancy
- Hypersense to drug
- mild infections
- infancy

Macrolides:

Ex: Erythromycin,

Roxithromycin, Clarithromycin and Azithromycin

-MOA:

- Macrolides act by inhibiting bacterial protein synthesis. They bind to 50s subunit of the bacterial ribosome and interfere with translocation.

- Erythromycin base is a labile and is destroyed by gastric acid. It is administered as enteric coated or as esterified forms.

- Macrolides are distributed well in the body but they do not cross BBB.

- Excreted in bile (generally).

-Adverse effects:

1. Hypersensitivity: skin rashes and fever
2. Cholestatic jaundice
3. Epigastric Distress

-Clinical uses:

- Erythromycin is used in patients who are allergic to penicillins and in those whom microorganisms have developed resistance to penicillin.

[against H-influenzae] etc

- diphtheria
- Tetanus
- Syphilis

- It is also the drug of choice in treatment of whooping cough.

- As a first choice drug for Atypical pneumonia caused by *Mycoplasma pneumoniae*.

Antibacterial Spectrum: All aminoglycosides are bactericidal.

- They are effective against many aerobic Gram -ve and some Gram +ve organisms.

Aminoglycosides:

Gentamicin
Streptomycin etc.

MOA:

- Aminoglycosides act by inhibiting bacterial protein synthesis. Susceptible organisms have an oxygen-dependent system that transports the antibiotic by active transport mechanism across the cell membrane. The antibiotic then binds to the separated 30s ribosomal subunit and interferes with the initiation of protein synthesis, block the translation of mRNA and prematurely terminate the synthesis. They have a minimal action against anaerobic organisms. They are bactericidal and the effect is enhanced by agents that interfere with cell wall synthesis.

Resistance:

Ex: M. tuberculosis etc.

1. Decreased uptake of drug when the oxygen-dependent transport system for aminoglycosides is absent.
2. An altered receptor where the 30s ribosomal subunit binding site has a lowered affinity for aminoglycosides.

3. Plasmid associated synthesis of enzymes such as acetyl transferases, nucleotidyl transferase and phosphotransferases that modify and inactivate aminoglycoside antibiotics.

□ Pharmacokinetics:

1. They are not absorbed in the GIT and are usually given IM or IV.

2. Do not cross the B.B.B.

All may cross the placental barrier.

3. They are rapidly excreted in urine.

□ Adverse Effects:

1. Ototoxicity

2. Nephrotoxicity

3. Allergic reaction / contact dermatitis

4. Local irritation

5. Neuromuscular paralysis

□ Therapeutic Applications:

↑ effective → organisms: M. tuberculosis, Shigella and E. coli
1. Streptomycin Proteus

i - treatment of tuberculosis

ii - " " plague

active against E. coli, Proteus, Pneumoniae,
Salmonellae

2. Gentamicin:

-It is very useful for preventing and treating respiratory infections in critically ill patients and in those with impaired host defence.

-It is often combined with penicillin/cephalosporin or other antibiotics.

3. Kanamycin. It is similar to streptomycin in all respects including efficacy.

4. Neomycin:

It is used topically for infected wounds, ulcers, burn etc.

□ Polyenes:

-The name polyene is derived from their double-bonded structure.

-Amphotericin B:

-It is the drug of choice in treatment of systemic mycoses.

-MOA:

Amphotericin binds to the ergosterol present in the cell membranes and interferes with permeability and with transport functions. This disrupts membrane function, allowing electrolytes and small molecules to leak from the cell, resulting in cell death. Amphotericin has a selective action, binding to the membranes of fungi and some protozoa, less ability to mammalian cells and not at all to bacteria.

□ Resistance:

Fungal resistance, though infrequent, is associated with decreased ergosterol content of the fungal membrane.

□ Pharmacokinetics:

1. It is poorly absorbed orally and is administered by intravenous infusion or applied topically.

Antifungal Spectrum: is active against a wide range of yeasts and fungi such as *Candida albicans* etc.

2. Amphotericin is highly protein bound and is distributed throughout the body.
3. About 60% of the drug is metabolised in liver
4. Excretion occurs slowly in urine and bile.

Adverse effects:

1. Fever and chills
2. renal impairment
3. Hypotension
4. CNS Toxicity
5. Anaemia

Uses:
 → Antifungal
 → Antiprotozoan → such as visceral leishmaniasis

1. It is used topically for oral, vaginal and cutaneous candidiasis and otomycosis
2. It is most effective for various types of systemic mycoses.
3. It is most effective drug for resistant cases of kala azar and mucocutaneous leishmaniasis.
4. is also commonly used in tissue culture to prevent fungi from contaminating cell cultures.

Polypeptide Antibiotics

- Polymyxin A and colistin:

MOA:

- They have cationic detergent properties and their mechanism of action involves interaction with the phospholipid of the cell membrane and disruption of its structure. They may also inactivate the bacterial endotoxin.

- They exhibit synergism with many other anti-bacterials by improving their penetration into the bacterial cell.

- Adverse effects:

1. neurological disturbances
2. neuromuscular blockade
3. nephrotoxicity

- Clinical uses:

1. They are used topically in combination with other antibacterials for skin infections, burns etc.
2. They are used orally for diarrhoea, especially in infants.

Quinolones:

- Quinolones are synthetic antimicrobials having a quinolone structure.

Nalidixic acid:

- It is effective against most of the Gram -ve bacteria that commonly cause urinary tract infections (E. coli, Proteus, Shigella etc).

MOA:

- It inhibits DNA gyrase and DNA topoisomerase IV.

The former action is direct and leads to arrest of DNA replication. The latter action blocks DNA replication by blocking the enzymes normal function. The activity of quinolones against Gram -ve bacteria is primarily due to action on DNA gyrase and on Gram +ve due to action on topoisomerase IV.

Pharmacokinetics:

- orally
- is highly plasma bound
- metabolism in liver

Excretion in urine

-Adverse effects:

Allergic reactions: rashes, fever etc
nausea

Vomiting

CNS problem: Headache etc.

-Clinical uses:

1. used as urinary antiseptic

2. It is also used in diarrhoea caused by *Proteus*,
Shigella or *Salmonella*.

□ Fluoroquinolones:

-These are quinolone antimicrobials having one or more Fluorine substitutions.

1. First generation Fluoroquinolones: Norfloxacin,
ciprofloxacin

2. Second generation F: levofloxacin etc.

□ Adverse effects:

1. CNS problems; nausea, headache

2. Nephrotoxicity

3. GI problems: vomiting, abdominal discomfort.

□ Clinical Uses:

- they are highly effective in gonorrhoea.
- They are used in complicated urinary tract infections, mild to moderate gastrointestinal infections and skin infections.

□ Antifungal Drugs:

- Infections caused by fungi are called mycoses and they can be divided into superficial infections (affecting skin, nails, scalp or mucous membranes) and systemic infections (affecting deeper tissue and organs).

□ Classification:

1. Antibiotics:

a - Polyenes: Amphotericin B, Nystatin

b - Griseofulvin

2 - Antimetabolites: Flucytosine

3 - Azoles:

a - Imidazoles: Miconazole

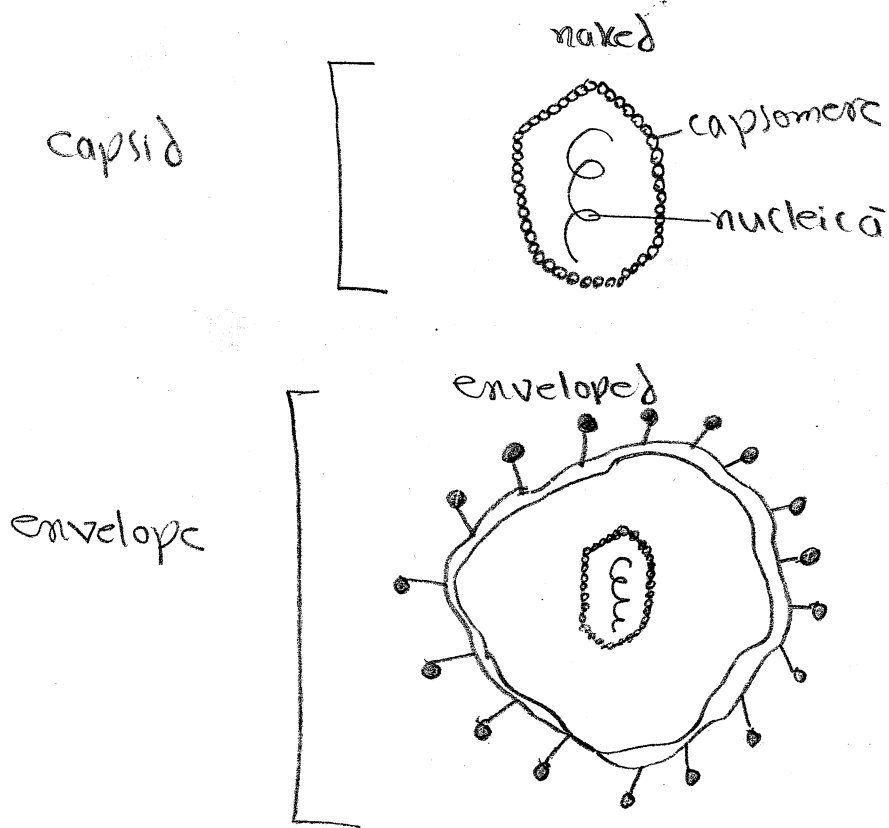
b - Triazoles: Fluconazole

4 - Allylamine: Terbinafine

5 - Other topical Agents: Benzofenone

Antiviral Agents:

- Viruses are the smallest obligate intracellular infectious agents containing only one type of nucleic acid, either DNA or RNA as their genome.



- After penetration into the target cell, viral replication occurs in following steps:

- Uncoating of viral nucleic acid strands
- Synthesis
- replication of viral DNA/RNA
- Late structural protein synthesis
- coating and maturation of viral particles and
- release of viral particles from the cell.

