NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

PHARMACOLOGY

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NSAIDs

- NSAIDs
- Analgesic
- Antipyretic
- Anti-inflammatory actions
- Compared to Morphine:
- Weaker analgesics
- Do not depress CNS Do not produce physical dependence
- No abuse liability.

Salicylates - Aspirin

- Salicylates - Aspirin
- • Prototype
- • Acetylsalicylic acid
- • It was obtained from „willow bark“ (Salicaceae) but is now synthesized
- • Methyl salicylate is a volatile liqiud derivate.
- • Irreversible inhibitor of COX
- • Nonselective inhibitor of COX (Counter irritant)

Aspirin – Pharmacological actions

1. Antiinflammatory action:

- Potent
- Exerted at high doses (3-6g/day or 100mg/kg/day)
- Signs of inflammation are suppressed.
- Acts mainly by inhibiting PG synthesis.

2. Analgesic action:

- Mild analgesic effect ≤ codeine
- Effective in non visceral pain
- Inhibition of peripheral PG synthesis

Aspirin – Pharmacological actions

- **3. Antipyretic action:**
- • Reduces body temperature in fever
- Resets the hypothalamic thermostat
- Rapidly reduces fever by heat loss
- But does not decrease heat production
- **4. Metabolic effects:**
- • These are significant at only at anti-inflammatory doses
- ↑ Cellular metabolism
- increased heat production
- ↑ Utilization of glucose

Aspirin – Pharmacological actions

- **4. Acid -base and electrolyte balance:**
- Significant changes at anti-inflammatory doses.
- Hypokalemia, Respiratory alkalosis(400µg500µg stimulation of respiratory centre inc. pO2), compensated respiratory alkalosis respiratory acidosis(higher doses500µg to 1mg medullary depress,inc.pCO2), uncompensated metabolic acidosis(poisoning) and dehydration(poisoning).

