Chapter 26:

ANTIPYRETIC, ANTI-INFLAMMATORY AND ANALGESIC DRUGS

(Non-narcotic or non-opioid (NSAID,s) and Aspirin like analgesics.)

Introduction & chemistry:

- Drugs grouped in this class having analgesic, antipyretic & anti-inflammatory effect of different measures.
- Having less analgesic effect when compared to narcotics.
- Having no CNS ↓, dependence & abusing liability.
- Bitter glycosides of willow bark (Salix alba) hydrolyzed to synthesis salicylic acid – used for many centuries.
- Na Salicylate introduced in 1875 for fever & pain.
- Acetyl salicylic acid introduced in 1899.
- 1st NSAID,s phenylbutazone discovered in 1949 and Indomethacin in 1963.
- COX inhibitors – ibuprofen and COX-2 inhibitors added recently.
- These are chemically diverse but mostly organic acid.

Inflammation:

A normal protective response of tissues injured by physical trauma, noxious chemicals or microbial agents. It is the body effort to destroy organism, remove irritation and restore the tissue reparation.

It may be triggered by innocuous agent (pollens) or autoimmune response (asthma, rheumatoid arthritis).

Chemical inflammatory mediators are histamine, 5-HT, PG,s, bradykinins, interleukines etc. It’s not possible to control all involved mediators.
Illustration of asthma/anaphylactic shock.

1. MAST CELL SENSITIZATION
First exposure to antigen causes production of specific IgE antibodies, which attach to surface of tissue mast cells and blood basophils.

   Antigen → Production of antibody → IgE antibody → Mast cell sensitization

   Monocytes

2. MAST CELL DEGRANULATION
Subsequent exposure to antigen results in binding to surface-bound IgE molecules. The sensitized mast cells are stimulated to release granules containing histamine, leukotrienes, prostaglandins, and other potent chemical mediators.

   Antigen (A) → Mast cell degranulation

   Rashes ← Asthma ← Anaphylactic shock

Synthesis of PGs, thromboxane & leukotrienes.

   Phospholipid (from cell membrane)

   Corticosteroids ——→ Phospholipase A₂

   5-lipoxygenase ——→ Arachidonic acid

   Prostaglandins (PG₂)

   Prostacyclin (PGI₂), Thromboxane A₂

   PGG₂, PGE₂, PGF₂α

   Leukotrienes

   Bradykinin, Angiotensin

   Cyclooxygenase ——→ NSAIDs

   Dipyridamole (see Chapter 20)
CLASSIFICATION:

A  **NSAID,s:** (Non-selective COX inhibitors)
   1  Salicylate - Aspirin
   2  Pyrazolon derivative - Phenylbutazone
   3  Indole derivative – Indomethacine, sulindac
   4  Propionic acid - Ibuprofen, flurbiprofen, naproxen
   5  Anthranolic acid derivative - Mefnamic acid (Fenamates)
   6  Aryl acetic acid derivative – Diclofenac, Ketorolac
   7  Oxicame derivative – Piroxicam, meloxicam

B  **preferential COX-2 inhibitors**
   Nimsulide

C  **Selective COX-2 inhibitors**
   Celecoxib, rofecoxib.

D  **Analgesic, antipyretic with poor anti-inflammatory effects.**
   1  Para-aminophenol derivative  Paracetamol (Acetaminophene)
   2  Pyrazolone derivative - Metamizole (dypron)

E  **Drugs for Arthritis:**
   Gold salts, chloroquine, D-Penicilline, immunosuppressants -methotrexate, cyclosporin.

F  **Drugs for Gout;**
   1  For acute gout;
      NSAID,s, colchicines, carticosteroids.
   2  For chronic gout/ hyperuricaemia;
      Uricosurics, probenecid, sulfinpyrazone.

26.1  **Salicylates** (aspirin)
   ✷  Aspirin is prototype of Salicylates
   ✷  Most common, less toxic & comparatively cheap.
   ✷  No sedation, dependence & tolerance (like morphine).
   ✷  Treatment coupled with H⁺ Pump ↓ or H2 blockers.
   ✷  Mostly weak organic acid.

**Dosage:**
   ➤  160- 325mg/ day MI, Post MI & coronary diseases.
   ➤  300mg tablet four time a day for analgesic effect.
   ➤  300mg 12-20 tablets/ day for pain & inflammation.
Pharmacokinetics:

- Local prep., oral administration and may be given rectally.

