Non steroidal Anti-inflammatory drugs

Prepared by

MRIDHULMOHAN

- Non steroidal anti-inflammatory drugs are aspirin type or non-narcotic or non-opioid analgesics. In addition, they have anti-inflammatory, anti-pyretic and uricosuric properties with out addiction liability.
- They act primarily on peripheral pain mechanism, but also in the CNS to raise pain threshold.

Classification

- **A. Non-selective COX inhibitors**
- **1**. salicylates- Aspirin
- **2**. propionic acid derivatives
- Ibuprofen, naproxen, ketoprofen, flurbiprofen
- **3**. Fenamate- Mephenamic acid
- **4.** Enolic acid derivatives
- Ketorolac, Indomethacin, Nabumetrone

- **5**. Pyrazolone derivatives.
- Phenyl butazone
- Oxyphen butazone
- **B. Preferential COX-2 Inhibitors**
- Nimesulide
- Diclofenac
- Aceclofenac
- Meloxicam
- Etodolac

- **C . Selective COX-2 inhinitors**
- Celecoxib
- Etoricoxib
- Parecoxib
- **D. Analgesic- Antipyretics with poor Anti-inflammatory action.**
- 1. Paraaminophenol derivative
- Paracetamol(Acetaminophen)
- 2. Pyrazolone derivatives- Metamizol, propiphenazone
- 3. Benzoxazocine derivatives- Nefopam

