### Autonomic Nervous System (ANS)

<table>
<thead>
<tr>
<th>ANS</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ganglionic</td>
<td>Post-ganglionic</td>
</tr>
<tr>
<td>Nucleus (Caudal)</td>
<td>Ganglia (outside)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Thoraco-lumbar nerves</th>
<th>Cranio-Sacral Nerves</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Situation</th>
<th></th>
<th>Near the organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Near the spinal cord</td>
<td>away from the organ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pre-ganglionic fibres</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-ganglionic fibres</td>
<td>Short</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuron</th>
<th>Pre-Ach (Secretion)</th>
<th>Pre-Ach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmitter</td>
<td>Post-Ach</td>
<td>Post-Adrenaline/ Noradrenaline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Adrenergic</th>
<th>Muscarinic and Alloautonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>β</td>
<td>α₁ &lt;br&gt; M₂ &lt;br&gt; M₃ &lt;br&gt; (Post-synaptic) &lt;br&gt; (Post-synaptic)</td>
</tr>
<tr>
<td>(Heart)</td>
<td>(GIT)</td>
<td>(Adipose)</td>
</tr>
<tr>
<td>(Vessels)</td>
<td>(Vessels)</td>
<td>tissue</td>
</tr>
</tbody>
</table>

| α₂ | β₂ | β₃ |
### Physiological Changes

<table>
<thead>
<tr>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart</strong></td>
<td><strong>Heart Rate</strong></td>
</tr>
<tr>
<td>Heart Rate Increase</td>
<td>Heart Rate Increase</td>
</tr>
<tr>
<td>B.P.</td>
<td>B.P. increase</td>
</tr>
<tr>
<td>B.P. decrease</td>
<td>Symptomatic</td>
</tr>
</tbody>
</table>

### Respiratory System

- Broncho constriction
- Bronchodilatation

### GIT

- Peristalsis increase (gastric)
- Peristalsis decrease
- Secretion increase (motility)
- Secretion decrease
  - (Salivary, Gastric Juice)

### Bladder

- Increase Urination
- Decrease Urination

### Eye

- Miosis (Pupil Contraction)
- Mydriasis (Dilation)

### CNS

- Depressive
- Stimulatory
Cholinergic System

- Cholinergic agonist \(\rightarrow\) Parasympathomimetics

Cholinergic (Same as Parasympathetic)

\[\text{Parasympatholytic} \rightarrow\] Anti-Cholinergic

\(\text{Parasympathetic} \rightarrow\) agonist

Classification

<table>
<thead>
<tr>
<th>Cholinesterase</th>
<th>Alkaloids</th>
<th>Anti-Cholinesterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Pilocarpine</td>
<td>Inhibited</td>
</tr>
<tr>
<td>Bethanocholine</td>
<td>Methacholine</td>
<td>Reversible</td>
</tr>
</tbody>
</table>
| Carbacholine | Muscarine | Irreversible

\[\text{Neostigmine}\]

\[\text{Physostigmine}\]

\[\text{Pyriddostigmine}\]
Classification of Cholinergic Drug

Cholinergic Drug

- Directly acting drugs
- Indirectly acting drugs

1. Cholinestersase
   - Acetylcholine
   - Bethanachol
   - Carbachol
   - Methacholine

2. Alkaloids
   - Neostigmine
   - Physostigmine
   - Pyridostigmine
   - Rivastigmine
   - Edrophonium

3. Irreversible
   - Malathione
   - Parathione
   - Dizolin
   - Tabun, Sarin

Pharmacological Basis of action of the cholinergic drug (Pilocarpine, Neostigmine)

1. CVS
   - Cholinergic (AcH) drug binds on m receptors of heart.
   - K+ channels open → hyperpolarisation
   - SA, AV nodes secretion decrease
   - Force of contraction decrease → Heart Rate decrease.
Respiratory System
- Cholinergic drug binds on M2 receptors of smooth muscle of Tracheo-Bronchial tree.
- Smooth muscle contraction occurs.
- Lumen becomes short.
- That's why it is contraindicated (unusual) in asthma.

3. GIT:
- Cholinergic drug binds on M1 receptors of tract.
- It stimulate contraction of smooth muscle of GIT.
- Increased peristalsis movement.
- Stimulate glands - Secretions are increased.

Bladder:
- Cholinergic drug binds on M3 receptors of bladder smooth muscle (detrusor muscle) wall.
- Contraction of detrusor muscle and relaxation of bladder trigone.
- Urination occurs.

Eye:
- aqueous humour production increases.
- ocular muscles.
Cholinergic drugs bind on iris and ciliary smooth muscles receptors.
and increase contraction of iris smooth muscles.
- Pupil → Constricted (diameter reduce) (Miosis)
- Trabecular outflow of aqueous humor increase → decrease intra ocular pressure.
- It is used in glaucoma.

Question: Pilocarpine used in glaucoma?

Pharmacological base of action of the indirect cholinergic drug?

- Anticholinesterase
  → They bind with cholinergic enzyme.
  → Inhibit the enzyme.
  → ACh destruction reduce.
  → ACh concentration increase.
  → Cholinergic drug action.
Uses of Cholinergic Drugs (Anticholinesterase Drug):

- Nostigmine,
- Phystigmine,
- Pyridostigmine,
- Edrostigmine,
- Rivastigmine

*Myasthenic Crisis*:
- It is an autoimmune disorder.
- Antibody is formed against acetylcholine receptors.
- Muscle paralysis (Muscle Weakness).
- When there is involvement of Respiratory muscles.
  
  Myasthenic Crisis.

Treatment:
- Anticholinesterase drugs (Neostigmine, Pyridostigmine).

Reasons:
1. Anticholinesterase inhibit Cholinesterase enzyme
   - So, Acetylcholine concentration increase.
   - Symptoms of myasthenia gravis Resolved.
2. Corticosteroids → Reduce antibody production.
3. Plasmapheresis → Removes the antibody from blood.

2.1 Glaucoma:
- Group of disorders in which there is damage to the optic nerve and retina.
- Most Commonly due to increase intraocular tension.
→ Aqueous humour production increase.
→ Outflow decrease.
→ Accumulation of fluid in chamber.
→ Increase pressure on lens.
→ Pressure transferred back and damage to retina and optic nerve.
→ Vision problem.

![Diagram of eye with labeled parts](image)

Iris
Cornial angle

Types:

→ Iritis
→ Iritis

Iritis caused angle open
Iritis caused angle closed

→ Pilocarpine is used.
→ Directly acting.
→ Binds on muscarinic receptors of Iris (Smooth Muscle)
→ Increase contraction of smooth muscle
→ Miosis
→ Increase outflow of Aqueous humour
→ Reduce intra ocular tension.
→ So, used in Glaucoma.

31 Post operative Urinary Retention:
→ Neostigmine can be used for post-operative Urinary Retention.
→ Because It increase bladder contraction.
→ So, Urine is passed.
1. Post operative Reversal of Neuromuscular Block:
   - If the muscles do not revert to contraction stage after operation.
   - Neostigmine can be given.
   - It will revert the neuromuscular block by increasing acetylcholine concentration at neuromuscular junction.

<table>
<thead>
<tr>
<th>Neostigmine</th>
<th>Physostigmine</th>
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<tbody>
<tr>
<td>Water Soluble</td>
<td>Lipid Soluble</td>
</tr>
<tr>
<td>Can not cross Blood</td>
<td>Can cross Blood, Brain Barrier</td>
</tr>
<tr>
<td>So, Peripheral effect</td>
<td>So, Central &amp; Peripheral effect</td>
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</table>

2. Belladono Poisoning (Ergot):
   - Physostigmine is used.
   - It is having central and peripheral effect.

3. Alzheimer's Disease:
   - In which Acetyl Choline (Ach) concentration is reduced in brain.
   - Neurophil degradation,
   - Dementia (Memory Loss).
   - Donepezil, Rivastigmine can be used for this.
Organophosphate Poisoning?

- Anticholinesterase Poisoning.

- Agents:
  - Organophosphate which binds irreversibly with Cholinesterase
  - Diflos
  - Gas form - Tabun
  - Parathione
  - Sarin
  - Malathione
  - Soman

- Exposure:
  - Inhalation
  - Injection
  - Skin contact

- Clinical Symptoms:
  - Bradicardia (Decrease Heart Pressure)
  - Blood Pressure fall down
  - Severe bronchoconstriction (Difficulty in Respiration)
  - Abdominal Cramps (Increase peristalsis)
    - Urine pass spontaneously
    - Stool Pass
    - Salivation increase.
  - Miosis (Pin Point Pupil)
  - Drowsiness
    - Coma -> Death (Due to Respiratory paralysis).
**Diagnosis:**
- History of exposure.
- Clinical features
- Cholinesterase Concentration test.

**Treatment:**
- Removal of person from further exposure.
- Remove the clothes, Wash with soap and water.
- Airway maintenance: Mechanical breathing
  - O2 therapy
  - Endotracheal Intubation (Tube insertion in P.T.)

  **Respiratory Tract:**
  - Circulation – IV fluid
  - IV diazepam - Calm and prevention of convulsion.
  - Gastric lavage.

  → **Specific Treatment:**
  - Anticholinergics
    - Atropin → 2 mg IV → Repeat at 10 to 15 minutes interval.
  - In 24 hrs → 200 mg maximum.
  - Use → Upto 7 to 10 days
    - Check: Dilated Pupil
    - Tachycardia
    - Comminution

- Oximus binds with cholinesterase enzyme at Anionic site.
- Dephosphorylates the enzymes
- Removes the organo-compound organophosphate compound.
- Activate enzyme.
- It should be given within 24 hours of organophosphate poisoning.
- So, reactivation is not possible.

- Pralidoxime Dose: 2 gms - at 8 hrs internal
- upto 7 days
- Dose will be dependant on the patient clinicale status.

* Classification of anticholinergic Drugs?

- Natural Anticholinergic Drugs:
  - Atropine
  - Hyoscine

- Semisynthetic Anticholinergic Drugs:
  - Homatropine
  - Pseudoephedrine Bromide
  - Triadocaine Bromide

- Synthetic Anticholinergic Drugs:
  a) Antisecretory and antispasmodic
    - Dicyclomine
    - Glycopyrrolate
  b) Mydriatic
    - Cyclopentolate
    - Tropicamide
- The main Antiparkinsonism Drug:
  - Benzexal
  - Bioperidine
  - Procyclidine

- 1. Vesicoselective:
  - Oxybutamine

- Atropine - Pharmacological: Base of Action:
  - Increase the force of contraction
  - Increase the heart rate
  - AV node conduction fast

- Activity:
  - excitement
  - Alterness
  - Inhibit cholinergic action of basal ganglia
    - Cholinergic
    - Dopaminergic

- Respiratory:
  - Smooth muscle of trachea-bronchial tree - Relaxation
    - Bronchodilatation
    - Because of m3 receptor blockage

- Glands:
  - Reduce secretion of glands
    - Salivary Glands
    - GI/GI Glands
5) GIT:
- Relaxation of GIT smooth muscles
- Reduce peristalsis
- constipation
- blockage

6) Excretory:
- Urine Retention ➔ Because of M3 receptor blockage

7) Eye:
- Block M3 receptor of constrictor pupil
- Mydriasis (dilatation of pupil).
- Passive Dilatation
- Lens become flatter
- Vision is fixed for short vision
- Accommodation reflex lost

* Quot: Atropin - Substitute

- Selective drugs are used for particular action on an organ.
- It results in adverse reaction, action become more selective.

- Eye:
  - Cyclopentolate and tropicamide → Ophthalmic examination
    - Fundoscopy
    - Retinoscopy
  - Atropin having longer duration
    ➔ blurring of vision ➔ longer duration
    ➔ Accommodation Reflex duration lost
- Cyclopentolate → 24 hr.
- Tropicamide 6-8 hrs. Observation → Preferred of action.

**Antispasmodic**

- Dicyclomine
  - More selective for SII smooth muscle.
  - So, used as antispasmodic (relaxation of smooth muscle).

- Dysmenorrhea
  - Dicyclomine is used.

**Preanesthetic medication**

- Glycopyrrolate
  - Having more selective action to block secretion.

**Parkinson's Disease**

- Benzerazide → Can work on CNS
- Biperiden
- Procyclidine
  - So, used in a parkinson's disease to reduce cholinergic activity of basal ganglia.

**Asthma**

- Ipratropium Bromide
- Tiotropium Bromide
  - Bronchoselective action.
  - Used in us inhalation.
Oxybutynin:
- Vasoactive
- Receptor M3 is in the more on urinary bladder
- Used for bladder spasm.

Vagolytic:
- Atropin: Vagus nerve action → block A-V node conduction fast
- Cardiac Block → it is used
  - Bradycardia

Adverse Drug Reaction of Anti-cholinergic Drug
- Dryness of mouth
- Constipation
  - Tachycardia
  - Cardiac arrhythmia
  - Excitement
  - Hallucination
  - Urinary Retention, difficulty of micturation
  - Accommodation Reflex - lost
  - Blurring of vision
Adrenergic transmission and metabolism

Presynaptic neuron

Synapse

MAO (monoamine oxidase) instead of MAO

In liver and peripheral tissue

Postsynaptic neuron

Acetylcholine (Ach)
Drugs directly acting on adrenergic receptors, known as directly acting adrenergic drug.

Metabolism of adrenergic agonist
- MAO
- COMT

Question: Pharmacological action of adrenaline?

Question: Types, distribution, and functions of adrenergic receptors?

Types of adrenergic receptors:

\[ \alpha \quad \beta \]
\[ \alpha_1 \quad \alpha_2 \quad \beta_1 \quad \beta_2 \quad \beta_3 \]

Distribution & Action:
1. Heart
   - Force of contraction increase
   - Heart rate increase
   - Conduction fast
   - Blood pressure increase

2. Kidney
   - Increase release of renin
   - Angiotensin increase
   - Vas constrictor
   - Blood pressure increase
Blood Vessels:
- $\alpha_1$ Stimulated $\rightarrow$ Vasconstriction
- $\beta_2$ Stimulated $\rightarrow$ Vasodilatation
- Blood Pressure Increase
- Blood Pressure Decrease

- Both stimulated:
  - $\alpha_1$ Skins vessels $\rightarrow$ Vasconestriction $\rightarrow$ Redistribution
  - Blood flow
  - More $\alpha_1$
  - Skeletal Muscle $\rightarrow$ Vasodilatation $\rightarrow$ Skeletal muscle

Eye:
- Contraction of radial muscles
- Myocyclis

Respiratory:
- $\beta_2$ Bronchodilatation
- Secretions inhibited
- Mast cell degradation step

Stomach:
- Decrease peristaltic movement
- Cell smooth muscle relaxation
1) Bladder:
- Bladder ß2 smooth muscle relaxation
- Bladder ß1 smooth muscle relaxation
- Urethra ß1 contraction
- Urinary Retention

2) Pregnant Uterus:
- Uterus Relaxation

3) CNS:
- ß1 presynaptic → Inhibitory action
- ß2 postsynaptic → Increase stimulatory action

4) Adipose Tissue:
- ß3 Lipolysis
- ß3 Lipogenesis

5) Liver:
- Glycogenolysis
- Glucagon synthesis


1. Pancreas:
   - Insulin Release Decrease
   - Glucagon Release.

2. For Vival:
   - IF → Itonotropic → Increase Force of contraction of cardiac muscle.
   - DC → Dromotropic → Increase Conduction velocity of heart action.
   - BF → Bethemotropic → Increase Exitability of cardiac action tissue.
   - CH → Chronotropic → Increase Heart Rate action.

3. Adrenaline action: $\alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3$.
   - Nore adrenaline action: $\alpha_1, \alpha_2, \beta_1$.
   - Isoprenaline action: $\beta_1, \beta_2, \beta_3$. 
Classification of adrenergic Drugs:

i. Drugs acting as CNS stimulant:
   - Amphetamine.
   - Mephentorhine.

ii. Drugs acting as Cardiac Stimulant:
   - Adrenaline
   - Dopamine
   - Dobutamine.

iii. Drugs used as pressure agent:
   - Noradrenaline
   - Dopamine

iv. Drugs used as Bronchodilator:
   - Salbutamol
   - Salmeterol
   - Formoterol

v. Drugs used as Uterine Relaxation:
   - Ritodrine
   - Isoxsuprine
   - Salbutamol

vi. Drugs acting as Mydriatic:
   - Phymylephrine.

vii. Drugs used as nasal decongestent:
   - Xylometazoline
   - Phymylephrine.
VIII. Drugs used as anaesthetics:
- Sibutramine.

IX. Local Vasconstrictors:
- Adrenaline.

Uses of adrenergic Drugs:
[A, B, C, D, E, F, G, H]

I. Anaphylactic Shock:
- It's a type-1 hypersensitivity reaction.
- In which antibodies are abnormally produced.
- They react with substances and mast cells.
- Degradation and vasodilation occurs.
- Blood pressure falls down.
- Redness on skin.
- This condition is known as anaphylactic shock.
- Adrenaline is used.
  - In IV dose (1:1000) 0.5 ml.
  - Adrenaline is a physiological antagonist of Histamine.

II. Bronchodilatation - [Asthma]
- In asthma - Constriction of bronchus.
  - Increased fluid secretion.
  - Breathlessness occurs due to this.
- Adrenaline e.g., subcutaneous or IV infusion can be used.
- But it's having more CVS stimulant action.
That's why
Heart Rate increase
Blood Pressure increase,

That's why more selective β2 agonist are used.

ex. Salbutamol, Salmeterol, Formoterol
lus: Inhalation (Use)

So cardiac stimulation is prevented.

iii) Cardiac Resuscitation

→ For cardiac arrest adrenaline is used.

→ Dose-
  1:1000 dilution → IM Use
  1:10000 dilution → IV Use.

→ In cardiac arrest → Heart has stopped or decreased functioning.

→ Adrenaline stimulate β1 receptor.

→ So, It increase force of contraction and increased conduction and increased heart rate.

iv) Increasing the Duration of Local anesthetic.

→ Adrenaline is administered locally, it produce vasconstriction.

→ So, Absorption of local anesthetic reduced.

→ and its action is increased.
Epistaxis - Bleeding from the nose known as Epistaxis.

Adrenaline through α1 receptor (nasal mucosa) produced vasoconstriction.

That will stop bleeding.

Glaucoma - Glaucoma is a group of disorders characterised by increase in intraocular pressure, tension and damage to the optic nerve & Retina.

Adrenergic drug (adrenaline) acts on α1 receptor and produce vasoconstriction and decrease formation of aqueous humor.

↓

decrease intraocular tension.

Q: Adverse Drug Reaction of Adrenaline?

A:

CNS:

- Tachycardia
- Hypertension
- Palpitation
- Cardiac Arrhythmia

CNS:

- Insomnia (Reduced Sleep)
- Anorexia (Decrease Food Intake)
- CNS stimulant
- Tremor

Smooth Muscles
- Urinary Retention
- Constipation
Uses of Adrenergic Drugs [5 marks]

- Dopamine

- It is directly acting catecholamine
- It acts on α₁, α₂, β₁ and β₂ receptors
- It is having dose-dependent action

- At Low Dose
  - < 2 μg/kg/min
  - β₁ receptor stimulated which dilates coronary and renal arteries afterload reducing
  - So, cardiac work is reduced peripheral resistance also reduced

- At Moderate Dose
  - 2 - 10 μg/kg/min
  - β₁ receptor is mainly stimulated which increases the force of contraction and increases heart rate

- At Higher Dose
  - > 10 μg/kg/min
  - α₁ receptor is mainly stimulated which produces vasoconstriction and increased peripheral resistance
  - Increase noradrenaline release → Blood Pressure increase
That's why dopamine is used as low or moderate dose.

[i. In cardiac shock.