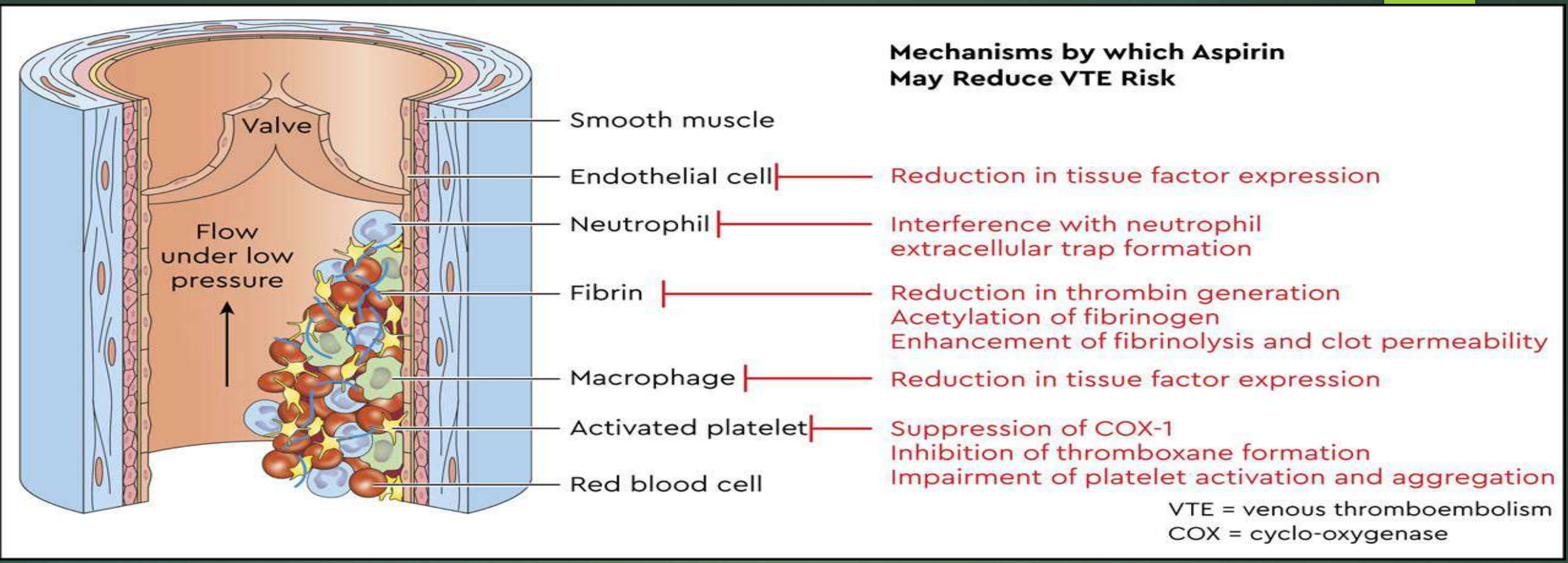
Aspirin – Pharmacological actions

- **5. CVS:**
- No direct effect in therapeutic doses
- Larger doses increase Cardiac Output (3g)
- Toxic doses depress VMC

- **6. GIT:**
- Irritate gastric mucosa and cause epigastric distress,
- nausea and vomiting
- “Ion trapping”
- Heart burn, dyspepsia, gers.astritis, erosion, Gastric ulcers.

Mechanism of action of aspirin to prevent venous thromboembolism

- Cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, catalyze the formation of prostaglandins, thromboxane, and levuloglandins.
- Aspirin inhibits COX activity (mainly COX-1) irreversibly.
- The suppression of COX-1 decreases the generation of thromboxane A2 (TXA2), an important cofactor for platelet activation and aggregation.
- Aspirin is also suspected to down regulate tissue factor expression, thrombin formation, and downstream thrombin-mediated coagulant reactions.
- In addition, aspirin may participate in the acetylation of various proteins to catalyze more efficient fibrinolysis.
- Aspirin may also exert influence COX-independent pathways to inhibit platelet aggregation and dense granule secretion.



composition of venous thrombosis and the antithrombotic effects of aspirin. Venous thrombosis typically originates in areas of slower blood flow, such as the venous anatomy near valves. Venous clots consist primarily of fibrin, red blood cells, and leukocytes. Platelets are involved, but are less prominent in comparison with the platelet-rich arterial thrombus. Aspirin exerts various antithrombotic effects on the participating cells and proteins of thrombus formation, and fibrinolysis via cyclooxygenase (COX) and COX-independent pathways.

Salicylate poisoning

salicylate poisoning, also known as aspirin poisoning, is the acute or chronic poisoning with a salicylate such as aspirin.

The classic symptoms are ringing in the ears, nausea, abdominal pain, and a fast breathing rate.

The severity of toxicity depends on the amount of aspirin taken.

Severity	Mild (150 mg/kg)	Moderate (150–300 mg/kg)	Severe (300–500 mg/kg)
Toxicity	No toxicity expected	Mild to moderate toxicity expected	Life-threatening toxicity expected
Symptoms	Nausea, vomiting, dizziness	Nausea, vomiting, ringing in the ears, headache, confusion, hyperventilation, tachycardia, fever	Delirium, hallucinations, seizures, coma, respiratory arrest

IBUPROFEN

Ibuprofen is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. It has **fewer side-effects** than other non-selective NSAIDs but its anti-inflammatory properties are **weaker**. It is unsuitable for conditions where inflammation is prominent, such as acute gout. Dexibuprofen is the active enantiomer of ibuprofen.

- Non selective COX inhibitor
- It has moderate anti-inflammatory effect potent analgesic effect.
- It is better tolerated than aspirin
- It can be used in children(**does not cause Reye's syndrome)**
- Oral and topical gel
- Dose: 400-600mg TDS(Three times a day)

- **Naproxen** is one of the first choices because it combines good efficacy with a low incidence of side-effects (but more than ibuprofen).
- **Fenoprofen** is as effective as naproxen, and flurbiprofen may be slightly more effective. Both are associated with slightly more gastro-intestinal side-effects than ibuprofen.

