PHARMACOGOLOGY-II- BP503T

UNIT : 2(NSAIDS)

CLASS: 11

TOPIC: NSAIDS definiiton and classification

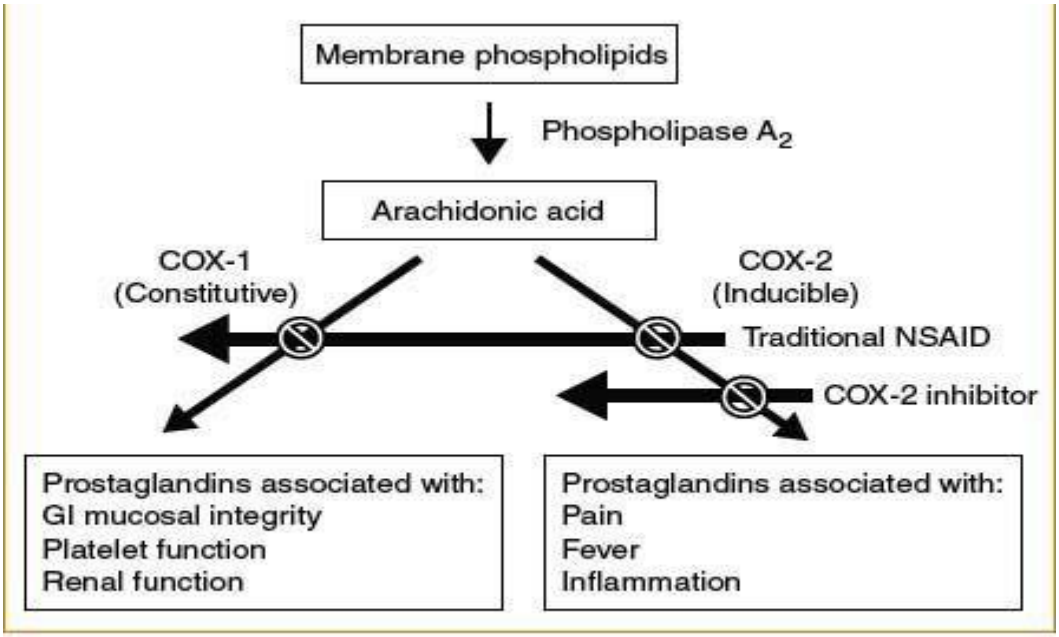
Definition: All drugs of NSAIDS has analgesic, antipyretic and antiinflammatory actions.
CLASSIFICATION

A. *Nonselective COX inhibitors (traditional NSAIDs)*
1. *Salicylates*: Aspirin.
2. *Propionic acid derivatives*: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. *Anthranilic acid derivative*: Mephenamic acid.
4. *Aryl-acetic acid derivatives*: Diclofenac, Aceclofenac.
5. *Oxicam derivatives*: Piroxicam, Tenoxicam.
6. *Pyrrolo-pyrrole derivative*: Ketorolac.
7. *Indole derivative*: Indomethacin.
8. *Pyrazolone derivatives*: Phenylbutazone, Oxyphenbutazone.

B. *Preferential COX-2 inhibitors:* Nimesulide, Meloxicam, Nabumetone.

C. *Selective COX-2 inhibitors:* Celecoxib, Etoricoxib, Parecoxib.

D. *Analgesic- antipyretics with poor antiinflammatory action*
1. *Paraaminophenol derivative*: Paracetamol (Acetaminophen).
2. *Pyrazolone derivatives*: Metamizol (Dipyrone), Propiphenazone.
3. *Benzoxazocine derivative*: Nefopam.



(From *The MGH Handbook of Pain Management*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2002.)

Salicylates:

ASPIRIN:

Aspirin: Aspirin is acetylsalicylic acid.