- Antiviral agents can target any one of the above steps.

Classification: ^{IRN H}

1. Anti-Herpes Virus: Idoxuridine, Acyclovir etc

2. Anti-Retro Virus:

a- Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

Zidovudine (AZT), Didanosine, Stavudine

b- Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs):

Nevirapine, Delavirdine

c- Protease Inhibitors:

Ritonavir, Lopinavir

3. Anti-influenza virus:

Amantadine, Rimantadine

4. Non-selective Antiviral Drugs:

Ribavirin, Interferons.

~~Anti-Herpes virus Agents~~

- Herpes viruses are associated with diseases such as cold sores, viral encephalitis and genital infections.

-The drugs that are effective against these viruses act mainly during the acute phase of viral infections. These drugs act mainly by inhibiting viral DNA polymerase or inhibition of attachment to the host cell.

2. Anti Retro-Virus Agents (Anti HIV drugs)

-These are the drugs which are active against human immuno deficiency (HIV), a retrovirus which is the cause for Acquired Immunodeficiency Syndrome (AIDS). The currently used drugs cannot eradicate the HIV infection, but when they are used in combination, they can decrease viral replication, improved immunologic status, and prolong survival.

□ Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Zidovudine (AZT):

-It is one of the most effective drugs used by HIV-infected individuals to improve immunological status. When the drug is given to pregnant women and to the new born infant, mother to baby transmission of HIV can be reduced.

-It also reduces neurological manifestations of AIDS and new Kaposi's lesions do not appear.

□ MOA:

Zidovudine is converted to its corresponding triphosphate by mammalian thymidine kinase. AZT triphosphate is then incorporated into the growing chain of viral DNA by reverse transcriptase. This terminates the chain synthesis of viral DNA.

Single-stranded viral RNA

↓ Virus directed reverse transcriptase
(inhibited by zidovudine triphosphate)

Double-stranded viral DNA

□ Resistance:

-Resistance to Zidovudine occurs by point mutations which alter reverse transcriptase enzyme, which has a lower affinity for the AZT-Triphosphate.

□ Pharmacokinetics:

-Orally, IV.

-Cross B.B.B.

-metabolism in liver, excreted by kidney.

Adverse Effects:-

- 1- toxic to bone marrow
 2. Severe anemia
 - 3- leukopenia
 - 3- Gastrointestinal disturbances
 - 4- Skin rash
 - 5- Fever
 - 6- Headache
- } in high doses.

-Non-Nucleoside Reverse Transcriptase Inhibitors:-

- These drugs like NRTIs inhibit reverse transcriptase but by different mechanism. These bind to the reverse transcriptase near the catalytic site and denature it. They are usually used in combination with NRTIs. They have no effect on human DNA polymerases and their major advantage is the lack of effect on the host blood-forming organs and lack of cross-resistance with NRTIs. Most of these drugs are inducers, substrates or inhibitors to cytochrome P450 enzymes.

Protease Inhibitors:

- These drugs reversibly inhibit the virus-specific protease that is essential for the final step of their proliferation.

HIV-treatment:

- The use of combination treatment changed the prognosis of HIV/AIDS. The combination therapy is known as highly active antiretroviral therapy (HAART). The combination used in HAART include two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or one or two protease inhibitors.

- Combination therapy aims to delay the development of drug resistance and to reduce the viral load and prolong the survival of the patient.

~~Non-Selective Antiviral Drugs~~

Ex: Ribavirin

Immunoglobulin

Interferon

-Immunoglobulin:

- Immunoglobulin contains antibodies that are active against viruses. The antibodies are directed against viruses to prevent their attachment to host cells.
- They are used before or after onset of symptoms to prevent measles, hepatitis etc.
- Hyperimmune globulin is used against hepatitis B etc.

□ Interferon:

-Interferons are a family of natural glycoproteins which inhibits virus replication and are produced by animals or cultured cells in response to viral infection or other non-viral inducers.

Types:

└ Type-I interferons:

1- α -interferon (IFN- α) - produced by monocytes and B lymphocytes. It has maximal antiviral activity.

2- β -interferon (IFN- β) - produced by fibroblasts and epithelial cells.

Has intermediate antiviral activity.

2. Type II interferons:

γ -interferon (IFN- γ) produced by activated T-cells.

- Now, Interferons are also produced by recombinant DNA technology.

- Interferons bind to specific cell receptors and affect viral replication at various steps such as viral penetration, synthesis of viral mRNA,

Adverse effects:

1. Hypersensitivity
2. Fever
3. Fatigue
4. Hearing loss

Therapeutic uses:

1. Chronic hepatitis B, C, D
2. All severe viral infections
3. used in multiple myeloma.
4. are used as second line drug in treatment of herpes simplex etc.

□ Chemotherapy of Tuberculosis:

- Tuberculosis is a chronic infectious disease, caused by several species of mycobacteria. *Mycobacterium tuberculosis* is one of the mycobacteria which can lead to serious infections of the lungs, genitourinary tract, skeleton and meninges. The disease is mainly spread by droplet infection.

- Drugs:

1. First line drugs:

- These drugs have high antitubercular activity and low toxicity and are used regularly.

Isoniazid, Rifampin, Streptomycin etc.

2. Second line Drugs:

- These drugs have low antitubercular activity or high toxicity or both. These are only used in special circumstances.

Ethionamide,

- Cycloserine, Amikacin and Fluoroquinolones etc.

- Monotherapy should never be used in tuberculosis, as this leads to rapid development of drug resistance.

-Compound drug therapy is employed:

a-A first initial phase of about two months consisting of three drugs used combinedly - Isoniazid, rifampin and pyrazinamide. Ethambutol is also used if the organism is suspected to be resistant.

b-A second continuation phase of four months, consisting of two drugs - Isoniazid and rifampin. Long term treatment is needed for patients with meningitis, bone/joint involvement or drug-resistant infection.

-Isoniazid:

MOA:

-Isoniazid acts mainly by inhibiting the synthesis of mycolic acid, an important constituent of the mycobacterial cell wall.

-It may also inhibit the formation of DNA and RNA and inhibit various oxidative mechanisms.

Resistance:

Resistance can occur due to reduced penetration and accumulation of drug by alteration of target enzyme or by production of excess amounts of enzymes. Cross-resistance with other antitubercular drugs is not reported.

Pharmacokinetics:

- Orally - distributed widely into all body fluids, cells, tubercular cavities, placenta etc.
- metabolism in liver
- Excrete in urine

Adverse effects:

- Peripheral neuritis
- fever
- Hepatotoxicity etc.

Ethionamide:

- It is structurally related to Isoniazid and is believed to act by the same mechanism.

pharmacokinetic: Same as isoniazid.

adverse:

- Hepatotoxicity
- nausea and vomiting
- impotence
- mental disturbances

Chemotherapy of Leprosy:

- Leprosy is caused by Mycobacterium leprae.
- The bacteria produces characteristic lesions in the skin and the peripheral nerves.
- Bacilli from the skin lesions or nasal discharge of infected patients enter susceptible individuals through the skin or respiratory tract.

Types:

1. Lepromatous
2. Tuberculoid
3. Indeterminate
4. Dimorphic (borderline)

- Lepromatous and borderline forms have plenty of bacilli in the lesions and are called multi bacillary leprosy whereas tuberculoid and indeterminate lesions show fewer bacilli and are called paucibacillary leprosy.

- Paucibacillary leprosy, which is mainly tuberculoid in type is treated for 6 months with dapsone and rifampin.

- Multibacillary leprosy, which is mainly lepromatous is treated for atleast 2 years with rifampin,

dapsone and clofazimine.

Dapsone:

Dapsone is chemically related to the sulfonamides...

Rifampin:

Clofazimine:

- Clofazimine is a phenazine dye with leprostatic and anti-inflammatory properties.

- It acts mainly by inhibiting the template function of DNA in M. leprae. It is bactericidal and has action against dapsone resistant organisms.

- It is well absorbed after oral administration and is retained in many tissues. It is excreted in the urine slowly for several weeks.

- Adverse:

- The skin and urine can develop a reddish colour and the lesions are a blue-black discolouration.

- nausea

- Headache

- Gastrointestinal disturbances.

Chemotherapy of Malaria:

- Malaria is also known as ague, malar fever, periodic fever or paludism.

- It is a communicable disease which occurs due to the presence of protozoan parasites in Red blood cells (RBCs).

- Causative Agents:

Malaria is caused by protozoan parasite belonging to the genus, Plasmodium (Plasmodium vivax, P. malariae etc.)

Mode of Transmission:

1- It is mainly transmitted through the bite of an infected Female Anopheles mosquito.