[ii. Heart failure with renal impairment.

[iii. Dopamine cannot cross Blood Brain Barrier. So, having no CNS effect.

Que: Dobutamine?

It is a catecholamine having β₁, β₂, and α₁ action.

It is not acting on Dopamine receptor (D₁, D₂).

Most commonly Dobutamine act on β₁ receptor.

It increases the force of contraction of heart.

It increases heart rate.

So, it is used in Congestive Cardiac failure and hypotension.

Adverse Drug Reaction:

Tachycardia

Hypertension

Que: α - Blockers?

Classification

Non Selective α Blockers

Reversible

Phentolamine

Irreversible

Phenoxybenzamine, Prazosine

Selective α Blockers

α₁ Blockers

Yohimbine

α₂ Blockers

Terazosine

Terazosine
Pharmacological Basis:

1. α blockers
   - Blocks the alpha receptors of CNT
   - and increases the peristalsis movement
   - Relaxes the sphincters

2. Blood vessels
   - Blood vessels - dilated
     - Peripheral Resistance decreases
     - Blood pressure decreases

3. Eyelid - Miosis
   - Due to radial muscle relaxation

4. Bladder:
   - Sphincter Relax
   - Urine Pass

5. CNS:
   - Depression
     - Reduced CNS activity

6. Vasodilatation
   - Retrograde ejaculation
      - α block
      - Sphincter of bladder Relax
      - Sperm is retrogradely enters into bladder
      - Sexual dysfunction occurs due to this

Urinary system
Uses:

i. Hypertension
- Alpha blockers used in hypertensive emergencies
- $\alpha_1$ receptors produce vasoconstriction
- $\alpha_2$ blockers, produce vasodilatation and reduce peripheral resistance so reduce blood pressure

ii. Hypertension emergency occurs in

i. Pheochromocytoma

[Note: Clonidine withdrawal]

iii. Pheochromocytoma
- It is a tumor of adrenal medulla
- So, increase production of adrenocorticotropic hormone
- Noradrenaline stimulation occurs
- For reducing the symptoms of pheochromocytoma, alpha blockers are used
- Definitive treatment is surgical removal of adrenal gland ("Tumor").
Benign Prostatic Hyperplasia

In this condition, size of the prostate gland increases.
- That compress urethra.
- The flow of urine is obstructed.
- Frequency of urination increases.
- Urgency will occur.
- Incomplete passing of urine.

\( \alpha \)-Blockers: Block the \( \alpha \) receptor of sphincter and relax the sphincter.
- So, urine flow can be increased.
- Selective \( \alpha_1 \) Blockers are used.

Along with
- \( \alpha \)-Blockers
- 5\( \alpha \) Reductase inhibitor is added
- To reduce the size of prostate.

IV. Peripheral Vascular Disease
- In peripheral vascular disease, there is vasoconstriction of peripheral vessels.
\( \alpha \) Blockers, block \( \alpha_1 \) receptors of peripheral vessels and produce vasodilation and reduce peripheral resistance.

\( \Rightarrow \) Male Sexual Dysfunction:

\( \Rightarrow \) \( \alpha \) Blockers used along with \( \text{papaverin} \) for erectile dysfunction.

\( \Rightarrow \) Adverse Drug Reaction:

\( \Rightarrow \) Tachycardia
\( \Rightarrow \) Postural hypotension
\( \Rightarrow \) Nasal stiffness.
\( \Rightarrow \) Importance due to retrograde ejaculation.

Que: Beta Blockers?

- Non-selective (\( \beta_1 + \beta_2 \))
  - \( B \) Blockers
    - Propranolol
    - Timolol
    - Sotalol
    - Pindolol
- Selective (Only \( \beta_1 \))
  - \( B \) Blockers
    - Atenolol
    - Metoprolol
    - Bisoprolol
    - Esmolol
Pharmacological Action:

- Propranolol is studied as a prototype.

Mechanism of Action:

- It blocks β₁ and β₂ receptors competitively.
- And reduce the sympathetic activity.

β blockers (propranolol) reduce the heart rate.
- Reduce the force of contraction of the heart.
- Inhibits the activity of SA and AV node.
- Reduce the conduction of impulse.
- Reduce the blood pressure (mainly due to decrease cardiac output).

Vascular System:
- β-blockers produce vasodeconstriction of peripheral vessels & vessels supplying muscle.
- It may increase the blood pressure but long term therapy of β-blocker reduces the blood pressure mainly due to reduced the cardiac output.
iii) Kidneys:
- β1 blockers reduce renin release from the aperstis.
- So, Angiotensin II concentration is decreased.
- Vasoconstriction is reduced.
- So, BP is reduced.

iv) Respiratory System:
- Non-selective β-blocker.
- Block β2 receptor of bronchial tree (bronchus).
- So, Bronchoconstriction occurs.
- Asthma attack may occur.

v) Skeletal Muscle:
- It inhibits contraction of skeletal muscle.

vi) CNS:
- β-blocker suppress the anxiety & produced the depression.

Metabolic Effects:
- β-blockers reduce the warning symptoms of hypoglycemia.

Uses:

i) Thyrotoxicosis:
- In thyrotoxicosis, thyroid hormone level is increased.
- Hypertension, tremor, Anxiety is produced.
- Non-selective β blockers are used to reduce the symptoms of thyrotoxicosis.
ii) Essential Tremor:
- Tremor produced due to excessive stimulation of β\textsubscript{2} receptor of muscle.
- Non-selective β-blocker is used to reduce these tremors.

iii) Angina Pectoris:
- There is chest pain due to blockage of coronary artery blood flow.
- Selective β\textsubscript{2} blocker reduces the cardiac output.
- Cardiac work is also reduced.
- So, demand of cardiac muscle is reduced.
- So, β-blocker is cardiac protective.

iv) Cardiac Arrhythmia:
- Abnormal impulse generation in the conduction system of heart.
- Which produces abnormal production.
- β-blocker reduces the conduction in heart.
- So, arrhythmia can be treated.

v) CHF (Congestive Heart Failure):
- When the heart is not able to pump the blood according to the need of body, it is known as heart failure.
- So, the blood is accumulated in heart known as congestion.
This is congestive cardiac failure.

Selective β2 blockers are used as chronic therapy (maintenance therapy) in CHF because of its cardio-protective action.


<table>
<thead>
<tr>
<th>Note:</th>
<th>Normal</th>
<th>Systolic</th>
<th>Diastolic</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Mild Hypertension Grade-I</td>
<td>140-159</td>
<td>90-99</td>
<td></td>
</tr>
<tr>
<td>Moderate Hypertension Grade-II</td>
<td>160-179</td>
<td>100-109</td>
<td></td>
</tr>
<tr>
<td>Severe Hypertension Grade-III</td>
<td>&gt;180</td>
<td>&gt;110</td>
<td></td>
</tr>
</tbody>
</table>

⇒ Increased Blood Pressure.
⇒ Selective β1 Blockers are used.
⇒ It reduce the force of contraction.
⇒ Reduce the conduction velocity.
⇒ Very effective in controlling systolic blood pressure.
⇒ Because of β1 Blockers reduce renin secretion.
⇒ So, reduce the effect of angiotensin II.
⇒ Which helps in reducing Blood Pressure.

⇒ vii.1. Pheochromocytoma.
⇒ It is the tumor of adrenal gland medullae.
⇒ Production of adrenaline and noradrenaline is increased.
⇒ So, sympathetic stimulation occurs.
⇒ For reducing the symptoms β Blockers (Non-selective) are used.
⇒ Distinctive treatment is "Removal of Tumor."
viii. Glaucoma:
- Glaucoma is a group of disorders characterised by damage to the retina or optic nerve.
- But mostly it occurs due to increased intraocular pressure (I.O.P.).
- β-blockers reduce aqueous humor production.
- So, Intraocular Pressure is reduced.
- Timolol is used for this.

ix. Myocardial Infarction:
- If there is reduced blood supply of myocardium, cells go into the stage of infection (Cellular Death).
- Selective β1-blockers are cardioprotective.
- They are used as long term Regulation of Blood Pressure after myocardial Infarction.
- They also prevent future attack (Prevent recurrence).

x. Migraine:
- Headache which mostly occurs due to vasodilatation of the vessels of dura mater.
- Non-selective β-blocker reduces vasodilatation and prevent migraine.

xi. Dissecting Aneurism:
- Aneurism means abnormal dilatation of artery.
- When blood flows from the layers of artery known as Dissecting Aneurism.
"β-Blockers used for reducing the chances of rupture of cataract by reducing B.P. and constrictive pupilation.

**Note:**

- Necrosis
  - Localised cell death
- Apoptosis
  - Programmed cell death followed by inflammation

---

**Drug for Glaucoma?**

⇒ **I/β-Blockers**: Timolol, Betaxolol,
⇒ **Ⅱ/α-blocker**: Pindolol, Timolol,
⇒ **Ⅲ/β-blocker**: Bimatoprost,
⇒ **Ⅳ/Prostaglandine analogue**: Latanoprost
⇒ **Ⅴ/Carbonic anhydrase inhibitor**: Acetazolamide, Dorzolamide
⇒ **Ⅵ/Cholinergic Drug (Miotics)**: Pilocarpine

**First-line drug** ➞ Latanoprost ➞ β-Blockers.
Autocoids

Instruction:
- "Self-healing substances"
  - Histamine,
  - Serotonin,
  - Prostaglandins,
  - Leukotriens.

Histamine:
- Tissue amine.
- Mainly produced by mast cells.
- Most cells are granulocytes.

Histamine (amino acid)
- Decarboxylation.

Most Cells

- Immediate in circulation.
- They rest in tissue and become mature.
- They are seen in subcutaneous tissue, lungs, air tract.

Classification of Antihistaminic Drugs:

- It is classified into two generations:
  - First Generation
    - Hydroxyzine
    - Diphenhydramine
    - Promethazine
  - Second Generation
    - Cetirizine
    - Levocetirizine
    - Azelastine
    - Pheniramine
    - Chlorpheniramine
The Pharmacological base of Antihistaminic Drug

There are 4 types of histaminic Receptors:

- H₁
- H₂
- H₃
- H₄

- Subcutaneous
- GIT
- Parasympathetic
- Cells
- Neuron
- Tissue
- Lungs

H₂ Receptors

Skin: Histamine → Increase vascular permeability and increase fluid filtration.

H₂ → Produce Oedema.

→ It increases inflammation.

→ Redness increase.

Histamine stimulates nerve endings and pain and itching.

Antihistamine → Completely blocks histamine receptor.

→ and it reduces inflammation.

→ it reduce Oedema.

→ it reduce itching.

→ That's why antihistaminic is used in allergic reactions.

Lungs: Histamine → Increase the contraction of smooth muscle of trachea and bronchi.

→ It increase fluid accumulation.

So, it induce the attack of asthma.
Antihistaminic → blocks the action of histamine and treats asthma.
(Receives the symptoms of asthma).
→ most commonly Antihistaminic used in allergic asthma.
→ mast cell stabiliser is better than antihistaminics.
→ Because they inhibit the release of histamine.

⇒ iii) CNS: Histamine → Stimulate reticular formation and necessary for wakefulness, alertness.
Antihistaminic → Blocks this receptors and produce sedation and reduce irritability.
→ But this is minor action.
→ Because of extra anticholinergic action.

⇒ First generation histaminic having anticholinergic action.
⇒ But second generation antihistaminic having anticholinergic action.
⇒ No anticholinergic action.

Qu: Difference between 1st generation and 2nd generation.

→ 1st generation
- Having anticholinergic action
- Produce sedation
- Cross Blood Brain Barrier
- Causes dry mouth
- Constipation
- Uterine contraction
- Blurring of eye

→ 2nd generation
- No anticholinergic action
- Can not produce sedation
- Can not cross BBB.
- Side effects are less.
Uses of Antihistaminic Drugs

i) Allergy:
   → Antihistaminic (H1) competitively block H1 receptor
     • So, it reduces permeability and fluid filtration into tissues and reduced inflammation
     • It reduces inflammation
     • Oedema is resolved.
   → So, antihistaminic used in the treatment of allergy.
     → e.g. Urticaria, Conjunctivitis, Allergic Asthma, Dermatitis, Pruritus

ii) Vomiting:
   → Histamin affects CTZ (Chemical Trigger Zone) and induce vomiting.
   → First generation antihistamines can cross Blood Brain Barrier and block [CNS] Histamine receptors and reduce vomiting.

 iii) Vertigo:
   → Rotatory sense of oneself or surrounding is known as vertigo.
   → It occurs due to abnormal stimulation at vestibular apparatus.
     • Two types of receptors in vestibular apparatus (M, H).
     • Antihistaminic blocks H1 receptor and reduce the stimulation at vestibular apparatus and reduce vertigo.
iv.1 Common Cold -

- In common cold, there is increase of vascular permeability of nasal mucosa.
- So, increase fluid filtration.
- This occurs due to histamine.
- Antihistaminic blocks H1 receptors and reduce nasal dripping (relieves this symptom).

v.1 Hypnotics and Sedatives -

- Antihistaminic (first generation) can cross Blood Brain Barriers and reduce irritability and consciousness.
- So, they are used as sedative as well as hypnotic (for inducing sleep).
- Histaminic do not produce dependence like benzodiazepines.

vi.1 Parkinson's Disease -

- Parkinson's disease is characterized by hypokinesia, rigidity, and tremor.
- Antihistaminics, along with centrally acting anticholinergic can reduce the symptoms.
- It is used in Drug induced Parkinsonism.

Psycosis | Parkinson
- Dopamin increase | Dopamin decrease

vii.1 Premarsthetic Medications -

- Antihistaminic can be used before giving anesthetic drug.
- Because it produce sedation and also reduce vomiting.
Blue: Adverse Drug Reaction:

- First Generation:
  - Dryness of mouth:
  - Urinary Retentions:
  - Constipation:
  - Blurring of vision:
  - Sedation:

- Second Generation:
  - Contact Dermatitis due to topical application.

20/07/16

Quiz:
Serotonin Receptors?

Production:
- Produced from tryptophan aminoacid.
- It's hydroxylation and decarboxylation occurs.
- Also known as 5HT (Hydroxy tryptamine)

Note

- There are seven types of receptors.
<table>
<thead>
<tr>
<th>Receptor</th>
<th>Site</th>
<th>Action</th>
</tr>
</thead>
</table>
| 5HT₁    | CNS  | • Autoceptors  
|         |      | Induce sleep  
|         |      | Works as neurotransmitter  
|         |      | Vasorestriction of cerebral vessels |
| 5HT₂    | Platelets | • Platelet aggregation  
|         |      | • Smooth muscle contraction of smooth muscles |
| 5HT₃    | CNTZ | • Vomiting |
| 5HT₄    | GIT  | • Peristalsis increase  
|         |      | • Gastric emptying |
| 5HT₅    | CNS  | • Vomiting treatment  

**Note**

- 5HT₁ antagonist → Ondesetron  
- 5HT₄ agonist → Metochlopamide
Due Drug therapy for Migraine

Migraine is disorder characterised by throbbing headache, visual disturbance (with aura), photosensitivity and vomiting.

Classification:

- **Mild**
  - One attack per year
  - Duration 8 hrs

- **Moderate**
  - Two to three attacks per month
  - Duration 2-24 hrs

- **Severe**
  - Three to four attacks per month
  - Duration 6-48 hrs
  - Visual disturbance

Person is not able to perform routine work.

Drugs:

- **NSAIDs**
- **Antiemetic Drugs (Stop Vomiting)**
- **Fentanyl Alkaloids**
- **Tryptans**

NSAIDs [Non-Steroidal Anti-inflammatory Drugs]:

- Paracetamol, Aspirin, Indomethacin, Diclofenac

They block the action of enzyme: "Cyclo-oxygenase".

And reduce the production of inflammatory mediators: PGE₂

They reduce pain and inflammation.

These are used for mild to moderate migraine.

Long-term therapy with these drugs are not advisable.
**Antiemetic Drugs:**
- Domperidone
- Ondansetron
- Metoclopramide
- They are used to relieve the symptoms of vomiting, nausea, and motion sickness.

**Exogenous Alkaloids:**
- Ergotamine
- It is a potent agonist at 5HT1A receptors.
- It induces vasoconstriction of cerebral vessels.
- It reduces the attack of migraine.
- It is used along with caffeine and 5-HT2 receptors.
- Caffeine increases the action of ergotamine.

- Dihydromergotamine
- It is prepared for parenteral administration.
  (I.M., I.V., S.C. Subcutaneously)  

**Tryptans:**
- Sumatriptan
- It is a 5HT1 agonist.
- It produces vasoconstriction of cerebral vessels.
- It terminates the migraine attack.
- Mostly used in severe migraine.
- Ergot alkaloid and tryptan should not be combined.
- Its action is fast and shorter lasting.
- ADP
- Causes hypertension, so contraindicated in cardiovascular disorders.
Question: Prophylaxis of Migraine?

- When the person suffering from moderate/severe migraine, prophylaxis is used.

- Drugs used as prophylaxis of migraine:
  - Anticonvulsants:
    - Sodium Valproate: Can be used as prophylaxis of migraine.
    - Note: When brain generates abnormal impulses, it produces seizures.
  - Beta Blockers:
    - Propanolol can be used as prophylaxis of migraine.
  - Calcium Channel Blockers:
    - Verapamil: Can also reduce the attack of migraine.
  - Antidepressants:
    - Tricyclic Antidepressants (TCA): Can be used as prophylaxis of migraine.
**Prostaglandins**? (Production and Action)?

**Production:**
- Membrane-bound phospholipids
  
  **Arachidonic Acid**
  
  $\text{COX}^1, \text{COX}^2$

  $\text{PGE}_2, \text{PGD}_2, \text{PGF}_2\alpha, \text{TXA}_2$

  **Prostaglandins:**
  - Vasodilation
  - Uterine contractility
  - Aggregation
  - Inhibition of platelet aggregation
  - Protection in physiological conditions

**Pharmacological Action:**
- Antiinflammatory
- Anti-inflammatory action a bit weaker than steroids

- i) **Gastrointestinal**:
  - Increase mucus protection
  - Protect against acid
  - Can be used in peptic ulcers

- ii) **Inflammation**:
  - Prostaglandins are responsible for inflammation
  - Stimulate nerve endings and produce pain


iii. Uterus:
- Prostaglandins (PGE2) increase the force of contraction of uterus.
- It helps in a delivery process.
- It prevents PPH (Post Partum Hemorrhage).
- Used for abortion.

iv. Eyes:
- PGE2 reduces the intracocular pressure.
- So, used in the treatment of glaucoma.

v. Blood:
- PGI2 - Inhibites platelet aggregation.
- TXA2 - Produces platelet aggregation.
- Aspirin at low dose inhibites TXA2 production.
- So, used as antiplatelet drug.

vi. CVS:
- PGE2 - Vasodilatation and reduce peripheral resistance and reduce B.P.
- PGE1 - Helpful for opening of ductus arteriosus.

Uses of PGI2:
iv. Abortion
- PPH (Post Partum Hemorrhage),
- Induction of labour.
- Glaucoma
- Peptic Ulcer
Adverse Drug Reaction:

- Nausea
- Vomiting
- Hypotension
- Flushing

**Classification of NSAIDs**: [Nonsteroidal Anti-inflammatory Drugs]

- Nonselective NSAIDs - (acting on COX1 and COX2)
  - Aspirin
  - Ibuprofen
  - Metamizol, etc.
  - Indomethacin, etc.
  - Piroxicam, etc.

- Preferential COX1 inhibition
  - Diclofenac
  - Aceclofenac

- Highly selective COX2 inhibition
  - Etoricoxib
  - Parecoxib

- Drug with antipyretic, analgesic, and poor anti-inflammatory action
  - Paracetamol
Aspirin?

