



Non Steroidal Anti-inflammatory Drugs (NSAIDs)

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Inflammation

- Inflammation is a complex response to cell injury that occurs in vascularized connective tissue and involves the immune response.
- The immune response may leads to chronic inflammation without resolution of the underlying injurious process

- Nonsteroidal antiinflammatory drugs (NSAIDs) relief pain &inflammation
- They are appropriate for the treatment of both acute and chronic inflammatory conditions.

The Treatment of Patients with Inflammation Involves two Primary Goals:

- The relief of symptoms and the maintenance of function
- The slowing or arrest of the tissue damaging process.

There are two Major Pathways in the Synthesis of the Eicosanoids from Arachidonic Acid

- Cyclooxygenase pathway.
- Lipoxygenase pathway.

Synthesis of Prostaglandins

- Prostaglandins are the important mediators of inflammation
- Arachidonic is the precursor of the prostaglandins.
- Release of Free arachidonic acid from tissue phospholipids occurs by the action of phospholipase A₂ via a process controlled by hormones and other stimuli.
- Arachidonic acid converts to the endoperoxide (precursors of prostaglandins) by cyclooxygenase enzyme

The Cyclooxygenase has at least 2 isoforms:

- COX-1 is expressed in noninflammatory cells
- COX-2 is expressed in activated lymphocytes, polymorphonuclear cells and other inflammatory cells.

