Non Steroidal Anti-inflammatory Drugs (NSAIDs)
4 signs of inflammation

• **Redness** - due to local vessel dilatation
• **Heat** - due to local vessel dilatation
• **Swelling** – due to influx of plasma proteins and phagocytic cells into the tissue spaces
• **Pain** – due to local release of enzymes and increased tissue pressure
Phospholipids in plasma membrane

Phospholipase A₂

Platelet-activating factor

Arachadonic acid

Cyclo-oxygenase

Prostaglandins Thromboxanes

Lipo-oxygenase

Leukotrienes
NSAIDs

- Cause relief of pain - analgesic
- Suppress the signs and symptoms of inflammation.
- Exert antipyretic action.
- Useful in pain related to inflammation.
  Esp for superficial/integumental pain.
Classification of NSAIDs

• **Salicylates**: aspirin, Sodium salicylate & diflunisal.
• **Propionic acid derivatives**: ibuprofen, ketoprofen, naproxen.
• **Aryl acetic acid derivatives**: diclofenac, ketorolac
• **Indole derivatives**: indomethacin, sulindac
• **Alkanones**: Nabumetone.
• **Oxicams**: piroxicam, tenoxicam
Classification of NSAIDs ..... 

- Anthranilic acid derivatives (fenamates): mefenamic acid and flufenamic acid.
- Pyrazolone derivatives: phenylbutazone, oxyphenbutazone, azapropazone (apazone) & dipyrrone (novalgine).
- Aniline derivatives (analgesic only): paracetamol.
Clinical Classif.

- Non selective Irreversible COX inhibitors
- Non selective Reversible COX inhibitors
- Preferential COX 2 inhibitors
  - 10-20 fold cox 2 selective
  - meloxicam, etodolac, nabumetone
- Selective COX 2 inhibitors
  - > 50 fold COX -2 selective
  - Celecoxib, Etoricoxib, Rofecoxib, Valdecoxib
- COX 3 Inhibitor? PCM
Cyclooxygenase-1 (COX-1):
- constitutively expressed in wide variety of cells all over the body.
- "housekeeping enzyme"
- ex. gastric cytoprotection, hemostasis

Cyclooxygenase-2 (COX-2):
- inducible enzyme
- dramatically up-regulated during inflammation (10-18X)
- constitutive: maintains renal blood flow and renal electrolyte homeostasis
Nonselective COX inhibitors

COX-1 (Constitutive)
- GI cytoprotection
- Platelet aggregation
- Renal electrolyte homeostasis
- Renal blood flow maintenance

COX-2 (Constitutive)
- Renal electrolyte homeostasis
- Renal blood flow maintenance

Selective COX-2 inhibitors

- Pain
- Fever
- Inflammation
Salicylates
Acetyl salicylic acid (aspirin).

**Kinetics:**

- Well absorbed from the stomach, more from upper small intestine.
- Distributed all over the body, 50-80% bound to plasma protein (albumin).
- Metabolized to acetic acid and salicylates (active metabolite).
- Salicylate is conjugated with **glucuronic acid and glycine**.
- Excreted by the kidney.
- Alkalinization of the urine increases the rate of salicylates excretion.
Aspirin....

- Low dose of aspirin 0.6 g is eliminated by 1st order kinetics and its t 1/2 is 3-5 h
- while high dose (more than 4 g/day) is eliminated by zero-order kinetics and its t 1/2 may increase up to 15 h.

**Mechanism of action:**

- Aspirin irreversibly inhibits cyclo-oxygenase enzyme, so blocks synthesis of prostaglandins and thromboxane A2.
Aspirin... *Pharmacological actions*

**Anti-inflammatory actions:**
Higher doses; 3-6 g/day, OA, RA, Rh fever

- Inhibits prostaglandin synthesis
- Blocks action of *kinins* which are mediated through prostaglandin synthesis.
- Inhibits granulocyte adherence to damaged vasculature.
- Stabilizes lysosomes.
- Inhibits migration of PMN leukocytes & macrophages into the site of inflammation.
Aspirin....