- It is non-selective COX inhibitor.

\[ \text{Arachidonic Acid} \]

\[ \text{Aspirin} \xrightarrow{\text{inhibit}} \text{Cyclooxygenase} \xrightarrow{\text{Prostaglandins}} \]

- COX (Cyclooxygenase Enzyme) present in skin, GIT.
- They are responsible for inflammation, pain, and fever.
- Aspirin inhibits COX enzyme and reduces the production of prostaglandins.
- And produces its action.

**Pharmacological Action**

**Analgesic**

- Prostaglandins stimulate the nerve endings and produce pain.
- Aspirin inhibit production of prostaglandins.
- So, nerve stimulation reduced.

**Pain is reduced [Analgesic]**

- So, it is used in headache, muscle pain, tooth pain, joint pain.
- Its action is less than opioid.
ii. Antiinflammatory:

- Prostaglandins increase vasodilation, Redness of site and chemotaxis of WBC.
- So, inflammation increased.
- Aspirin inhibit the production of prostaglandins and reduce vasodilation, Redness and chemotaxis of WBC swelling.

iii. Antipyretic:

- Prostaglandins reach hypothalamus.
- and they affect thermostatic set point.
- Fever is Produced.
- Aspirin inhibit prostaglandins and reset the body temperature.
- That's how it reduce fever.

iv. Antiplatelet:

- Aspirin at low dose inhibit the production of TxA2 [Thromboxane]
- So, platelet aggregation is reduced.
- [50 mg - 325 mg].

v. Kidney:

- Aspirin increase retention of sodium and water.
- High dose → Increase excretion of urine acid.
VI. COX-2

- Aspirin inhibitor for enzyme COX-2 and reduce the production of mucus.
- So, chances of peptic ulcer increased.

Note:
- Aspirin is used along with proton pump inhibitor and the blocker (Pepcid). So, chances of peptic ulcer decrease.

VII. Uterus

- Prostaglandins increase uterine contraction.
- Aspirin inhibit production of PG and delay labour.
- Increase the chances of PPH (Post Partum Haemorrhage).

VIII. Respiratory System

- Aspirin - Increase chances of Respiratory alkalosis. [CO₂ evasbout]
- Followed by Metabolic acidosis.
Adverse Drug Reaction:
- Nausea, Vomiting
- Gastrointestinal irritation
- Gastro, Peptic Ulcers
- Hypersensitivity reactions
- Respiratory alkalosis & metabolic acidosis
- Bleeding
- Reye's Syndrome: In children suffering from hepatitis if aspirin used.
  - The chances of liver failure increase: [Encephalopathy]

Uses:
- Analgesic in headache, Tooth pain, Joint pain, muscular pain
- Fever
- Antiplatelet after myocardial infarction for reducing thrombosis
- Rheumatoid arthritis, Caut.
Gallisylate Poisoning or Overdose of Aspirin?

- Clinical Features:
  - Alunemia
  - Vomiting
  - Gastritis
  - Diarrhea
  - Fever
  - Acid-Base imbalance
    - Hyperventilation (RR↑)
    - Electrolyte disturbance (Oedema)
    - Concentration decrease
    - Convulsion
    - Coma → Death

- Treatment:
  - Hospitalisation
  - Gastric lavage (with activated charcoal powder)
  - Injection of [Sodium bicarbonate] is given.
    - M.O.A:
      - Make urine alkali (Basic)
      - Aspirin is acidic. So, it is excreted more into basic alkaline urine.

  - Fluid therapy
  - Electrolyte therapy
  - External Cooling
  - Hemodialysis
  - Vitamin K.
Uses of Other NSAIDs

i) Ibuprofen -
   - Muscular pain
   - In children aspirin is contraindicated but ibuprofen can be used.

iii) Diclofenac -
   - It is concentrated in synovial fluid of joints.
   - It is used in joint pain.

iii) Indomethacin -
   - It is used for closing the patent ductus arteriosus.
   - Also used as analgesic and antipyretic.

iv) Mephenamic Acid -
   - Dysmenorrhea (Painful Menstruation)
   - Analgesic and Antipyretic.

Some specific indications of different NSAIDs:

- Indomethacin: Indicated for conditions like peritonitis, myocardial infarction, and acute gout.
- Diclofenac: Indicated for conditions like head injury and acute cholecystitis.
- Ibuprofen: Indicated for conditions like myocardial infarction and acute cholecystitis.
- Mephenamic Acid: Indicated for conditions like nausea and vomiting.

Question: Difference between Selective COX-2 inhibitor and Non-selective COX inhibitor?

Selective COX-2 inhibitor: It has analgesic effect. It has antipyretic effect. It has anti-inflammatory effect. No antiplatelet effect.

Non-selective COX inhibitor: It has analgesic effect. It has antipyretic effect. It has anti-inflammatory effect. Having antiplatelet effect.

Selective COX-2 inhibitors do not cause damage to gastric mucosa and do not produce peptic ulcers.

Non-selective COX inhibitors increase the chances of thrombosis, increase the chances of cardiac damage.

Examples: Etoricoxib, Parecoxib, Mefenamic acid.

Question: Aspirin (Paracetamol)

M.O.A.: Inhibit cyclooxygenase enzyme and reduce the production of prostaglandins.

- It is good antipyretic and analgesic.
- But weak anti-inflammatory.

Route: Oral or Parenteral.
Dosage: 10 mg/kg [TDS]

Uses:
1) Analgesic - headache, muscle pain, toothache
2) Antipyretic - for reducing fever

It can be used in child and [pregnant woman]

Adverse effects:

Paraacetamol is very safe drug, general tolerance.

Side effects rarely occur excepting:

- Due to chronic misuse, poisoning take place
- Hepatic toxicity
- Renal failure
- Paracetamol Poisoning

Antidote: Acetylcysteine
**Gout Biochemistry and Pathophysiology**

- **Xanthine Oxidase**
  - Allopurinol (m.o.a.)
  - Alloxanthine
  - Hypoxanthine
  - Xanthine
  - Uric acid

- **Purine Nucleotides**
  - Resin use (in children)
  - Probenecid

- **Uric Acid Excretion into Urine**

- **Hyperuricemia (High uric acid in blood)**
  - Deposited into joint (Sodium urate crystals)
  - Macrophage comes
  - Cytokine
  - Neutrophils also come

- **Inflammation into Joint**
  - Swelling and pain into joint
  - Known as Gout

- **Inhibit the action**
- **Increase the action**
**Classification of drugs used in Gout**

There are two types of drugs used in Gout:

1. **Acute Condition**
   - Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
     - Diclofenac
     - Indomethacin
   
2. **Chronic Condition**
   - (for long term)
     - Uricosuric Drugs
       - Probenecid
   
3. **Medications**
   - Corticosteroids
     - Prednisolone
     - Methylprednisolone
   
4. **Other Medications**
   - Allopurinol
   - Triumeclonol

**Q2. Colchicine used in Gout**

*It is an alkaloid.*

**M.O.A.:**

- Colchicine inhibits the release of cytotoxicity protein from macrophage.
- Inhibits chemotaxis of neutrophils.
- Used directly inhibits inflammation.
- It is not acting directly for reducing pain.

**Use:**

- It is used in acute gout.
- For long term use.
ADR:
- Nausea, Vomiting, Abdominal pain.
- Due to long-term use: Bone marrow affected,
  - Aplastic anemia.
  - WBC reduced. 

**Q1:** NSAIDS used in Gout?

- NSAIDS inhibit COX enzyme.
  - So, reduce prostaglandins production.
  - So, they reduce inflammation and swelling of joint.
  - Gives symptomatic relief in the Gout.

**Q2:** Glucocorticoids used in Gout?

- Glucocorticoids are strong anti-inflammatory.
- They inhibit inflammation and relieves the symptoms of gout.
- Multiple joints affected → Give glucocorticoids via systemic route.
- Single joint affected → Give glucocorticoid directly into joint (Intraarticular).<sup>1</sup>

**Q3:** Probeneoid used in Gout?

- m.o.a.:
  - Probeneoid inhibit reabsorption of uric acid from renal tubules.
  - So, uric acid excreted more into the urine.
It is used in long-term treatment of gout.

- Care:
  - It should not be used in renal failure.
  - It should be avoided in acute gout.

- ADR:
  - Gutt disturbances
  - Abdominal pain
  - Rash.

**Due:** Allopurinol used in Gout.

**M.O.A.**:
- Allopurinol is converted into alloxanthine.
- Alloxanthine inhibits enzyme Xanthine Oxidase (irreversibly) (permanently).
- So, uric acid production is reduced.
- And it stops further progression of gout.

**Use**:
- It is used in early stage of gout.
- It is used for long-term therapy.
- Used in secondary gout like gout due to renal failure or leukemia.
ADRs:
- Gastrointestinal disturbance, Nausea, Vomiting
- Hypersensitivity reaction -> rash, itching
- It is contraindicated in pregnancy, lactation, children.

Drug Resinase used in Children:

M.O.A.
- Resinase make uric acid soluble
- So, uric acid dilute in the urine and excreted via renal way or urinations

Drug interactions:
- Drug interactions are uncommon with the use of resinase
- It is essential to monitor the patient's response to the medication

Interaction details:
- If there is an interaction, the patient should be monitored closely
- Medication adjustments may be necessary to ensure the patient's well-being
**Gastro Intestinal Tract (GIT)**

**Question:** Mechanism of production of vomiting?

- Vomiting is a protective reflex.
- It is "reverse peristalsis" movement.
- It is necessary for elimination of toxic substances present into GIT.

**Reflex of vomiting:**

- Sensory - GIT mucosa
  - Smell
  - Vision
  - Psychological factors
  - Taste

**Nucleus:** Medulla oblongata

- Area postrema
  - CTZ (Chemical trigger zone) (BBB absent)
  - NTS (Nucleus Tractus solitarius)
  - Vagus Nerve

**Cortex**

- Ane release
  - GIT smooth muscle contraction

**CTZ**

- 5HT3, M, H1, D2

**Toxin**

- Blood

**GIT**
Classification of drugs used to prevent vomiting (as antiemetics)

- 5HT3 antagonists
  - Ondansetron
  - Granisetron
  - Palonosetron

- Peripherally acting dopamine receptor antagonists
  - Metoclopramide [5HT3, D2 Antagonist]
  - Domperidone [D2 antagonist]

- Anticholinergic
  - Hyoscine
  - Dicyclomine

- Antihistaminic
  - Promethazine
  - Diphenhydramine

- Neuroleptic (Antipsychotic) [Anticholinergic and Antihistaminic]
  - Prochlorperazine
  - Haloperidol
  - Chlorpromazine

- NK1 receptor antagonist
  - Apretidipt
vii. Dronabinol [Sedation]

viii. Adjuvant Drugs:
   a. Glucocorticoids:
      - dexamethasone
      - Methylprednisolone
   b. Benzodiazepines:
      - Diazepam
      - Lorazepam
**5HT3 Antagonist**

- **Ondansetron** is a produg.

- **Mechanism of Action:**
  - It blocks 5HT3 receptors.
  - It affects peripheral 5HT3 as well as central receptors.
  - By blocking 5HT3 peripheral receptors, it inhibits effector impulse to CTZ.
  - By blocking central 5HT3 receptors, inhibit effector impulse for vomiting.

- **Pharmacokinetics:**
  - It is very well absorbed orally.
  - Also effective via parenteral route.
  - Transdermal patch is also available for long-acting.

- **Uses:**
  - It is used for inhibiting the vomiting which is induced by chemotherapy or radiotherapy.
  - It is used for post-operative vomiting.
  - It is used for pregnancy-time vomiting.
=> ADR:

- This drug is very well-tolerated and very less side effects.
- Diarrhea
- Headache

Due to:

- Metoclopramide

- It is a prokinetic drug.

=> M.G.A:

- It is 5HT3 antagonist.
- It is 5HT4 agonist.
- Do antagonist

- It is potent drug.
- It can cross Blood Brain Barrier and also have central effect.

=> Action is done by:

- increase lower esophageal sphincter tone.
- relax pyloric sphincter.
- increase gastric emptying.
- increase peristalsis of small intestine.
Prophylaxis i- Gluza

→ (Use)

i.1 Postoperative Vomiting:

→ Due to any surgical procedure, vomiting is common.

→ So, as prophylaxis, this drug can be used.
   (Treatment)

ii. Drug induced vomiting:

→ Drug therapy, most commonly, associated with nausea and vomiting.

→ This drug can be used as prophylaxis for preventing vomiting.
   → ex. Antiparkinson's drugs "Lecodope" which increase chances of vomiting

→ Domperidone is preferred than metochlorpromamide.
   → Metochlorpromamide can cross Blood Brain Barrier.
   → So, it inhibits central action of levodopa.
   → Domperidone did not cross Blood Brain Barrier.
   → So, it does not interfere with levodopa action.

iii. GERD (Gastro-Esophageal Reflex Disease):

→ In which content of stomach reflexly go back to esophagus and damage to esophagus.

→ Metochlorpromamide increases tone of lower esophageal sphincter and helps in relieving symptoms.
PPI (Proton Pump Inhibitor) and H₂ blockers are preferred more than metochloramide.

**Mastic Emptying**

- Metochloramide relax pyloric sphincter.
- And increase gastric emptying.
- So, it is used before any operation for GIT emptying.

**Vomiting due to chemotherapy and radiotherapy**

- Anticancer drugs induce vomiting.
- So, metochloramide is used for preventing chemotherapy induced vomiting.
- Ondesetron is prepared over metochloramide because of less side effects.

**ADR**

- It can produce parkinsonism.
  - Hypokinesia
  - Muscle rigidity
  - Tremor
  - Diarrhea
  - Headache
  - Dohemina inhibits prolactin release
  - Dohemina antagonists increase prolactin
  - Menstrual irregularities release
  - Alimentary
**Domperidone:**

- It is a prokinetic drug.

- M.O.A.
  - D2 antagonist.
  - It is less potent than metochlopramide.
  - It can not cross Blood Brain Barrier.
  - So, central (CNS) side effects are not there.

- Uses
  - Drug induce the vomiting
    - used along with levodopa
    - Gastric emptying.

- ADRs
  - Increase prolactin level
  - Gastrosthesia
  - Menstrual irregularities
  - Gynaecomastia
  - Diarrhoea
Anticholinergics are used as antiemetic.

- Anticholinergic blocks mucous and receptors of GIT track and inhibits abnormal contraction.
- So, hyoscine and dihydrocoleamine can be used as antiemetic.
- It also blocks impulse from vestibular apparatus.
- So, used in motion induced vomiting.

Antihistamines used as antiemetics.

- First generation H1 blockers also having anticholinergic and sedative action.
- So, it can stop vomiting.
**Q1:** Mechanism of secretion of HCl

- HCl is secreted by parietal cells of gastric mucosa.
- $\text{H}^+ - \text{K}^+$ ATPase pump is the final step for the acid secretion.
- Muscarinic receptors in stomach stimulates acid production.
- Histaminergic receptors ($H_2$) in stomach stimulates acid secretion.

**Q2:** Prostaglandins - (PyEg):

- Increase the mucus production.
  - So, mucus protects stomach wall from HCl.
- Bacteria (H. Pylori) infects stomach and increases acid production.

**Q3:** Classify the drugs used for peptic ulcer?

- Proton pump inhibitors: $\text{H}^+ - \text{K}^+$ ATPase antagonist
  - Omeprazole
  - Esomeprazole
  - Pantoprazole
  - Rabeprazole
  - Lansoprazole
⇒ ii. H2 blocker
- Ranitidine
- Famotidine
- Cimetidine
- Roxatidine

⇒ iii. Anticholinergics:
- Pirenzepine

⇒ iv. Prostaglandine analogues:
- Misoprostol

⇒ v. Ulcer protective:
- Sucralfate
- CBS (Cerium Bismuth Subsalicylate)

⇒ vi. Neutralise the acid secretion:
(a) Local actions:
- Magnesium hydroxide
- Aluminium hydroxide
- Calcium Carbonate

(b) Systemically acting
- Sodium bicarbonate
- Sodium citrate
Antibiotics (Antibiotics' drugs)
- Amoxicillin
- Metronidazole
- Tinidazole
- Clarithromycin

PPI
Proton Pump Inhibitor? or Omeprazole
Or PPI or H⁺-K⁺ ATPase inhibitors?

H₂O, B. I.

It orally taken, reach to intestine than absorbed into the blood, then reach to parietal cell of stomach.

It converted into active metabolite (Sulfonamide)

That active metabolite binds irreversibly with H⁺-K⁺ ATPase pump

Final step of acid secretion is inhibited.

So, it reduce acid production and secretion.

It is also used intravenously.

It is taken before meal (before 30 minutes)

Food interferes in its absorption.

Uses:

Peptic Ulcer:

Damage to the GUT mucosa by increased HCl (acid) secretion produce ulcer, which is known as Peptic Ulcer.
It is twin type.

i) Gastric Ulcer — When occurs in stomach.

ii) Duodenal Ulcer — When occurs in duodenum.

Proton pump inhibitors reduced acid secretion and gives time for healing of ulcer.

Under due to H. pylori → PPI + Antibiotic used.

Stress ulcer → PPI are very effective.

→ H2 blockers are also used.

→ Bleeding peptic ulcer → PPI are effective.

Zollinger Ellison Syndrome is synonymous.

It is due to “gastrin secreting tumour”.

Gastrin production is high.

Gastrin stimulates acid production.

So, [PPI] are used to reduce acid secretion.

Permanent treatment is “Surgical removal of tumor”.

[29/08/16]

GERD = (Gastro-esophageal reflux disease)

Abnormal function of the lower oesophageal sphincter.

Content of stomach reflex goes into the oesophagus.

Those content damage mucosa of oesophagus.

Pain is felt on epigastrium region.

PPIs are most commonly used drug in GERD.

→ because they are more potent than others.
PPIs reduce acid secretion.
So, they are used preoperatively used for reducing the chances of aspiration.

ADR:
- Diarrhea
- Abdominal discomfort
- Reduced absorption of vitamin B12
- Reduced the absorption of minerals

Intrinsic Factor (IF) produced in the stomach stimulates absorption of vitamin B12.

H2 blockers:
- Name: Ranitidine
  - Famotidine
  - Cimetidine
  - Roxatidine
m. o. a.:

- On parietal cells of stomach, they block H2 receptors competitively.
- Reduced acid secretion and production.
- They reduced acid secretion during all the phases of gastric secretion. (Cephalic, Gastric, Intestinal).
- They are less potent than PPIs.
- They are most commonly used drugs.
- Used orally as well as parentally.

Uses:

- i. Peptic ulcer:
  - Stress ulcer
  - H2 blocker is most commonly used.
- ii. GERD
- iii. Zollinger Ellison's syndrome.
- iv. Preoperatively.

ADR:

- Diarrhea
- Abdominal discomfort.
- Cimetidine can cross Blood Brain Barrier, so it can cause confusion, hallucination, convulsion.
- Cimetidine increase prolactin level so gynecomastia, menstrual irregularity.
- So, cimetidine not used.
**Anticholinergic Used in Peptic Ulcer?**

- Pirenzepine is an anticholinergic drug which blocks muscarinic receptors and reduces acid production.
- So, it can be used in peptic ulcer.
- But it is not used routinely because it is less potent and having more side effects.

**CBS Used in Peptic Ulcer?**

(Codominal Bismuth Substitute)

- CBS (Bismuth)
  - Precipitates protein and helps in healing of ulcer.
  - Increases PGE production, mucus production, and bicarbonate production ( Acid nutrition)
  - Reduce the growth of *H. pylori*.
Anti H. pylori Drugs?