Absorbed through skin i.e. methyl salicylate.
Unionized salicylate passively absorbed from Gut.
Slow & unreliable rectal absorption.
Solubility ↑ at higher pH & absorption ↓.
PPB: 80%, Cross BBB & placenta.
T½ 3-5, 8-12 & 30 Hrs with C-max 10, 20, 60mg/ml

- Water soluble metabolites/ conjugates are
  1. Glucuronidation-ether/ester glucuronides
  2. Glycine conjugation- salicyluric acid
  3. Oxidation- Genitiscic acid
  1st order reaction at C-max 10mg/ml.
  Zero order at C-max 20 & above.

- Glomerular filtration, renal tubular excretion.

Mechanism of action:

- Irreversible acetylation of COX.
- Deacetylated by estrase to producing active salicylate.
- ↓ Pg,s synthesis at Thermoregulatory centre (hypothalamus) and peripheral target tissues.
- ↓ Subcortical (thalamus, hypothalamus) and peripheral (chemical/ mechanical) sensitivity of receptors for pain.
Pharmacological actions:

**Analgesic:**
- Lower than morphine, 600mg:60mg
- Obtund/ block peripheral pain receptors and prevent Pgs mediated sensitization of nerve endings.

**Antipyretic:**
- Reset hypothalamic thermostat & ↓ fever.
- ↑ Heat loss by sweating, cutaneous vasodilatation.

**Anti-inflammatory:**
- At ↑ dose 3-6 g/ days or 100mg/kg/day.
- Progression of underlying disease in rheumatic/ osteoarthritis, rheumatic fever not affected.
Metabolic effects:

- ↑ Cellular metabolism (in skeletal M.) at higher dose.
- ↑ Glucose utilization (diabetes) & liver glycogen depletion.
- Large chronic use ↓ plasma Free FA & cholesterol level by ↑ conversion of proteins into carbohydrates. / oxidation of ketone bodies is also ↑

Respiration:

- At higher dose respiration rate ↑, because of ↑ CO2 level that stimulate central (medulla) & peripheral receptors.
  - Salicylate poisoning
  - Hyperventilation.

  - ↑ Salicylate level
  - Resp. depression → Resp. failure → Death

- Respiratory alkalosis compensated by kidney.

GIT:

- Prostacyclin ↓ gastric acid secretion, PgE2 & PgE2α ↑ protective mucous secretion.
- ↑ acid, ↓ mucous synthesis, ↑ Epigastric distress, ulceration & hemorrhage, erosive gastritis

Platelets:

- TXA2 synthesis ↓ that ↑ platelet aggregation. endothelial TXA2 synthesis remained unaffected.
- ↓ thrombosis, ↑ bleeding time.

Kidney:

- NSAID.s ↓ PgE2, PgI2 – responsible of maintenance of renal blood flow, therefore ↑ H2O, Na retention, edema & hypokalemia.

Therapeutically uses:

1. Anti-pyretic and analgesics.
2. External application:
   - Corns, calluses, epidermophytosis (mycotic eruption), counter irritation in liniments (methyl salicylate/oil of winter green), Analgesia, Rheumatoid arthritis

Aspirin renal effect.
Cardiovascular application:
Platelet aggregation, transient ischemia, angina, coronary artery diseases/thrombosis & closure of patent ductus arteriosus.

Colorectal cancer

Adverse effects:
1. GIT: Epigastric distress, nausea, vomiting.
2. CVS: ↑Bleeding time
3. Respiratory effect: ↓Respiration.
4. Metabolism:
Uncouple oxidative phosphorylation, ATP synthesis ↓, pyretic effect ↑ at toxic dose.
5. Hypersensitivity:
Urticaria, bronchoconstriction, angioneurotic edema, anaphylactic shock.
6. Reye syndromes:

Salicylism:
Mild: Tinnitus, headache, mental confusion.
Sweating, thirst, Dimness of vision, dizziness, lassitude.
Sever: Restlessness, delirium, hallucination, respiratory/metabolic acidosis, convulsions skin eruptions, coma and death.

Treatment:
► Measurement (pH calculation)
& correction of acid base/electrolytic balance.
► ↑ Fluid administration
► Hemodialysis and peritoneal dialysis.
► Forced dieresis with alkalinizing solution

Contra-interaction:
Nephritis, hepatitis, surgery, lesions, gastric ulceration, piles etc.