DICLOFENAC

- **Diclofenac sodium** and **aceclofenac** are similar in efficacy to naproxen.

Preferential COX 2 inhibitor

- It has potent anti-inflammatory effect.
- It gets concentrated in synovial fluid, hence preferred in inflammatory conditions(arthritis)of joints.
- Incidence of hepatotoxicity is more.
- Oral, i.m, rectal, topical gel and ophthalmic preparation(eye drops)
- Dose: 50mg BD or 100mg sustained release preparation OD

INDOMETHACIN

- It is a non-selective COX inhibitor.
- It has a potent anti-inflammatory effect.
- It inhibits migration of **neutrophils to inflamed area.**
- It is very effective in ankylosing spondylitis, acute gout and arthritis
- It has prominent GI side effects.
- CNS side effects are severe headache, confusion, hallucinations, etc.
- It is contraindicated in epileptics, psychiatric patients and drivers.
- Oral, eye drops and suppository
- Dose:- 50mg TDS

MEFENAMIC ACID

- Mefenamic acid (used in ≥12 year-old) as minor anti- inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment.
- Non selective COX inhibitor
- It has analgesic, antipyretic and weak anti-inflammatory effect
- It is used in dysmenorrhoea ,osteoarthritis, rheumatoid arthritis.
- Oral Dose:-250-500mg TID

CELECOXIB

- • **Celecoxib** is significantly more selective for inhibition of COX-2 than of COX-1
- • Used for treatment of RA(Rheumatoid arthritis), osteoarthritis, and pain.
- • Do not affect platelet aggregation.
- **Less gastric effect**
- • High cardiotoxicity, electrolyte imbalance
- • Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects
- • Dose 200mg

- **Tenoxicam** is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration.

- **Ketorolac trometamol** and the selective inhibitor of cyclo- oxygenase-2, parecoxib, are licensed for the short-term management of postoperative pain.

- The selective inhibitors of cyclo-oxygenase-2, etoricoxib and celecoxib, are as effective as non-selective NSAIDs such as naproxen. Available evidence appears to indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin.

PARACETAMOL(ACETAMINOPHEN)

- • Non selective inhibitor of COX
- • Acetaminophen inhibits prostaglandin synthesis in the CNS hence have a potent analgesic and antipyretic effect
- • but have less effect in tissue PG synthesis so have poor anti- inflammatory activity.
- **PCM USES**
- As antipyretic:- To reduce body temperature during fever
- As analgesic:-To relieve headache, toothache, myalgia, dysmenorrhoea etc.
- is the preferred analgesic and antipyretic in patients with peptic ulcer, haemophilia, bronchial asthma and children.
- Dose 500 mg oral

PCM ADR

- **PCM ADR**
- 1. Side effects are rare, occasionally causes skin rashes and nausea.
- 2. Hepatotoxicity :with acute overdose or chronic use.
- 3. Nephrotoxicity is commonly seen on chronic use.

- **PCM POISONING**
- • 20 gm PCM is lethal in Adult
- • Acute overdosage • causes hepatotoxicty-the symptoms are nausea, vomiting, diarrhoea, abdominal pain, hypoglycaemia, hypotension, coma etc.
- • Death is usually due to hepatic necrosis.

MECHANISM OF TOXICITY

- • N-acetyl-p-benzoquinoneimine (NABQI) is a highly reactive metabolite of paracetamol
- • This is detoxified by conjugation with glutathione in liver.
- • When a very large dose of paracetamol is taken, conjugation capacity is saturated
- • more of the metabolite is formed - hepatic glutathione is depleted and this metabolite binds covalently to proteins in liver cells (and renal tubules) causing necrosis.