- H. pylori is gram negative bacteria, rod shaped
- It resides into the mucosa of stomach.
- It damage the mucosa and produce inflammation of mucosa.
- So, it produce gastritis, peptic ulcers and gastric carcinoma.
- Mechanism of production of damage:
  - Urease enzyme of bacteria produce ammonia and that ammonia may damage mucosa.
- Combination of different drugs are used for the treatment of H. pylori infection.
- Objective for combination of drugs:
  - For prevention of resistance.
  - For faster effect.
  - For prevention of relapse.
  - For eradicate the H. pylori bacteria (Completely remove).

Diffent combinations are describe below:

i. Omeprazole / lanzoprazole
   Amoxicilidine
   Clarithromycin.

ii. Omeprazole
   Tetracycline
   Metronidazole
   CBS (Bismuth)  
   →Duration of treatment 8 weeks and PPI then continued for further 6 weeks.
Diarrhea:

- Loose stools passing 3 or more than 3 times in a 24 hrs
- They are two types:
  - Acute diarrhea
  - Chronic diarrhea
  - Mostly due to infection
  - May be due to unknown etiology

Management of diarrheaa:

Anti-diarrheal drugs or Drugs used in diarrheaa

i) Non-specific therapy:
   a) Oral rehydration therapy (ORS).
   b) Parenteral therapy.

ii) Antisecretory and antimotility drugs:
   a1) Opioids → Codeine, loperamide.
   b1) ß-adrenergic agonist → Clonidine
   c1) Octreotide
   d1) Racercadotril.

ii) Specific treatment - Antimicrobials.
   a) Antibiotic → Ofloxacin, Ciprofloxacin.
   b) Antiparasitic → Albendazole.
   c) Antiamoebic → Metronidazole, Tinidazole, Omidazole.
**Q. ORS (Oral Rehydration Solution):**

- It is used as Rehydration therapy for diarrhea.

**Contents of ORS:**

- Sodium Chloride 2.6 gm.
- Potassium Chloride 1.5 gm.
- Sodium Citrate 2.9 gm.
- Glucose 13.5 gm.

- It is mixed with 1 liter of drinking water.

- ORS is hypoosmolar 245 m osm/l (milliosmolar)

\[
\begin{align*}
\text{(1) Sodium} & \quad 75 \\
\text{Glucose} & \quad 75 \\
\text{(2) Chloride} & \quad 65 \\
\text{(2) Citrate} & \quad 10 \\
\text{Potassium} & \quad 20 \\
\hline
\text{245 m osm/l} \\
\end{align*}
\]

**M.O.A.:**

- Solute and water containing solution increase the absorption of contents from GIT in Blood.
- It replenish the electrolytes into the body and reduce the diarrhea by increasing absorption from GIT.
- It symptomatically treat the person.

- Uses:

- Diarrhea
- Dehydration [Mild to Moderate]
- Heat stroke
- Burns

- Home base ORS preparation:
  - Boiled rice water
  - Juice [Containing salt and sugar]
- Recently with added zinc (Zn) in to ORS [10 - 14 days therapy].

Q: Opioid analogue for diarrhea?

- Codeine:
  - It is natural opioid analogue.
  - M.D.A.
    - Acts on μ receptor of AIT tract.
    - and increases the tone of sphincter.
    - So, sphincter are closed.
    - Decrease the AIT motility.
    - So, diarrhea frequency is reduce.
2. Loperamide:

- It is more potent opioid analogue for diarrhea.

- **M.O.A.**
  - Acts on μ-receptor of GIT tract.
  - und. increases the tone of sphincter.
  - So, sphincters are closed.
  - Decrease the GIT motility
  - So, diarrhea frequency is reduced.

- **ADR**:
  - Constipation
  - Toxic megacolon
  - Increased chances of perforation of GIT mucosa.
  - Should not be used in children less than 7 yrs of age.

- **Uses**:
  - In Traveller's Diarrhea.
  - for decreasing the frequency of diarrhea.
Que: Raltegravir:

- **M.O.A.**
  - It is a phosphatase inhibitor.
  - Encephalamin degradation is done by encephalinase.
  - Raltegravir inhibits encephalaminase and increases concentration of encephalaine.
  - It reduces secretion from intestinal mucosa.

- **Use:**
  - In secretory diarrhea (watery diarrhea).

Que: Octreotide:

- **M.O.A.**
  - It is somatostatin analogue.
  - It inhibits the release of SHT (Hydroxy treptamin).
  - So, secretion and movement of GIT tract reduced.

- **Use:**
  - In the secretory diarrhea.
**CVS (Cardio Vascular System)**

1. **Renin - Angiotensin - Aldosterone System**

   - **Renin** is an enzyme secreted from the **JG apparatus**.

     
     \[
     \text{Angiotensin} \\
     \downarrow \text{Renin} \\
     \text{Angiotensin I} \\
     \downarrow \text{(ACE - Angiotensin Converting Enzyme)} \\
     \text{Angiotensin II}
     \]

   (i. **Vascular System**  (ii. **Aldosterone**  (iii. **Sympathetic**  (iv. **Cardiac**

   - **Vasoconstriction**

     \[
     \downarrow \text{Na}^+ \uparrow \text{Reabsorption} \\
     \downarrow \text{Water} \uparrow \\
     \downarrow \text{Urine} \rightarrow \text{Blood} \\
     \downarrow \text{Blood volume} \uparrow \\
     \downarrow \text{Cardiac Output} \uparrow \\
     \downarrow \text{Blood Pressure} \uparrow
     \]
Write a short note on ACE inhibitor [Name of ACE inhibitors, MOA, Uses, ADR]

Name of ACE inhibitor:
- Captopril
- Enalapril
- Ramipril
- Lisinopril
- Perindopril

MOA:
- This drug binds with the ACE enzyme and inhibits the conversion of AT (Angiotensin I) into AT II (Angiotensin II).
- So, vasoconstriction is reduced
  - Angiotensin II level is reduced.
  - Sympathetic activity is reduced.
  - Cardiac remodelling & hypertrophy is decreased
- So, blood pressure is reduced.

Uses:
- i) Hypertension:

  Blood pressure: Systolic Diastolic
  - Stage I: 140 - 159 90 - 99
  - Stage II: 160 - 179 100 - 109
  - Stage III: ≥ 180 ≥ 110

- ACE inhibitor reduce the level of angiotensin II into the blood.
- So, vasoconstriction, sympathetic activity is reduced.
So, BP is also reduced.

ACE inhibitors are used as oral or parenteral medication.

They are used in all stages of hypertension.

Acute Myocardial Infarction:
When blood supply to the cardiac wall is reduced, cells of myocardium go into the stage of Necrosis, known as Myocardial infarction.
Cardiac remodeling occurs during Myocardial infarction.

ACE inhibitors inhibit cardiac remodeling and sympathetic stimulation.
So, ACE inhibitors are cardioprotective and used in myocardial infarction.

Congestive Cardiac Failure:
When the heart is not able to pump enough amount of blood, known as congestive failure.
And congestive changes occur into the heart, known as congestive cardiac failure.
ACE inhibitors prevent cardiac remodeling.
↓ Blood volume → ↓ Cardiac Workload
So, ACE inhibitor used in CCF.

Diabetic Nephropathy:
Due to diabetes, chances of atherosclerosis and Renal vascular and glomerular changes occurs.
ACE inhibitors produce dilation of arteries and improve renal blood flow.
ADR: [C, APTOPRIL]

→ i) Cough: Bresykinin ↑
   
   Vasodilation and effect
   
   Respiratory tract.

→ ii) Angioedema: Oedema at lips, larynx.

→ iii) Proteinuria: Occurs Rarely.

→ iv) Teratogenicity: Growth retardation of fetus, Renal damage, Renal death.

→ v) Hypotension: May occur.

→ vi) Neutropenia: Rarely occurs.

→ vii) Rash

→ viii) Itching

→ ix) Loss of testes sensation.

→ x) Hyperkalaemia: Increased K⁺

⇒ It is contraindicated during Renal artery stenosis.
**Question:** Angiotensin Receptor Blockers (ARB) Name the drug, M.O.A., Uses and ADR.

- Name of ARBs:
  - Losartan
  - Irbesartan
  - Candesartan
  - Telmisartan
  - Valsartan
  - Olmesartan

- **M.O.A.**:

  - ARB competitively blocks angiotensin receptors and antagonise the action of angiotensin-II.

- Angiotensins are two types:
  - AT1, AT2.
  - ARB mainly binds with AT1 receptors.
  - So, it inhibits the binding of Angiotensin-II.
  - So, the action of angiotensin-II is reduced.
  - So, Hypertension is reduced.
  - Aldosterone secretion is reduced.
  - Sympathetic activity is reduced.

- **Uses:**
  - i. Hypertension
  - ii. Myocardial infarction
  - iii. Chronic Cardiovascular Failure
  - iv. Diabetes Nephropathy
NOTE:
- If the person suffers from cough due to ACE inhibitor then patient should be shifted on to the ARB.
- ARB do not affect ACE enzyme.
- So, metabolism of brendifarin is not affected.
- and cough is not produced.

Classified as antihypertensive Drugs.

i) ACE inhibitor:
- Captopril
- Enalapril
- Ramipril
- Lisinopril
- Perindopril

ii) ARB (Angiotensin Receptor Blocker):
- Losartan
- Olmesartan
- Candesartan
- Irbesartan
- Telmisartan
- Valsartan
Diuretics:

1. Thiazides:
   - Hydrochlorothiazide
   - Chlorthalidone
   - Indapamide

2. Loop Diuretics:
   - Furosemide

3. K⁺ sparing Diuretics:
   - Spironolactone

Calcium Channel Blockers:

- Verapamil
- Diltiazem
- Nifedipine
- Amlodipine

Sympatholytic Drugs:

1. β- blockers:
   a. Selective β-blockers:
      - Atenolol
      - Bisoprolol
      - Metoprolol
      - Esmolol
   
   b. Non-selective β-blockers:
      - Propranolol
2. Centrally Acting:
   - Clonidine
   - \( \alpha \)-Methyl dopa

3. \( \beta \) blockers with additional \( \alpha \)-blocking action:
   - Labetalol
   - Carvedilol

Due to Thiazides as Antihypertensive (Diuretics)

(Name, Uses, ADR):

=> Name of Drugs:

- Thiazides
- Hydrochlorothiazide
- Chlorthalidone

=> M.O.A.

- Thiazides block \( \text{Na}^+ \)-\( \text{Cl}^- \) Sympathetic channel at the DCT of Nephron.
- \( \text{So, Na}^+ \) is excreted in urine.
- \( \text{So, water is also excreted along with Na}^+ \) ions.
- Cardiac output is reduced.
- \( \text{So, B.P. is also reduced.} \)
- Due to \( \text{Na}^+ \) excretion peripheral resistance is also reduced.
- B.P. is reduced.
Advantages of Thiazides as antihypertension:

- Thiazides are well tolerated.
- Effective in mild to moderate hypertension.
- They are combined with other antihypertensive.
- Cheap drugs.
- Preferred in elderly patients.
- Longer duration of action.

ADR:
- Hypokalemia (low K⁺ in blood);
- Hyperglycemia;
- Hypercalcemia;
- Impotence;
- Decreased libido (sexual desire).
**Que:** CCB (Calcium Channel Blockers) as antihypertensive

- Neurmes of CCB:
  - Verapamil
  - Diltiazem
  - Amlodipine
  - Nifedipine

- M.C.A.:

  - Calcium Channel Blockers block calcium channel situated at smooth muscles of vessels and cardiac tissue.

- Inhibit Calcium Current:
  - Prevent the entry of calcium inside the cells.
  - So, smooth muscles contractibility is reduced.
  - Vasodilatation occurs.
  - Peripheral resistance reduce.
  - Blood Pressure is reduced.
  - Cardiac contractibility is also reduced.
  - So, Blood Pressure is reduced.
  - Verapamil and diltiazem reduce AV conduction.
  - So, heart rate is also reduced by them.

- CCB is hypotensive:
  - Very effective drug as monotherapy as well as combination with other.
  - Good for elder patient.
  - It is preferred in patient suffering from osthema.
Peripheral vascular disease, Diabetes.

ADR:

- Nifedipine (Reflex Tachycardia)
- Amlodipine

- Verapamil (AV block)
- Diltiazem

- Pseudohypertension, Headache, Swellings.

Q: Amlodipine can be combined with β-blocker?

- Amlodipine produces reflex tachycardia.
- β-blockers can reduce tachycardia.
- Both have different mechanisms of action for reducing blood pressure.
- So, they can be combined with antihypertensive effect.

Q: Verapamil, Diltiazem should not be combined with β-blocker?

- Verapamil, Diltiazem act on AV node and reduce conduction.
- β-blockers also reduce conduction.
- So, if they are combined, person may suffer from heart attack.
- So, they should not combined.

ma.
Questions: β-blockers as Antihypertensive.

1. Name of β-blockers:
   - Atenolol
   - Bisoprolol
   - Metoprolol
   - Famotidine

2. i. Selective β1-blockers:
   ii. Non-selective β blockers:
      - Propranolol

3. Mechanism:
   β-blockers block β1-receptor of heart
   Cardiac contractibility is reduced.
   Cardiac output is also reduced.
   So, blood pressure is reduced.

4. Non-selective β-blockers produce vasoconstriction
   So, selective β1 blockers used more commonly.

5. β-blockers reduce Renin Release.
   So, conversion of angiotensinogen to angiotensin-I is reduced.
   RAAS is suppressed.
   So, blood pressure is controlled (Reduced).
β - blockers used as Antihypertensive:

- In young patient.
- The patient having higher functioning of RAS.
- Patient having MI, Angina pectoris, other cardiac disorder.
- Should not be used in Asthma patients.

Q: Clonidine is Antihypertensive?

S.Q.

- Clonidine acts on α2 receptors on presynaptic membrane of neuron.

Presynaptic

- Reduce the sympathetic outflow.

α2

Synapse

- Reduce release of noradrenaline at synapse.

Post synaptic

- Blood Pressure is reduced.

→ It can cross Blood Brain Barrier.

→ Used:

- Severe hypertension.
**Question:** Treatment of Hypertension?

- **Systolic B.P.**  ≥ 140 mm of Hg.
- **Diastolic B.P.**  ≥ 90 mm of Hg.

Considered as hypertension.

**Stage of Hypertension:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>140 - 159</td>
<td>90 - 99</td>
</tr>
<tr>
<td>II</td>
<td>160 - 179</td>
<td>100 - 109</td>
</tr>
<tr>
<td>III</td>
<td>≥180</td>
<td>≥110</td>
</tr>
<tr>
<td>Severe Hypertension</td>
<td>≥220</td>
<td>≥120</td>
</tr>
</tbody>
</table>

⇒ Non-pharmacological treatment for early stage of hypertension:
- Patient should be advised for
  - weight reduction.
  - Reduce NaCl diet.
  - Regular exercise
  - Less oil containing diet (Saturated food).
  - Stop smoking.
⇒ Pharmacological treatment for hypertension:
- ACE inhibitor, ARB, β-blockers, calcium channel blockers,
  - Diuretics are commonly used.
  - They are used as monotherapy in early stage of hypertension.
  - Combination therapy may be used for uncontrolled hypertension or severe hypertension.
Drugs

- Hydrochlorothiazide (Diuretics)
  - Mild Hypertension

- Captopril, Enalapril, Ramipril
  - Mild to severe hypertension

  - In young age.

  - [If person suffers from cough due to ACE inhibitor then use ARB]

  - Diabetic patient

- Atenolol; Metoprolol (β-blocker)
  - In young age.

  - If hypertension due to over sympathetic stimuli

  - Systolic hypertension

- Propranolol
  - Contraindicated in asthma patient

- Amlodipine; Nifedipine (Calcium Channel Blockers)
  - Old age

  - Hypertension due to PVD (Peripheral vascular disease)

  - Mild to severe hypertension
Hypertension in Pregnancy:
- Α-methyldopa and niphedipine can be used in hypertension in pregnancy.

Therapy in severe hypertension:
- Intravenous sodium nitroprusside can be used.
- Esmolol, Clonidine, Hydralazine, furosemide can be used.

25% of hypertension should be reduced first
- B.P. → 160/100 mm of Hg should be maintained in 2-6 hrs.

Due: Angina Pectoris:  
(Classification of drugs used in angina pectoris)?

Angina pectoris also known as chest pain.
There are three types of Angina Pectoris.

1. Stable Angina:
   - In which angina pectoris occurs due to exercise or excessive work.

2. Unstable Angina:
   - In which angina occurs frequently and at resting stage also.

3. Variant Angina:
   - In which angina occurs due to severe vascular spasm.
**Pathology of Angina:**

- Decreased O₂ supply to the myocardium
  - Artherosclerosis
  - Thrombosis

- Increased O₂ demand of body tissue
  - Increased heart rate
  - Ventricular hypertrophy

**Treatment approach for angina:**

- Increased O₂ supply to the myocardium
  - PCI (Percutaneous coronary intervention)
  - CABG (Coronary artery bypass grafting)
  - Nitrate - Antiplatelet drugs
    - Thrombosis

<table>
<thead>
<tr>
<th>Nitrate</th>
<th>Beta-blockers</th>
<th>CCB</th>
</tr>
</thead>
</table>

**Antianginal drugs:**

- Nitrates:
  - Short acting:
    - GTN (Glyceryl trinitrate)
  - Long acting:
    - Isosorbide dinitrate
    - Isosorbide mono-nitrate

**Date:** 21/09/16
1. β-blockers:
   - Atenolol, Metoprolol, Esmolol, Bisoprolol.

2. Calcium Channel Blockers:
   - Verapamil
   - Diltiazem
   - Amlodipine
   - Nifedipine

3. K⁺ Channel Blocker:
   - Nicorandil

4. Other Drugs:
   - Antiplatelet Drugs:
     - Aspirin, Clopidogrel
   - Statins
     - Atorvastatin

Que: M.O.A., Pharmacological base; Use; A.D.R. of Nitrates

5. Nitrates:
   i. Short Acting:
      - GTN
   ii. Long Acting:
      - Isosorbide dinitrate
      - Isosorbide mononitrate
- Nitrates produce Nitrogen Oxide.
- It increases the activity of Guanyl Cyclase.
- So, AMP concentration increases.
- Camp (Cyclic AMP) decreases Ca²⁺ concentration in the cell.
- So, it inhibits muscular contraction (smooth).
- Vasodilatation occurs.

**Pharmacological base of Action:**

1. **Vein:**
- Nitrates produce NO (Nitrogen Oxide).
- So, it relaxes smooth muscles of vein.
- Vasodilatation occurs.
- Venous return to the heart is reduced.
- So, cardiac output and workload is reduced.
- So, Anginal pain is reduced.

2. **Artery:**
- Nitrates produce arteriolar dilatation.
- So, peripheral resistance is reduced.
- So, cardiac workload is reduced.
- Angina pain can be reduced.

3. **Heart (Coronary Vessels):**
   - Nitrates increase the blood flow towards ischemic area of heart.
   - It is known as the redistribution of blood.
1.1 Angina Pectoris:
- Due to decreased blood supply to the myocardium, angina pectoris occurs.
- ATN is used in acute attack of angina.
- It is given sublingually because it is faster absorbed and bypasses the first pass metabolism.
- If pain is relieved and person starts developing headache than person should spit out tablet.
- Maximum 3 tablets can be used at a time.
- Long acting nitrates are used for prophylaxis of angina.
- Prophylaxis should be used in unstable angina.
- Due to long term treatment with nitrates, tolerance develops against its action.

2.1 Myocardial Infarction:
- Infarction of myocardium due to reduced blood supply to myocardium.
- Nitrates can be used in acute attack of myocardial infarction.
- But it alone cannot reduce the pain of myocardial infarction.
- Blood pressure should be monitored during nitrate therapy.
- Should be stopped if hypotension occurs.
3) CCF: - (CHF):

- If heart is not able to pump, according to demand of body tissue known as heart failure.
- Blood is accumulated in heart chamber known as CCF.
- Nitrates reduced preload and afterload so, cardiac workload is reduced.
- B.P. monitoring should be done.