- **Analgesia**: inhib of PG: 300-600mg, 6-8 hrly
- **uses**
- **Antipyretic axn.**: inhib of PG: resets the “hypothalamic thermostat”
- **Inhibition of platelet aggregation**: low doses: irreversibly inhibit platelet COX, antiplatelet effect lasts 8-10 days. (acts on TXA2, no effect on PGI2)
Aspirin...

- **Uses:**
  - Antiplatelet: M imp
  - Analgesic
  - Antiinflammatory
  - Antipyretic
  - Misc.
  - Colonic Ca
  - Pre eclampsia
  - Alzheimer’s Ds
  - Familial polyposis
  - Niacin induced flush
Adverse effects

- **CNS:** Headache, Tinnitus, dizziness, blurred vision, irritability, hyperventilation *(Salicylism)*
- **Cardiovascular:** fluid retention, HT, edema, CHF (rarely)
- **GIT upset:** abd pain, nausea, vomiting, peptic ulceration & bleeding
- **Hypersensitivity:** bronchial asthma, angioedema & rashes,
- **Thrombocytopenia, Hypoprothrombinemia and bleeding tendency** as aspirin competes with vitamin K, so decreasing prothrombin synthesis.
Aspirin ADRs ....

• Renal effects: inhibition of PGE2 mediated vasodilation in response to ATII : renal insufficiency, renal failure, hyperkalemia, proteinuria. Analgesic nephropathy on chronic use

• Hepatic: Liver function abnormalities, rarely liver failure.
Reye’s Syndrome

- Aspirin and derivatives may be a trigger.
- Hepato encephalopathy.
- Highly Lethal
- Do not give in children with chickenpox or influenza B infection.
Aspirin Overdose

- Acid-base disturbance.
- **Respiratory Alkalosis** (400-500 microgm/ml).
- Direct stimul of the respiratory centers: salicylism; renal mech compensate by increasing excretion of HCO3
- **Metabolic Acidosis** (0.5-1 mg/ml)
- Medullary depression. Depletion of HCO3, accumulation of salicylic acid & deriv., absolute uncoupling of oxidative phosp. >> accum of lactic acid, pyruvic & acetoacetic acid
**Aspirin Overdose**

<table>
<thead>
<tr>
<th>Blood Salicylate Level (μg/mL)</th>
<th>Effect</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-100</td>
<td>Analgesia, antipyresis</td>
<td>Tinnitus, dizziness, nausea</td>
</tr>
<tr>
<td>150-300</td>
<td>Antiinflammatory</td>
<td>Respiratory alkalosis</td>
</tr>
<tr>
<td>200-350</td>
<td>Salicylism</td>
<td></td>
</tr>
<tr>
<td>≤350</td>
<td>Hyperventilation</td>
<td>Metabolic acidosis, dehydration, hyperthermia, respiratory acidosis, delirium, convulsions, coma</td>
</tr>
<tr>
<td>450-800</td>
<td>Disrupted carbohydrate metabolism, sweating, vomiting, uncoupled oxidative phosphorylation, depressed respiration, increasing acidosis and body temperature</td>
<td></td>
</tr>
</tbody>
</table>
Acute aspirin poisoning

S/S : Restlessness, tremors, convolution, vomiting, dehydration, hypotension, hyperventilation, hyperreflexia, hyperpyrexia & coma.

Treatment:

• Activated charcoal 50g p.o to adsorb salicylates and prevents its absorption.

• Alkalization of urine (to enhance excretion) by i.v Na HCO3 which also corrects acidosis.

• Anticonvulsant e.g. i.v diazepam.

• Cold fomentation and ice bags.
**Acute aspirin poisoning...**

- Correct dehydration by i.v fluids (5% dextrose).
- Correct acid / base balance (alkalosis or mixed alkalosis/acidosis need no specific treatment).
- Correct hypoprothrombinemia by i.v vitamin K.
- Hemodialysis may be needed.
Contraindications:

- Peptic ulcer,
- esophageal varices,
- bronchial asthma,
- idiosyncrasy, allergy,
- viral infection in children,
- bleeding tendency and
- small dose in gout (competes with uric acid excretion).
Interactions

• Aspirin displaces oral anticoagulants and oral hypoglycemics from their plasma protein binding sites, so increasing their activities and may lead to toxicity.