TREATMENT OF TOXIXITY

- TREATMENT OF TOXIXITY • Antidote N-acetylcystine is given intravenously.
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- Gastric lavage should be done
- Activated charcoal is administered to decrease absorption of paracetamol from the gut.
- Haemodialysis may be required in cases with acute renal failure.

Choice

- The selection of an NSAID is based primarily on patient preference, convenience, cost, and safety.
- **Indomethacin** penetrates the blood–brain barrier better than any other NSAID, achieving levels in the cerebrospinal fluid of up to 50% of serum levels. As a result, the incidence of central nervous system side effects of indomethacin such as dizziness often precludes the use of optimal anti-inflammatory doses, particularly in the elderly.

- **Piroxicam**, a longer acting NSAID, has been associated with a higher frequency of peptic ulcer disease and GI bleeding and, therefore, should be avoided.

Dental and orofacial pain

- Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include **ibuprofen, diclofenac sodium,** and **diclofenac potassium.**
- Aspirin alters hemostasis most significantly and should be **discontinued before surgery**, even for minor procedures like **tooth extraction.**
- **COX-2 inhibitors** are not expected to alter platelet function because COX-2 is not found in platelets.

Asthma

- Asthma Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.
- Aspirin hypersensitivity, especially in association with asthma, is cause for serious concern; challenge with aspirin in these patients can precipitate an acute, life-threatening, bronchospastic reaction.
- Between 6% and 15% of asthmatics have a history of aspirin- induced bronchospasm; it occurs more often among middle-age women than men and rarely in children. The prevalence of aspirin-induced asthma increases with the presence of nasal polyps, rhinitis, and a personal or family history of atopy.

Asthma

- Asthma Aspirin-sensitive patients can experience a high degree of cross-reactivity (over 90%) to all nonselective NSAIDs; therefore, nonselective NSAIDs should be avoided in patients who have experienced aspirin-induced asthma.
- On the other hand, COX-2 inhibitors have been used safely in aspirin-sensitive asthmatics.
- Paracetamol is usually safe in patients sensitive to aspirin and cross-sensitivity to paracetamol has been calculated as about 7%.

Hypersensitivity

- **Hypersensitivity** Contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom **attacks of asthma, angioedema, urticaria or rhinitis** have been precipitated by aspirin or any other NSAID.

- Some use a formal challenge with a **300-mg oral dose of aspirin** to confirm a diagnosis of NSAID sensitivity but others consider this to be a dangerous technique and use **inhalation of lysine aspirin** which they consider to be a safer and more predictable alternative. Intranasal challenge with lysine aspirin has also been used.

Pregnancy

- Pregnancy Although NSAIDs, including aspirin, are not teratogenic, they must be used cautiously in women who are pregnant and who plan to breast-feed infants.
- NSAIDs should be avoided during the third trimester because use is associated with a risk of closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of the newborn. In addition, the onset of labour may be delayed and its duration may be increased.
- Fetal effects of NSAIDs also include possible increased cutaneous and intracranial bleeding, transient renal impairment, and a reduction in urine output.
- Pregnancy High doses of aspirin (greater than 3 g/day) and NSAIDs can inhibit uterine contractions, resulting in prolonged labor.
- The use of NSAIDs can also increase peripartum blood loss and anemia.
- Aspirin and nonaspirin NSAIDs should be used sparingly and at the lowest effective doses during pregnancy and discontinued at least 6 to 8 weeks before delivery to minimize adverse fetal and maternal effects.

Breast Feeding

- Breast Feeding Aspirin generally should be avoided for women who plan to nurse their baby because salicylate serum concentrations in breast-fed neonates raise concerns about the potential for metabolic acidosis, bleeding, and Reye syndrome. (Reye's syndrome is a rare but potentially fatal disorder characterized by acute encephalopathy and fatty degeneration of the liver. It occurs almost exclusively in young children).