4) Hypertensive Emergencies:
- Intravenous nitrates can be used in the treatment of hypertension.

5) Biliary Colic:
- Due to obstruction of bile duct; pain occur known as biliary colic.
- Nitrates relax bile ducts and relieves pain.

6) Cyanide Poisoning:
- Cyanide inhibits cytochrome enzyme and inhibits cellular metabolism.
- MOA of nitrates in cyanide poisoning.
Nitrites

\[ \text{Hemoglobin} \xrightarrow{+} \text{Methemoglobin} \]

\[ \xrightarrow{+} \text{Cyanide} \]

\[ \{ \text{Cyanmethemoglobin} \}
\]

I.V.

\[ \{ \text{Sodium thiosulphate} \}
\]

\[ \text{Sodium thiocyanate} \]

\[ \text{Excreted in Urine} \]

\[ \Rightarrow \text{A.D.R. i-} \]

- Headache
- Hypotension
- Tachycardia
- Palpitation
- Methemoglobinemia.
**Respiratory System**

- What is cough? Types of cough.

  → Cough is a protective reflex for removal of substances from the respiratory tract.

  ⇒ Types:

  → i.) Productive Cough:

     • Cough with substances coming out known as productive cough.

  → ii.) Non-productive Cough:

     • Cough without sputum (substance) known as non-productive cough.

  ⇒ Mechanism of production of cough:

  → i.) Local irritation:

     • Irritation to the respiratory tract mucosa produce the cough.

  → ii.) Central Regulation:

     • Cough centre is located into the medulla oblongata.

     • When the central is stimulated, it can produce cough.
Classification of drugs used in treatment of cough:

1. Pharyngeal demulcents:
   - Lozenges.
   - Licorice.

2. Antitussive:
   a) Opioid Antitussive:
      - Codeine.
      - Pholcodeine.
   b) Non-Opioid Antitussive:
      - Noscapine.
      - Dextromethorphan.
   c) Antihistaminic:
      - Chlorpromazine.
      - Promethazine.

3. Mucolytics:
   - Bromhexine.
   - Ambroxycole.

4. Expectorants: (Secretion Enhancers):
   - Sodium citrate.
   - Potassium citrate.
   - Guapheesine.
   - Ammonium chloride.
   - Bulatum of tolu.
Describe M.O.A., pharmacological base, ADR of antitussive:

Name of antitussive drugs:

- Opioid: Codeine,
  Pholcodeine

- Nonopioid: Nasacpine,
  Dextromethorphone

- Antihistaminics: Chlorpromazine,
  Promethazine

M.O.A.:

These drugs can act on central cough centre.
They suppress the cough centre.
So, cough can be stopped.

Pharmacological base with ADR:

- Opioid:
  These drugs are very potent in suppressing cough.
  Should be used in nonproductive cough.
ADR:
- It inhibits intestinal movement and produce constipation.
- It produce dependence.
- It produce drowsiness.
  - Bronchospasm.

Non Opioids:
- This drugs also acts similar to the opioids.
- But side effects like constipation and dependence is less.

ADR:
- Headache
- Bronchospasm.

Antihistaminics:
- 1st generation antihistaminics which are also having anticholinergic action.
  - They reduce the cough and reduce secretion.
  - They are good for emetogenic type of cough.

ADR:
- Dryness of mouth.
Definition -
Asthma -
- Hyperresponsiveness of tracheobronchial tree, which results in bronchoconstriction and difficulty in breathing known as asthma.

Types of asthma -
1. Acute asthma
2. Chronic asthma
3. Status asthmaticus
   - Continuous attack of asthma.

Classification of drugs used in asthma -

1. Bronchodilators -
   1. ß2 - Agonist selective -
      - Sulbutamol
      - Salmeterol
      - Formeterol
      - Terbutaline
   2. Non-Selective agonist (Sympathomimetic)
      - Adrenaline
ii) Methylxanthine:
- Thiophyline
- Aminophyline

iii) Anticholinergics:
- Ipratropium bromide
- Tiotropium bromide

⇒ 2) Moist Cell Stabilizers:
- Sodium chromoglycate
- Ketotifen

⇒ 3) (Leukotriens) LT antagonists:
- Montelukast
- Zafirlukast

⇒ 4) Glucocorticoids:
   ⇒ 1) Inhaled Steroids:
   - Budesonide
   - Fluticasone
   - Ciclesonide

⇒ 2) Systemic Steroids:
- Hydrocortisone
- Prednisolone
- Methylprednisolone

⇒ 5) Anti Ig E antibodies:
- Omalizumab
**β-agonist in asthma**

- Name of β-agonist used in asthma.
  - Salbutamol
  - Salmeterol
  - Formoterol
  - Terbutaline

- Non-selective
  - Adrenaline

- M.O.A.:
  - It acts on the smooth muscle of tracheo-bronchial tree.
  - On the β2 receptors.
  - Increase cAMP concentration inside cell.
  - Smooth muscle of tracheo-bronchial tree relax.
  - Bronchodilatation occurs.
  - Also acts on mast cells.
  - Reduce the action of inflammatory mediator

- Description of β-agonist:

  1. Salbutamol:
     - Onset of action - fast.
     - Duration of action - short (up to 6 hr).
     - So, used in the acute therapy for asthma.
     - Due to short duration of action, it is not used for chronic asthma.
ii) Salmeterol:

- Onset of action → slow
- Duration of action → long (up to 12 hr)
- So, it is used in chronic therapy of asthma.
- Not used in acute attack of asthma.

iii) Formoterol:

- Onset of action → fast
- Duration of action → long
- So, it can be used in acute asthma and as chronic therapy of asthma.

⇒ ADR:
- Tremor
- Tachycardia
- Arrhythmias
- Palpitation

Methylxanthines (Phosphodiesterase inhibitor)

⇒ Name of methylxanthine:
  i.) Thiophylline
  ii.) Aminophylline
  iii.) Etofylline
  iv.) Doxophylline
Methylxanthines are inhibitors of phosphodiesterase enzyme. Function of phosphodiesterase enzyme (PDE) is to metabolise cAMP. Methylxanthines inhibit PDE and increase cAMP. So, smooth muscle relaxation occurs. Bronchodilatation occurs.

Uses:

Thiophylline → Used orally
→ As poor water soluble, IV not used.

Aminophylline → Orally used.
→ As irritant, it should be used slowly for IV therapy.

Methylxanthines are used in asthma and COPD patients.

Due to more side effects, their use is limited.
ADRL:

On CNS:
- Restlessness, insomnia, convulsion.

On CVS:
- Tachycardia, arrhythmia, hypotension.

On GIT:
- Nausea, vomiting, gastric & peptic ulcer.

On Kidney:
- Diuresis.

ADR according to dose of each drug.

Q: Anticholinergic in Asthma

⇒ Name of Drugs
  - Ipratropium bromide
  - Tiotropium bromide.
m.o.a:-
- These drugs blocks (antagonise) the 
  muscarinic receptors of treachiobronchial 
  tree.
- So, produce bronchodilation.

Use:-
- It is less potent than β-agonist
- It is used in acute attack of asthma 
  along with β-agonist
- Combination therapy of anticholinergic 
  with β-agonist is more effective.
- Used via inhalation route.

A.D.R:-
- Dryness of mouth.
- Tachycardia.

Ques. Must Cell Stabilizer?

Name of Drugs:-
- Sodium Chromoglycate.
- Ketotifen.

m.o.a:-
- This drug stabilize the mast cell 
  membrane and prevents the degradation of 
  mast cell.
- So, release of histamine, PGE2, Prostaglandins 
  leukotriens are reduced.
- So, asthma attack is prevented.
1.7 Allergic Asthma

- In allergic reaction, mast cells play a key role for production of asthma.
- So, mast cell stabiliser can be used.
- It is not affected usually.

1.7.1 Allergic Conjunctivitis
1.7.2 Allergic Rhinitis
1.7.3 Allergic Dermatitis

⇒ ADR:
- Local irritation.
- Cough
- Headache.
**Leukotrienes Antagonist**

- **Name of Drugs:**
  - Monteleukast
  - Zafirlukast

- **M.O.A.**
  - These drugs block LT\(_2\) receptors of smooth muscles of tracheobronchial tree.
  - So, leukotriens which are inflammatory mediator not able to bind with LT\(_2\) receptor.
  - So, bronchodilator is produced, inflammation is reduced and asthma is treated.

- **Uses:**
  - Used in moderate to severe asthma.
  - Orally well absorbed and plasma protein binding is more.
  - Preferred in children.
  - They are well tolerated.

- **ADRs:**
  - Headache
  - Rashes
  - Rash Eosinophilia
Steroids in asthma:

Name of the glucocorticoids used in asthma:

Inhaled Steroids:
- Beclomethasone.
- Budesonide.
- Ciclesonide.
- Fluticasone.

Systemic Steroids:
- Hydrocortisone.
- Prednisolone.
- Methyl Prednisolone.

M.O.A.:
- Steroids inhibit phospholipase enzyme and reduce production of inflammation mediator.
  - So, steroids [Reduce inflammation.]

  Steroids prevents antigen - antibody production.
  - So, it works as [anti-allergie.]

  Reduce antibody production.
  - So, it works as [immunosuppressant.]
Uses:

i. For moderate asthma:

- When asthma attack is ≥ 1 per day known as moderate dose.
  - Inhaled steroid with long acting β2 agonist is used.
  - Steroids prevent the tolerance of β2 agonist.

ii. For Severe Asthma:

- Continuous attack of asthma for long duration is known as status asthmaticus.
  - Intravenous systemic steroids are used for the treatment.

iii. For Status Asthmaticus:

- Continuous attack of asthma for long duration is known as status asthmaticus.
  - Intravenous systemic steroids are used for the treatment.

⇒ ADRs:

- Dryness of mouth
- Fungal infection of oral cavity
- Suppression of hypophysial-pituitary axis
- Osteoporosis
- Hypertension
- Muscle weakness
For prevention of AAR of steroids.

- Rinsing (wash) the mouth after each inhaled dose.
- Use the spacer.

**Diagnosis:** Status Asthmaticus

- Continuous attack of asthma for long time is known as status asthmaticus.
- It is associated with upper respiratory tract infection.

**Therapy:**

- Start humidified O₂.
- Give intravenous hydrocortisone 100 mg stat followed by 100 mg 4-8 hourly.
- Give β₂ agonist (salbutamol) (faster acting) by nebuliser.
- Start IV fluid therapy.
- Start appropriate antibiotic therapy.
- If patient do not respond to the nebuliser therapy, then intubation is done and bronchodilators are given.
- Tracheostomy is done if intubation is difficult.
- Mechanical ventilation is done.
- If person suffers from hypokalemia, potassium therapy is given.
- If acidosis occurs → IV sodium bicarbonate.
**Blood**

**Coagulation:**

→ It is the process of conversion of fibrinogen into fibrin and formation of clot.

→ Pathway of coagulation:

- There are two pathways of coagulation:
  - **Extrinsic Pathway**
  - **Intrinsic Pathway**

Tissue Factor (III) → VII → VIIa → X → Xa → XIII → XI → Fibrinogen → Fibrin

Prothrombin → Thrombin

Insoluble clot formation.
Q1: Classification of anticoagulant drug

1.3 Anticoagulant used In Vitro:

   - Heparin
   - Sodium Citrate
   - Sodium EDTA [Ethylene Diamine Tetraacetate]
   - Sodium Oxalate

2.1 Anticoagulant used In Vivo:

   \[ \Rightarrow \]

   i.1 Parenteral:
   - Heparin (UFH → Unfractioned heparin).
   - LMWH (Low Molecular Weight Heparin).
     - Enoxaparin,
     - Rivaroxaban.
   - Synthetic
     - Fondaparinux.

   \[ \Rightarrow \]

   ii.1 Oral:
   - Coumarin Derivative:
     - Warfarin.
     -Dicumarol.
   - Thrombione Derivative:
     - Phenindione.
   - Factor Xa Inhibitor:
     - Rivaroxaban.
**Uses and ADR of Heparin**

- Heparin is a mucopolysaccharide.
- It is a negatively charged organic acid.
- It is plasma protein bound.
- It is normally present in the human body.
- It is a very large molecule.

**M.O.A.:**

- Heparin indirectly inhibits coagulation.
- Heparin activates antithrombin.
  - and that anti-heparin anti-thrombin inactivates the thrombin.
  - and prevents clotting.
- Heparin also affects the coagulation factors X, X, XI, IX, VIII.
  - and prevents coagulation.
- Heparin is used subcutaneously (SQ) or intravenously (IV).

**Uses:**

**1. Deep Vein Thrombosis:**

- Thrombosis occurs into the deep veins of the body.
- It mainly occurs due to long-term immobilisation.
- It occurs due to abnormal clotting into the vessels.
1. Heparin prevents the clotting into the vessels.
2. Heparin can not produce lysis of thrombus but it can prevent further clotting.
3. Heparin is used SC or IV than patient is shifted on oral anticoagulant.

2) Myocardial Infarction:

Heparin is used in acute myocardial Infarction (MI) for prevention of thrombosis.

3) Unstable Angina:

Heparin is used to prevent thrombosis in unstable angina.

4) Atrial fibrillation:

Abnormal rhythm of atria.

Heparin is used as precaution.

5) DIC (Disseminated Intravascular Coagulation):

In DIC abnormal coagulation occurs in intravascular compartment.

Heparin is used to inhibit that abnormal coagulation.
6. Vascular Surgery

7. Other Uses:

- Bypass surgery
- Prosthetic heart valve surgery

⇒ ADR:

⇒ 1. Bleeding ⇒ Hematuria
   ⇒ GIT bleeding
   ⇒ Internal bleeding

⇒ 2. Thrombocytopenia

⇒ 3. Hypersensitivity Reaction ⇒ Rashes

⇒ 4. Osteoporosis

⇒ 5. Alopecia
**Q1:** LMWH is preferred over UFH?

- Size of LMWH is lower than UFH.
- LMWH is faster absorbed via subcutaneous route.
- Action of LMWH is longer.
  - So, once a day used.
- Side effects of LMWH are lesser.
  - Like thrombocytopenia, osteoporosis, alopecia is lower with LMWH.
- Monitoring with APTT (Activated Partial Thromboplastin Time) is not required for LMWH.
  - LMWH acts on factor Xa.
  - It is not affecting thrombin.
  - So, APTT is not affected by LMWH.

**Q2:** Oral Coagulation?

- Name of oral coagulation:
  1. Coumerine Derivative:
     - Warfarin
     - Dicumarol
  2. Rivaroxaban
  3. Phenindiones.
Blue to Description of Warfarin:

\[ \text{It is coumarin derivative.} \]

\[ \text{M.O.A.} \]

\[ \text{Liver} \]

Conversion into active coagulation factor

\[ \text{π, VII, IX, X} \]

\[ \text{Vitamin K} \rightarrow \text{Inactive Vitamin K} \]

\[ \text{Epoxide Reductase} \]

\[ \text{Warfarin} \]

\[ \text{Coagulation factors π, VII, IX, X are activated by 'γ-Carboxylation'.} \]

\[ \text{Vitamin-K is necessary for 'γ-Carboxylation' of this factors.} \]

\[ \text{During this reaction vitamin-K is converted into inactive (Vit-K epoxide) form.} \]
Warfarin inhibit Epoxide Reductase enzyme and 'γ-carboxylation' of coagulation factors inhibited.

So, it takes time (1-5 days) for action of warfarin.

Uses:

i.) Deep vein thrombosis.
ii.) Myocardial Infarction.
iii.) Unstable angina.
iv.) Disseminated Intravascular coagulation.

ADR:

1. Bleeding
   - Internal bleeding
   - External bleeding

2. Skin Necrosis

3. Diarrhea; abdominal pain.

4. Teratogenic effect
   - Warfarin can cross the placenta and affects the fetus.
   - Hypoplasia of organs.
   - Bleeding tendency increased.
   - Intrauterine death.
**Contraindication:** (Do not use):

- Bleeding Disorder (Hemophilia);
- Peptic Ulcer;
- Liver Damage;
- Pregnancy;
- Hemorrhage;

**Fibrinolytics:**

- The drugs which increase the breakdown of fibrin known as fibrinolytics.

⇒ **Name of drugs used as fibrinolytics:**

1. Streptokinase
2. Urokinase
3. Alteplase
   - Retreplase
   - Tenecteplase

⇒ **M.O.A.**

```
Fibrinolytics → Plasminogen → Plasmin → Fibrin → Fibrin degraded products
```

*classmate*
Fibrinolytics convert plasminogen into plasmin.

Plasmin produces degradation of fibrin.

So, clot is removed from the circulation.

Revascularisation of tissue occurs.

Uses:

1. Myocardial Infarction:
   - Thrombosis inside coronary artery produces Infarction of myocardium.
   - Fibrinolytics is used immediately after starting of symptoms.
   - Best result is possible if they are used within an hour of starting of symptoms.
   - They are alternative of PCI.

2. Pulmonary Embolism:
   - Fibrinolytic removes the embolus from the circulation.
3. Deep Vein Thrombosis:

Fibrinolytics can remove thrombus of deep vein.

⇒ Description of Fibrinolytics:

1.7 Streptokinase:

⇒ It's a protein which we get from β-hemolytic streptococci.

⇒ It is analgenic.

⇒ Antibodies are produced against it.

⇒ It can produce anaphylaxis Reaction.

⇒ so, it should be used only for 1 time.

⇒ ADRI:

- Bleeding chances are more.
- Hypotension.

2.1 Urokinase:

⇒ Enzymatic protein.

⇒ It is obtained from human fetal kidney cell culture.
It is not antigenic.

It is not producing hypersensitivity reaction.

ADR:
- bleeding.
- hypertension.

3) Alteplase:

It is obtained by R-DNA technology.

Alteplase is more selective plasminogen activator.

Non-antigenic.

Costly.

ADR:
- less chances of bleeding.
**Antiplatelate Drugs**

- The drugs which inhibit aggregation of platelets known as antiplatelet drugs.

**Classification**

1. Thromboxane A2 Inhibitor:
   - Aspirin (Low dose 50-325 mg).

2. Phosphodiesterase Inhibitor:
   - Dipyridamole.

3. P2X Receptor Antagonist:
   - Ticlopidine.
   - Clopidogrel.
   - Prasugrel.

4. GP IIb/IIIa Receptor Antagonist:
   - Abxicimab.
   - Eptifibatide.

**Aspirin (as antiplatelet drug)**?

**M.D.A.**

- Aspirin is COX enzyme inhibitor.

- So, it reduce the concentration of thromboxane A₂.
Thromboxane A2 is responsible for platelet aggregation.

Aspirin reduces Tx A2 concentration so it works as an antiplatelet drug.

\[ \text{Arachidonic Acid} \xrightarrow{\text{COX}} \text{Aspirin} \]
\[ \text{Tx A2} \]
\[ \text{Platelet Aggregation} \]

At higher doses of Aspirin:

Aspirin inhibits PGI2 synthesis.

PGI2 is inhibiting platelet aggregation so at higher dose aspirin's antiplatelet aggregation action is lost.

*Q:* Phosphodiesterase Inhibitor? (as antiplatelet?)

Dipyridamole

m.o.a.:

Dipyridamole inhibits phosphodiesterase enzyme.

So, cAMP metabolism is reduced.
So, CAMP concentration increase.

CAMP inhibits platelet aggregation.

So, Dipyridamole is used as an antiplatelet drug.

Phosphodiesterase \( \xrightarrow{\text{enzyme}} \) Dipyridamole

\( \xrightarrow{\text{degradation}} \) CAMP

Inhibits platelet aggregation.