MOA

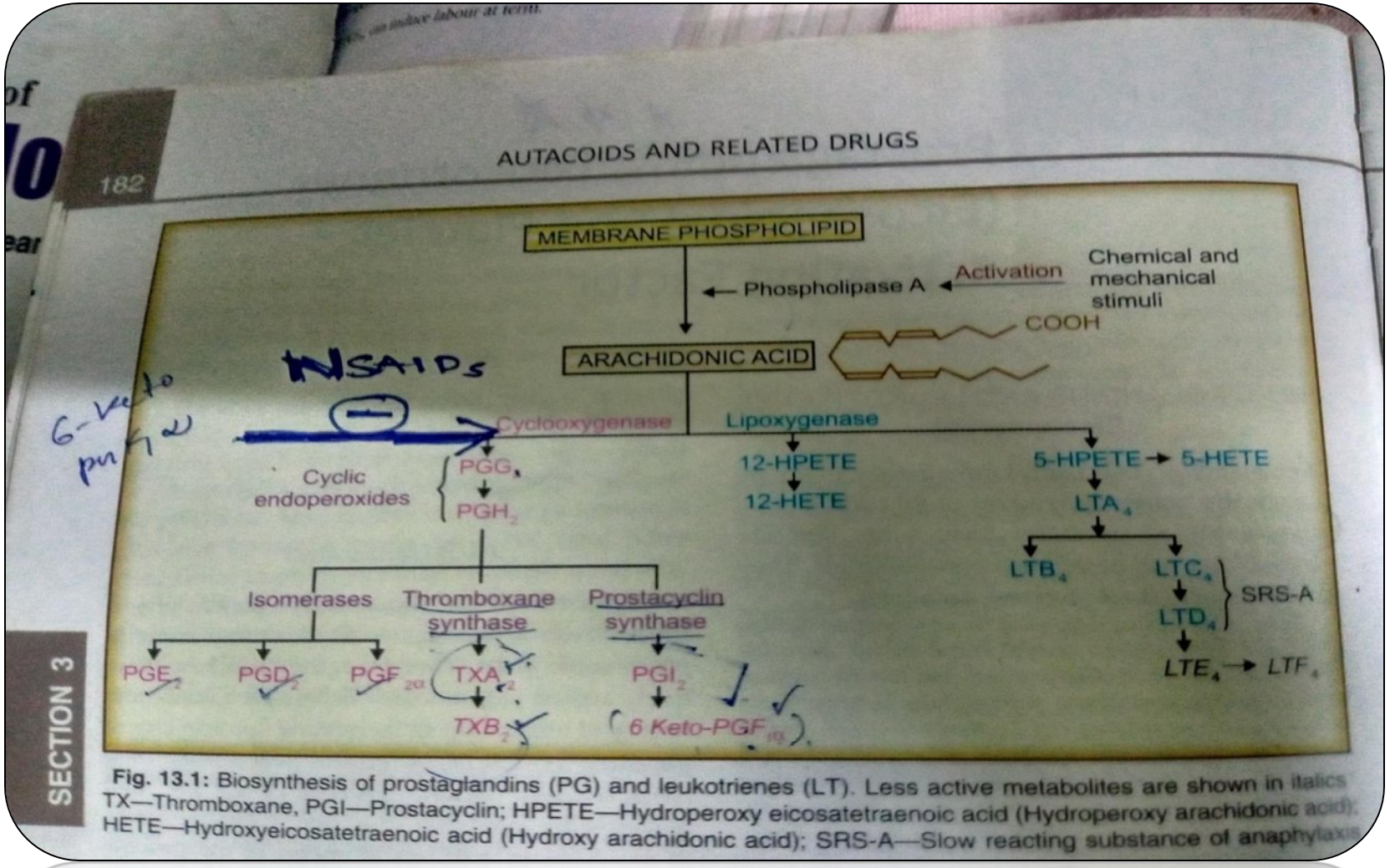


Fig. 13.1: Biosynthesis of prostaglandins (PG) and leukotrienes (LT). Less active metabolites are shown in italics
TX—Thromboxane, PGI—Prostacyclin; HPETE—Hydroperoxy eicosatetraenoic acid (Hydroperoxy arachidonic acid);
HETE—Hydroxyeicosatetraenoic acid (Hydroxy arachidonic acid); SRS-A—Slow reacting substance of anaphylaxis

- During inflammation arachidonic acid liberated from membrane phospholipids is converted to prostaglandins(PGs) catalysed by the enzyme cyclo oxygenase(COX).
- These prostaglandins produce hyper analgesia. They sensitize the nerve endings to pain caused by other mediators of inflammation like bradykinin and histamine.
- NSAIDs inhibit the PG synthesis by inhibiting the enzyme cyclo-oxygenase and is the major mechanisim responsible for pharmacological effects of aspirin.

- Aspirin is an irreversible inhibitor of COX while the others are reversible competitive COX inhibitors.
- There are two forms of cyclo-oxygenase, COX1 and COX2
- COX1 is found in most of the normal cells and is involved in maintaining tissue homeostasis.
- Cox2 is induced in the inflammatory cells by cytokinines and other mediators of inflammation.
- COX2 catalyzes the synthesis of prostanoids which are the mediators of inflammation.
- Most NSAIDs inhibits both COX1 and COX2 while some newer agents like celecoxib and rofecoxib selectively inhibit only COX2.

Salicylates (Aspirin)

- Aspirin is Acetylsalicylic acid.
- It is rapidly converted in the body to salicylic acid which is responsible for most of the actions.

Pharmacological actions

- 1. **Analgesic effect**
- Aspirin is good analgesic and relieves pain of inflammatory origin. This is because PGs are formed during inflammation and they sensitize the tissue to pain and aspirin inhibits PG synthesis.
- Pain originating from the integumental structures like muscles, bones, joints and pain in connective tissues is relieved. But is relatively ineffective in severe visceral and ischaemic pain.

- These drugs relieve pain with out causing sedation, respiratory depression, tolerance and dependance.
- They are less efficacious than morphine.
- Aspirin produces analgesia at doses of 2-3g/day.

- **2. Antipyretic action**
- The thermoregulatory centre is situated in the hypothalamus.
- Fever occurs when there is a disturbance in hypothalamic thermostat.
- In fever, pyrogen, a protein, circulates in the body and this increase the synthesis of PGs in the hypothalamus, there by raising its temperature set point.

- NSAIDs reset the hypothalamic thermostat and reduce the elevated body temperature during fever.
- They promote heat loss by causing cutaneous vasodilation and sweating.
- They do not affect normal body temperature.
- The antipyretic effect is mainly due to inhibition of PGs in the hypothalamus.
- The dose of aspirin for antipyretic effect is 2-3g/day.

- **3. Anti-inflammatory effect**
- Anti-inflammatory effect is seen at high doses.
- Aspirin- 3-6g/day in divided doses
- These drugs produce only symptomatic relief.
- They suppress sign and symptoms of inflammation such as pain, tenderness, swelling, vasodilation and leukocyte infiltration. But they do not affect the progression of underlying disease.

- The anti-inflammatory action of NSAIDs is mainly due to inhibition of PG synthesis at the site of injury.
- They also affect other mediators of inflammation(bradykinin, histamine, serotonin etc.), thus inhibit granulocyte adherence to the damaged vasculature.

