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 A<sub>2</sub>

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

- COX-2 (Inducible)
  - Pain
  - Fever
  - Inflammation

Selective COX-2 inhibitors
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**: inhibit of PG: 300-600mg, 6-8 hrly
- uses
- **Antipyretic** axn.: inhibit 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 uncou[pling of oxidative phosp. >> accum of lactic acid, pyruvic & acetoacetic acid
### TABLE 36-6  Relationship Between Blood Salicylate Level and Therapeutic and Toxic Effects

<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></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>Metabolic acidosis, dehydration, hyperthermia, respiratory acidosis, delirium, convulsions, coma</td>
</tr>
</tbody>
</table>
Acute aspirin poisoning

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

Treatment:

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

- **Alkalinization 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, Valdecoxisb, .

*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 TXA$_2$ 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.
**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:
- Treatment:
  - Methionine (oral) or N-Acetylcyctysteine (I.V)
  - Methionine or N-acetylcyctysteine conjugates of toxic metabolite - Excreted

Oxidation of SH group of hepatic and renal cell proteins
- 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