2. It may also get transmitted directly through blood transfusions, usage of non-sterilized needles etc.

3. It is very rarely transmitted congenitally (from mother to neonates).

- Symptoms:

Stage 1: Fever with chills and rigor

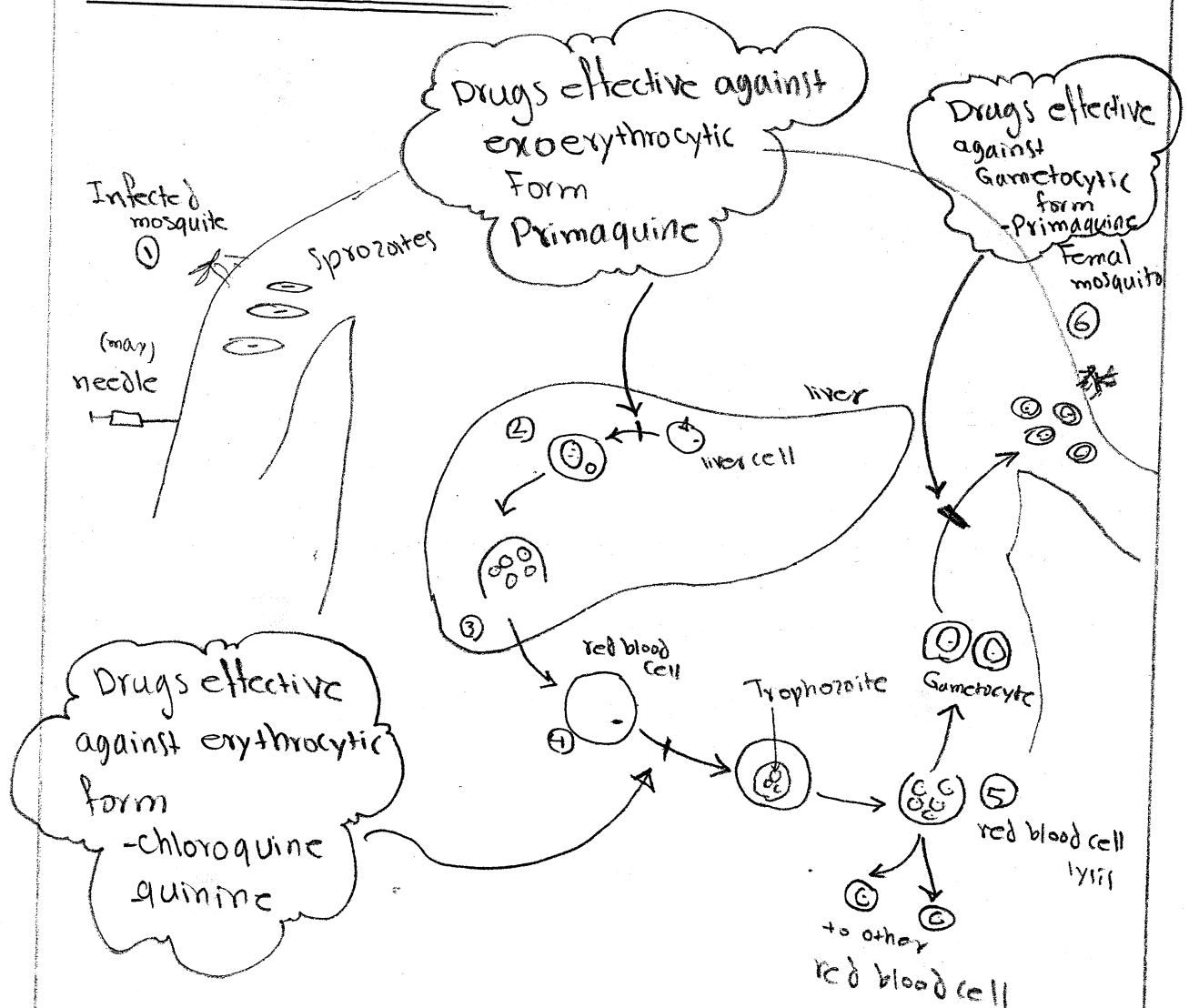
- Stage 2 (Hot Stage)

Severe headache and burning hot sensation occurs due to rise in body temp.

Stage 3:

Profuse sweating.

Life-cycle of malaria:



- 1- Infected mosquito injects Sprozoites.
- 2- Sprozoites migrates to liver cell where they form merowite.
3. Merozoites are released and invade red blood cells.
4. In red blood cells the merozoites become Trophozoites.
5. Rupture of red blood cells release merozoites which can infect other red blood cells.
- 6- Female mosquito picks up Gametocytes from infected individual.

Antimalarial Drugs:

- clinically, malarial infections can be controlled by using drugs that act at different stages of the life cycle of the parasites.

Drugs used to Treat acute attack:

- Acute attack can be treated by employing blood schizonticidal agents.

- They act on erythrocytic forms and suppress actual attack, but exoerythrocytic forms can cause relapses later.

-The drugs belonging to this group are quinine, mefloquine, chloroquine etc.

-They are also used in combinations along with antibiotics such as tetracycline and doxycycline.

#Drugs that effect Radical Cure

These drugs are tissue schizonticidal agents that act on parasites in the liver. These drugs also destroy the gametocytes, reducing the spread of infection.

Ex:

Primaquine

#Drugs Used for Chemoprophylaxis:

-Chemoprophylactic agents block the link b/w exoerythrocytic stage and erythrocytic stage and thus prevent the development of malarial attacks.

-The drugs are chloroquine, mefloquine, dapson etc. These are also used in combination.

- Chemoprophylactic agents are used by individuals who intend to travel to areas where malaria is endemic. They are to be administered one week

before entering the area and should be continued throughout stay and for at least one month afterwards.

Drugs used to Prevent Transmission:

Drugs that destroy gametocytes prevent the transmission of malaria b/w mosquito and humans.

Drugs: primaquine, proguanil and pyrimethamine.

Antimalarial drugs:

1. Cinchona Alkaloids: Quinine, Quinidine
2. Quinoline Derivatives
 - a- 4-aminoquinolines: Chloroquine, Hydroxy quinoline etc.
 - b- 8-aminoquinolines: Primaquine
 - c- Quinoline - methanol: Mefloquine
3. Anti folates:
 - a- Biguanides: Proguanil
 - b- Diamino Pyrimidines: Pyrimethamine
 - c- Sulfonamides and sulfones: Sulfadoxine, Papicon
4. Artemisinin Compounds: Artesunate, Artemether
5. Antimicrobials: Tetracycline, Doxycycline

□ Chloroquine:

-MOA:

- Chloroquine which is unionized at neutral pH diffuses freely into the parasite lysosome. At the acidic pH of the lysosome, it is converted to a protonated, membrane impermeable form and is trapped inside the parasite. At high concentrations, it inhibits the synthesis of protein RNA and DNA synthesis.

- Chloroquine acts mainly on haem disposal by preventing digestion of haemoglobin by the parasite and thus reducing the supply of amino acids necessary for survival of parasite.

- It also inhibits the enzyme haem polymerase that polymerises toxic free haem to haemozoin, rendering it harmless.

Adverse effects:

1- nausea

2- Vomiting

3- Headache

4- Dizziness

5. hepatic dysfunction

- Pharmacokinetics:

- administration: orally (in severe malaria condition, IM or S.C injection followed by IV infusion)
- distribution: throughout the body, cross placenta and penetrates into the cerebrospinal fluid.
- Metabolism: hepatic microsomal enzyme system
- Excretion: in urine

- Uses:

- 1- Malaria
- 2- hepatic amoebiasis
- 3- manifestation of lepra reaction
- 4- anti-inflammatory action.

Chemotherapy of Protozoal infections.

1. Chemotherapy of Amoebiasis.

- Amoebiasis (amoebic dysentery) is an infectious disease caused by protozoa, Entamoeba histolytica, which is produced by the ingestion of cysts of this organisms.

- The ingested cysts develop into trophozoites and adhere to the colonial epithelial cells in the intestine. These trophozoites then lyse the host cell and invades the submucosa. This produces the amoebic ulcers and cause acute dysentery or chronic intestinal amoebiasis.

- The parasite may also pass into blood stream and invades the liver causing liver abscesses.

Symptoms:

mild diarrhoea to fulminating diarrhoea.

Drugs:

1. Systemic amoebicides:

a) For both intestinal and extraintestinal amoebiasis

Nitroimidazoles:
Metronidazole

Alkaloids:

Emetine,
dehydroemetine

b- For extraintestinal amoebiasis only: Chloroquine

2- Luminal Amoebicides

a- Amides: Nitazoxanide

b- 8-Hydroxyquinolines: Quiniodochlor

c- Anti-biotics: Tetracyclines

Metronidazole

-MOA:

Metronidazole is selectively toxic to anaerobic organisms and amoebae. Some anaerobic protozoan parasites possess ferredoxin like, low-redox potential, electron transport proteins that participate in metabolic electron removal reactions. The nitro group of metronidazole accepts electrons, forming reduced cytotoxic compounds that binds to proteins and DNA causing cell death.

-Pharmacokinetics:

- Administration: orally

- Distribution: in the body and therapeutic concentrations are achieved in vaginal secretion, semen, saliva, and cerebrospinal fluid.

- Metabolism: liver

- Excretion: urine

Adverse effects:

- 1- Gastrointestinal disturbances
- 2- nausea
- 3- abdominal cramps
- 4- vomiting
- 5- rarely headache, dizziness

Uses:

- 1- Amebiasis
- 2- Giardiasis

Chemotherapy of Giardiasis:

Giardia lamblia is a flagellate protozoan parasite that mostly lives in the small intestine. It is transmitted from man to man by faecal contamination of food and water. This protozoa invades the mucosa and causes diarrhoea which requires treatment. The trophozoites divide by binary fission and form cysts occasionally which pass out in stool. It often exists in association with *E. histolytica* infection.

The drugs:

- Metronidazole
- Tinidazole
- Paramomycin
- Furazolidine
- Quinacrine

□ Pharmacology of Anthelmintic Drugs:

- Helminths are a poly phyletic group of eukaryotic parasites.

- They are worm-like organisms living in and feeding on living hosts, receiving nourishment and protection while disrupting their host's nutrient absorption, causing weakness and disease. Those that live inside the digestive tract are called intestinal parasites. They can live inside humans and other animals.

Symptoms:

- intestinal obstruction

- insomnia

- vomiting

- Weakness

- Stomach pain

□ Anthelmintic Drugs:

- Are drugs that expel parasitic worms (helminths) from the body, by either stunning or killing them.

- They may also be called vermifuges (stunning) or vermicides (killing).

Classification:

1. Broad Spectrum Anthelmintics:

a- Drugs effective in round worms, thread worms, hook worms, tape worms and flukes.

Ex: Mebendazole

b- Drugs effective in round worms, thread worms and hook worms:

Ex: Albendazole

2. Narrow Spectrum Anthelmintics:

a- Drugs effective in round worm and thread worm and hook worms.