• inhibits the uricosuric effects of sulphipyrazone and probenecid.

• Barbiturates increase the analgesic effect of aspirin.

• Alcohol:
Locally acting salicylates

• *Salicylic acid*: keratolytic, antiseptic & fungistatic.
• *Methyl salicylate* (wintergreen oil): used as counterirritant for muscle and joint pain.
• *Sulfasalazine*: it is a combination of sulfapyridine and 5-aminosalicylic acid (5-ASA). Sulfasalazine liberates 5-ASA in the colon where it blocks the synthesis of leukotriene B4 locally and used in ulcerative colitis.
PROPIONIC ACID DERIVATIVES

• Ibuprofen, Naproxen, Fenoprofen.
• Very similar in mechanism of action and effects (compared to aspirin).
• More effective as analgesics
• Ibuprofen and Fenoprofen half-life of 2 hrs.
• Naproxen has a longer half-life (13 hrs).
• Use: Dysmenorrhea.
• Adverse effects are similar: nephrotoxicity, jaundice, nausea, dyspepsia, edema, rash, pruritus, tinnitus.
• Interactions and contraindications: same as aspirin.
ACETIC ACIDS

• **Indomethacin** : indole AA : Most potent inhibitor of prostaglandin synthesis (COX-1) more effective but **more toxic** than aspirin. May also inhibit phospholipase A₂, C

• Orally absorbed, highly bound to plasma proteins, half-life 2hrs.

• Metabolized in liver, excreted in bile and urine.

• A/E : GI, severe migraine (20-25%), dizziness, confusion and depression, risk of fluid retention, hyperkalemia and blood dyscrasias.

• **Contraindicated** in pregnancy and in patients with psychosis.
Indomethacin

• **Uses:** Treatment of patent ductus arteriosus in premature babies.

• Acute gouty arthritis, ankylosing spondylitis, osteoarthritis.

• **Sulindac:**

  • Is a pro-drug closely related to Indomethacin.
  • Converted to the active form of the drug.
  • Indications and toxicity similar to Indomethacin.
Diclofenac

- Short half life (1-2 hrs), high 1st pass metab., accumulates in synovial fluid after oral admn.
- GI S/E: in about 20% pt. Severe effects like GI distress, GI bleeding, gastric ulceration less frequent than other NSAIDs and similar to celecoxib.
- High doses impairs renal function. Elevates liver enzymes.
- CI: children, pregnant women and nursing mothers
FENAMATES

• Mefenamic acid,
• Analgesic, anti-inflammatory properties less effective than aspirin, more toxic.
• Short half-lives, should not be used for longer than one week and never in pregnancy and in children.
• Diarrhea and abdominal pain.
• Enhances oral anticoagulants.
PYRAZOLONE DERIVATIVES

- **Phenylbutazone**: Withdrawn from the market.
- **Adverse effects**: agranulocytosis, aplastic anemia, hemolytic anemia, severe gastric irritation
- **Oxyphenbutazone**: one of the metabolites of phenylbutazone. Apazone.- Similar to phenylbutazone, but less likely to cause agranulocytosis
OXICAMS

• Piroxicam.


• High doses inhibits PMN migration, decrease oxygen radical production, inhibits lymphocyte function.

• Used in osteoarthritis, ankylosing spondylitis and rheumatoid arthritis.

• Adverse effects: GI symptoms, dizziness, tinnitus, headache, rash. **Peptic ulcer (9.5 higher).**
Ketorolac

- Analgesic, no anti-inflammatory effect.
- Can replace morphine in mild to moderate postsurgical pain.
- IM, IV.
- Similar toxicities. Renal toxicity common with chronic use.
Nimesulide

- Rel weak PG synth inhib, 5-10 COX 2 sel.
- Other mech – reduced SO prod, free radical scavenger, inhib of PAF synth & of metalloproteinase act in cartilage
- NOT FDA approved, Banned in many countries d/t hepatotoxicity
- NOT TO BE USED IN CHILDREN
Preferential COX 2 inhibitors

• 10-20 fold cox 2 selective
• meloxicam: longer acting
• etodolac: less GIT tox,
• nabumetone: non acidic, prodrug, longer acting
Selective COX 2 inhibitors

- > 50 fold COX -2 selective
- Celecoxib, Etoricoxib, Rofecoxib, Valdecoxib, .