- **4. Metabolic effect**
- Salicylates enhance the cellular metabolism due to uncoupling of oxidative phosphorylation.
- More of oxygen is used and more CO2 is produced, especially in skeletal muscles, leading to increased heat production.
- In toxic doses, hyperpyrexia, increased protein catabolism with resultant aminoaciduria and negative nitrogen balance are seen

- Enhanced utilization of glucose leads to mild hypoglycaemia. But in toxic doses, hyperglycaemia occurs due to central sympathetic stimulation which increases adrenaline levels.

- **5. Respiration**
- In therapeutic doses 4-6g/day salicylates increase consumption of oxygen by skeletal muscles.
- As result, there is increased CO2 production. This increased CO2 stimulates the respiratory centre.
- Salicylates also directly stimulate the medullary respiratory centre, both these actions increases the rate and depth of respiration. These effect are dose dependent.

- In toxic doses, the respiratory centre is depressed leading to respiratory failure.

- **6. Acid- base and electrolyte balance**
- In anti-inflammatory doses, salicylates produce significant respiratory stimulation, more CO2 is washed out resulting in respiratory alkalosis; pH become alkaline.
- This is compensated by increased excretion of HCO3- in the urine accompanied by Na+, K+ and water. pH then return to normal. This stage is known as **compensated respiratory alkalosis**.

- With toxic doses, salicylates depress the respiratory centre directly. As a result, CO2 accumulates because more CO2 is produced than exhaled. Thus plasma CO2 rises and pH decreases.
- Since the concentration of HCO3- is already low due to enhanced renal excretion, the change results in uncompensated respiratory acidosis.

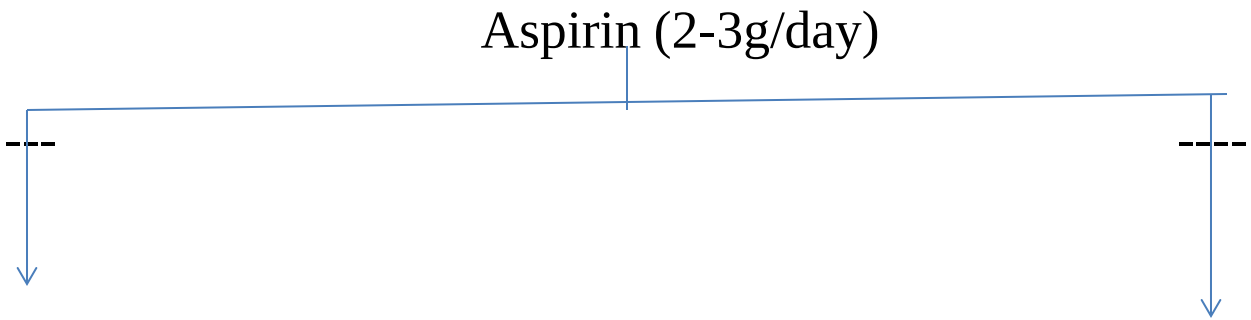
- **7. CVS**
- Aspirin has no direct effect on heart or blood vessels in therapeutic doses.
- Larger doses increase cardiac output.
- Toxic dose depress vasomotor centre, BP may fall because of increased cardiac work as well as sodium and water retention.
- They may precipitate CHF in patient with low cardiac reserve.

- **8. GIT**
- Aspirin is a gastric irritant
- Irritation of the gastric mucosa leads to epigastric distress, nausea, vomiting and dyspepsia.
- Aspirin also stimulate the CTZ to produce vomiting.

- Aspirin → inhibits PGs in gastric mucosa → increase in HCl production → gastric irritation and peptic ulcer.
- Aspirin → acidic pH of stomach → exists in unionized form → enters the mucosal cell → pH 7.1 → ionized and become indiffusible → Acute ulcers, erosive gastritis and Haemorrhage

- **9. Immunological effects**
- In higher doses, salicylates suppress several antigen- antibody reactions including inhibition of antibody production.
- **10. Urate excretion**
- Dose related effect is seen.
- Aspirin, in therapeutic doses, inhibit urate secretion in to the renal tubule and increase the plasma urate levels.
- In high doses, salicylates inhibit the reabsorption of uric acid in the renal tubules and produce uricosuric effect.

- **11. Blood**
- Aspirin in low doses(50-325mg/day) irreversibly inhibits platelet TXA2 synthesis and produce Anti-platelet effect, which last for 8-10 days.
- Aspirin in high doses(2-3mg/kg) inhibits both PGI2 and TXA2 synthesis. Hence anti-platelet effect is lost.



PGI2(it cause vasodilatation and inhibits platelet aggregation)

TXA2(TXA2 cause vasoconstriction and promotes platelet aggregation)

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low dose aspirin(50-325mg)

- **12. local effect**
- Salicylic acid when applied locally is a keratolytic.
- It also has mild antiseptic and fungistatic properties.
- Salicylic acid is also an irritant for the broken skin.