Ex: Piperazine

b- Drugs effective in filariasis:

Ex: Diethyl carbamazine

c- Drugs effective in tap worm:

Ex: Chloroquine

d- Drugs effective in flukes:

Ex: Praziquantel

□ Chemotherapy of Cancer (Neoplasms):

- Neoplasm or tumor is defined as growth or mass of abnormal tissue formed due to excess and un-coordinated cell proliferation.

Types:

1. Benign Tumours: they are slow growing and do not invade other parts of the body. They are removed by normal surgery and does not lead to death.

2. Malignant Tumours:

- These are cancerous tumours which are fast growing and invade other body parts. they cannot be removed by surgery as there is no clear demarkation b/w normal cells and tumour cells. These tumors may lead to death.

Etiology of tumours:

1. Epidemiological Factors:

i- Familial and Hereditary Factor

ii-Geographical Factors

iii-Environmental and cultural Factors

a-Smoking

b-Excess alcohol consumption

iv. Age

v. Sex

-Pathogenesis:

-The basis for tumour formation is change in genetic factors which leads to non lethal genetic damage of cells. There are two types of regulatory genes in the body which protects it from mutation and tumor. But, during development of cancer, these 2 genes are the primary targets.

1- Oncogenes

2- Tumor suppressor genes.

-General Principles of cancer Chemotherapy:

-Cancer chemotherapy is aimed either to kill cancer cells or modify their growth. The anticancer

Drugs generally attack the metabolic sites that are essential in cell replication. For ex, these drugs reduce the availability of purine and pyrimidine precursors that are used in synthesis of DNA or RNA.

- In some non curative cases of cancer, drugs are used for palliation or as an adjuvant to surgery or radiotherapy and immunotherapy.

Anti-cancer drugs:

1. Cytotoxic Drugs:

(a) Alkylating agents:

i- Nitrogen mustards: Cyclophosphamide, Chlorambucil

ii - Alkyl sulfonate: Busulfan

iii - Nitrosoureas: Carmustine, Lomustine

iv. Triazine: Dacarbazine

(b) Anti-metabolites:

i. Folic acid antagonist: Methotrexate

ii - Purine Antagonist: 6-Mercaptopurine

iii - Pyrimidine Antagonist: 5-Fluorouracil

① Plant derivatives

Vinblastine

Vincristine

Etoposide

② Antibiotics:

Actinomycin D, Mitomycin C

③ Hormones:

Prednisolone

Hydroxyprogesterone

Flutamide

④ Miscellaneous:

- Hydroxyurea

- Cisplatin

□ Alkylating Agents

- An alkylating antineoplastic agent is an alkylating agent used in cancer treatment that attaches an alkyl group (C_nH_{2n+1}) to DNA.

The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring.

- Since cancer cells, in general, proliferate faster and with less error-correcting than healthy cells, cancer cells are more sensitive to DNA damage - such as being alkylated.

Alkylating agents are used to treat several cancers. However, they are also toxic to normal cells (cytotoxic), leading to damage, in particular in cells that divide frequently, as those in the gastrointestinal tract, bone marrow etc.

- Cyclophosphamide:

- As a prodrug, it is converted in the liver to active forms that have chemotherapeutic activity.

- Pharmacokinetics:

- prefer orally or IV

- metabolites are excreted in minimal quantities into faeces or urine.

Adverse effects:

- nausea
- Vomiting
- bone marrow depression
- renal toxicity

Therapeutic uses:

1. breast cancer
2. some form of brain cancer
3. leukemia
4. Autoimmunodisease treatment

□ Nitrosoureas:

- Nitrosourea is both the name of a molecule and a class of compounds that include a nitroso ($R-NO$) group and a urea.

Ex:

- Carmustine
- Lomustine

- Nitrosourea compounds are DNA alkylating agents and are often used in chemotherapy.

- They are lipophilic and thus can cross the BBB, making them useful in the treatment of brain tumors.

- Carmustine: IV / lomustine: orally

Adverse effects:

- 1- renal toxicity
- 2- nausea.
- 3- Vomiting
- 4- bone marrow depression

b- Antimetabolites:

- Antimetabolites are structurally related to normal components of DNA or of coenzymes involved in the nucleic acid synthesis. These generally interfere with the availability of purine or pyrimidine nucleotide precursors by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.

Folate Antagonists:

Methotrexate:

MOA:

- Folic acid is essential for the production of the coenzyme, tetrahydrofolic acid (THF). The conversion of folate to THF is carried out by an enzyme, folate reductase. Methotrexate competes with folic acid for this enzyme by binding irreversibly to folate reductase, thus inhibiting the production of THF. Lack of the coenzyme THF leads to inhibition of DNA synthesis and consequently of cell rep.

- Pharmacokinetics:

Administration: orally (usually), IM, IV

Adverse effects:

1. depression of bone marrow
2. nephrotoxicity

- Therapeutic uses:

1. Breast cancer
2. as immunosuppressant

Purine Antagonists:

6-Mercaptopurine:

MOA:

- It is an analogue of purine and is highly effective anticancer drug. The drug is converted in the cells to ribonucleotide of 6-Mercaptopurine, which then suppress the de novo biosynthesis of purines and hence of DNA.

Pharmacokinetics:

Administration: orally

Distribution: throughout the body except CSF.

Metabolism: in liver

Excretion: in the urine

Adverse effects:

1. Bone marrow depression
2. Hepatotoxicity
3. Nausea
4. Vomiting
5. Diarrhoea

- Uses:

- 1- choriocarcinoma
- 2- Solid tumours
3. Acute leukaemia

Pyrimidine antagonists:

5-Fluorouracil:

- MOA:

- Is an analogue of uracil (pyrimidine). 5-Fluorouracil must be converted in the body to the corresponding deoxynucleotide, which inhibits thymidylate synthesis and blocks the conversion of deoxyuridilic acid to deoxythymidilic acid. The result is inhibition of DNA synthesis but not RNA or protein synthesis.

- Pharmacokinetics:

- 1- IV to prevent first-pass metabolism.
- 2- well distributed in the body.
- 3- metabolism in liver

- Adverse effects:

- 1- bone marrow depression
- 2- Gastrointestinal disturbances.

-Therapeutic uses:

1- breast, ovarian, pancreatic cancer, colon, urinary bladder, liver etc.

Plant Derivatives:

Vinblastine, Vincristine

-MOA:

-These act by inhibiting mitosis. They bind to tubulin and inhibit its polymerisation into microtubules and thus prevent spindle formation in mitosing cells and cause arrest of metaphase. Hence, they are both cycle specific and phase-specific.

Pharmacokinetics:

-IV

-metabolism in liver

-bile and faeces

-Adverse effects:

-nausea

-vomiting

-diarrhoea

-alopecia

- Clinical uses:

Vincristine:

- 1 - Wilm's tumor
- 2 - Hodgkin's disease

Vinblastine is used in combination with bleomycin and cisplatin for treating Hodgkin's disease and testicular carcinoma.

Antibiotics:

- Actinomycin D:

The drug intercalates into the minor groove of double helix b/w guanine-cytosine base pairs of DNA and interfere with the movement of RNA polymerase along the gene and thus preventing transcription. It may also cause strand breaks and stabilise DNA-topoisomerase II complex.

- Pharmacokinetics:

- IV

- Do not cross B.B.B.
- liver
- bile and urine

-Adverse effects:

- 1-Vomiting
- 2- diarrhoea
- 3- bone marrow depression
- 4- alopecia

-Uses:

- Actinomycin D is effective in combination with methotrexate against gastrointestinal choriocarcinoma.
- + Vincristine for treatment of wilm's tumour and some soft tissue sarcomas.

-Bleomycins:

-MOA:

- These antibiotics degrade preformed DNA, causing chain fragmentation and release of free bases. This action is produced by chelation of copper or iron ions which produces superoxide ions that intercalates b/w DNA strands causing chain scission. It is most effective in G_2 phase of cell cycle and mitosis.

Pharmacokinetics:

- IV, S.C, IM. Intracavity
- Excreted through urine.

- Adverse effects:

- 1- Fever - chills
- 2- cough
- 3- pulmonary toxicity
- 4- pulmonary Fibrosis

Uses:

1. testicular tumors in combination with vinblastine.
2. Squamous cell carcinoma of skin, oral cavity, head, neck.

Hormones:

Ex: prednisone

Synthetic anti-inflammatory corticosteroid.

MOA:

- Prednisone itself is inactive and must first be reduced to prednisolone by 11- β Hydroxysteroid dehydrogenase.

- The steroid binds to the receptor that triggers the production of specific proteins.

- Prednisolone irreversibly binds with glucocorticoid receptors (GR) α and β .

- The steroid/receptor complexes dimerise and interact with cellular DNA in the nucleus, binding to steroid response elements and modifying gene transcription. They induce synthesis of some proteins, and inhibit synthesis of others.

Pharmacokinetics:

- Orally

- bound to plasma albumin

- Cyto 11- β -Hydroxylase $\rightarrow$ to prednisolone in liver

- in urine.

Adverse effects:

Hyperglycemia

glaucoma

change in mood

constipation

Uses:

1. Asthma

2. Acute lymphoblastic leukemia

3. Kawasaki disease

3. COPD

4. Myasthenia gravis

5. as an antitumor drug

-Tamoxifen:

(is an anti-estrogen)

-MOA:

-Tamoxifen competitively binds to estrogen receptors on tumor cells and other tissue targets, producing a nuclear complex that decreases DNA synthesis and inhibits estrogen effects.

- Tamoxifen causes cells to remain in the G_0 and G_1 phase of the cell cycle. Because it prevents (pre) cancerous cells from dividing but does not cause cell death, tamoxifen is cytostatic rather than cytotoxic.

Pharmacokinetics:

- Effective on oral administration
- partially metabolized in the liver
- Excretion: bile and faeces.