Inhibit prostacyclin (COX-2) in sites of inflammation.

- Do not block “housekeeping” effect of COX-1.
- Antipyretic, analgesic and anti-inflammatory effect.

- Gastro –protective as compared to non selective NSAIDs ; BUT SAME potential for renal and hepatic dysfunction ,While INCREASED risk of thrombotic CVS disorders.
COX-2 Selective

• Celecoxib:
  • Osteoarthritis (100-200mg BID), rheumatoid arthritis, dysmenorrhea, acute gouty attacks, acute musculoskeletal pain.
  • Being a sulphonamide can cause skin rash & hypersensitivity rxn., occasional oedema & HT.
• A/E:
  • Etoricoxib, parecoxib
Rofecoxib (Vioxx®) & Valdecoxib

- Withdrawn from the market.
- Higher incidence of cardiovascular thrombotic events.
- Inhibit prostacyclin (PGI2) in vascular endothelium, letting TXA₂ act freely and promote platelet aggregation.
Paracetamol / Acetaminophen

Analgesic and antipyretic actions equivalent aspirin.

• No anti-inflammatory effects---can inhibit Cox 1 poorly in presence of superoxides at inflamm sites
• No occult bleeding or gastric irritation , do not inhibit platelet aggregation, or affect prothrombin time.
• No relationship with Reye’s syndrome.
• Does not antagonize the effects of uricosuric drugs.
• Proposed as COX 3 inhibitor – involved in pain perception & fever NOT in inflamm.
Paracetamol Metabolism

Metabolized by liver glucoronyl transferase to form an inactive compound.

Minor CYP-dependent pathway produces a N-acetyl-para-benzoquinonimine (NAPQI) a reactive metabolite that is inactivated by glutathione.

In serious overdose glutathione becomes depleted, and metabolite damages hepatocytes.

Alcohol enhances liver toxicity via induction of CYP2E1 enzyme.
**Fig 26.1** Mechanism of Paracetamol Poisoning and its Treatment.

- **Paracetamol**
  - Major pathway: Glucuronide or Sulfate Conjugation
  - Minor pathway: Cytochrome P-450 → N-acetyl-p-benzoquinone imine (A toxic metabolite)

**For normal therapeutic doses**
- Glutathione
  - Glutathione conjugate of toxic metabolite (being non-toxic, excreted)
  - Produce more

**In toxic doses**
- Oxidation of SH group of hepatic and renal cell proteins
- Methionine (oral) or N-Acetylcysteine (I.V)
  - Methionine or N-acetylcysteine conjugates of toxic metabolite - Excreted
  - Cell proteins get covalently bound to toxic metabolite → cell death
Acute PCM Toxicity

• PCM usual doses - 325-650 TID –QID (Max 2.6 g/day -latest FDA , ).

• Acute ingestion of > 7.5 g can result in toxicity---severe liver damage.

• The signs & symptoms of toxicity start within 12-24 hrs: N, V, D, abdominal pain, dizziness, elevated plasma transaminases. Signs of hepatic damage appear over 2-4 days. Renal tubular necrosis may occur. Onset of hepatic encephalopathy or worsening of coagulopathy beyond this pd. Indicates poor prognosis.
Management

• Severe liver damage with pl. conc>300 microgm/ml at 4 hrs or 45 microgm/ml at 15 hrs after ingestion.
• Activated charcoal- within 4hrs ↓PCM absb by 50-90%
• Antidote- N-acetylcysteine (NAC)- detoxifies NAPQI- both repletes glutathione store and may conjugate with NAPQI by serving as GSH substitute. Also has antioxidant and anti-inflamm properties.
• Oral loading dose of 140 mg/kg , followed by 70mg/kg q 4hrly for 17 doses. If available IV LD-150mg/kg IV inf in200ml of 5%D over 1 hr, followed by 50 mg/kg in 500ml 5%D over 4hrs then 100mg/kg in 1000ml 5%D over 1