*Purinergic receptor antagonist (as antiplatelet)*

- Ticagrelor
- Clopidogrel
- Prasugrel

**M.C.A.**

These drugs inhibit the action of ADP.

ADP (Adenosine Diphosphate) is increasing platelet aggregation.

These drugs inhibit ADP release and action.
So, they inhibit platelet aggregation.
ADP $\rightarrow$ Platelet aggregation

$\Theta$

Purinergic receptor blocker

Quer: GP IIb/IIIa receptor antagonist (as antiplatelet)

$\Rightarrow$ Name of Drugs:

- Abxiramab
- Eptifibatide

$\Rightarrow$ M.O.A.

$\Rightarrow$ GP IIb/IIIa receptors are present on platelets.

$\Rightarrow$ They take part into final step of aggregation of platelet.

$\Rightarrow$ GP IIb/IIIa antagonist inhibit this receptor.

$\Rightarrow$ and prevents platelet aggregation.

$\Rightarrow$ These are more selective and potent drugs.
Uses: (Some in above three questions):-

i.) Myocardial Infarction:

→ Aspirin can be given at the initial stage of myocardial infarction.

→ Aspirin + Clopidogrel is used for long time for prevention of myocardial infarction.

ii.) Acute Coronary Syndrome:

→ Antiplatelet drug is used as treatment and prevention of acute coronary syndrome.

iii.) Angina Pectoris:

→ Antiplatelet drugs used for the prevention & treatment of angina pectoris.

iv.) Peripheral Vascular Diseases:

v.) Prostatic Heart Valve Surgery:

After surgery to prevent thrombosis on the valve.

vi.) Transient Ischemic Attack:

→ Antiplatelet drugs are used for the prevention & treatment of TIA.
ADRI

Bleeding

Aspirin -> Contraindicated in pregnancy
    -> Ray's Syndrome.

Dipyridamole -> Diarrhea.

Blue: Iron Therapy

Oral Preparations:
    - Ferrous Gluconate
    - Ferrous fumarate
    - Ferrous Sulfate
    - Colloidal ferric hydroxide
    - Carbonyl iron.

Parenteral Preparations:
    - Iron Solubil
    - Iron dextran
    - Ferrous Carboxymethyl.
Oral iron is used for the iron deficiency.

Uses:
- Iron deficiency anemia,
- Pregnancy,
- Menstrual bleeding.

In pregnancy:
- Iron (100mg) along with Folic acid (0.5mg) used.
- During 2nd trimester of pregnancy for around 100 days.

In Iron deficiency anemia:
- Iron around 200mg is used.
- It is given along with vitamin C because vitamin C increase the absorption of oral iron.

Duration: In 4-8 weeks hemoglobin count is corrected.
- Then therapy should be continued for almost 3-6 months to replenish iron store.

Indication for parenteral iron therapy:
- Severe anemia
- Intolerant (vomiting, nausea, GIT disturbances) to oral therapy
- Poor pregnancy of oral therapy.
- Malabsorption of iron.

**ADR**
- Metallic Taste
- Nausea, Vomiting.

→ **Dose of iron in parenteral therapy** is calculated by following equation.

\[ \text{Dose of \ Iron (In mg)} = 4.4 \times \text{Body Weight (of \ Person)} \times \text{Deficient \ Hemoglobin} \]

→ **Intramuscularly**

→ Parenteral iron can be administered deep intramuscular injection.

→ It is done by 'Z' technique.

→ Iron solution do staining of the skin.

→ By 'Z' technique, solution which is administered at the site, do not come back and staining is prevented.

→ Daily recommended dose in adult is 100 mg/day.

→ **Intravenous Therapy**

→ Calculated dose is diluted in 500 mg of saline.

→ It is complete within 6-8 hrs.
Infection should be stopped.

- If person starts developing breathlessness
  - chest discomfort.

For iron toxicity antidote is → desferoxan

ADRs:
- Painful injection.
- Abscess.
- Skin → staining.
- Nausea ; Vomiting.

**Ques.** Skeletal muscle Relaxant:

- skeletal muscle Relaxant.

1.) Centrally acting:
- Benzodiazepine
  - Diazepam
  - Lorazepam
  - Midazolam
- Methocarbamol
- Clobazamine

2.) Peripheral acting:

a) Dopolarizing:
  - (Non-competitive):
  - Succinyl choline
  - Decamethonium
as ii) Competitive (Non - depending)

- DTC (Tuber curonium).
- Vecuronium.
- Rocuronium.
- Pencuronium.
- Atracurium.
- Mivacurium.

as iii) Directly acting on Skeletal Muscle

- Dantrolene.

But Succinyl choline acts skeletal muscle relaxant.

- Succinyl choline is a depolarising, a depolarising skeletal muscle relaxant.
- Non - competitive action.

- m.0.A

- It acts at neuromuscular junction.
- It depolarise the skeletal muscle.
- So, muscle do not respond to Ach.
- So, it leads to flaccid paralysis of muscle.
- And muscle relaxation occurs.
- It is metabolised by pseudocholinesterase.

- Its action is short-lasting (3-8 mins).

- **Uses:**
  1. It is used along with general anesthesia for producing good muscle relaxation.
     (during surgery; minor orthopedic procedures; endoscopic surgery).
  2. Short surgical procedure.
  3. In status epilepticus for reducing trauma.

- **Adr:**
  - Apnea (stoppage of respiration).
  - Muscle pain.
  - Vagal stimulation → brevycardia.

**Question:**

- Hypolipidemic Drugs:

- The drugs which lower plasma *lipoproteins* cholesterol levels.

- Classification is given below.
Classification

1. HMG CoA Reductase Inhibitor
   - Atorvastatin
   - Rosuvastatin
   - Lovastatin
   - Simvastatin

2. Bile acid binding Resins
   - Cholestyramine

3. Dietary Cholesterol absorption inhibitors
   - Ezetimibe

4. Nicotinic acid

5. HMG CoA Reductase Inhibitor
   => M.O.A.
   - It prevents cholesterol synthesis

\[ \text{HMG CoA} \quad \text{HMG CoA Reductase} \quad \text{Mevalonate} \quad \text{several steps} \quad \text{Cholesterol} \]
- So, LDL and VLDL production is also reduced.

- Uses:
  - It is used in hyperlipidemia
  - Post myocardial Infusion for prevention of atherosclerosis.
  - In Diabetes Mutilus for prevention of hyperlipidemia.

- ADRs:
  - Hepatotoxicity.
  - Nausea, Vomiting, Diarrhea
  - Headache.
Treatment therapy for myocardial infarction

- Pharmacotherapy for myocardial Infarction.

Death of the cells of myocardial known as myocardial Infarction which most commonly occurs due to reduce blood supply.

- Most commonly because of thrombosis of cardiac vessels.

**Clinical Features:**

- Severe chest pain
- Pain is radiating towards upper border of upper limb and jaw.

**Diagnosis:**
- ECG
- Cardiac Markers

**Treatment:**

- Aspirin at low dose (62.5-325 mg)
  (antiplatelet drug) (Table)
- If the patient having allergy for aspirin then clopidogrel is used.
- O2 therapy, 2-4 L/min
- For pain relief -> Opioids - [Morphine] (10 mg)
  (Infraavenous)
- For removal of thrombus
  - Thrombolytic Therapy - streptokinase, urokinase, alteplase
  - PCI (Percutaneous Coronary Intervention)
- Parenteral Anticoagulant - Heparin

\[ LMWH \text{ (Low Molecular Weight Heparin)} \]

- \( \beta \)-blockers: It is used if the patient is not hypotensive.
  - But as a regular therapy it is used because it is cardioprotective.

- Nitrites: Intravenous Nitrites to reduce pain and cardiac workload.

- ACE Inhibitors: It is used for prevention of cardiac remodeling.

- Acidocid: Sodium bicarbonate should be given.

- Statins: For reducing cholesterol level in blood.

As after termination of acute attack drug therapy used are:

- Antiplatelet Drug
- Statin
- \( \beta \)-blocker / ACE inhibitor
Question: Treatment therapy for Congestive Heart Failure?

- When the heart is not able to pump enough amount of blood known as heart failure.
- It leads to accumulation of blood within the heart known as congestive heart failure (CHF).

![Diagram]

- Back Pressure → Pulmonary Edema → Blood to Tissue is decreased → Renin-Angiotensin aldosterone → Vasconstriction.
- Preload ↑ → System is stimulated → Na⁺, Water retention → Edema

⇒ Treatment Goal:

⇒ Reduce Preload:

- Diuretics:
  - Loop diuretics → Furosemide
  - Thiazides → Hydrochlorothiazide
  - K⁺ spurring diuretics → Spironolactone

- Arterial and Venodilators:
  - ACE Inhibitors → Enalapril; Captopril; Benepril
  - ARB → Losartan; Condesartan; Valsartan

⇒ Treatment Goal:
- Nitrites:
  - GTN
  - Isosorbide dinitrate
  - Isosorbide mononitrate

- Hydralazine

For increase force of contraction:

- β-Sympathomimetics:
  - Dopamin
  - Dobutamin

- Cardiac glycosides:
  - Digoxine

For prevention of cardiac arrhythmia & Overstimulation of heart:

- β-blockers
  - Atenolol
  - Metoprolol
  - Bisoprolol

CHF is classified into different stages:

i.) Mild CHF
ii.) Moderate CHF
iii.) Severe CHF
iv.) Refractory CHF
Cardiac Glycosides

**Name of Drugs:**
- Digoxin
- Digitoxin

**Mechanism of Action:**
- Glycosides inhibit Na⁺-K⁺ ATPase pump.
- Na⁺ concentration is increased intracellularly.
- Ca²⁺ is increased intracellularly.
- Cardiac muscle contractility increase.
- Force of contraction is increased.
- Cardiac output is increased.
- But heart rate is not increased.

**Uses:**
1. **CHF:**
   - In this condition heart is not able to pump enough amount of blood.
   - Cardiac glycosides increase force of contraction & increase cardiac output.
   - So, CHF is treated.

2. **Cardiac Arrhythmias:**
   - Cardiac glycosides reduce the impulse production & increase PR interval.
   - So, they can be used to treat arrhythmia.
ADRs:
- Nausia, vomiting
- Headache
- Gynecomastia
- Restlessness
- Body accumulation
- AV block
CENTRAL NERVOUS SYSTEM

Sedatives & Hypnotics

- Sedatives: Substances which reduce the excitement and calm the patient.
- Hypnotics: Substances which induce the sleep.

Introduction

Physiology of sleep

There are two types of sleep.

1. NREM Sleep (Non-Rapid EyeBall Movement)
   - Stages: 0, 1, 2, 3, 4.

2. REM Sleep (Rapid EyeBall Movement)
   - Rapid EyeBall Movement Sleep.
   - Dreams occur during this sleep.
   - 20% - 30% of sleep.
During sleep there is a cycle of (NREM - REM) sleep.

Person spends majority of the time in stage 2; NREM movement.

Particular system of brainstem is responsible for consciousness and awakening.

Sedative and hypnotics affect reticular system.

---

**Question:** Classification of Sedatives and Hypnotics?

---

1. **Barbiturates**
   - **Long acting:** Phenobarbitone
   - **Short acting:** Butabarbital
   - **Ultra short acting:** Thiopentone Sodium

2. **Benzodiazepines**
   - **Antianxiety**
     - Diazepam
     - Alprazolam
     - Temazepam
   - **Anticonvulsant**
     - Sodium Lithium
     - Carbamazepine

3. **Non-Benzodiazepine Hypnotics**
   - Zolpidem
   - Zopiclone
   - Zaleplone
M.O.A.: Pharmacological action; Therapeutic action and ADR of Diazepam (Benzodiazepine)?

M.O.A.:

- Benzodiazepines binds to the benzodiazepine receptors of GABA channels.

\[ \text{GABA} \rightarrow \text{and open the chloride channel.} \]

- Chloride goes inside neurone
- It produce inhibition of neurone
- It affects reticular system, midbrain and limbic system.

(DIAZEPAM Ac.) (Pharmacological action)

- Diagnosis & Minor operation
- Insomnia
- Z
- E
- Preanesthetic Medication
- Anxiety
- Muscle Relaxant
- Alcohol withdrawal
- Conscious sedation.
Pharmacological action & Therapeutic Uses:

1. Insomnia:
   - Difficulty in initiation of sleep known as Insomnia.

Types:
- Transient Insomnia → < 3 days.
- Short Term Insomnia → 3 days - 3 weeks.
- Long Term Insomnia → > 3 weeks.

- Benzodiazepines are preferred (used) for insomnia.
- They are better than barbiturates because:
  - Dependence is less.
  - Tolerance is less.
  - Morning clumsiness and headache is less.
  - Sleep pattern is not disturbed.
  - Benzodiazepines affects (increase) stage II NREM sleep.
- Benzodiazepines do not affect REM pattern.
- Benzodiazepines should not be used for long time. Otherwise they also produce dependence and tolerance.

2. Diagnosis and Minor Operation:
   - Diagnosis can be used in minor surgery because it produce Amnesia; Anxiety effects also.

3. Preanesthetic Medication:
   - Diazepam reduce the anxiety and calm the patient.
   - So, used as preanesthetic medication.
4) Anxiety
- Diazepam also affects neurons of the limbic system and reduce the anxiety.

5) Muscular Relaxant
- Diazepam is centrally acting skeletal muscle relaxant.

6) Alcohol Withdrawal
- Diazepam can be used to relieve the symptoms of alcohol withdrawal.

7) Anticonvulsant
- Diazepam reduce the impulse sensation.
- So, it can be used to treat convulsion.
- e.g., febrile convulsion, status epilepticus.

8) Conscious Sedation
- For unco-operative patient, diazepam can be used to calm the patient.

ADR
- Dependence
- Tolerance
- Drynesses → In the morning (after sleep)
- Headache
- Amnesia
- Hypotension (B.P.)
- Respiratory depression.
Diazepam Toxicity:

Antidote → Flumazenil (IV) (antagonist Benzodiazepine Receptor).

Barbiturates:

Name of barbiturates:
- Phenobarbitone.
- Butobarbitone.
- Thiopentone Sodium.

M.O.A.
- Barbiturates binds with GABA channel on [barbiturate receptors] γ-2/β.
- Opens the chloride channel.
- Chloride goes inside the neuron.
- Hyperpolarisation of neuron.
- Neuron → inhibited.

Pharmacological action & Uses:

1.) Insomnia:
- Barbiturates can be used.
- Barbiturates affects normal pattern of sleep.
- They affect REM, NREM stage II, IV sleep.
- Safety margin is less.
- Drowsiness, headache chances are less.
1. Induction of General Anesthesia:

- Thiopentone sodium is used for induction of General Anesthesia.
- It is faster acting and acts for very short duration.

2. Anticonvulsant:

- Barbiturates block impulse generation in neurons.
- So, they can be given as an anticonvulsant.

4. Enzyme Induction to Jaundice:

- Phenobarbitone induces enzymes of bilirubin conjugation.
- So, it can be used for jaundice in child.

Adverse Drug Reactions:

- Dependence
- Tolerance
- Drowsiness
- Headache
- Respiratory depression
- Rebound increase in sleep (REM)
- Hypotension
- Anemia
Nonbenzodiazepines Hypnotics

Name of Drugs:
- Zolpidem
- Zaleplone
- Zopiclone

M.O.A:
- These drugs binds with GABA channel.
- Open chloride channels.
- Chloride goes inside the neurone.
- Hypopolarization of neurone occurs.
- Neuronal inhibition.

Pharmacological action and use:

Insomnia:
- These drugs are good for insomnia.
- Because
  - Short acting;
  - Morning drawiness; headache less;
  - Dependance less;
  - Tolerance is less;
- These drugs are less anti-anxiety, Anticonvulsant and muscle relaxant.
**ADRs:**
- Nausea
- Vomiting
- Headache
- Drowsiness

**Drugs used in Parkinson's Disease:**

**I. Drugs affecting the Dopaminergic System:**

**I.1 Dopaminergic Precursors:**
- Levodopa

**I.2 Peripheral Decarboxylase Inhibitors:**
- Carbidopa

**I.3 COMT Inhibitors:**
- Entacapone
- Tolcapone

**I.4 MAO Inhibitors (Mono Amin Oxidase):**
- Selegiline

**I.5 Dopamin Agonists:**
- Bromoapetine
- Ropinirole
- Pramipexole

**I.6 Dopamin Facilitators:**
- Amantidine
1. Drug affecting Cholinergic System:

1.1. Centrally acting anticholinergic:
   - Benzhexol
   - Biperidene
   - Procyclidine

1.2. Antihistaminic:
   - Promethazine
   - Orphenadrine

Que: M.O.A.; Pharmacological action; and ADR of Levodopa

→ It is a dopamine precursor drug.

→ As dopamine can not cross Blood Brain Barrier;
Dopamine is given in the form of Levodopa.

M.O.A.:

→ Levodopa crosses the Blood Brain Barrier
   and reach to the brain tissue.

→ Levodopa is converted into dopamine.

→ Dopamine acts on D2 receptor of Basal ganglia:
   - Because it is D2 receptor agonist.
   - And inhibits the neurons.

→ So, symptoms of parkinson's disease is resolved.
   - Rigidity, Tremor, Hypokinesia is resolved.
Levodopa is used to treat Parkinson's disease.

Levodopa is combined with carbidopa. Why?

- Levodopa is decarboxylated into peripheral tissue.
- So, very less amount is reaching into the brain.
- And peripheral side effects are increase.
- Carbidopa cannot cross Blood Brain Barrier.
- It is acting on peripheral decarboxylase enzyme.
- So, peripheral conversion of levodopa is prevented.
- And high amount of levodopa reach into the brain.

ADRs -

- It produce nausea and vomiting by stimulating CTZ (Cemo Trigger Zone) of brainstem.
- Hypotension
- Tachycardia; Arrhythmia
- Hallucination; irrelvent thinking process like condition.
- Confusion; Headache.
- Behaviour Changes.
- Ataxia.
On and Off phenomena:

- Drugs effect goes → and symptoms start "Off"

- Drug is taken → Symptoms disappear "On"

- Due to long term treatment with levodopa,
  - On-off phenomena occurs.

  - Levodopa is combined with other drugs for prevention of 'On-Off' effects.
Coxbomazepine 1

- Coxbamazepine is from iminostilbene group.

- M.O.A.

- Coxbamazepine increase duration of inactivated sodium channel or prolongation of inactivated sodium channel.

- So, that neuronal stimulation is reduced and epilepsy treated.

- It is bound to protein.

- It is having ADH like action.

- It can reduce urine volume and produce water intoxication.

- It is having autoinduction effect.

- It increase it's own metabolism.

- Uses:

  - i.) GTCS (Generalise Tonic Clonic Seizure)
  - ii.) EPS (Simple Partial Seizure)
  - iii.) CPS (Complex Partial Seizure)
  - iv.) Trigeminal Neuralgia (Pain along the distribution of trigeminal nerve)
  - v.) Acute Mania.
  - vi.) Bipolar Disorder.
- ADR:
  - Drowsiness.
  - Sedation.
  - Vertigo.
  - Urinary Retention.
  - Hypersensitivity reaction.
  - Hepatitis.
  - Bone marrow suppression.

**Question:** Valproic Acid - or Sodium Valproate?

- Broad spectrum anti-epileptic drug.