Pharmacokinetics

- Salicylates being acidic are rapidly absorbed from the stomach and the upper small intestine.
- When administered as micro fine particles, absorption increases.
- They are highly bound to plasma proteins.
- Aspirin is de-acetylated in the liver, plasma and other tissues to release salicylic acid which is the active form.
- Plasma t1/2 of aspirin is 3-5hrs.
- Salicylates are excreted in the urine.

Dosage regimen for aspirin

- **1. Analgesic dose**
- 2-3g/day in divided doses
- **2. Anti-inflammatory dose**
- 4-6g/day in divided dose
- **Antiplatelet dose**
- 50-325mg/day(low dose aspirin)

ADR

- **GI tract-** nausea, epigastric distress, vomiting, erosive gastritis, peptic ulcer
- Nephrotoxicity- almost all NSAIDS can cause nephrotoxicity after long term use.
- Salt and retention with hypertension, and impaired renal function with acute interstitial nephritis, acute papillary necrosis.
- **CNS-** headache, dizziness, confusion

- **Allergic reactions**
- Rashes
- Urticaria
- Pruritus
- Photosensitivity
- Angioedema
- Bronchospasm

- **Haemolysis-** salicylates can cause haemolysis in patient with G6PD deficiency.
- NSAIDS can also rarely cause thrombocytopenia and neutropenia.
- Hepatotoxicity with hepatic necrosis and cholestatic jaundice can also occur when high dose of NSAIDS are used over a long period.

- **Salicylism**
- Higher doses given for a long time as in treatment of rheumatoid arthritis may cause chronic salicylate intoxication termed salicylism.
- The syndrome characterised by
- Headache, vertigo, dizziness, vomiting, mental confusion, diarrhoea, sweating, difficulty in hearing, thirst and dehydration.

- **Reyes syndrome**
- This syndrome seen in children is a form of hepatic encephalopathy which may be fatal.
- It develops a few days after a viral infections especially influenza and varicella.
- An increased incidence of this syndrome has been noted when aspirin is used to treat fever.
- Hence aspirin and other salicylates are contraindicated in children and young subjects < 20 year old with viral fever.
- Paracetamol may be used to trat fever in such chilldren.

Aspirin poisoning(salicylate poisoning)

- Poisoning may be accidental or suicidal.
- It is more common in children.
- 15-30g is the fatal dose of aspirin.
- **Clinical symptoms**
- Dehydration
- Hyper-pyrexia
- GI irritation
- Vomiting

- Haematemesis
- Acid base imbalance
- Restlessness
- Delirium
- Hallucination
- Metabolic acidosis
- Tremors
- Convulsions
- Coma
- Death due to respiratory failure and cardiovascular collapse.

- **Treatment**

- There is no specific Antidote for salicylate poisoning
- Treatment is symptomatic
- Gastric lavage to eliminate unabsorbed drug or by administration of activated charcol(adsorb toxic material)
- IV fluids to correct acid base imbalance and dehydration.
- Temperature is brought down by external cooling with alcohol or cold water sponges

- If haemorrhagic complications are seen blood transfusion and vitamin K are needed.
- The IV fluid should contains Na+, K+,HCO3- and glucose(to treat hypokalaemia and acidosis)
- Blood pH should be monitored
- In severe cases, forced alkaline diuresis with sodium bicarbonate and a diuretics like frusemide is given along with IV fluids.
- Sodium bicarbonate ionizes salicylates making them water soluble and enhances their excretion through kidneys.

CONTRAINDICATIONS

- Peptic ulcer
- Liver diseases
- Viral fever in children
- Pregnancy
- Breast feeding mothers
- Diabetics
- Bronchial asthma

DRUG INTERACTIONS

- NSAIDS and glucocorticoids – potentiation of GI complications- nausea, vomiting , dyspepsia, epigastric pain, ulceration and GI bleeding.
- NSAIDS potentiate the effect of oral anticoagulants,oral hypoglycaemics, and methotrexate by displacing them from plasma protein binding sites.
- Aspirin displaces warfarin, naproxen, sulfonyl ureas,phenytoin, and methotrexate from binding sites on plasma proteins- toxicity of these drugs may occur.
- Some NSAIDS (piroxicam) can impair the clearance of lithium leading to its toxicity.

