

On and off phenomenon: Add COMT inhibitors or Dopamine Agonist. Use controlled release Levodopa

Levodopa ADR: Nausea, vomiting, Dyskinesia, Tachycardia & arrhythmias, Wearing off and on-off phenomenon.

Levodopa + Carbidopa (DDC inhibitor) 1:4 ratio.
Advantages: prolongs action, minimises systemic toxicity, less on and off phenomenon and better efficacy.

Levodopa-Prodrug crosses the BBB, 3% reaches the CNS, 97% metabolised to DA peripherally, causing systemic SE: Tachycardia, nausea, vomiting, postural Hypotension.

COMT inhibitors: enhance and prolong the therapeutic effect of levodopa. **E.g.** Tolcapone, Entacapone.
Tolcapone: Central & Peripheral effects, known to cause liver toxicity. Entacapone -Peripheral action and no liver toxicity.

Dopamine agonist: Directly binds to dopamine receptors.
Ergot derivatives: Bromocriptine, cabergoline. Cabergoline long acting ($t_{1/2}$: 80 hours) **non-ergot derivatives** Pramipexole, ropinirole-used in early PKD, ADR-gambling tendencies.

Dopamine Facilitator: Amantadine: Antiviral agent, used in Early PKD. It prevents DA reuptake and facilitates presynaptic dopamine receptors. Weak antimuscarinic action, Blocks glutamate NMDA receptor.

MAO-B inhibitors: Selegiline, Rasagiline. Has anti-parkinsonism action when used alone. In combination with levodopa, prolongs levodopa action.

Non-pharmacological management:
Deep brain stimulation
Gait training
Cognitive training
Speech therapy

- **Bradykinesia**
- **Rigidity**
- **Tremors**

Pathophysiology
- DA Neuronal degeneration

Low



Drugs for PKD

Drugs acting at the Cholinergic level

Centrally acting anticholinergics:
Trihexyphenidyl, Procyclidine, Biperiden.
Trihexyphenidyl is most commonly used. Used in drug induced parkinsonism.

Antihistaminic:
Orphenadrine and promethazine.
Rarely used, but can produce anti-parkinsonism effect through anticholinergic action.

Anti-histaminic agents

L-histidine



Histidine decarboxylase

Histamine

Histamine stored
in mast cells



Histamine, after release, binds to H₁ receptor

Location of H₁ receptor: Smooth muscles, CNS & Endothelial cells.

Histamine: is a neurotransmitter and neuromodulator. secreted mast cells' granules, gastrointestinal tract (enterochromaffin cells, intestine), and lungs, plays important role in hypersensitivity reactions.

Pharmacological actions:

- CVS: Vasodilatation-Fall in BP & increase permeability.
- RS: Bronchoconstriction.
- GIT: smooth muscle contraction of the intestine.
- CNS: Stimulation of sensory nerve endings- itching and pain.

H₁ receptors- Antagonist

First-generation Anti-histaminics

Has antihistaminic and antimuscarinic action.
Not recommended in children and elderly patients.
Highly sedative.
Diphenhydramine, Pheniramine, Chlorpheniramine,
Cyclizine, Orphenadrine and Promethazine.

Second-generation Anti-histaminics

Has antihistaminic and antimuscarinic action.
Safe for children and used in elderly patients
without dose alteration. Minimal sedation.
Cetirizine, Levocetirizine, Fexofenadine,
Loratadine. Rupatadine.

Therapeutic uses:

1. Allergic conditions: anaphylaxis, hay fever, and pruritus to relieve symptoms.
2. Common cold and cough: cetirizine and levocetirizine for symptomatic relief.
3. Motion Sickness: Promethazine, half an hour before the start of the journey.
4. Insect or sting bite: cetirizine and levocetirizine reduce swelling and oedema in patients with insect bites.
5. Preanesthetic medication: Promethazine is used to prevent vomiting and reduce oral and laryngeal secretions.
6. Vertigo: Cinnarizine, H₁ antagonist, acts as a Ca⁺⁺ channel blocker that reduces the vasoconstriction caused by released mediators.

ADR: Sedation: promotes sleep and diminishes the reflex action; hence, it should not be prescribed to drivers and other skilled workers. Also causes dryness of the mouth and blurring of vision (Anticholinergic action). Decrease in alertness.

Routes of drug administration

- **Enteral**
- **Parenteral**
- **Topical**
- **Novel drug delivery**

Oral: most convenient, BA 30-70%, not suitable for drugs with high first pass metabolism, not useful in an emergency and for an unconscious patient. Example: Paracetamol tablet.

Sublingual route: drug placed under the tongue. Bypass first-pass metabolism. E.g. Nitro-glycerine tablet.

Rectal route: Used in patients with vomiting, gastric irritant drugs may be administered. The route is inconvenient. E.g. Diazepam suppository in Febrile convulsions.