Cyclooxygenase Enzymes

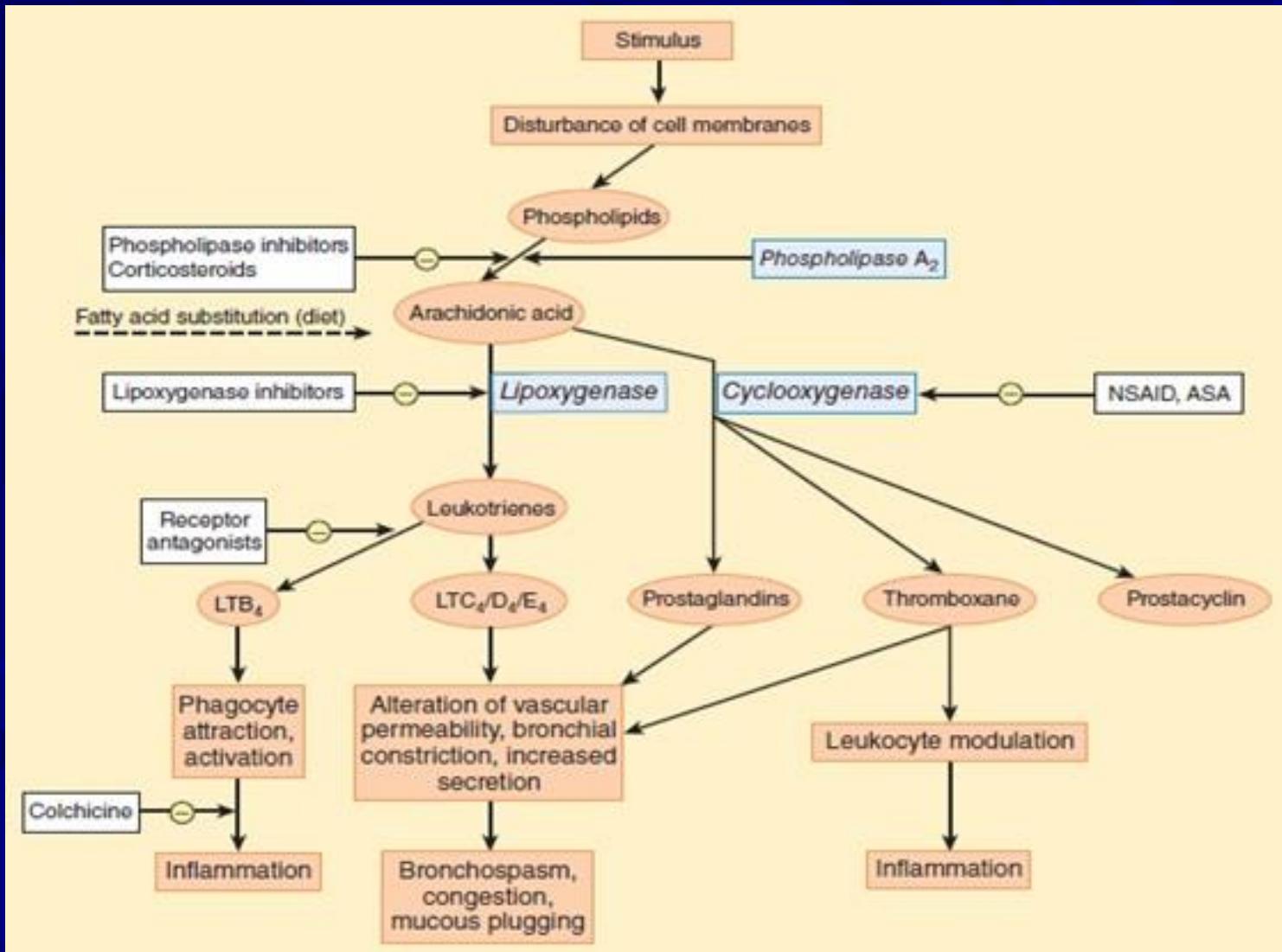
COX-1

- Responsible for the physiologic production of prostanoids.
- Regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function.
- Present in every organ

COX-2

- Causes production of prostanoids in sites of disease and inflammation
- Expressed in the brain, kidney and bone.

Prostanoid mediators derived from arachidonic acid and sites of drug action.



NSAIDs

Aspirin

Other
nonselective
NSAIDs

COX-2
inhibitors
(celecoxib)

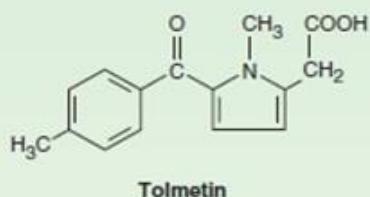
Chemical Classes of NSAIDs

Propionic acid derivative



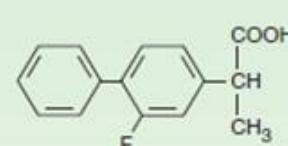
Ibuprofen

Pyrrolealkanoic acid derivative



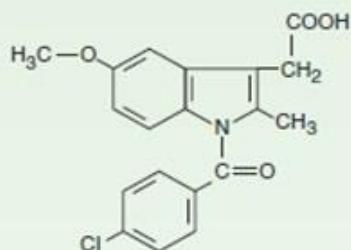
Tolmetin

Phenylalkanoic acid derivative



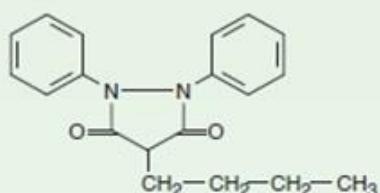
Flurbiprofen

Indole derivative



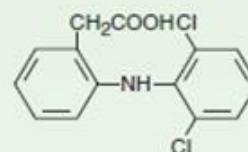
Indomethacin

Pyrazolone derivative



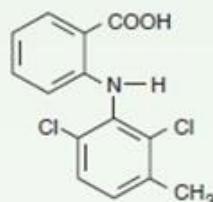
Phenylbutazone

Phenylacetic acid derivative



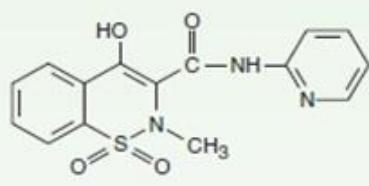
Diclofenac

Fenamate



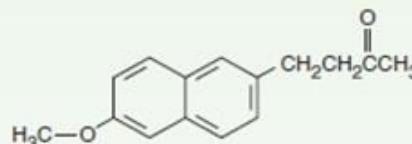
Meclofenamic acid

Oxicam



Piroxicam

Naphthylacetic acid prodrug



Nabumetone

NSAIDs-therapeutic Effects

- Anti-inflammatory
- Antipyretic
- Analgesic effects

Mechanisms of Action of NSAID

- NSAIDs inhibits COX activity, it diminishes prostaglandins and inhibits the inflammation which is mediated by prostaglandins
- Aspirin irreversibly acetylates and blocks platelet cyclooxygenase, while the non-COX-selective NSAIDs are reversible inhibitors.
- Inhibition of chemotaxis
- Down-regulation of interleukin-1 production
- Decreased production of free radicals and superoxide