PHARMACOLOGICAL ACTIONS

1. **Analgesic, antipyretic, anti-inflammatory actions:** The analgesic action is mainly due to inhibiting of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings.
   Anti-inflammatory action is exerted at high doses.
2. **Metabolic effects** These are significant only at anti-inflammatory doses. Cellular Chronic use of large doses cause negative N2 balance by increased conversion of protein to carbohydrate. Plasma free fatty acid and cholesterol levels are reduced.
3. **Respiration** The effects are dose dependent. At anti-inflammatory doses, respiration is stimulated by peripheral (increased CO2 production) and central (increased sensitivity of respiratory centre to CO2) actions.
4. **Acid-base and electrolyte balance:** Anti-inflammatory doses produce significant changes in the acid-base and electrolyte composition of body fluids.
5. **CVS** Aspirin has no direct effect in therapeutic doses. Larger doses increase cardiac output to meet increased peripheral O2 demand and cause direct vasodilatation.
6. **GIT** Aspirin and released salicylic acid irritate gastric mucosa →□cause epigastric distress, nausea and vomiting.

7. **Blood** Aspirin, even in small doses, irreversibly inhibits TXA2 synthesis by platelets. Thus ,it interferes with platelet aggregation and bleeding time is prolonged to nearly twice the normal value.

Kinetics:
ROA: oral
Absorption: git
M: in liver through glucuronic acid
E: in urine.

ADR:

1. *Hypersensitivity and idiosyncrasy*
2. *Antiinflammatory doses* (3–5 g/day) produce the syndrome called salicylism—dizziness, tinnitus, vertigo, reversible impairment of hearing and vision, excitement and mental confusion, hyperventilation and electrolyte imbalance. The dose has to be titrated to one which is just below that producing these symptoms;
3. *Acute salicylate poisoning* It is more common in children. Vomiting, dehydration, electrolyte imbalance, acidotic breathing, hyper/hypoglycaemia, petechial haemorrhages, restlessness, delirium, hallucinations, hyperpyrexia, convulsions, coma and death due to respiratory failure+ cardiovascular collapse.

Precautions and contraindications

• Aspirin is contraindicated in peptic ulcers pts, liver disease pts and chronic heart failure pts.

Interactions

1. Aspirin displaces warfarin, naproxen, sulfonylureas, phenytoin and methotrexate from binding sites on plasma proteins: toxicity of these drugs may occur.

USES:

1. *As analgesic*
2. *As antipyretic*
3. *Acute rheumatic fever*
4. *Rheumatoid arthritis*
5. *Osteoarthritis*

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TOPIC: PROPIONIC ACID DERIVATIVES:

Ibuprofen:

- Alternative to aspirin.
- The analgesic, antipyretic and anti-inflammatory efficacy
- All inhibit PG synthesis, naproxen being the most potent;

Adverse effects:

- Gastric discomfort, nausea and vomiting.
- CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.
- Rashes, itching and other hypersensitivity phenomena

Kinetics:
absorbed orally,
Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and beta□blockers.

Uses:

- Analgesic
- Anti-pyretics
- Used for treatment of RA and Osteoarthritis
- Treatment of soft tissue injuries, fractures, vasectomy, tooth.

Naproxen
Ketoprofen
Other drugs are same.

ANTHRANILIC ACID DERIVATIVE (FENAMATE)

Mephenamic acid:
An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits COX as well as antagonises certain actions of PGs.

ADR:
Diarrhoea
Skin rashes, dizziness
Haemolytic anaemia

Pharmacokinetics

ROA: Absorption
Partly metabolized and excreted in urine.

USES:
Analgesic in muscle
Treatment of joint and soft tissue pain
Useful in some cases of rheumatoid and osteoarthritis

ARYL-ACETIC ACID DERIVATIVES:

Diclofenac sodium
Actions: Analgesic-Antipyretic, anti-inflammatory drug
Kinetics: ROA: Oral
Metabolism: in liver
Excreted: in urine

Adverse effects:

- Epigastric pain, nausea, headache, dizziness, rashes.
- Gastric ulceration and bleeding are less common.