Adverse effects:

- 1- Skin rash
- 2- Vaginal bleeding
- 3- nausea
- 4- Vomiting
- 5- Hypercalcemia

Uses:

- 1- Treatment of breast cancer
- 2- " " mania in patients with bipolar disorder.

treatment of

3. Infertility in women with anovulatory disorder

Treatment Protocols:

- Some combination regimens and their uses :-

- POMF: Methotrexate + Oncovin (vincristine) + Prednisone + Purimethol (mercaptopurine) used in lymphocytic leukaemia.

- VAMP: Vincristine + Amethopterin (Methotrexate) + 6-Mercaptopurine + Prednisolone used in acute leukaemia.

- COAP: Cyclophosphamide + Oncovin + Ara-c + Prednisolone

- Controlling of Emesis:

- Nausea and vomiting are induced by many chemotherapeutic agents in cancer.

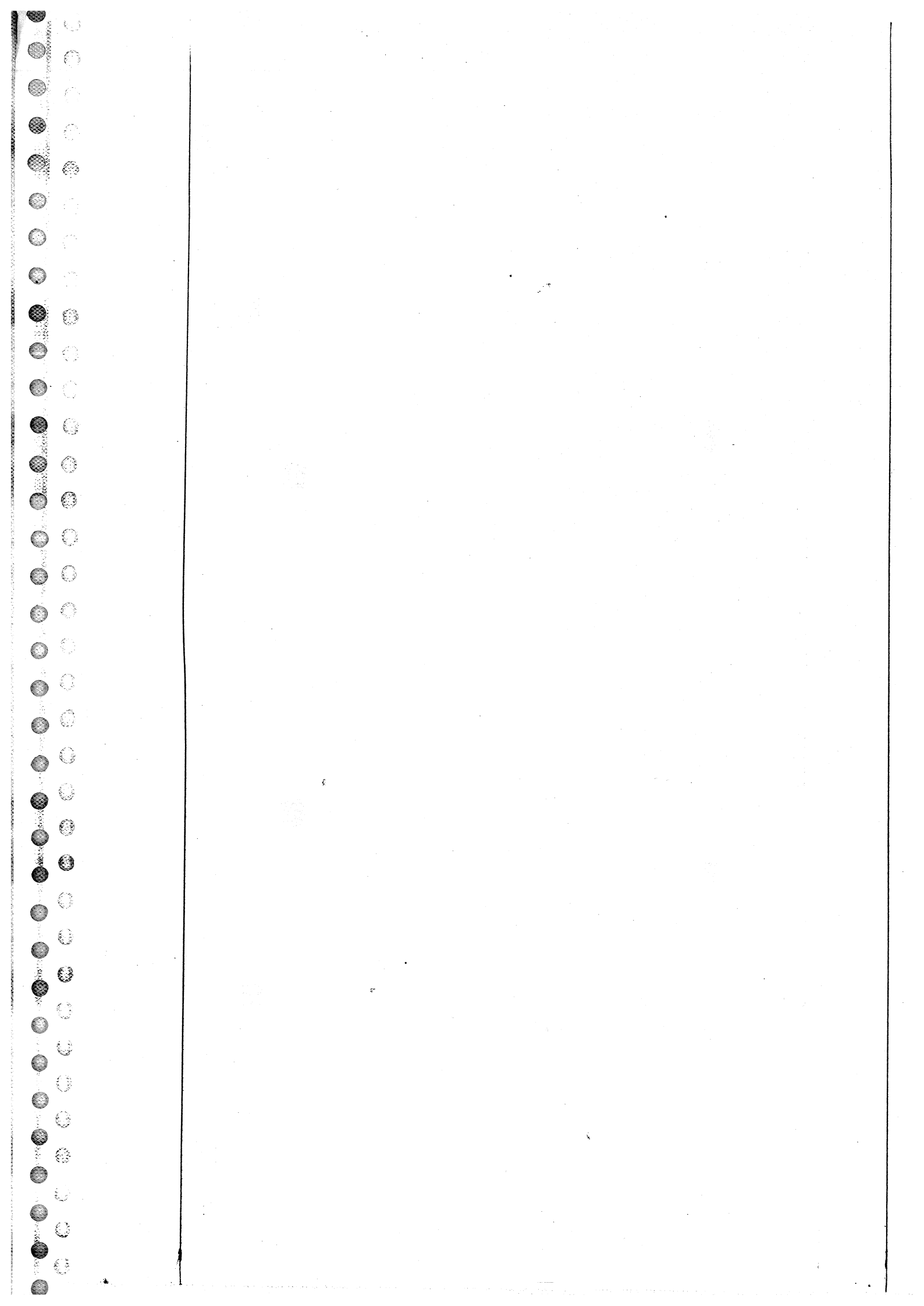
- 5-HT₃ receptor antagonists such as ondansetron or granisetron are effective against cytotoxic-drug induced vomiting.

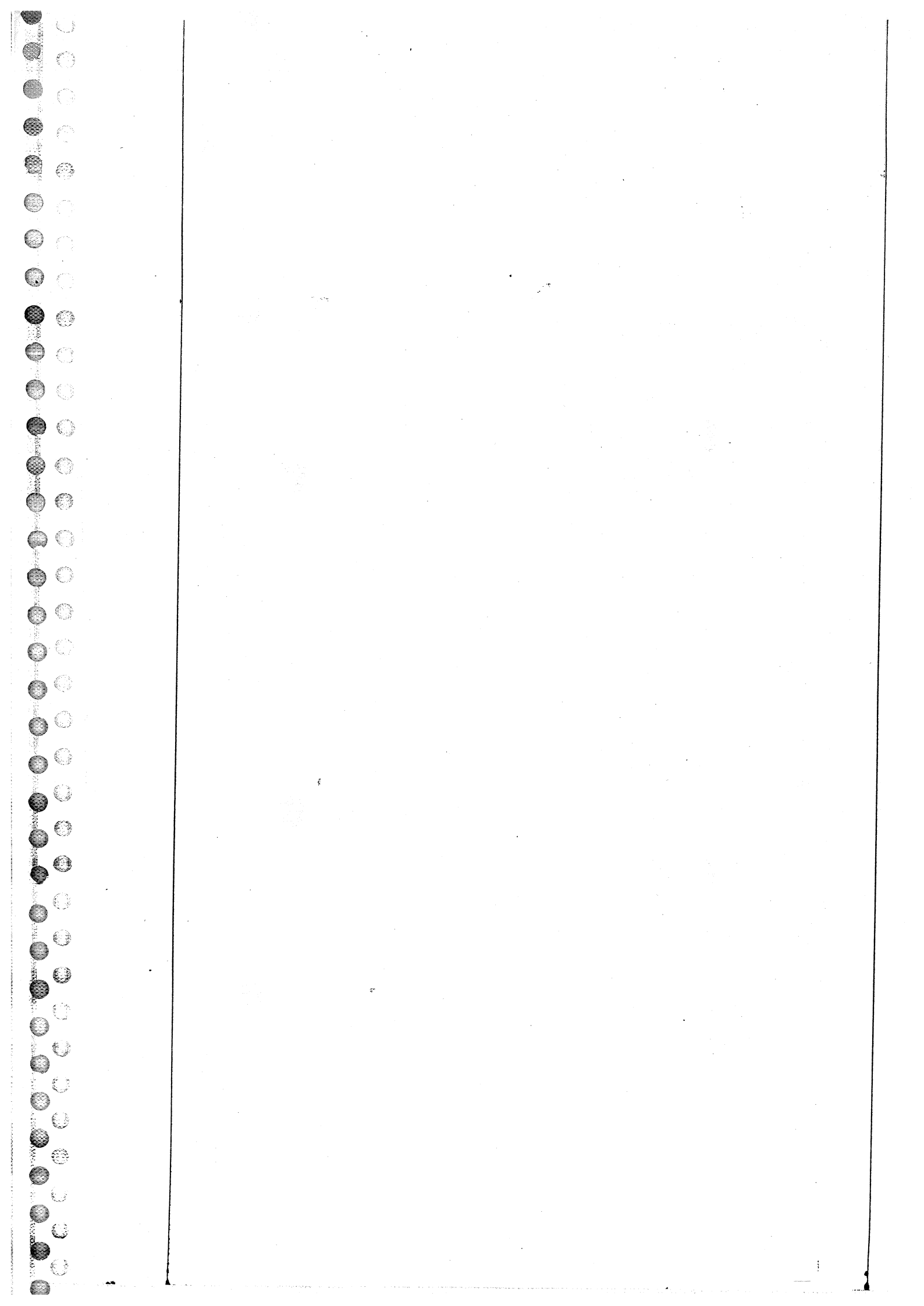
Other drugs: Metoclopramide and diphenhydramine

-Controlling of Myelosuppression:

-Myelosuppression is the main unwanted effect of anticancer agents.

-To overcome this problem, some of patient's bone marrow is removed prior to cancer chemotherapy, ^{collected} purged it of cancer cells and is replaced after therapy. Harvesting stem cells from blood after administering molgramostim and multiplying them in vitro with relevant haemopoietic growth factors is frequently used now.





6

- Biological assays (Bio-Assays) are prescribed where the potency of a drug substance or its preparation cannot be adequately determined by chemical or physical means, but where it may be possible to observe the biological effect of the drug on some type of living matter.

Definition:

- Bio-assay may be defined as the estimation of the nature, constitution or potency of a material by means of the reaction that follows its application to living matter.

- Bio-assay may also be defined as a procedure for determining the quantitative relationship b/w the dose (or concentration) of a drug and the magnitude of the biological response it evokes.

- Unlike the physical and chemical methods, bio-assays are always comparative. The effect of the test substance is compared with that of the reference standard.

Bioassay

Define + different types [Explain] - Discuss any one method involved in the bioassay of insulin.
Lcom, Jan 2014.

- Discuss the types of Bioassay [5M, Mar 2013]

- The Reference standard can be produced from the "Expert Committee on Biological Standardisation" of W.H.O.

- In India, "Central Drug Research Institute" and "Central Drug Research Lab".