THERAPEUTIC USES

- As analgesic – in painful conditions like headache, toothache, backache, bodyache , muscle pain, joint pain, neuralgias and dysmenorrhoae.
- As antipyretic- To reduce elevated body temperature in fever, paracetamol is preferred.
- Acute rheumatic fever –Aspirin is the preferred drug, it reduce fever, relieves swelling and joint pain.

  Dose 4-6 g/day in 4-6 divided dose. The dose is reduced after 4-7 days and maintenance dose of 50 mg/kg/day are given for 2-3 weeks.

- Rheumatoid arthritis

NSAIDS have anti inflammatory effects and can produce only symptomatic relief but they do not alter the progression of disease.

Aspirin – 3-5 g / day

Aspirin relieves pain swelling and redness of joints.

- Osteoarthritis – in mild cases, paracetamol is used.
- Post myocardial infarction and post stroke (Thromboembolic disorders)

Aspirin inhibits platelet aggregation,and this may lower the incidence of reinfarction in a low dose of 60- 100 mg /day.

PARA AMINO PHENOL DERIVATIVES (Acetaminophen, Paracetamol)

- Phenacetin was the first drug used in this group but, due to severe adverse effects,it was withdrawn.
- Paracetamol is the de- ethylated active metabolite of phenacetin.

PHARMACOKINETICS

- Paracetamol is effective in oral, parenteral routes. It is well absorbed, widely distributed all over the body.
- Metabolised in the liver by sulphate and glucuronide conjugation.
- The metabolites are excreted in urine.

Pharmacological actions

- Paracetamol has analgesic, good antipyretic and weak anti inflammatory properties.
- The inflammatory sites are rich in peroxides which are generated by the leukocytes.
- In the presence of peroxides, paracetamol is a weak inhibitors of COX and thereby PG synthesis.Hence paracetamol has poor anti inflammatory actions.
- Paracetamol is active on cyclooxygenase in the brain which account for its antipyretic action.

- It does not stimulate
- It has no actions on acid base balance, cellular metabolism, cardiovascular system and platelet function.
- It does not produce gastric irritation.

ADR

Side effects are rare.

- Ocassionally causes skin rashes and nausea.
- Hepatotoxicity (chronic use)
- Nephrotoxicity is commonly seen on chronic use.

THERAPEUTIC USES

- As antipyretic
- As analgesics - To relieve headache, toothache, myalgia, dysmenorrhoea

  Dose -250-650 mg/kg(adults)

  10-15 mg/kg (children)

PARACETAMOL POISONING

- In antipyretic dose, paracetamol is safe and well tolerated.
- When large doses are taken acute paracetamol poisoning results
- Acute overdosage of paracetamol mainly causes hepatotoxicity.
- Children are more susceptible because their ability to conjugate by glucuronidation is poor.
- 10-15 g in adults causes serious toxicity.

Clinical symptoms

- Nausea, vomiting, diarrhoea, anorexia, abdominal pain, hypoglycemia, hypotension, hypoprothrombinaemia, coma, death is usually due to hepatic necrosis.
- Paracetamol is hepatotoxic and can cause severe hepatic damage.
- Symptoms are seen within 2-4 days and include increased serum transminase, jaundice, liver tenderness, prolonged prothrombin time.

Mechanism of Toxicity

- A small portion of paracetamol is metabolised to a highly reactive intermediate N-acetyl-p-benzoquinone-imine (NAPQI) which is detoxified generally by conjugation with glutathion.
- However, when large doses of paracetamol are taken,hepatic glutathion is depleted and the toxic metabolite binds to sulphydryl groups in hepatic proteins resulting in hepatic necrosis.

Treatment

- If the patient is brought early, vomiting should be induced or gastric lavage done.
- Activated charcoal is given orally to prevent further absorption.
- Other supportive measures as needed should be taken.
- Specific antidote- **N- acetyl cysteine-** 150 mg/kg should be infused IV over 15 m followed by the same dose IV over the next 20 hrs.

- Alternatively 75 mg/kg may be given orally every 4-6 hrs for 2-3 days.
- N-acetyl cysteine partly replenishes the glutathion stores of the liver and prevents binding of the toxic metabolites to the cellular constituents.

DRUG	DOSE
Ibuprofen	400- 600 mg TDS
Diclofenac	50 mg BD
	100 MG OD
Indomethacin	50 mg TDS
Piroxicam	20 mg OD
Ketorolac	10-20 mg QID
Mefenamic acid	250-500 mg TDS
Naproxen	500 mg BD
Celecoxib	100-200 mg OD or BD
Etoricoxib	60, 90,120 mg tab.