**Explanation:**

- It do prolongation of inactivated sodium channel.
- It inhibits calcium current in the neurons.
- It activates GABA channel
  - By increasing GABA production and decreasing GABA production.
    - So, Cl- goes inside.
    - Hyperpolarisation of neuron occurs.
- Thus, sodium valporate inhibit neuron stimulation by 3 different channels.
- It is plasma protein bound.
- It is metabolise into liver and excreted through urine.
Use:

1) First line drug in
   - Absence Seizure
   - Myoclonic Seizure
   - Atonic Seizure

2) Second line drug in
   - GTCS (Generalised Tonic Clonic Seizure)
   - GDS (Simple Partial Seizure)
   - CPS (Complex Partial Seizure)

3) Acute Manic.
4) Bipolar Disorder.
5) Paroxysmal of Migraine.

ADR: (VALPROATE)

- Vomiting
- Anorexia
- Liver Damage
  - It is not given in children less than 3 years of age.
  - Because it produce fulminant hepatitis in children.
- Elevated liver enzyme
- Pancreatitis
- Rash
- Alopecia (Choir loss)
- Teratogenic effect
  - Neural tube defect (spina bifida)
- Oral - furial dermatitis
**Due:** Status Epilepticus

- When epilepsy attack continue > 30 minutes or person having two or more than two attack without gaining consciousness in between.

**Treatment 1:**

- Hospitalise the patient.
- Maintain airway.
- Administer oxygen.
- Blood sample for testing.
- Water and electrolyte balance (Glucose, Electrolyte)

**Step 1:**

- Lorazepam 0.1 mg/kg IV
- Diazepam 10 mg/kg IV

Repeate after 10 min if necessary.

- Or
- Fosphenitine 20 mg/kg IV
- Or
- Pheniton 20 mg/kg IV

If seizure continues.
Step II:

- Phenobarbitone 10 - 15 mg/kg IV

- If seizure continues.

Step III:

- General anaesthesia
  - i.v. Midazolam
  - or
  - i.v. Propofol

- BP measurement continuous
- Maintain ventilation.
Epilepsy:

**Introduction:**

- PCD: Paroxysmal Cerebral (Sudden brain) Dysrhythmic
  (Abnormal impulse generation).

- Epilepsy is a neurological disorder in which sudden uncontrollable abnormal impulse generation occurs into the brain.

- It can be sensory and motor.

- Motor epilepsy also known as convulsion.

**Types**

<table>
<thead>
<tr>
<th>Generalised Seizure</th>
<th>Partial Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTCS: Generalised Tonic Clonic Seizure</td>
<td>Simple Partial Seizure</td>
</tr>
</tbody>
</table>

- There is general involvement of whole body muscle.

- Absence Seizure:
  - Mostly child affected
  - Visible become fixed
  - Loss of consciousness
  - Amnesia.

- Atomic Seizure:
  - Muscle tone is lost.

- Complete Partial Seizure:
  - Group of muscle involved + other symptoms
  - Loss of consciousness
  - Mental disturbance.

- Partial Seizure:
  - Group muscle involved.
- Myoclonic Seizure
  - Simple Partial Seizure

  Shock like momentary may become generalised
  construction of muscle

- Question: Classification of drugs used in epilepsy as
  Antiepileptic drugs?

- Phenytoin
  - Forphenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Valporate acid (Sodium Valproate)

- Barbiturates
  - Phenobarbitone

- Benzodiazepines
  - Diazepam
  - Lorazepam
  - Clonazepam

- GABA Pentane
  - Etho sucinide

- Newer Antiepileptics
  - Levetiracetam
  - Topiramate
  - Vigabatrine
Phenytoin binds with Na⁺ channel and it prolongs the inactivation of Na⁺ channel. So, Na⁺ channels do not activate. So, impulse generation is reduced. So, epilepsy is treated.

Use:
1. GTCS (Generalized Tonic Clonic Seizure)
2. Partial Seizure
3. Status-epilepticus - Continuous attack of Seizure > 30 min.
4. Trigeminal Neuralgia

Phenytoin can relieve the attack of trigeminal Neuralgia.
ADR

- Hirsuitism: Abnormal hair growth on face on female.
- Hypertrophy of gum.
- Hypersensitivity reaction.
- Hypoplastic bone marrow - megaloblastic anemia
- Hepatic damage

- Pregnancy fetal hydantoin syndrome
  - Cleft palate
  - Microcephaly
  - Hare lip

CNS
- M - Mental Confusion
- D - Drowsiness
- B - Behavioural Disturbance
- H - Hallucination
- A - Ataxia
- V - Vertigo

CVS
- Hypotension
- Cardiac arrhythmia

GI
- Nausea
- Vomitting
Opioids

It is an alkaloid which we get from a plant Papaver Somniferum.

- Morphine is natural.
- We have different type of opioids analgesic.

1. Classification of Opioids?

⇒ Naturally:
- Morphine
- Codeine
- Papaverine
- Noscapine

⇒ Semi Synthetic:
- Pholcodeine
- Hydromorphone

⇒ Synthetic:
- Pathidine
- Tramadole
- Fentanyl
- Alphentenyl
- Remiphenyl

⇒ Opioid Agonists:
- Pentazocine

⇒ μ-receptor agonist, κ-receptor antagonist:
- Buprenorphine.
Pharmacological Action:

I. CNS:
- Morphine acts on M, K, S receptors located at spinal and supraspinal region.
- It modifies the pain conduction.
- Morphine stimulates analgesic pathway so that pain pathway is inhibited.
- So, subjective feeling of pain is reduced.
- Anxiety and fear is reduced.
- Person becomes calm.
- It also produces euphoric effect.
- Reduce consciousness.

II. Eye:
- Morphine acts on midbrain on 3rd cranial nerve nucleus and stimulates it.
- Produce miosis.

III. Respiratory System:
- Morphine suppress respiratory centre and produce reduction in respiratory rate.
- Increase CO2 accumulation.

IV. Physiological & Psychologicale:
- Morphine reduce physical and psychological dependence.

V. C.V.S.:
- Morphine increase histamine release and produce peripheral vasoconstriction.
- Vagal stimulation.
- Hypotension is produced.
vi.) GIT-
  → Morphone stimulate GIT sphincters and close them.
  → Mostly anal sphincter and pyloric sphincter are closed.
  → So, it produce constipation.

vii.) Urinary Bladder:
  → Morphone increase tone of bladder sphincter
  → Closing of bladder sphincter.
  → Urinary Retention.

viii.) Cough:
  → Morphone inhibits cough centre and suppress cough.

ix.) Hypothermia:
  → Morphone reduce body temperature.

x.) GIT:
  → Morphone stimulates vomiting centre and produce Nausea and vomiting.

xi.) Skin:
  → Morphone stimulates histamine release in skin and produce itching.
xii. Billiary Tract:
- Morphine stimulates sphincter of a urinary tract and close it.

⇒ Uses:

i. Analgesic:
- Opioids are preferred drug for relieving pain.
- Their efficacy for reducing pain is higher than NSAIDS.
  - e.g. Myocardial Infarction.
    - Burns
    - Bullet Injuries
    - Pain due to accidental injuries
    - Concex
    - Renal Stone Pain.

ii. Preanaesthetic Medication:
- Opioids reduce Anxiety and calm the person.
- Minor operations can also be performed after giving opioids.

iii. Diarrhea:
- Opioids produce symptomatic relief in diarrhea by reducing frequency of passing stool.

iv. Cough:
- Opioids suppress cough centre and reduce production of cough.
- So, they are used in dry cough.
Pulmonary Oedema:

- Opioids produce peripheral vasodilatation.
- So, blood is distributed towards peripheral parts of the body.
- So, fluid accumulation in lung is reduced.
- Symptomatic Relief occurs.

Adverse Effects:

- Difficulty in vision.
- Respiratory depression.
- Physicole & Psychologicale dependance.
- Hypotension
- Itching
- Nausea & Vomiting
- Sedation
- Euphoria
- Constipation
- Difficulty in micturation.

Contraindications:

- Bannchi asthma
- Head injury → because morphine increase intracranial tension by decrease CO2 expiration.
- Hypotension
- Infants → Morphine produce severe respiratory depression in infants.
**Question:** Difference between Morphine & Pethidine.

<table>
<thead>
<tr>
<th>Morphine</th>
<th>Pethidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is natural opioid.</td>
<td>It is synthetic opioid.</td>
</tr>
<tr>
<td>Analgesic dose → 10 mg</td>
<td>Analgesic dose → 100 mg</td>
</tr>
<tr>
<td>10th time more potent</td>
<td>1/10th time potent dose</td>
</tr>
<tr>
<td>than pethidine than</td>
<td>than morphine.</td>
</tr>
<tr>
<td>morphine</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>Less with</td>
</tr>
<tr>
<td>→ more with</td>
<td>Constipation</td>
</tr>
<tr>
<td>Urinary Retention</td>
<td>→ less with</td>
</tr>
<tr>
<td>Morphine</td>
<td>Urinary Retention</td>
</tr>
<tr>
<td>Miosis</td>
<td>Pethidine</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
</tr>
<tr>
<td>Having cough suppressant</td>
<td>It is not having cough</td>
</tr>
<tr>
<td>effect</td>
<td>suppressant effect.</td>
</tr>
<tr>
<td>Produce severe Respiratory</td>
<td>Pethidine produce less</td>
</tr>
<tr>
<td>depression</td>
<td>respiratory depression.</td>
</tr>
<tr>
<td>Rapid action but long</td>
<td>Rapid action and short</td>
</tr>
<tr>
<td>duration of action</td>
<td>duration of action.</td>
</tr>
</tbody>
</table>
**Question:** Morphine Poisoning?

- When morphine is consumed in higher dose, produce poisoning.

**Clinical Features are as below:**
- Miosis (Pin Point Pupil)
- Sedation; Drowsiness
- Respiratory Depression
- Hypotension
- Nausea; Vomiting
- Constipation; Urine Retention
- Coma
- Death (May be due to Respiratory Failure)

**Treatment:**
- Stop further intake of Morphine
- Hospitalisation of patient
- Airway Support
  - Stunt Ventilation
- Maintain Circulation
  - Fluid Therapy
- Gastric Lavage
  - Potassium Permanganate (KMNO₄) is used for gastric lavage
- Naloxone (Opioid Antagonist) (0.4 - 0.8 mg IV)
- Stop Naloxone after the Respiratory become normal
- Maintain vital function.
**Question:** Classification of Antipsychotic Drugs

**Typical:**
- Chlorpromazine
- Trihexyphenidyl
- Haloperidol
- Trifluoperazine
- Prochlorperazine

**Atypical:**
- Risperidone
- Olanzapine
- Clozapine
- Ziprasidone
- Aripiprazole

**Question:** M.O.A, Pharmacological action, Uses, and ADR of Chlorpromazine (CPZ)

**M.O.A.**
- Chlorpromazine blocks D2 receptors of limbic system and other cortical areas.
- So, Antipsychotic effect is produced.

**Other Actions of Chlorpromazine:**
- Block CTZ → Stop Nausea, Vomiting.
- Block α1 → Postural Hypotension.
- Block D2 receptor → EPS (Extra Pyramidal Side Effects) of Basal Ganglia (Parkinson's disease like condition).
- Block Muscarinic → Dryness of mouth, receptor → Decrease secretion → Constipation.
Pharmacological Action-

- CNS:
  - Chlorpromazine reduces thinking, reduces hallucination.
  - Reduces insomnia, changes the behaviour, & anxiety.
  - By blocking Basal Ganglia, produce rigidity and tremor.

- CVS:
  - Chlorpromazine blocks α1 receptors and produces hypotension.

- GIT:
  - CPZ reduces nausea and vomiting.
  - By Antimuscarinic action → reduce secretion, decrease peristalsis and constipation.

- Urinary Bladder:
  - May produce urinary retention.

- Endocrine:
  - CPZ blocks D2 receptors and increases prolactin level.
  - In female → Oligomenorrhea, Amenorrhea.
  - In male → gynecomastia.
Use of CPZ:

- Mania: Person having elevated mood, fights of idea, Insomnia.
  - CPZ is used for treating Mania.
  - In acute mania, Haloperidol is used by Intravenous Route.

- Antiemetic: CPZ is used to reduce nausea and vomiting.

- Schizophrenia: It is psychological disorder in which person is not able to understand difference between reality & dreams.
  - It is characterised by Hallucination, delusion, abnormal social behaviour.
  - CPZ can be used to treat schizophrenia.
  - Now a days Atypical anti psychotics are used more.

- Interactive Hiccough: CPZ can be used for treating Hiccough.

ADRs:

- Parkinson's Disease:
  - Hypokinesia (4 Movement)
  - Rigidity
  - Tremor
  - Abnormal Muscular Movement
  - Hypotension
  - Dryness of mouth
Oligomenorrhea; Amenorrhea
Gynecomastia
Urinary Retention
Constipation
Weight gain
Hypersensitivity reaction
Loss of Libido (i.e., Sexual Desire).

22/12/16

Atypical Antipsychotics

Name of Atypical Antipsychotics:
- Clozapine
- Olanzapine
- Ziprasidone
- Risperidone
- Amitrazole

M.O.A.

These drugs Acts by blocking 5HT2 receptors of limbic cortex.
So, Antipsychotics produce antipsychotic effect.

What are the benefits of atypical antipsychotics over typical antipsychotics?
Atypical antipsychotics having very weak D2 blocking action.
So, extra pyramidal side effects (Parkinson's Disease) are not produced.
Also block D1 and muscarinic receptors.
Uses:

1) Schizophrenia:
   - Atypical antipsychotics are preferred.
   - They treat positive (hallucination) as well as negative (lack of motivation; social withdrawal) symptoms of schizophrenia.

2) Mania:
   - Person having elevated moods; flights of ideas; Insomnia.
   - CPZ is used for treating mania.
   - In acute mania; Haloperidol is used by Intravenous route.

ADRI:
   - Weight Gain;
   - Abnormal Muscular Movement;
   - Sedation;
   - Drowsiness.

**Antidepressants**

- Depression is a condition associated with low mood or sadness.

Other Symptoms:
- Lack of interest.
- Sleep disturbance.
- Suicidal Ideas.
- The drugs used to elevate the person's mood work as antidepressants.
Classification of Drugs:

i) TCA - (Tricyclic Antidepressants):
   - Trimipramine
   - Imipramine
   - Amitriptyline
   - Nortriptyline
   - Doxepine
   - Chlomipramine

ii) SSRI - (Selective Serotonin Reuptake Inhibitors):
   - Fluoxetine
   - Sertraline
   - Escitalopram
   - Citalopram
   - Paroxetine

iii) SNRI - (Serotonin Noradrenaline Reuptake Inhibitors):
   - Duloxetine
   - Venlafaxine

iv) Atypical Antidepressant:
   - Trazodone
   - Bupropion
   - Mianserine

v) MAO-A Inhibitors:
   - Clorgyline
   - Moclobemide
**M.O.A. ; Uses and ADR of TCA**

**Drugs:**
- Imipramine
- Trimipramine
- Chlomipramine
- Amitriptyline
- Nortriptyline
- Doxepine

**M.O.A.:**
These drugs inhibit reuptake of Noradrenaline (NA) and increase concentration of Noradrenaline (NA) into synapse.

- It stimulates the neuron.
- Person's mood is elevated.

**Other Mechanisms:**
- TCA also inhibit reuptake of Serotonin.
- Increase availability of serotonin at synapse.
- Person's behaviour and mood changes.
- TCA also inhibit α receptor and produce postural hypotension.
  - Cardiac Arrhythmia.
- TCA also produce anticholinergic action.
  - Dryness of mouth.
  - Blurring of vision.
  - Constipation.
- Produce sedation.
- Reduce seizure threshold.
Uses:

i.) Depression:
- "Low Mood" state of the person is known as Depression.
- TCAs used in depression.
- It may take few weeks for its action.
- It increases person's mood and person starts taking interest in surroundings.

ii.) OCD: (Obsessive Compulsive Disorder):
- It is the disorder in which person having an obsession which is followed by compulsion (Check)
- ex. Checkers, Washers.
- TCA can be used in OCD.
- It prevents the frequency of obsession & compulsion and prevents the fluctuation in mood.

iii.) ADHD: (Attention Deficient Hyperkinetic Disorder)
- Person is hyperkinetic (excessively active) but not able to focus on one thing.
- TCA are also effective in ADHD.

iv.) Nocturnal Enuresis:
- Person pass urine in bed during sleep known as Nocturnal Enuresis.
- Psychotherapy (Counseling) is more useful in Nocturnal Enuresis.
- TCA can be used in the treatment of Nocturnal Enuresis.
v) Prophylaxis of Migraine:
- TCA can be used in the prophylaxis of migraine.
- It prevents the frequency of attacks of migraine.

vi) Neuropathic Pain:
- Pain because of abnormal stimulation to neurons.
- TCA can be used to treat such pain.

ADR:
- Postural Hypotension.
- Cardiac arrhythmias.
- Dryness of mouth.
- Constipation.
- Blurring of vision.
- Sedation.

Contraindicated in:
- Glaucoma.
- IHD.
- Epilepsy.
**Q.** SSRI (Selective Serotonin Reuptake Inhibitor).

**Name of the Drugs:**
- Fluoxetine
- Fluvoxamine
- Sertraline
- Citalopram
- Escitalopram
- Paroxetine

**M.O.A.:**
- These drugs inhibit serotonin reuptake.
- So; concentration of serotonin increase in the synapse.
- Serotonin helps for mood elevated.

**Benefits of SSRI over TCA:**
- SSRI do not act on α1 receptor.
  - So, postural hypotension is not occurring.
- SSRI do not have anticholinergic activity.
  - So; dryness of mouth; constipation; blurring of vision not occurring.
- SSRI produce very less sedation.
- SSRI do not produce weight gain.
- SSRI do not produce convulsion.
- SSRI better tolerated.
- Less cardiac toxicity.
м

Usage-

1. Depression-

"Low mood" state of a person is known as Depression.

SSRI used in Depression.

It may take few weeks for its action.

It increase person's mood and person starts taking interest in surrounding.

2. Anxiety-

Person having "increased (high) mood".

Person having increased consciousness; Alertness; increased thoughts.

SSRI helps in Reduction of Anxiety.

3. OCD - (Obsessive Compulsive Disorder)-

It is the disorder in which person having an obsession which is followed by compulsion. (e.g.)

ex. Checkers; Washers.

SSRI can be used in OCD.

It prevents the frequency of obsession & compulsion.

and prevents the fluctuation in mood.
iv) Premature ejaculation:

- Ejaculation occurs immediately during sexual intercourse.
- Which occurs due to subjective Anxiety, or
  sympathetic stimulation.
- SSRI can be used to treat Premature ejaculation.

Adverse effects:
- Insomnia;
- Headache;
- GI disturbances;
  - Nausea;
  - Vomiting;
- Loss of libido.

Question:
Bipolar Disorder (Drugs used in bipolar disorder):

- Person's mood is changing from mania to Depression and Depression to mania, known as Bipolar Disorder.

- Mood stabiliser used for the treatment of bipolar disorder.
Name of the Drugs:

- Carbamazepine (antiepileptic)
- Valproic acid (Sodium Valproate)
- Olanzapine
- Risperidone (Antipsychotics)
- Haloperidol
- Lithium

**Lithium**

**M.O.A.**

- Lithium inhibits secondary messenger (IP₃) formation.
- Lithium mimics the action of sodium.
- Acts instead of sodium (Na⁺)
- It reduces the release of Dopamine & Noradrenaline.
- It stabilises the person's mood.
- So; it is used for Bipolar Disorder.

Use:

- **Bipolar Disorder**
  - Lithium stabilises the person's mood.
  - So, it prevents mania as well as depression.
  - It takes time for it's action.
  - So, lithium is used as a precaution for bipolar disorder.
Lithium can be used for unipolar mania.