Principles:

CITER

P₁: All Bioassays must be comparative, compared against a standard drug or preparation (In order to overcome or minimise errors due to biological variations.)

P₂: The standard and the new drug should be as far as possible, identical to each other. Thus, when it is so, their dose-response curves will have the same slope and would be parallel.

P₃

- The method for comparing the unknown and std should preferably test the therapeutic property of the drug. Ideally an anal-

- Describe the principles and general methods of bioassay [10m, Sep 2011]
- Write the principle of bioassay [5m, Mar 2011, Aug 2010]

gesic is tested for analgesic activity and anticonvulsant for the anticonvulsant a.

- However, this is not always convenient or possible to do so, eg: for estimating the potency of insulin the lowering of blood glucose level would be the ideal index.

P4:

- The method should eliminate, as far as possible and allow an estimation of the error due to biological variation in different animals/ persons at any one time and in the same animal/ person at different times.

- These include the selection of suitable animals/ preparations and also the selection of the experimental condition.

P5:

- The results of the test should be subject to Statistical ^{anal} analysis to minimise errors due to biological variations.

-Methods:

- depende upon type of response
- I- Quantal
- II- Graded

① Bioassays based on quantal Responses:

- In this form of bioassay at least two groups of animals are employed. The response is either +ve or -ve. there is no intermediate response, eg: the animal receiving a convulsant either shows convulsion or does not.

- It is employed for bioassay of a substance in the following ways:

- A. Comparision of threshold responses
- B. Comparson of ED_{50} (or LD_{50})

② Threshold Response Assays:

- In this type of assay procedure the std and the unknown are administered to two different groups of animals continuously until a fixed end point (threshold) is reached. These end points may be systolic arrest of the heart or etc. The

- Define + principles + merits and demerits [10m Feb 2010]
- Principle + applications [Sep 2009, Feb 2010] [5m]

- What is bioassay. principles + write the bioassay of oxytocin IX. 1996 [UOM, Oct 2007]

threshold doses are determined in a large no. of animals and the mean threshold dose of the std and the test drug is determined.

$$\text{Concentration of test substance} = \frac{\text{Threshold Dose of the std}}{\text{" " " " unknown}} \times \text{Concn of the std}$$

Ex:

The assay of digitalis is carried out by infusion of the extract containing digitalis into a vein of guinea pig at a constant rate till the heart stops and the blood pressure falls to 0. The amt of drug in the fluid administered is the threshold dose, i.e., the minimal lethal dose of digitalis in guinea pig. Comparing it with a std the potency of the extract can be determined.

B. Comparision of ED_{50} (or LD_{50}):

- Different doses of the drugs are administered to different groups of animals and the quantal response in the percentage of animals in

each group recorded. The concentration of the [or the responses are plotted in a graph. From the graph the respective ED_{50} or LD_{50} are determined. The concentration of the unknown can be calculated by the formula.]

Test substance may then be ^{حساب} computed by comparing it with the std drug:

$$\text{concentration of the Test Sub} = \frac{\text{ED}_{50} \text{ (or LD}_{50}) \text{ of the Std}}{\text{ED}_{50} \text{ (or LD}_{50}) \text{ of the Unknown}} \times \text{concentration of the Std}$$

Eg:

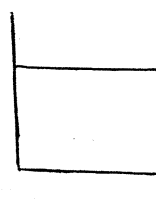
In assay of typhus vaccine - LD_{50} in guinea pig is used for the assay.

II. Bioassays Based on Graded Responses:

- These are called as graded response assays because the responses to varying doses of a drug are graded and measured.

- The effect of the std drug and of the unknown are measured repeatedly on the same tissue.

- Accordingly the graded response bio-assays may be divided into.

- 
- 1- Graded bio-assays using the entire animals
 - 2- " " " " " part of the "

A. Graded Bioassays using Entire animals:

- These bio-assays include the estimation of potencies of various substance during the entire animals.

- Gradually increasing doses are administered to the intact animals and the responses produced are recorded.

- The same animal may be used to record the changes in responses, with the administration of different dose or different animals may be used for different doses;

Name	Activity Assayed	Animal	route	End point of Assays.
1- Diuretics (Eg: theophylline)	Diuresis	Rat/Dog	I.P	↑se in the urine out put
2. Glucagon	Blood-Sugar level	Anaesthetized Cat	I.V	Elevation of blood sugar level

B: In these assays part of the animals are employed for recording the response to a given substance.

- These preparations include the isolated tissues from the healthy animals.

Tissues	Animal	Substances Assayed
1. Ileum	Guinea pig	Histamine, ACh
2. Uterus	Rat	oxytocin, Adrenaline
3. GI Smooth muscle	Rabbit	Adr, nor-Adr

- Usually the dose dependent contractions or the relaxations of the isolated tissue preparations are recorded on a kymograph, the heights of the contractions or relaxation are measured and compared with that of the standard drug doses.

Methods:

1. Bracketing or Matching dose assays

2. Interpolation assays:

- a- Three-point (2+1) assays
- b- Four-point (2+2) assays

1. Bracketing or Matching Dose Assay:

- Simplest form
- In this type of assay the test substance and the standard drug are applied and

the responses obtained are matched by trial and error process until they produce equal effects.

-This may also be said to be analytical dilution assay as the assay involves the determination of the factor by which the test substance is diluted or concentrated in order to produce a response that is equal to that of a known amount of the standard drug.

Adv:

It does not depend on the assumption of a dose response relationship.

Disadv:

i. Experimental error cannot be determined from the assay itself.

ii. The matching is purely subjective.

-The working dose of the std is first determined in the sensitive part of the dose-response curve.

-This dose of the Std drug is kept constant, throughout the experiment, in order to have some idea about the change in the sensitivity of the tissue with time.

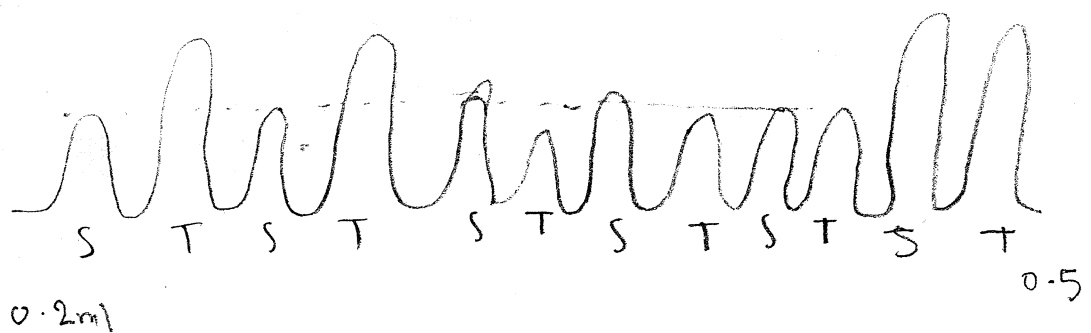
-The response to test substance is matched or bracketed b/w two response of the std.

-Depending upon the response of the first dose of test substance the next responses are obtained by $\uparrow$ ing or $\downarrow$ ing the dose so as to obtain responses just larger or smaller than the average of those of the std flanked on either side.

Close bracketing given more accurate results.

-The matching becomes perfect if almost identical responses are obtained by giving 2 or 3 times the equivalent doses of the std and the test substance.

Ex: graph of bioassay of histamine like substance.



□ Interpolation Assays:

- In these assays the dose-response curve is first obtained from the responses to different doses of the std substance and the test substance.

The submaximal doses of the standard and the test substance are chosen from the curve.

- In order to reduce the effects of irregular fluctuations in the sensitivity of the pharmacological preparation, several responses for the same doses of the std and the test substances chosen are obtained and the mean values (or total values) are used in the final calculation.

$$\text{Potency ratio (m)} = \frac{n_1}{+} \text{Antilog} \left[\frac{T-s_1}{s_2-s_1} \log \left(\frac{n_2}{n_1} \right) \right]$$

9. Three point assay:

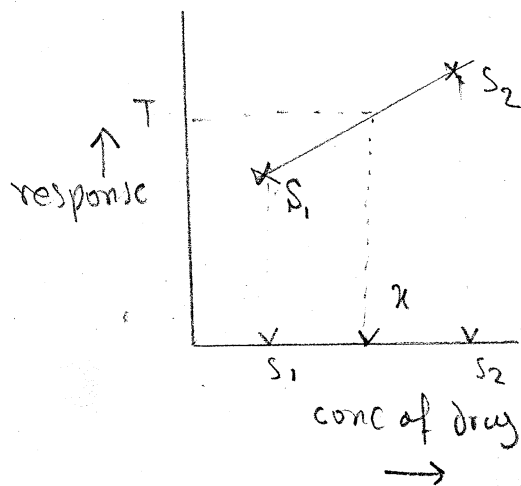
- From the dose response relationship or curve two doses of the std drug are chosen which lie on the straight part of the curve.

- Then a dose of the test substance is chosen which give a response that is in b/w the responses of the two doses of the std.

- Now the responses to the two doses of the std (S_1 and S_2) and the test (T) are obtained by changing the order in successive cycles, such as in the order:

$$S_1, S_2, T : S_2, T, S_1 : T, S_1, S_2$$

From these responses the average response for each dose is obtained and the amt of the substance in test soln is obtained from the graph.



Strength of unknown soln (Test) = concentration of $\times$ Dilution factor for test soln $\times$ Potency ratio $\times M \rightarrow$

n_1 = lower volme of std

n_2 = Higher " " "

t = Volume of test.

S_1, S_2, T - mean response.

b) Four point Assay:

- As in the previous assay two doses of the std (S_1 and S_2) and two doses of test (T_1 and T_2) are chosen, such that they lie on the steeper part of the curve.