IV route: 100% BA, onset of action is fast, Useful in an emergency. Strict aseptic precautions is must. Can cause thrombophlebitis. E.g. Injection Ceftriaxone.

IM route: The most common site is the deltoid or gluteal muscle. Predictable absorption and depot injections can be given. The route is painful and can cause abscess formation if aseptic precautions are not taken. E.g. Injection Procaine Penicillin.

SC route: smooth and slow absorption. Irritant drugs can cause necrosis. E.g. Injection Insulin.

Intradermal route: Drug administered within the layers of skin. The route has diagnostic utility. E.g. BCG vaccination using tuberculin syringe.

Other routes: Intra-thecal (used for anaesthesia), intraperitoneal (used rarely), intra-arterial (used for diagnostic purposes), intraosseous (used in paediatric patients), etc.

Topical route: the drug is given in the form of ointment, solution, suppositories, drops or spray. Topical medications are instilled into the mucous membranes of the eye, ear and nose in the form of ointment or aqueous solutions of drugs,

Novel drug delivery

Developed for sustained and prolonged action, providing site-specific delivery of the drug. **Transdermal Route:** A transdermal patch is applied to the skin, and the required dose of medicine is delivered through the skin by diffusion into the blood circulation in a steady and sustained manner. E.g. Scopolamine TD patch.

Inhalational Route: Selective action at the lungs, drug delivered through a special device such as a nebuliser, inhaler or rotahaler. Reduces systemic side effects.

Prodrug: inactive form of a drug, metabolised into a pharmacologically active compound. E.g. Levodopa.

Liposomes: Drugs are encapsulated into phospholipid bilayer vesicles and targeted at the site of action. E.g. Amphotericin B liposomal drug delivery.

Nanoparticles: particle size: 1 to 100 nm, used as drug carriers for targeted drug delivery in cancer therapy.

Monoclonal antibodies: Developed by using "hybridoma technology."

Bioavailability (BA)

Active concentration of the drug in the systemic circulation. (F) IV route, F= 100%

Factors modify BA: Pharmaceutical: lipid soluble, non-ionised, Amorphous form and small-sized particle drugs have better BA and vice versa. Physiological factors: BA is less after food, and decreased gastric emptying enhances drug absorption. Disease-related: Malabsorption and Gastroenteritis reduce BA. Misc: oral route variable BA, poor compliance reduces BA.

First Pass Metabolism: the drug gets metabolised in the liver before reaching the circulation. Drugs with high first metabolism (Nitroglycerine-NG), BA is less if given orally. Alternative route: SL, IV, IM. Example: SL Ngin Angina.

Inactive substance--- active metabolite.
Active metabolite--- active substance.
Active substance--- inactive metabolite

Phase I Reactions: non-synthetic: oxidation, reduction and hydrolysis. (catalysed by microsomal enzymes). Addition or exposure of functional groups (-OH, -NH₂, -SH, -COOH), e.g., Paracetamol, adrenaline.

Enzyme Induction: slow process (2-3 weeks), stimulates smooth endoplasmic reticulum--accelerate metabolism of the drug, which is co-administered with an inducer—reduced therapeutic efficacy.

Example: Rifampicin + OC pills-failure of contraception. Phenobarbitone in preterm labour enhances conjugation activity and conjugates the bilirubin.

Enzyme inhibition: a decrease in the expression of a specific enzyme in the presence of a particular drug (inhibitor), causes cumulative toxicity or prolongation of the action. Fast process.

Example: Warfarin + erythromycin (enzyme inhibitor) = bleeding.

Phase II Reactions: Mainly conjugation reactions. (Catalysed by non-microsomal enzymes). E.g. Isoniazid, chloramphenicol.

BBB: separates blood and brain and regulates the access of drugs inside the brain. Lipid-soluble drugs cross the BBB. Dopamine, a tertiary amine compound unable cross the BBB, so its prodrug- levodopa, is used for the treatment of Parkinsonism.

Placental Barrier: separates the placenta from the maternal blood. Teratogenicity (congenital malformations, developmental disorders) if the drug crosses the barrier. Thalidomide-causes Phocomelia.

Plasma protein binding: (PPB) Drug + protein=Drug=protein complex. Acidic drugs (Warfarin, Sulfonamide) bind to Albumin, and basic drugs (Quinidine, Propranolol) bind to α_2 acid glycoprotein. PPB prolongs drug action; displacement reactions are common.

Absorption

Distribution

Pharmacokinetics

Metabolism

Excretion

enzyme-mediated chemical changes.

Routes of drug elimination: Renal (most common), biliary, faecal and alveolar.

First order kinetics: Constant fraction eliminated. Plasma half life constant

Zero order kinetics: Constant amount is eliminated. Plasma half-life variable.