PROPIONIC ACID DERIVATIVES
(Ibuprofen, Flurbiprofen, Ketoprofen, Naproxen)
► Anti-inflammatory, analgesic & antipyretic effect is less than higher aspirin dose.
► Ibuprofen was 1st member of this class introduced in 1969.
► It has replaced Aspirin and having same pharmacodynamic with different potency & T max.
►↓ Platelet aggregation & ↑ bleeding time.
Pharmacokinetics:

Oral preparation, injectables, local application, rectal preparations. ⇒ PPB is more than 85% (albumin).

T½ : (Ketoprofen) 1.8 – 58 (Oxaprazin).
Flurbiprofen: T½ 3.8, 300mg tid.
Ibuprofen: T½ 2, 600mg qid.
Naproxen: T½ 14, 375 mg bid.
Cross BBB & Placenta.

Urinary and biliary excretion. ⇐ Majorly metabolized in liver - Hydroxylation and glucuronide conjugation.

Mechanism of action:

Reversible inhibit COX and ↓ Pg synthesis.

Therapeutical uses:

Osteo-arthritis, rheumatic arthritis, analgesic, anti-inflammatory.

Adverse effects:

G.I. disturbance (nausea, vomiting), dyspepsia, bleeding, CNS effects, headache, tinnitus, dizziness, thrombocytopenia, skin rashes, blurred vision.

Contraindications:

Pregnancy, lactation.

Drug Interactions:

Antagonize the natriuretic and antihypertensive effects of furosemide, thiazides diuretics, antihypertensive effect of β-adrenergic blocking agents, inhibitors of ACE.

INDOL DERIVATIVE/ ACETIC ACID DERIVATIVE
(Indomethacin, Sulindac)

Introduced in 1963.
Analgesic, anti-inflammatory and not recommended for fever.
↓ Neutrophil motility, ↓ T cell & B cell proliferation.
↓ Phospholipase A & C.

Pharmacokinetics:

Oral administration, 50-70 mg tid, T½ 4.5-8 average about 2.5 hrs.
Indomethacin - 90% PPB, liver metabolism and renal excretion.

Mechanism of action:

Reversible non-selective COX ↓.
↓ Pg, ↓ Neutrophil motility.
At toxic dose uncouple oxidative phosphorylation and depresses the biosynthesis of mucopolysaccharides.
**Therapeutical uses:**
Gouty arthritis, ankylosing spondylitis, osteo-arthritis of hip, rheumatic arthritis, sweet syndrome, juvenile rheumatoid arthritis, pleurisy, nephrotic syndrome, diabetes insipidus, Urticaria vasculitis, post-episiotomy pain, heterotropic ossification in arthroplasty.

**Adverse effects:**
Abdominal pain, diarrhea, G.I. hemorrhage, pancreatitis, thrombocytopenia, aplastic anemia, hyperkalemia, hepatitis, jaundice, neutropenia.

**Contraindications:**
Pregnancy, lactation, person operating machinery patients with psychiatric disorders, epilepsy or parkinsonism, renal disease, ulcerative lesions of stomach and intestine.

**PYRAZOLONE DERIVATIVE**
(Phenylbutazone, Oxyphenbutazone, Propiphenazone)
- Phenazone and amidopyrin introduced in 1884 as antipyretic & analgesic but banned because of association with agranulocytosis.
- Phenylbutazone introduced in 1949 and usually not recommended now because of bone marrow depression, agranulocytopenia and reactions.
- Not suggested more than one week.
- Strong anti-inflammatory and poor analgesic & antipyretic.
- Mechanism of action: COX

**Pharmacokinetics:**
- Oral absorption, PPB 98%, T½ 60 Hrs.
- Complete liver metabolism – hydroxylation & glucuronidation.

**Therapeutical uses:**
Rheumatic arthritis, ankylosing spondylitis, acute gout.

**Adverse effects:** (More toxic than aspirin)
Nausea, vomiting, peptic ulceration, diarrhea, edema, hypersensitivity, bone marrow suppression, skin rashes, vertigo, insomnia, blurred vision, hematurea, goiter (iodine absorption).
Summary of Non steroidal anti-inflammatory drugs

Figure 41.11
Cumulative incidence of gastro-duodenal ulcers over twelve weeks in patients treated with NSAIDs.

Figure 41.12
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). *As a group, with the exception of aspirin, these drugs may have the potential to increase myocardial infarctions and strokes.