- Then the average values of the responses of different doses of the std and test are obtained from the responses obtained by changing the order in which they are added to the tissue preparation in successive cycles eg: in the following order.

$$S_1 S_2 T_1 T_2 : S_2 T_1 T_2 S_1 : T_1 T_2 S_1 : T_2 S_1 S_2 T_1$$

- Then the concentration of the substance in the test soln is calculated as follows:

$$\text{potency ratio} = \frac{x_1}{y_1} \times \text{antilog} \left[\frac{T_2 - S_2 + T_1 - S_1}{T_2 - T_1 + S_2 - S_1} \times \log \frac{x_2}{x_1} \right] = M$$

x_1 = lower volume of the std drug (S_1)

x_2 = higher " " " " " (S_2)

y_1 = lower " " test soln (T_1)

S and T = mean responses.

$$\begin{array}{l} \text{concentration} \\ \text{of} \\ \text{unknown} \\ \text{soln} \end{array} = \begin{array}{l} \text{concentration} \\ \text{of} \\ \text{std drug} \end{array} \times \text{Dilution} \times \text{Potency ratio} \times \text{Factor} \quad (M)$$

Applications:

1. To measure the pharmacological activity of new or chemically undefined substances.
2. To measure the concentration of known substance (e.g. Ach etc) in a tissue extract or body fluids.
3. To measure ED₅₀ or LD₅₀ of a drug.
4. To measure drug toxicity and unwanted effects.

Demerits:

1. The effect measured in test animals often is not that which the drug is intended to produce in treating patients.
2. The techniques and ^{شرح، توضیح} interpretations involved may often vary with different operators.

Merits:

1. For samples where no other methods of assays are available.
2. Bioassays can be performed on whole animals either singly or in groups or on isolated tissues or even cells.

3. They not only help to determine the concentration but also the potency of the sample

4. The sensitivity and specificity of the bioassays made them a very important tool in pharmacology.

- Immunology is the study of Immunity, which is the ability of the body to resist infection.

→ natural immunity

→ acquired immunity

- Immunosuppressants are the drugs used to suppress immunity.

- They are used in the therapy of autoimmune disease and to prevent and/or treat organ transplant rejection.

□ Classification (based on their MOA):

1. Drugs that inhibit IL-2 production or action

Ex: ciclosporine

2. Drugs that inhibit cytokine gene expression

Ex: corticosteroids

3. Drugs that ^{inhibit} synthesis of purine or pyrimidine

Ex: Azathioprine

4. Drugs that block Tcell surface molecules involved in signalling.

Ex:

Monoclonal antibodies

- Write the MOA and adverse effects of cyclosporins. [5M, Jan 2014]

- Cyclosporine [2M, Sep 2011]

Pharmacology of immuno suppressant [5M, 2010]

Cyclosporine:

- MOA:

- Cyclosporine enters the target cell (T cell) and binds to cyclophilin and form a complex that binds to and inactivates calcineurin. Calcineurin is responsible for dephosphorylating cytosolic nuclear factor of activated T cells. The cyclosporine/calcineurin complex cannot carry out this reaction and thus further reactions required for the synthesis of a no. of cytokines including IL-2. The final result is ↓ in IL-2 which is the main stimulus for increase in no. of T lymphocytes.

- The other actions of cyclosporine are:

a. reduced induction of and clonal proliferation of cytotoxic T cells from CD8⁺ precursor T cells.

b. Reduced function of the effector T cells that mediate cell-mediated responses.

- Pharmacokinetics:

- Orally or IVly
- metabolism in liver
- excretion in bile

-Adverse effects:

Nephrotoxicity

Hypertension

Hepatotoxicity

Uses:

-in prevention and treatment of organ transplant rejection reaction.

-It is also used as second line drug in autoimmune diseases such as bronchial asthma.

Pharmacology of Immunostimulants:

- Immunostimulants are agents that enhance immunological and nonspecific host defenses.

MOA:

1. Increasing the humoral antibody responses
2. Enhancing the phagocytic activity of macrophages or
3. Modifying the cell-mediated immune responses.

Ex:

Amantadine

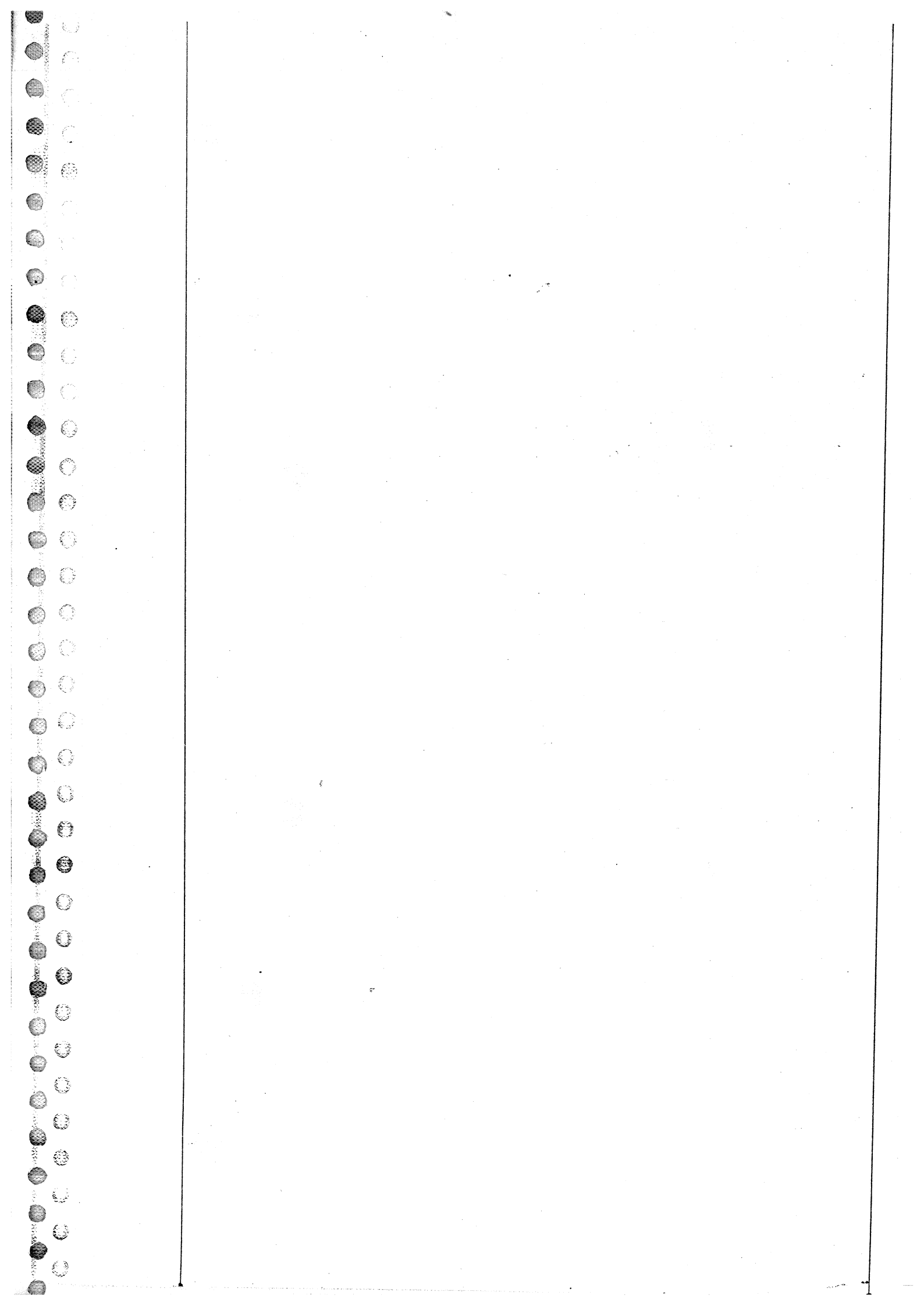
Tilorane

- Immunoglobulins: contain antibodies against various viruses. The antibodies are directed against the viruses in preventing them to attach to host cells.

- Interferons which are a family of inducible proteins having complex effects on immunity. IFN γ which is termed as immune interferon is produced mainly by T lymphocytes as a part of an immunological response to both viral and non-viral antigens.

These are synthesised in mammal cells or can be produced by recombinant technology.

-Interferons have a beneficial effect in certain lymphoreticular and other cancers, in multiple sclerosis and hepatitis B.



□ Drug interactions before administration:

→ Certain drugs react with each other and get inactivated if their solns are mixed before administration.

→ In practice situations, these in vitro interactions occur when injectable drugs are mixed in the same syringe or infusion bottle.