OXICAM DERIVATIVES
Piroxicam It is a long-acting potent NSAID with anti-inflammatory

MOA: It is a reversible inhibitor of COX;

Pharmacokinetics:
ROA: Rapidly and completely absorbed:
Metabolism: 99% plasma protein bound; largely metabolized in liver by hydroxylation and glucuronideconjugation;
Excretion: excreted in urine and bile;

Adverse effects:
The g.i. side effects are more than ibuprofen
Rashes and pruritus

Uses
Treatment of : Rheumatoid and osteo-arthritis, ankylosing spondylitis, acute gout, musculoskeletal injuries, dentistry, episiotomy, dysmenorrhoea etc.,

PYRROLO-PYRROLE DERIVATIVE
Ketorolac:
Novel NSAID with potent analgesic and modest anti-inflammatory activity.

Remaining from notes

PREFERENTIAL COX-2 INHIBITORS

Nimesulide

This newer NSAID is a relatively weak inhibitor of PG synthesis and there is some evidence to indicate relative COX-2 selectivity.

Anti-inflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNF□ □release, free radical scavanging, inhibition of metalloproteinase activity in cartilage.

Remaining from notes

SELECTIVE COX-2 INHIBITORS (Coxibs)

- **COX-2 inhibitors** cause little gastric mucosal damage; occurrence of peptic ulcer and ulcer bleeds is clearly lower than with traditional NSAIDs.
- They do not depress TXA2 production by platelets (COX-I dependent); do not inhibit platelet aggregation or prolong bleeding time, but reduce PGI2 production by vascular endothelium.

- Currently, 3 selective COX-2 inhibitors *Celecoxib*, *Etoricoxib* and *Parecoxib* are available.
- Moreover, they should be avoided in patients with history of ischaemic heart disease/hypertension/cardiac failure/cerebrovascular disease, who are predisposed to CV events.

Paracetmol:

Actions:

- The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral anti-inflammatory component. Analgesic action of aspirin and paracetamol is additive.
- Paracetamol is a good and promptly acting antipyretic.
- Paracetamol has negligible anti-inflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on COX in the brain.

Pharmacokinetics

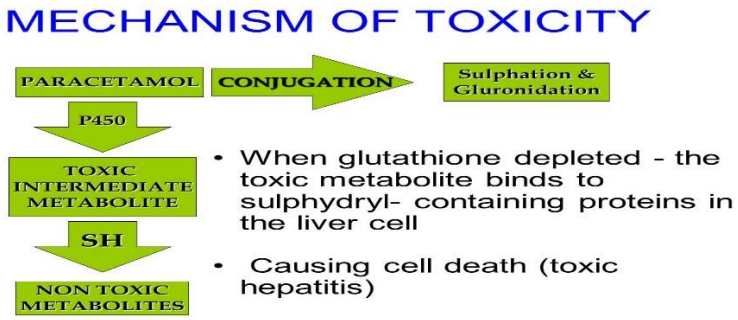
- Paracetamol is well absorbed: orally, plasma and it is uniformly distributed in the body. Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are
- excreted rapidly in urine. Plasma t½ is 2–3 hours.

ADR:

- *Analgesic nephropathy*
- *Acute paracetamol poisoning:* It occurs especially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur.

- Early manifestations are just nausea, vomiting, abdominal pain and liver tenderness with no impairment of consciousness.

Mechanism of toxicity



Uses: Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea, etc. but is relatively ineffective when inflammation is prominent.

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TOPIC: ANTIRHEUMATOID DRUGS

Rheumatoid arthritis (RA) is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage.

Classification:

A. *Disease modifying antirheumatic drugs (DMARDs)*

1. *Immunosuppressants:* Methotrexate, Azathioprine, Cyclosporine
2. Sulfasalazine
3. Chloroquine or Hydroxychloroquine
4. Leflunomide
5. Gold sod. thiomalate, Auranofin
6. d-Penicillamine