Plasma half-life: It is the time taken by the drug to reduce the concentration of the drug to half of its original value.

$$t_{1/2} = \frac{0.693}{K}$$

(K= elimination constant)

Drug name	Plasma Half-life
Adenosine	10 seconds.
Oxytocin	3 to 5 mins.
Amoxicillin	2 hours.
Amiodarone	15-140 days.

Steady state plasma concentration: Rate of absorption= rate of elimination. It takes 4-5 half-lives.

Primarily used in the treatment of inflammation, fever & pain. The basic mechanism behind pain, inflammation and fever is activation of the cyclooxygenase pathway, leading to the synthesis of PGs.

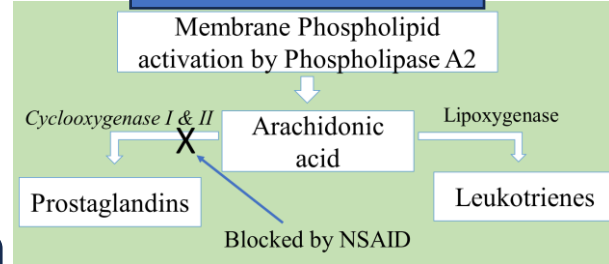
Classification: Non-selective COX inhibitors:

Salicylates: Aspirin. Propionic acid derivatives: Ibuprofen, Ketoprofen. Acetic acid derivatives: Diclofenac sodium, Aceclofenac sodium, Ketorolac. Para-aminophenol derivatives: Paracetamol. Enolic acid derivative: Piroxicam, tenoxicam. Fenamates: Mefenamic acid.

Classification:

Selective COX II inhibitors: Coxibs: Celecoxib, parecoxib, etoricoxib. Non-Coxibs: Nimesulide, Meloxicam, Etodolac.
Miscellaneous drugs: Nefopam, Diacerin.

Mechanism of action



An irreversible inhibitor of COX, used as a cardioprotective drug in post MI & Stroke.

ADME: available as an enteric-coated tablet, follows dual kinetics of elimination.

Therapeutic uses: Analgesic (Dysmenorrhoea, toothache), Anti-inflammatory (RA, OA, Gout), antiplatelet, PDA, prevention of colonic and rectal cancer, reduces progression of cataract. pre-eclampsia.

Adverse effects: gastric mucosal ulceration, respiratory alkalosis, Analgesic nephropathy (Chronic use), Reye's syndrome (under 12 years-hepatic injury), Acute Salicylism (tinnitus, vertigo, decreased hearing).

Toxicity: Acute salicylate poisoning: in children, doses > 20g/day. Gastric lavage with activated charcoal. Alkalinization of urine, Haemodialysis in resistant cases.

Ketorolac: a non-selective reversible COX inhibitor with potent analgesic and moderate

ADME: Oral and parenteral) and local routes (Nasal and Eye drops).

Therapeutic uses: Postoperative pain, metastatic pain, dental pain, Spasmodic and muscular pain, post-cataract pain.

ADR: risk of peptic ulceration, rash and pruritus, increase in transaminase levels.

A
s
p
i
r
i
n

N
S
A
I
D

P
a
r
a
c
e
t
a
m
o
l

OTC drug, used in all age groups, pregnancy & Lactation.

ADME: Oral route- exceptional bioavailability, peak in 1 hour.

Uses: Analgesic (body ache, backache, and headache), Antipyretic, poor anti-inflammatory (OA), and migraine headache.

Acute paracetamol poisoning: > 2 g/day. Presents with nausea, vomiting, abdominal pain, jaundice and coma. Treated with: Gastric lavage with activated charcoal, N-acetyl cysteine (detoxify NABAI).

COXIBs

Selective COX II inhibitors: Celecoxib, Rofecoxib, Valdecoxib, Parecoxib and Etoricoxib.

Advantages: Superior GI safety, no antiplatelet action, no bronchoconstriction. Preferred in patients with peptic ulcer.

Disadvantages: increases the risk of cardiovascular thrombosis. MI.

Nimesulide: banned due to severe hepatic toxicity.

K
e
t
o
r
o
l
a
c

Diclofenac sodium

In addition to COX inhibition, also reduces the Arachidonic acid concentration in leukocytes.

Therapeutic uses: As an anti-inflammatory agent: in RA, OA. As an analgesic in patients with primary dysmenorrhoea and renal colic. Equally effective in producing analgesia in post-operative pain. Diclofenac suppositories are used to alleviate pain caused by haemorrhoids. Topical use: Topical applications are used to relieve pain due to minor strains, sprains, and bruises.

Adverse effects: 1/5th suffer from nausea, vomiting and dyspepsia, high cardiovascular risk, rash, itching and photosensitivity. Rarely Stevens-Johnson's syndrome. Hepatic injury: in 15% of individuals.