ADRs:

Renal:
- Decrease ADH release
  - Increase frequency of urine
  - Polyuria
  - Polydipsia (thirsty)
  - Known as Diabetes Insipidus

GIT:
- Nausea
- Vomiting

CNS:
- Headache
- Confusion
- Ataxia

Lithium overdose may produce:
- Cardiac arrhythmia
- Coma & Death
- Hypothyroidism
- Death
Treatment:

- Stop the further treatment with lithium.
- Give intravenous Mannitol.
- Give Normal saline to increase Na⁺.
- Hemodialysis can be done.
**Excretory System**

**Diuretics**

- These are the drugs which increase urine volume.

**Classification:**

1.1 High efficacy diuretics (Na\(^+\) - K\(^+\) - 2Cl\(^-\) Inhibitors):
   - Furosemide
   - Torasemide
   - Bumetanide

2.1 Medium efficacy diuretics:
   - Thiazides:
     - Hydrochlorothiazide
     - Hydroflumethiazide
   - Thiazides like:
     - Chlorothalidone
     - Indapamide

3.1 Weak diuretics:
   - Carbonic anhydrase inhibitor:
     - Acetazolamide
   - K\(^+\) sparing diuretics:
     - Spironolactone
     - Amiloride
   - Osmotic Diuretics:
     - Mannitol
     - Glycerol
Eurosemide:

- It is high efficacy diuretics.

M.O.A:

- Eurosemide inhibit Na\(^+\) - K\(^+\) - 2Cl\(^{-}\) channel at ascending limb of Henle of nephron.
- So, Na\(^+\), K\(^+\), Cl\(^{-}\) ions absorption into the blood is reduced.
- Ion concentration in urine is increased.
- At DCT; Na\(^+\) is exchanged by K\(^+\).
- K\(^+\) excretion is more increased.
- It is known as Diuresis.

Uses:

- i.) Oedema:

  - Accumulation of fluid in the intestinal space (ECF) known as Oedema.
  - Eurosemide increase excretion of fluid in urine.
  - Intravascular fluid is reduced.
  - So, extracellular fluid is shifted into intravascular compartment.
  - So, accumulated fluid in intestinal space is reduced.
  - Oedema is reduced.
  - Eurosemide is used in:
    - Cardiac Oedema
    - Pulmonary Oedema
    - Hepatic Oedema
    - Cerebral Oedema
ii.) Hypertension

- Furosemide increases urine formation.
- Decrease water content of intravascular fluid.
- So, Cardiac output is reduced.
- So, Blood pressure is reduced.
- So, Furosemide can be used in the treatment of hypertension.
- It is not used as long term therapy of hypertension.

iii.) Hypercalcemia

- Furosemide increases calcium excretion in urine.
- It is used with normal saline.
- So, furosemide is used in hypercalcemia.

iv.) Fluid Overload

- Furosemide increases fluid excretion into urine.
- So, it can be used in fluid overload conditions.
- Ex. after blood transfusion.

- ADR

- 1) Hypokalemia [K⁺ concentration in blood]
- Furosemide increases K⁺ excretion.
2) Hyponatremia (Low Na⁺ Concentration in blood):
   - Furosemide increases Na⁺ excretion.

3) Hypocalcemia / Hypomagnesemia:
   - Because of increased excretion of Ca²⁺ and Mg²⁺.

4) Hyperglycemia:
   - Because of decreased insulin.

5) Hyperlipidemia:
   - Because of increased LDL concentration.

6) Hyperuricemia:
   - Because of decreased uric acid excretion.
   - Contraindicated in patients of gout.

7) OTC toxicity:
   - Because of ion imbalance.
   - Tinnitus (Ringing of ears).
   - Vertigo.

8) Cardiac arrhythmia:
   - Because of hypokalemia.

9) Hypersensitivity Reaction:
   - Because of rashes and itching.
**Que:** Thiazide Diuretics

**Ans:**

- Thiazides inhibit $Na^+ - Cl^-$ symport channel at DCT of nephron.
- So, absorption of $Na^+ , Cl^-$ reduced from proximal nephron.
- So, water is excreted along with ions.
- Volume of urine is increased.
- That is known as \textit{Diuresis}.
- It is having less efficacy than furosemide.
- $Na^+$ is exchanged by $K^+$.
- So, $K^+$ is excreted more which results into hypokalemia.
- Other ions $HCO_3^-, Mg^{2+}$ also excreted in urine.

**Uses:**

- 1.3 Hypertension:
  - Thiazides increase excretion of $Na^+, Cl-$.
  - Fluid is more excreted in urine.
  - So, intravascular fluid is reduced.
  - So, Cardiac output is reduced.
  - and blood pressure is also reduced.
  - Thiazides used as long term therapy for hypertension.
  - They are also combined with other anti-hypertensive drugs.
2.) Oedema-

- Thiazides increase urine volume excretion.
- Intravascular fluid reduced.
- Fluid shift from ECF to intravascular compartment.
- And oedema is reduced.
- Used in cardiac oedema; Hepatic oedema; Pulmonary Oedema.
- Thiazides are less efficacious than furoside in reducing oedema.

3.) Hypercalcemia-

- When calcium is excreted more into the urine known as hypercalcemia.
- Thiazides reduce calcium excretion.
- So, it can be used in hypercalcemia.

4.) Diabetes Insipidus-

- Thiazide reduce frequency and water filtration in urine in case of Diabetes insipidus.
- Mechanism of this effect is not properly understood.
Probable Explanation:

- Thiazides increase excretion of Na⁺, Cl⁻ along with water.
- Electrolytes in blood reduced.
- They are more absorbed from proximal tubule.
- Water along with that ion also more absorbed.
- Diabetes insipidus symptoms reduced.

ADRI-

- i) Hypokalemia - [↓ K⁺ Conc. in blood]
  - Thiazide increase K⁺ excretion.

- ii) Hyponatremia - [↓ Na⁺ Conc. in blood]
  - Thiazide increase Na⁺ excretion

- iii) Hypomagnesemia -
  - Bez of increase excretion of Ca²⁺ and Mg²⁺

- iv) Hyperglycemia -
  - Bez of decrease insulin.

- v) Hyperlipidemia -
  - Bez of ↓ increase LDL concentration.

- vi) Hyperuricemia -
  - Bez of decrease uric acid excretion.
  - Contraindicated in patient of gout.
Q1. Aldosterone Antagonist?

or

K⁺ sparing diuretics?

⇒ Name of the drugs:

- Spironolactone.

⇒ M.O.A.:

⇒ Aldosterone Action:

→ Aldosterone is a mineralocorticoid.

→ It reaches into the cells of DCT.

→ It binds with its intracellular receptors.

→ Stimulates DNA; transcription occurs and RNA formed.

→ Translation occurs and protein formed.

→ This protein absorbed Na⁺ and excrete K⁺ into urine.

⇒ Spironolactone Action:

→ Spironolactone binds with aldosterone receptors.

→ Blocks the action of aldosterone.

→ So, Na⁺ is excreted more into urine.

→ Water absorption from urine reduced.

→ Urine volume increased.

→ K⁺ excretion is reduced.

→ So, it is K⁺ sparing diuretics.
Uses:

- It is used along with other diuretics (Thiazide/furosemide).
- Thiazide/furosemide increase K⁺ excretion and hypokalemia occurs.
- Spironolactone reduce K⁺ excretion.
- So, hypokalemia is reduced.

Side Effects:

- Oedema
- Hypertension: Resistant hypertension. (In case of hypokalaemia)
- ADR:
  - Nausea
  - Vomiting
  - Diarrhoea
  - Gynecomastia
  - Loss of libido.

5Q: Spironolactone should not be combined with ACE inhibitor /ARB?

- Because ACE inhibitor /ARB produce hyperkalemia
- Spironolactone also produce hyperkalemia.
- So, combination of both leads to cardiac arrhythmia.
**Question:** Carbonic anhydrase inhibitor (Antagonist) →

**Name of Drugs:**
- Acetazolamide
- Dorzolamide

**Diagram:**

<table>
<thead>
<tr>
<th>Tubular Lumen</th>
<th>Tubular Cell</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO₃</td>
<td>H₂O + CO₂</td>
<td>H₂CO₃</td>
</tr>
</tbody>
</table>

**In Tubular Cells:**

- H₂O and CO₂ combine with the help of carbonic anhydrase enzyme to form H₂CO₃.
- H₂CO₃ dissociates into H⁺ and HCO₃⁻.
- H⁺ is exchanged with Na⁺ via Na⁺ - H⁺ antiport (antiport) channel.
- Remaining HCO₃⁻ of tubular lumen binds with H⁺ and forms H₂CO₃.
- This H₂CO₃ is dissociated into H₂O and CO₂ with the help of carbonic anhydrase.
- H₂O and CO₂ diffuse into Tubular cells.
- Na⁺ and HCO₃⁻ of Tubular cells diffuse into blood.
along with them water is also absorbed.

- Carbonic anhydrase inhibitor inhibit carbonic anhydrase enzyme and prevent the binding of H$_2$O and CO$_2$

- So; Na$^+$ and HCO$_3^-$ ions reabsorption reduced

- They pass into urine.

- So, Diuresis occurs.

**Uses:**

**i.) As Diuretic:**
- CA inhibitor is weak diuretic
- It is used as diuretic along with other diuretics.

**ii.) Glaucoma:**
- CA inhibitor reduce aqueous humor production.
- So; reduce intraocular tension.
- So; used in glaucoma.

**iii.) Alkalization in Urine:**
- CA inhibitor decrease NaHCO$_3$ absorption from PCT.
- So; increase excretion of Na$^+$ and HCO$_3$.
- Because of that urine becomes alkaline.
- So; it is used in acidic drug poisoning.

**iv.) Mountain Sickness:**
- For symptomatic relief by reducing CSF production.
ADRs:
- Drowsiness
- Metabolic acidosis
- Hypokalemia
- Headache
- Renal stone.

**Osmotic Diuretics**

**Name of Drugs:**
- Mannitol
- Glycerol

**M.O.A.**
- Osmotic diuretics are present in intravascular compartment.
- They create osmotic pressure.
- Increase water absorption from intestinal space to intravascular compartment.
- They are freely filtered into urine.
- Increase the volume of urine.
- That's how diuresis occurs.
- They decrease oedema.

**Uses:**

*Oedema:*
- Mannitol is preferred in oedema.
- It is preferred in cerebral oedema after head injury.
- Because it prevents rise in intracranial tension.
ii) **Glaucamal**

- In acute angle closure glaucoma, IV mannitol is used to reduce intraocular tension (pressure).

iii) **Maintenance of volume of intravascular fluid**

- After dialysis
- During cardiovascular shock; prevent renal damage.

iv) **ADRs**

- Headache
- Nausea; Vomiting
- Pulmonary edema
  - Due to rapid use.
Central Nervous System

Antidiuretics:

→ These are the substances which reduce urine volume.

\[SN\]: Vasopressin or ADH:

→ It is produced in supraoptic nucleus of hypothalamus.
→ Stored in posterior pituitary gland.
→ It is peptide hormone.

\[aw\]: M.O.A.:

→ **V₁** receptor mediated:
  Vessels → Vasconstriction
  JVP ↑
  AII → Peristalsis ↑
  Platelets → Aggregation
  Uterus → Contraction

→ **V₂** mediated actions:
  Kidney → Vasopressin
  Reach of collecting tubule
  → Increase production of water in channel.
  → Increase absorption of water from urine into blood.

→ Regulation in Body:
  Body osmolality ↑ → ADH ↑
  Body osmolality ↓ → ADH ↓
Desmopressin:
- It's a synthetic analogue.
- It is V2 receptor agonist.
- It is more potent than vasopressin.
- It can be used by oral, nasal and parenteral route.

Terlipressin:
- Prodrug in vasopressin.
- It is having selective V1 agonist action.

Uses:

1) Diabetes Insipidus:
- It occurs because of deficiency of ADH.
- So, water content in urine is increased.
- Polyuria:
  - Increased frequency and volume of urine.
  - Only water is excreted.
- It is two types.
  1. Pituitary DI: ADH concentration is reduced.
  2. Nephronic DI: ADH is normal but Renal tubules are resistance to ADH (not responding).
- Desmopamine is used in the treatment of DI. It will reduce urine volume by absorption of water from urine to blood.
ii) **Nocturnal enuresis** -
- Desmopressin can be used in nocturnal enuresis.
- It reduces urine volume and decreases the chances of passing urine in blood.

iii) **Esophageal Varices** -
- Bleeding from esophagus due to rupture of vessels.
- Which mostly occurs in portal hypertension.
- Blood vomiting occurs.
- Terlipresin can be used to produce vasoconstriction of vessels and reduce bleeding.

**ADRI** -
- Nausea
- Vomiting
- Hypertension
- Increase chances of angina.
- Diarrhea
- Increase thrombosis.

**General Anesthesia** -
**Features of GA** -
- Reversible loss of consciousness.
- Reversible loss of sensations.
- Analgesia.
- Amnesia.
- Muscle relaxation.
- Loss of reflexes.
Classification of GA.

Inhalation:
- Gas:
  - Nitrous Oxide
- Volatile Liquids:
  - Halothane
  - Isoflurane
  - Desflurane
  - Sevoflurane
  - Ether

Intravenously:
- Inducing Agent:
  - Thiopentone Sodium
  - Propofol
  - Etomidate

Slowly Acting:
1. Benzodiazepines:
   - Diazepam
   - Lorazepam
   - Midazolam
2. Dissociative Anaesthetics:
   - Ketamine
3. Opioids:
   - Fentanyl
   - Sufentanyl
   - Alfentanil
   - Remifentanil
Quer: Stages of Anaesthesia?

→ There are four stages of anaesthesia.

**Stage - I:**
- Stage of analgesia.
- Person is conscious but drowsy.

**Stage - II:**
- Stage of excitement, excitement.
  - Patient loses consciousness.
  - Sympathetic activity increased
  - HR ↑
  - BP ↑
  - Pupil → dilatation
  - Muscle tone → increase
  - Breathing → irregular

**Stage - III:**
- Stage of surgical anaesthesia.
  - Reflexes lost
  - Breathing regular
  - Intercostal muscle → paralysed

**Stage - IV:**
- Stage of medullary paralysis.
  - Respiratory centre → depressed
  - Vasomotor centre → depressed
  - Person may go into the stage of coma
  - Death can also occur.
**Question:** Ether:

- Volatile liquid.

**Characteristics:**

- Irritant
- Explosive
- Inflammable
- Very good analgesic

**Good:**

- Potent anesthetic
- It has a wide margin of safety.
- It is cheap.
- It does not sensitize the heart for catecolamine.
  (adrenaline, noradrenaline).

**ADR:**

- Post operative nausea and vomiting.
- Less hepatotoxicity.

**Question:** Halothane:

- It is volatile liquid.

**M&A:**

- It is faster absorbed from urine.
- Mix into blood and reach CNS.
- It reduces the neuronal activity.
- And produces anesthesia.
Benefits:

- Non-irritant.
- Non-explosive.
- Well tolerated.
- Induction & recovery is faster.
- Preferred in children.

Drawbacks:

- Poor analgesic.
- It sensitized the heart for catecolamines and produce cardiac arrhythmia.
- Respiratory depression.
- Hepatotoxicity.
- It's costly.

Guer Nitrous Oxide (N2O) 9

- It is a gaseous general anaesthetic.

M.D.A.:

- It is absorbed faster from alveoli.
- Absorbed into blood.
- It reduces neuronal activity (Block impulses).

Benefits:

- Induction and recovery is faster.
- Non-irritant.
- Non-inflammable.
- Wide margin safety.
- Excellent analgesic.
- Having less effect on heart and blood pressure.
- It's cheap.
**Disadvantages**

- Poor anesthetics.
- Poor muscle relaxation, relaxant.
- It produces diffusion hypoxia.
- Increase intracranial tension.

*Quiz*

Halothane is combined with nitrous oxide.

- Dose requirement of Halothane for production of anesthesia is reduced.
- Halothane is potent anesthetic but poor analgesic.
- Nitrous oxide (N₂O) is potent analgesic but poor anesthetic.
- Combination is beneficial as effects are combined.
- Nitrous oxide (N₂O) is rapidly diffuse and it also increase diffusion of halothane. Earlier effects are produced.

*Quiz*

Propofol

- It is a parenterally (intravenously) used general anesthetic.

*Notes*

- It binds with GABA channel.
- Increase Cl⁻ current (Conc.) is neurons.
- Hyperpolarisation of neurons.
- Decrease neuronal activity (4 impulse generation).
Benefits:

- Induction and recovery is faster.
- Non-irritant.
- Non-inflammable.
- Good for outpatient surgery (day care surgery).
- Good for producing sedation in ICU.
- Can be used for controlling convulsion in case of status epilepticus.
- Preferred in asthmatics.

Disadvantages:

- Fall in blood pressure.
- Pain at injection site.
- Acidosis.
- Respiratory depression.

Ques: Thiopentone Sodium?

- Ultra short acting barbiturates.

Mechanical:

- It acts on barbiturates receptors of GABA channel.
- Increase chloride current.
- Neuronal potential becomes negative.
- Impulse generation reduced.
Benefits / Advantages / Uses:

- It is rapidly acting.
- Used as induction of anesthesia.
- It also work as anti-convulsant.
- At low dose it can be used as Narcounalysis.
- Its action is terminated fast.

ADRs / Disadvantages:

- Respiratory depression.
- Depression of vasomotor centre.
- Poor analgesic.
- Poor muscle relaxant.

Redistribution of Thiopentone Sodium:

- First thiopentone reaches to the organs having higher blood flow (brain).
- Then, it is redistributed to the organs like muscle; fat.
- So, its action is terminated.

Questions:

- Ketamine:
  - It is "dissociated anesthesia".
  - It is good analgesic.
  - It produce sedation and amnesia.
Ketamin acts on NMDA (N-methyl-D-aspartate) type of glutamate receptor.

- Block the action of glutamate.
- Reduce neuronal activity.

Advantages:

- Bronchodilation → Preferred in asthma patients.
- Do not produce hypotension.
  - So, can be used in hypovolemic patients.
- It is well tolerated by children.
- Preferred for surgery of head & neck region.
- It can be used by IV, IM, oral or rectal route.

Disadvantages:

- Hypertension, increase HR
- Hallucination
- Delirium (false belief)
- Increase intracranial tension.

Preanesthetic Medication:

- The drugs which are given before anesthesia to make anesthesia safe and pleasant known as preanesthetic medication.
For reduction of secretion (Antisecretory):

- Glycopyrrolate which is anticholinergic used to reduce secretions.
- Anesthetic drugs increase nasopharyngeal secretions and increase the chances of aspiration.
- So, antisecretory drugs are used as preanesthetic medications.

For reducing anxiety and reducing sleep:

- Benzodiazepines (Diazepam, Lorazepam) can be used to reduce anxiety and increasing sleep in patient.

For reducing pain preoperatively as well as postoperatively:

- Opioids (Fentanyl, Remifentanil) can be used to reduce pain.
- NSAIDS (Diclofenac) can also be used for low grade of pain.

For prevention of Nausea and vomiting:

- Antimitotic Drugs - 5HT3 antagonist ondansetron is used.
- It is very effective and safe for prevention of Nausea and vomiting.
For increasing gastric emptying:

- Prokinetic drug → Metoclopramide is used.
- It increase the gastric emptying.

For reducing acid secretion:

- Proton pump inhibitors → Omeprazole; Pantoprazole can be used.
- They reduce acid production.
- Reduce the chances of aspiration pneumonia.

Classification of local anesthetics?

According to clinic use.

1) Surface anesthesia:
   - Cocaine
   - Lignocaine
   - Tetracaine
   - Benzocaine

2) Injectable anesthesia:
   a) Short acting with low potency:
      - Procaine
      - Chlorprocaine
   b) Intermediate acting with intermediate potency:
      - Lignocaine
      - Mepivacaine
   c) Long acting with high potency:
      - Tetracaine
      - Ropivacaine
      - Bupivacaine