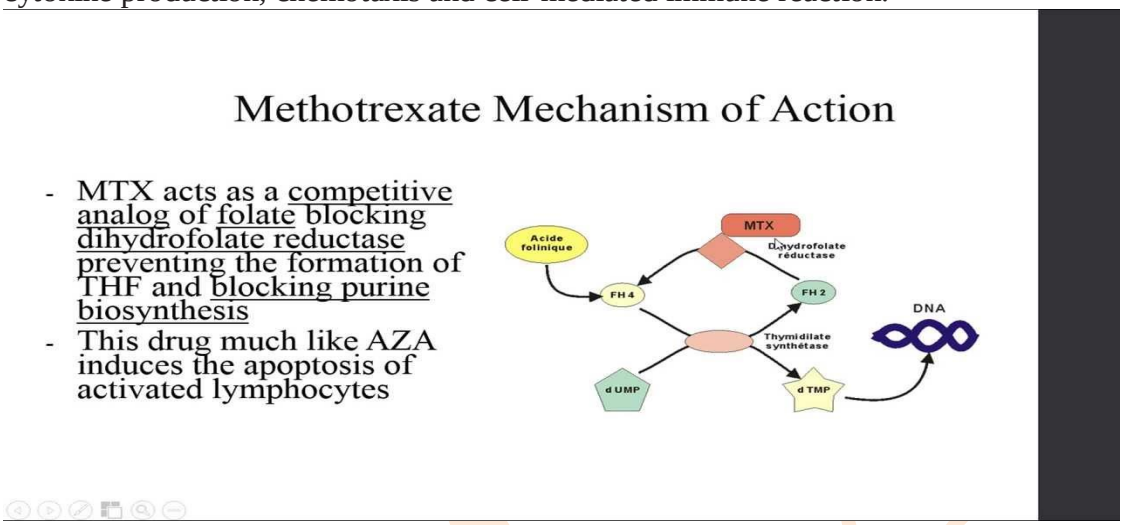
B. *Biologic response modifiers (BRMs)*

1. *TNFα inhibitors:* Etanercept, Infliximab, Adalimumab
2. *IL-1 antagonist:* Anakinra

C. *Adjuvant drugs*
Corticosteroids: Prednisolone and others

Immunosuppressants:

Methotrexate (Mtx) This dihydrofolate reductase inhibitor has prominent immunosuppressant and antiinflammatory property. Beneficial effects in RA are probably related to inhibition of cytokine production, chemotaxis and cell-mediated immune reaction.



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CLASS: 13

TOPIC: Drugs in Gout

Gout It is a metabolic disorder characterized by hyperuricaemia (normal plasma urate 1–4 mg/ dl). Uric acid, a product of purine metabolism, has low water solubility, especially at low pH. When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue.

For acute gout	*For chronic gout / hyperuricaemia*
NSAIDs	*Uricosurics Synthesis inhibitor*
Colchicine	Probenecid Allopurinol
Corticosteroids	Sulfinpyrazone

Acute gout manifests as sudden onset of severe inflammation in a small joint (commonest is metatarso phalangeal joint of great toe) due to precipitation of urate crystals in the joint space. The joint becomes red, swollen and extremely painful: requires immediate treatment.

NSAIDS:

One of the strong antiinflammatory drugs, e.g. ***indomethacin, naproxen, piroxicam, diclofenac*** or ***etoricoxib*** is given in relatively high and quickly repeated doses. They are quite effective in terminating the attack, but may take 12–24 hours, i.e. response is somewhat slower than with colchicine, but they are generally better tolerated; majority of patients prefer them over colchicine.

Colchicine:

Colchicine is neither analgesic nor anti-inflammatory, but it specifically suppresses gouty inflammation.

They start an inflammatory response, chemotactic factors are produced – granulocyte migration into the joint; they phagocytose urate crystals and release a glycoprotein which aggravates the inflammation by:

(i) Increasing lactic acid production from inflammatory cells → local pH is reduced → more urate crystals are precipitated in

(ii) Releasing lysosomal enzymes which cause joint destruction. Colchicine does not affect phagocytosis of urate crystals but inhibits release of the glycoprotein and the subsequent events. By binding to fibrillary protein tubulin, it inhibits granulocyte migration into the inflamed joint and thus interrupts the vicious cycle. Other actions of colchicine are:

(a) Antimitotic: causes metaphase arrest by binding to microtubules of mitotic spindle. It was tried for cancer chemotherapy but abandoned due to toxicity. It is used to produce polyploidy in plants.

(i) (b) Increases gut motility through neural mechanisms.