Ex:

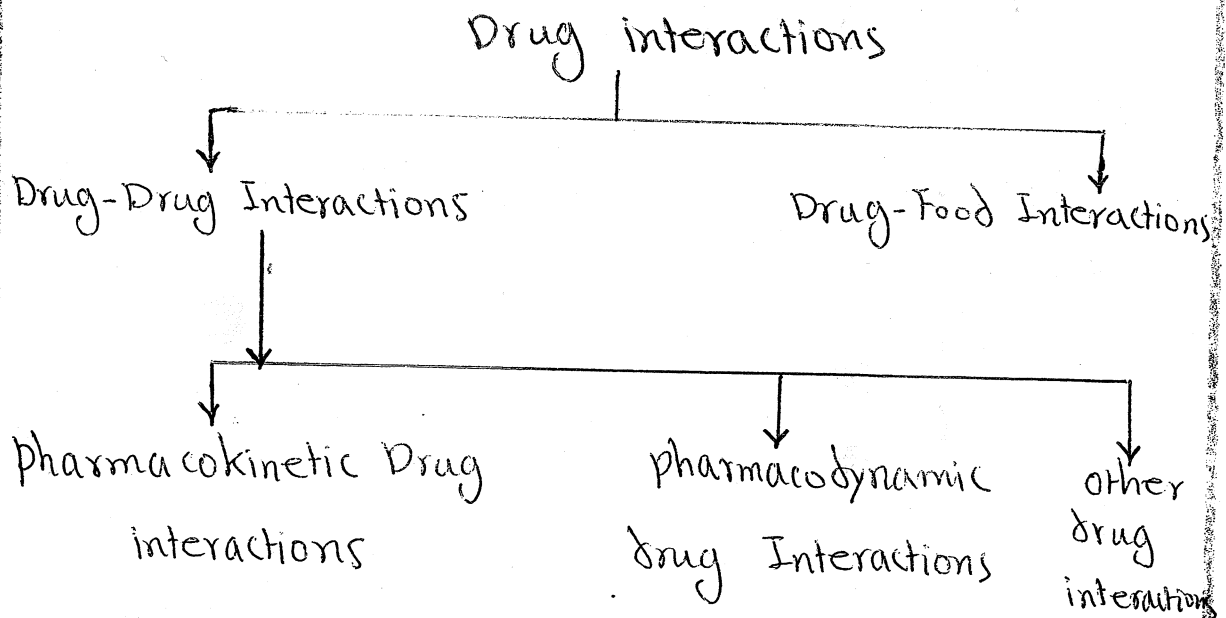
- 1- Penicillin G mixed with gentamicin.
 - 2- thiopentone sodium when mixed with succinyl choline or morphine.
 3. Heparin when mixed with penicillin / gentamicin / hydrocortisone.
 - 4- Noradrenaline when added to sodium bicarbonate soln.
- In general, it is advisable to avoid mixing of any two or more parenteral drugs before injecting.

□ Drug Interactions:

- Modification of pharmacological activity of one drug by the ^{معان} concomitant or ^{مزامن} concurrent administration of another drug is known as "Drug Interactions".

- This result in synergistic (enhanced) or antagonistic (decreased) effects, may be harmful or beneficial.

- Classification:



Drug Interactions:

- Drug-Drug Interactions:

a) Pharmacokinetic Drug Interactions:

- It includes alterations of drug absorptions,

-What are different forms of drug interactions? Discuss on in vivo type of drug interactions + Exs Lion, Feb 2010 / Sep 2009]

Distribution, metabolism, excretion etc.

i) Alteration of Drug Absorption from the GIT:

- Drug absorption from the GIT may be diminished by concurrent administration of another drug.

- This is due to many factors:

1. Change in pH:

- Lipid soluble drugs (non-ionised form) are readily absorbed from the GIT than the water soluble drugs (ionized form).

Case 1: Antacids and Acidic Drugs

- Absorption of acidic drugs (i.e. aspirin etc) can be diminished in the presence of antacids.

Case 2: Antacids and Basic Drugs:

- Absorption of basic drugs (i.e., ephedrine) can be enhanced in the presence of antacids.

2. Complex Formation and Adsorption:

-Complexation:

Case 1: Tetracyclines and metal ions.

-Tetracycline forms complexes with most of the metal ions like Ca^{2+} , Mg^{2+} , Fe^{2+} , Al^{3+} etc. which causes poor absorption for tetracycline from the GIT. Hence, antacids, calcium, iron preparations, and milk should be avoided with tetracycline.

Adsorption:

-Phenothiazine, digoxin etc. can be adsorbed by the concurrent administration of adsorbents (i.e. kaolin). This leads to decreased absorption of digoxin and phenothiazine. Hence, adsorbents (anti-diarrhoeals) should not be given during digoxin and phenothiazine therapy.

3. Gastric Motility:

- Certain drugs like laxatives can enhance the gastric motility. It results in shortening of gastric emptying time. So acidic drugs get

- Pharmacodynamic drug-drug interactions [5M, Ag 2010 / Oct 2007]
- Briefly Explain pharmacokinetic type of drug-drug interactions [5M, Sep 2017]

readily absorbed (which remains unionised at gastric pH) and basic drug get poorly absorbed in the presence of gastric motility enhancers.

Case 1: Digoxin and Metaclopramide

- Digoxin is poorly absorbed in the presence of metaclo-pramide i.e, antiemetic ($\uparrow$ se the g.m).

Case 2:

- Digoxin and Propantheline

- Digoxin is rapidly absorbed in the presence of propantheline ($\downarrow$ se the g.m). Hence, proper care should be taken during digoxin therapy.

4. Gastric Enzymes:

Case: Folic acid, phenytoin and oral contraceptive

- Folic acid is essentially found in the dietary sources as folic acid polyglutamate (poorly absorbed form). This polyglutamate gets converted into folic acid mono-glutamate (readily absorbed form) by the action of intestinal conjugase enzyme. This enzyme is inhibited by

phenytoin and oral contraceptives, which causes poor folic acid absorption. This leads to anaemia. Hence, during phenytoin therapy anaemia can be observed in the patients due to folic acid deficiency.

ii) Alteration of Drug Distribution:

1. Displacement from plasma protein Binding Sites:

- Concurrent administration of two drugs may compete for the same binding site. Thus, one drug can displace another drug from the receptor binding site. This results in increased effect of the unbound or free form of the drug which causes toxicity. This type of interactions can be only seen in case of drugs which are highly protein bound ($>90\%$) and have a small V_D .

Ex: Tolbutamide, Warfarin etc.

case: Tolbutamide and Salicylates, phenylbutazone

-Tolbutamide can be displaced from sites by salicylates and phenylbutazone. This results in hypoglycaemic toxicity.

-Case 2 warfarin sodium, clofibrate and salicylates

-Warfarin sodium can be displaced from the binding site which results in haemorrhage.

iii) Alteration of Drug metabolism:

1. Enhancement of metabolism (Enzyme induction)

-Metabolism of one drug can be stimulated by another drug by enzyme induction. (Enhancement of microsomal enzyme activity is known as enzyme induction.) This results in decreased therapeutic activity of the subsequent drug. The drugs which causes enzyme induction are known as enzyme inducers or enzyme inducing agents.

-Ex: Alcohol, Barbiturates etc.

Case 1: Barbiturates and oral Anticoagulants.

-Barbiturates can induce the metabolism of anticoagulants (warfarin sodium).

-Case-2

-Phenytoin and vit D

-Phenytoin can induce the metabolism of vit D, which leads to the development of osteomalacia.

2-Inhibition of Metabolism (Enzyme Inhibition):

-Metabolism of one drug can be inhibited by another drug by enzyme inhibition. (Inhibition of microsomal enzyme activity is known as enzyme inhibition). This results in increased plasma drug concentration, which causes prolonged and intensified drug action. Sometimes it may lead to toxicity. The drugs which cause enzyme inhibition are known as enzyme inhibitor.

-Examples:

-Disulfiram can inhibit the metabolism of warfarin and phenytoin. This results in increased activity of warfarin and phenyt.

iv) Alteration of Drug Excretion:

1. Urinary pH changes:

- Ionised drugs (acidic and basic) are readily excreted from urine, whereas non-ionised drugs are poorly excreted because they are reabsorbed into the blood. So any ionised drug either acidic or basic can effect the excretion of weakly acidic or weakly basic drugs by altering the pH of urine.

-Ex:

- Excretion of weakly acidic drugs (i.e. salicylates, barbiturates etc) can be enhanced by urinary alkalinising agents (i.e. sodium bicarbonate, sodium citrate etc) which makes the urine alkaline.

- Excretion of weakly basic drugs (amphetamine) can be enhanced by the urinary acidifying agents (i.e. ascorbic acid, barbiturate) etc).

2. Interference with Excretion of urine:

- Case 1: Probenecid and Penicillin.

- Probenecid inhibits the excretion of penicillin by competing with it for renal (or tubular) excretion. This prolongs the therapeutic activity of penicillin.

- Case - 2: Quinidine and Digoxin

- Quinidine inhibits the renal excretion of digoxin. As a result, the concentration of digoxin in the plasma increases which may lead to its toxicity.

b) Pharmacodynamic Drug interactions:

- It includes alteration of pharmacological action of the drug.

- Alteration of pharmacological Action:

1. Antagonistic Effect:

- Case 1: Atropine and Acetyl choline

- Atropine (anticholinergic drug) and acetyl choline (cholinergic drug) shows antagonistic effect on the GIT.

- Case-2: Adrenaline and Histamine

- Adrenaline (bronchodilator) and histamine (broncho-constrictor) shows antagonistic effect on bronchial smooth muscles.

2. Synergistic Effect:

- Case - 1: Alcohol and CNS depressants (i.e., Anti-Histamines, Barbiturates etc) exhibits synergistic effect which results in enhanced CNS depression.

- Case - 2:

 sulphonamides and Trimethoprim
- They show synergistic effect which results in enhanced anti-microbial activity.

c) Other Drug Interactions:

- At the same or different receptor sites:
- Therapeutic effect of some drugs can be produced by their action on particular receptors. They may act on the same or different receptors.

- Some drugs act at the same receptor when subsequently administered. They may show either additive effect or antagonistic effect on the another.

- Ex:

- Morphine (CNS depressant) and Nalorphine (antagonist of morphine) acts on the same receptor, but the later shows antagonistic effect against morphine.

- Nandrolone (anabolic steroid) enhances the anticoagulant effect of warfarin by acting on the same receptor as that of warfarin.

- Drug-Food interactions:

- Food can alter the drug absorption from the GIT. It can be associated with:

a) changes in Gastric Emptying time

b) Drug complexation

c) Drug dilution.

- Drug-Food interaction [2m, Jan 2014, Mar 2013] [5m, Mar 2017]

Examples:

1. Absorption of tetracycline can be reduced in the presence of milk due to formation of insoluble complex.

2. Absorption of Ranitidine and Famotidine (antiulcer) gets delayed in the presence of food. Hence, they should be taken on empty stomach or two hours after meals or before meals.

3. Absorption of Griseofulvin (lipid soluble drug) gets enhanced in the presence of fatty food. Hence, griseofulvin should be taken immediately after meals or within two hours of meals.

4. Tyramine in food (e.g. in cheese, chocolate etc) shown in below:

