جَـامعة
المَـنارة
MANARA UNIVERSITY

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Inflammation

- A normal response to tissue damage and infection and associated with:

- Pain
- Fever

- Inflammation is caused by chemicals released from damaged tissue and circulating blood cells .

Chemicals involved in the inflammatory response are:

- Lipids) prostaglandin (PGs), leukotriens (LT), tromboxanes (TXs), platelets activating factor (PAF) or **(AGEPC)**
- (Amines (histamine, serotonin).
- peptides (bradykinin).

Classification of anti-Inflammatory drugs

1. Non-steroidal anti-inflammatory drugs (NSAIDs).
2. Drugs used for treatment of gout.
3. Drugs used for treatment of rheumatoid arthritis.
4. Steroidal anti-inflammatory drugs (Glucocorticoids).

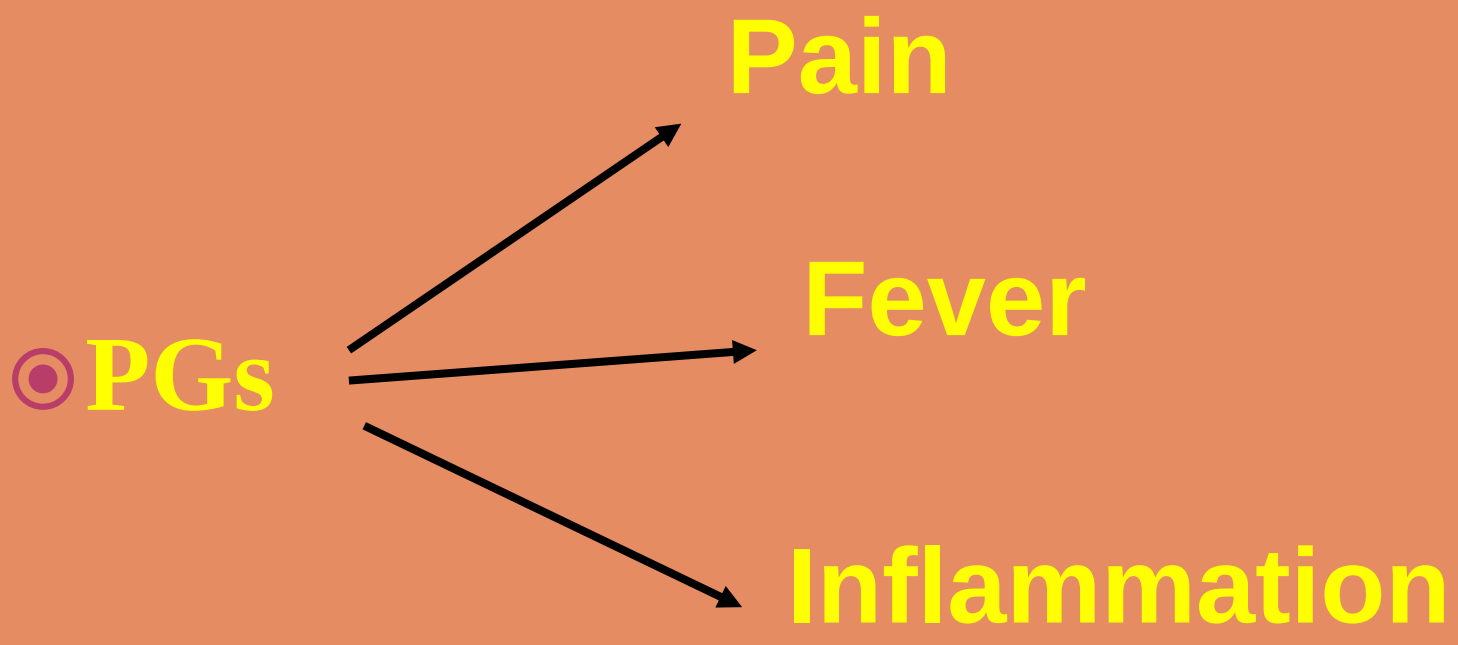
Non-steroidal anti-inflammatory drugs (NSAIDs) :

1 .Analgesic

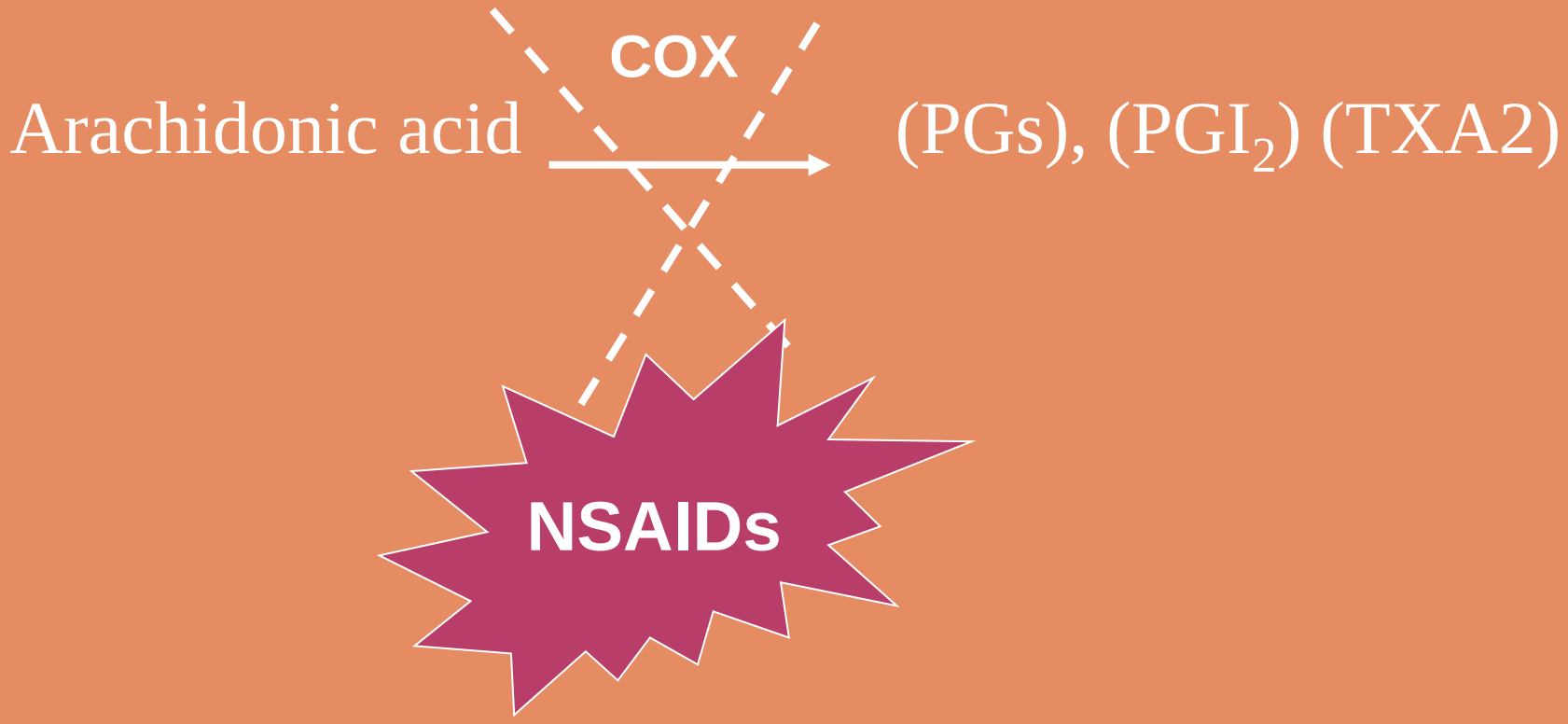
2 .Antipyretic

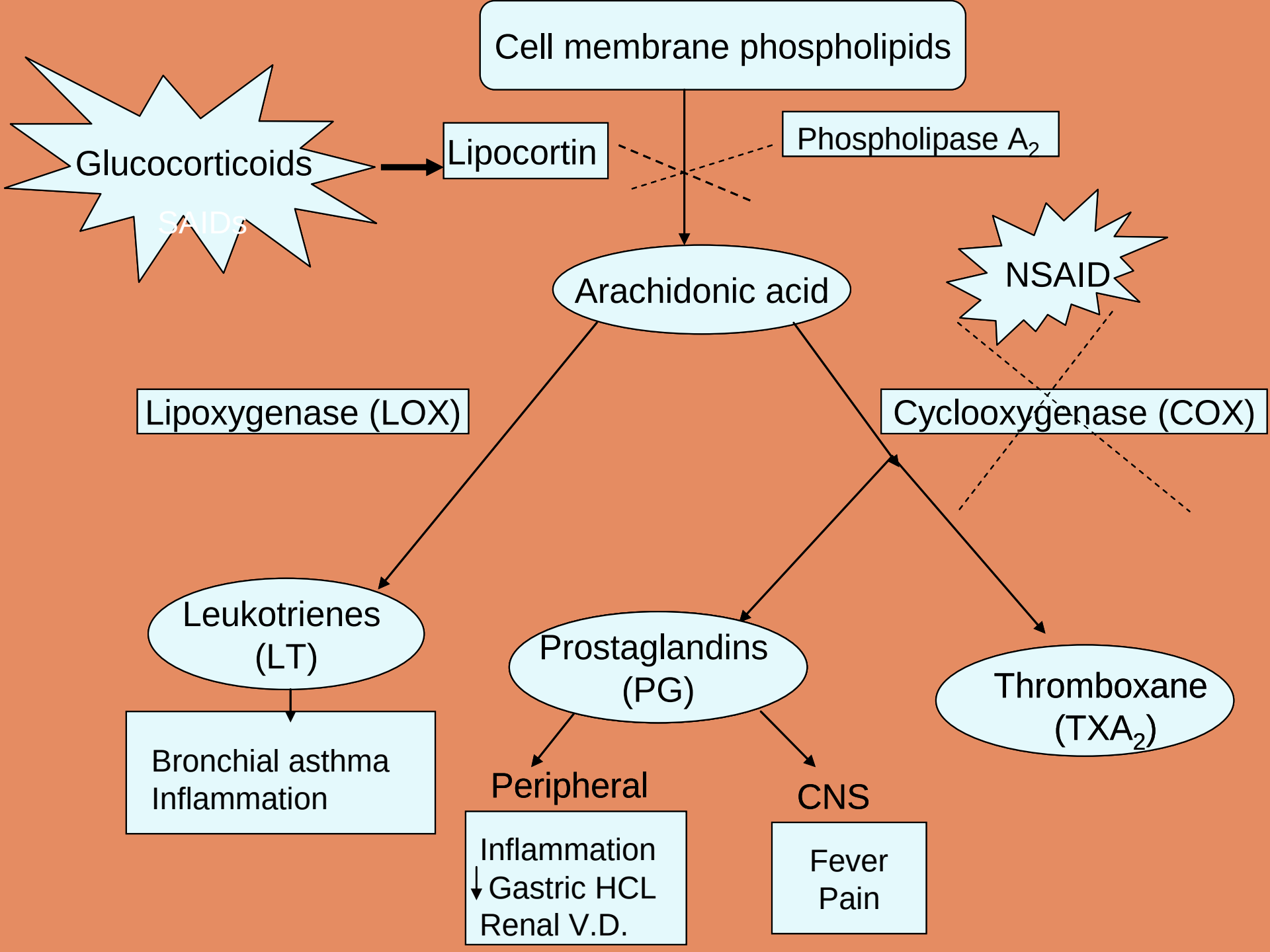
3 .Anti-inflammatory

Mechanisms of action of NSAIDs:



NSAIDs act by inhibition of PGs synthesis


COX
Arachidonic acid
(PGs), (PGI_2) (TXA2)
NSAIDs


Cell membrane phospholipids
Glucocorticoids
SAIDs
Lipocortin
Phospholipase A_2
Arachidonic acid
NSAID
Lipoxygenase (LOX)
Cyclooxygenase (COX)
Leukotrienes (LT)
Prostaglandins (PG)
Thromboxane (TXA_2)
Bronchial asthma
Inflammation
Peripheral
CNS
Inflammation
↓ Gastric HCL
Renal V.D.
Fever
Pain

Types of cyclo-oxygynase enzymes (COX)

1. COX-1: It is expressed constitutively in most cells, including: Platelets
GIT
Kidney
} (physiological) Cytoprotective

2. COX-2: It is inducible by:
Inflammation
Cancer
} (Pathological)

3. COX-3: : It is found in CNS It inhibited by **paracetamol.**

Classification of NSAIDs

A. Non selective COX inhibitors (Classical NSAIDs)

Most of NSAIDs are non-selective COX inhibitors (i.e. inhibit both COX-1 and COX-2).

B. Selective COX-2 inhibitors (Newer NSAIDs)

- This group of drugs were selective COX-2 inhibitors (i.e. inhibit COX-2 ***without*** affecting action of the COX-1)

A. Non selective COX inhibitors (Classical NSAIDs)

1. **Salicylates:**

Acetyl salicylic acid (Aspirin)

2. Para-aminophenol:

Paracetamol (acetaminophen)

Phenacetin , metamizole*(4 methylaminoantipyrine) 4 dimethylaminoantipyrine

3. Acetic acid derivatives:

a. Indole acetic acid: Indomethacin,

b. Phenylacetic acid: Diclofenac

4. Pyrazolone derivatives:

Phenyl-butazone, Oxyphen-butazone

5. Propionic acid derivative:

Ibuprofen, Ketoprofen, Naproxen

6. Fenamic acids:

Mefenamic acid, Meclofenamic acid

7. Oxicams:

Piroxicam, Tenoxicam

2. Selective COX-2 inhibitors)Newer NSAIDs.(

- Celecoxib
- Meloxicam
- Rofecoxib
- Valdecoxib

A. Non selective COX inhibitors (Classical NSAIDs)

1. **Salicylates:**

Example:

Aspirin, or acetylsalicylic acid (ASA) is the prototype of NSAIDs

Acetyl salicylic acid (Aspirin) (prototype)

- Aspirin, or acetyl salicylic acid is a salicylate drug .
- Hydrolyzed in moist air to salicylic acid & acetic acid.
- It is OTC (over the counter) drug, cheap and effective drug.
- Used as an

Analgesic to relieve minor aches and pains, as an **A**ntipyretic to reduce fever and as an **A**nti-inflammatory medication.

Mechanism of action

- It is inhibit the synthesis of PGs,TXs and PGI2
- Aspirin ⟶ **irreversible** inhibition of both COX-1 and COX-2 both in CNS and periphery.
- This makes aspirin different from other NSAIDs (such as diclofenac and ibuprofen...), which are **reversible**.srotibihni

- It is useful analgesic for pain associated with skeletal muscle, toothache, headach and arithrits.

- It is not effective for visceral pain (e.g renal and myocardial infraction)

.3Antinflammatory & antirheumatic action

a. Aspirin → COX-2 induced by inflammation → ↓ PGs synthesis → action of → inflammatory mediator such as bradykinin, histamine and cytokines → Anti-inflammatory

b. Aspirin also inhibit the migration of polymorphs and macrophages to the site of inflammation (inhibit the release of lymphokines from T cell)

c. Stabilization of lysosomal membrane (inhibit the release of proteolytic enzymes)

- The aspirin’s antiplatelet effect lasts 8-10 days (the life of the platelet), this causes prolongation of bleeding time .

Aspirin used as prophylaxis against thromboembolic disease.

To prevent bleeding complication aspirin should be withheld for tow weeks befor surgery.

.Hepatic and renal effects

- Large dose of aspirin → hepatotoxicity and nephropathy

- PG → Renal vasodilator (RV) → Regulate blood flow

- Aspirin → PG → Renal vasoconstraction → Renal blood flow → salt and water retention → acute reduction of renal function

Reye's syndrome

- Aspirin in some children with viral infection causes encephalopathy and hepatotoxicity.

Effect on Respiration

- Aspirin ⟶ bronchial asthma
- Production of leukotriens (LT) which responsible for bronchial asthma
- So aspirin contraindicated in asthmatic patients.

Pharmacokinetics

- Rapidly absorbed orally.
- A peak plasma salicylate level within 1-2 hours.
- Bound to plasma protein) 50-80.(%
- Crosses the BBB and placental barrier.

Metabolism:revil yB

- mostly conjugation with glucuronic acid and glycin (inactive metabolite)

- Little by oxidation (active metabolite)

- **Excretion:** degnahcnu yltrap eniru yB detagujnoc yltrap ,(dica cilycilas eerf)

Side effects

1. **GIT:**

- Epigastric distress, nausea, vomiting, microscopic GI bleeding (occult blood in stools).

-This effect can be reduced by taking drug with food and a large volum of fluid .

-

2 **.Blood :**

-Prolongation of bleeding time .

-It should not be taken for at least one week prior surgery.

-Doses of anticoagulants should be reduced when taken with salicylates.

3 .Hypersensitivity :

-Urticaria, bronchoconstriction

-LOX inhibitor (Zileuton) useful in treatment of aspirin-induced bronchial asthma.

4 .Reye's syndrome :

-Aspirin in some children with viral infection causes encephalopathy and hepatotoxicity, so it is best avoided in children.

Toxicity of aspirin

1. **Acute aspirin toxicity (15-30 gm)**
   - Fever
   - Dehydration (sever electrolytes imbalance)
   - Hypoprothrombinemia
   - Tremors, convulsions, hallucination and coma.

Death from aspirin over dose is caused by respiratory and renal failure.

Contraindication

1. Allergy to salicylates
2. Bleeding tendency
3. Peptic ulcer
4. Bronchial asthma
5. Virus infection in children because of the risk of Reye’s syndrome.
6. Small doses in patient with gout.

Drug interactions of salicylates

1. Displace drugs from plasma proteins e.g. oral anticoagulants and oral hypoglycemics

2. Antagonize the action of other uricosuric agents (e.g. probenecid)

3. Ammonium chloride enhances toxicity (because it acidifies the urine and decrease the renal excretion of salicylates)

4. NSAID, corticosteroids and alcohol increase ulcerogenic effect of salicylates

5. Phenobarbitone increase the metabolism of salicylates

2. Diflunisal (diflurophenyl derivative of salicylic acid)

- It is more potent than aspirin as anti-inflammatory drug.
- It is has no antipyretic effects (poor penetration into CNS)
- It is 3-4 times more potent than aspirin in treatment of osteoarthritis.
- It doesn’t produce tinnitus and cause fewer and less intense GIT and antiplatelates effects compared with aspirin.

II. Para-aminophenol derivatives:

1. **Paracetamol = acetaminophen**

   Used as analgesic and antipyretic medication It has no significant anti-inflammatory effects

   It is well tolerated, lacks many of the side-effects of aspirin.

   Available over-the-counter (without prescription)

Mechanism of action

- It inhibits central but not peripheral COX.
- It inhibit COX-3 enzyme in CNS with weak peripheral effect.
- It has analgesic and antipyretic effects but no significant anti-inflammatory action.

Pharmacological action:

1. Analgesic, antipyretic effect similar to aspirin (central action)

2. It has no significant anti-inflammatory action (no peripheral action)

3. It has no effect on platelet aggregation

4. No gastric irritation so it can be used by patients with peptic ulcer

5. No bronchospasm and no effect on uric acid levels so it is safe to use by asthmatic patients and gout.

Pharmacokinetics

- Absorption: orally and it is related to gastric emptying, slightly bound to plasma proteins

- Metabolism :
- → %95Conjugation with glucuronic acid & sulfate **Inactive metabolite** →

- → %5Cytochrom P450(→ **(NABQ)**

N-acetyl-p-benzo-quinone (Toxic metabolite) →
Conjugation with Glutathion-SH → Non toxic

Toxic metabolite (NABQ) is normally detoxificated by glutathione

Large doses of paracetamol

↓

Depletion of glutathione-SH

↓

Accumulation of N-acetyl-p-benzo-quinone

↓

Hepatotoxicity and nephrotoxicity

Therapeutic uses

1. Analgesic, antipyretic in patients allergic or intolerant to aspirin.

2. Safe in pregnancy
3. Does not affect the closure of the fetal ductus arteriosus as NSAIDs.

4. Safe in children, it is not associated with a risk of Reye's syndrome in children with viral illnesses .

.5Safe to be used by patient with hemophilia or history of peptic ulcer, bronchial asthma and gout.

.6 It doesn’t antagonize the effect of uricosuric agents.

Adverse effects and toxicity (toxic dose 10g in adult and 4g in children)

- In therapeutic doses are usually well tolerated.
- Skin rash and other allergic reactions occur occasionally.
- Excessive use of paracetamol cause fatal Hepatotoxicity and nephrotoxicity .
- Toxicity from paracetamol is not from the drug itself but from its metabolites N-acetyl-p-benzo-quinone (NABQ)

Treatment of acute toxicity

- Antidote **N-acetylcysteine** (neutralize the toxic metabolites).
- The antidote N-acetylcysteine (rich in SH) acts as glutathione substitute, binding the toxic metabolite as it is being produced
- A liver transplant may be required for patients with hepatic failure.

2. Phenacetin

- It is not used now.
- It is nephrotoxic

Phenacetin (active) prodrug → metabolized → Acetaminophen (Active metabolite)

↓

more toxic than its active metabolite

III- Acetic acid derivatives:

1. Indole acetic acid:

a. Indomethacin

- Is a potent non-selective COX inhibitor it inhibits both central and peripheral COX.

- It is a powerful anti-inflammatory agent.

- Must not be used as an analgesic or antipyretic (side effects).

Pharmacokinetics

- Rapidly and almost completely absorbed from GIT after oral ingestion.
- Metabolized in liver, highly bound to plasma proteins (90%).
- Concentrated in synovial fluid.
- Excreted in urine, bile and feces (unchanged and as metabolite), so undergoes enterohepatic circulation

Adverse effects

1. GIT side effects (anorexia, nausea, diarrhea and abdominal pain).

2. CNS disturbance include, severe frontal headache, dizziness, vertigo, mental confusion, severe depression, psychosis and hallucinations.

3. Corneal opacity and blurred vision.

Therapeutic Uses

1. A potent anti-inflammatory drug used in treatment of rheumatoid arthritis.

2. Very effective in treatment of acute gout.

3. To close patent ductus arteriosus in neonates.

4. Tocolytic agent to suppress uterine contraction in women with preterm labor.

Contraindications

Indomethacin should not be used in Pregnant women

Psychiatric disorders

Epilepsy

Parkinsonism.

Renal disease

Ulcerative lesions of the stomach or intestines

b. Sulindac

It is similar to indomethacin but less potent, less toxic and longer duration of action.

Sulindac (prodrug) → sulindac sulfide (active metabolite)

↓

- long duration of action (t 1/2 = 18 hrs) (enterohepatic cycle)
- less gastric irritation

It allowed in patients with mild renal insufficiency.

Therapeutic Uses

- Rheumatoid arthritis
- Osteoarthritis
- Acute gout

b. Phenylacetic acid

Diclofenac

- It is non-selective COX inhibitor, it inhibit both central and peripheral COX-1 and COX-2.

- It has analgesic, antipyretic and anti-inflammatory activities. It is more potent than indomethacin.

Pharmacokinetics

- Diclofenac is rapidly and completely absorbed after oral administration and it is highly bound to plasma proteins (99%).

- Diclofenac accumulates in synovial fluid after oral administration..

- Diclofenac is metabolized in liver to hydroxydiclofenac; the metabolites are excreted in the urine (65%) and bile (35%).

Adverse effects

1. Gastrointestinal distress, occult gastrointestinal bleeding, gastric ulceration.

2. Diclofenac at dosage of 150 mg/day appears to impair RBF & GFR

3. Skin rashes and allergic reaction.

4. Fluid retention and edema.

Therapeutic Uses

1. Use in treatment of rheumatoid arthritis, osteoarthritis

2. Postoperative pain e.g. Prevention of postoperative ophthalmic inflammation

3. Dysmenorrhea

IV. Pyrazolone derivatives:

1. Phenyl-butazone

Pharmacological action

1. It is a potent anti-inflammatory drug used in treatment of rheumatoid arthritis.
2. Because of its toxicity phenyl-butazone should not be used routinely as an analgesic or antipyretic.
3. It has a mild uricosuric effect and it is useful for the treatment of chronic gout.
4. Phenylbutazone cause significant retention of sodium and chloride which may lead to edema.

Pharmacokinetics

- Phenyl-butazone is rapidly and completely absorbed from the GIT or the rectum.
- It is highly bound to plasma proteins (98%).
- Phenyl-butazone metabolised in liver and change to oxyphenbutazone

Therapeutic Uses

- At the present time phenyl-butazone because of its toxic effect it is not considered to be the drug of choice for any condition.

Adverse effects

- Bone marrow depression (agranulocytosis)
- Liver and renal toxicity
- GIT effects such as nausea, vomiting, epigastric discomfort, diarrhea, and edema.
- Hypertension and skin rash.

Drug interaction

Displaces other drugs from plasma proteins:

- Oral anticoagulants
- Oral hypoglycaemics
- Sulfonamides
- Thyroxin

2. Apazone

- It is very similar to the phenyl-butazone but it is much less toxic.
- It is anti-inflammatory, analgesic and antipyretic.
- It is used for treatment of rheumatoid arthritis, osteoarthritis.
- It is also a potent uricosuric agent so it is useful for treatment of acute gout.

V. Propionic acid derivative:

Ibuprofen

- It has analgesic, antipyretic and inflammatory action

- It inhibit both COX-1 and COX-2 both central and peripheral

Pharmacokinetics

- Ibuprofen is rapidly absorbed after oral administration and is extensively (99%) bound to plasma proteins.

- Ibuprofen metabolized in liver, and more than 90% of an ingested dose is excreted in urine as metabolites.

Therapeutic Uses

- Rheumatoid arthritis
- Osteoarthritis
- Dysmenorrhea
- Postsurgical dental pain.
- Closing patent ductus arteriosus in preterm infants

Adverse effects

- Gastrointestinal side effects (epigastric pain, nausea, heartburn).
- The incidence of these side effects is less with ibuprofen than aspirin or indomethacin.
- Rash, tinnitus, dizziness, headache, blurred vision and fluid retention.

2. Naproxen

- It is approximately 20 times more potent than aspirin.
- It half life =14 hrs.
- It is effective in treatment of acute attack of gout.

VI. Fenamic acids:

- Mefenamic acid, Meclofenamic
- They inhibit both COX-1 and COX-2 both central and peripheral.
- They have analgesic, antipyretic and anti-inflammatory activity
- They are used for treatment of dysmonorrhea, rheumatoid arthritis and osteoarthritis .

VII. Oxicams:

Piroxicam

- Piroxicam is an effective analgesic, antipyretic and anti-inflammatory.
- It is used for treatment of rheumatoid arthritis, osteoarthritis and postoperative pain.
- Long half life, which permits the administration of a single daily dose.
- Main side effects: It can cause gastric erosions and it prolongs bleeding time.

2. Selective COX-2 inhibitors (New NSAIDs)

- They have analgesic, antipyretic and anti-inflammatory effects similar to those non-selective COX inhibitors but fewer GIT side effects and with out affecting platelets.

Mechanism of action

They inhibit PG synthesis by COX-2 enzymes induced at site of inflammation without affecting the action of COX-1 enzymes

- Recently COX-2 enzyme found to be constitutive in many tissues:
  - Brain
  - Kidney
  - Vascular endothelium.

Thus COX-2 inhibition is associated with both beneficial and adverse effects .

Beneficial effects:

- They have anti-inflammatory with less risk of gastric ulceration.
- They decrease progression of Alzhiemer disease.
- They decrease the risk of colorectal cancer.
- They have no effect on bleeding time.

Adverse effects:

- Nephrotoxicity.
- Increase risk of stroke and myocardium infraction (COX-2 is responsible for PGI2 synthesis).

- **1. Celecoxib**
- It is a selective COX-2 inhibitor and it is effective as other NSAIDs in the treatment of rheumatoid arthritis and osteoarthritis with fewer gastrointestinal side effects.

- It does not affect platelet aggregation at usual doses. Other adverse effects are similar to those of other NSAIDs.

2. Etoricoxib

It is a second generation COX-2 selective inhibitor (highly selective).

It is used for treatment of the sign and symptoms of osteoarthritis, rheumatoid arthritis, acute gouty arthritis and for relief of acute musculoskeletal pain.

3. Meloxicam

- It is related to piroxicam
- It is used in treatment of rheumatoid arthritis and osteoarthritis.
- It associated with fewer clinical GIT symptoms and complications than piroxicam, diclofenac.

4. Valdecoxib

- It is a new highly selective COX-2 inhibitor.
- It is used in the treatment of osteoarthritis rheumatoid arthritis and painful menstruation.
- It was approved to use by US in 2001 and it was withdrawn from the market in the USA in 2005
- It is Possible increases risk of heart attack and stroke and Stevens Johnson syndrome.

.5Rofecoxib

- It is a NSAID use for treatment of osteoarthritis, acute pain conditions, and dysmenorrhoea.
- It was approved to use by US in 1999 and it was withdrawn from the market in the USA in 2004
- It increases risk of heart attack and stroke associated with long-term, high-dosage use .

Thank you