- Decrease PG synthesis, repress the sensation of pain (Prostaglandin is sensitize nerve endings to the action of bradykinin, histamine)
- Affect lymphokine production from T lymphocytes, Reverse the vasodilation of inflammation.
- ↓PG synthesis, lower body temperature in patients with fever & resets the hypothalamic thermoregulatory center.
- Inhibit platelet aggregation (except COX-2-selective & the Nonacetylated salicylates).

Indication of NSAIDs

1. Rheumatoid arthritis
2. psoriatic arthritis
3. Arthritis associated with inflammatory bowel disease
4. Osteoarthritis
5. Musculoskeletal syndromes (eg, sprains and strains, low back pain)
6. Gout (except tolmetin which is ineffective in gout).

Pharmacokinetics

- Highly protein-bound
- Variable half life time
- Good absorption
- Hepatic metabolism, phase I followed by phase II mechanisms and others by direct glucuronidation (phase II) alone.
- Renal excretion is the most important route for final elimination
- All undergo varying degrees of biliary excretion and reabsorption (enterohepatic circulation).

Nonsteroidal anti-inflammatory Drugs.

Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Aspirin	0.25	<2%	1200–1500 mg tid
Salicylate ¹	2–19	2–30%	See footnote 2
Celecoxib	11	27% ³	100–200 mg bid
Diclofenac	1.1	<1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	<1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	<1%	300 mg tid
Ibuprofen	2	<1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	<1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid ⁴
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone ⁵	26	1%	1000–2000 mg qd ⁶
Naproxen	14	<1%	375 mg bid
Oxaprozin	58	1–4%	1200–1800 mg qd ⁶
Piroxicam	57	4–10%	20 mg qd ⁶
Sulindac	8	7%	200 mg bid
Tolmetin	1	7%	400 mg qid

Adverse Effects of NSAIDs

- 1. Central nervous system:** Headaches, tinnitus and dizziness.
- 2. Cardiovascular:** Fluid retention, hypertension, edema and rarely, myocardial infarction and congestive heart failure.
- 3. Gastrointestinal:** Abdominal pain, dysplasia, nausea, vomiting rarely and ulcers or bleeding. COX-2-selective agents cause less GI irritation than aspirin.
- 4. Hematologic:** Rare thrombocytopenia, neutropenia.
- 5. Hepatic:** Abnormal liver function tests
- 6. Skin:** Rashes, pruritus.
- 7. Pulmonary:** Asthma
- 8. Renal:** Renal insufficiency, renal failure, hyperkalemia and proteinuria decrease renal prostaglandin which is responsible for autoregulation of renal blood flow

Nonselective COX Inhibitors

- **Aspirin (acetylsalicylic acid)** is the prototype
- **Aspirin, ibuprofen, indomethacin, piroxicam & sulindac** are somewhat more effective in inhibiting COX-1.
- Vary in potency, analgesic, anti-inflammatory effectiveness & duration of action.
- **Indomethacin** has greater anti-inflammatory effectiveness
- **ketorolac** has greater analgesic effectiveness.

Aspirin and Other Salicylic Acid Derivatives

Aspirin

Aspirin is now rarely used as an anti-inflammatory medication, it have anti-platelet effects (81–325 mg once daily).

Dosage

- **Low dose** is effective in reducing platelet aggregation
- **Intermediate doses** have antipyretic and analgesic effects
- **High doses** (2400–4000 mg/d) are used for an anti-inflammatory effect.

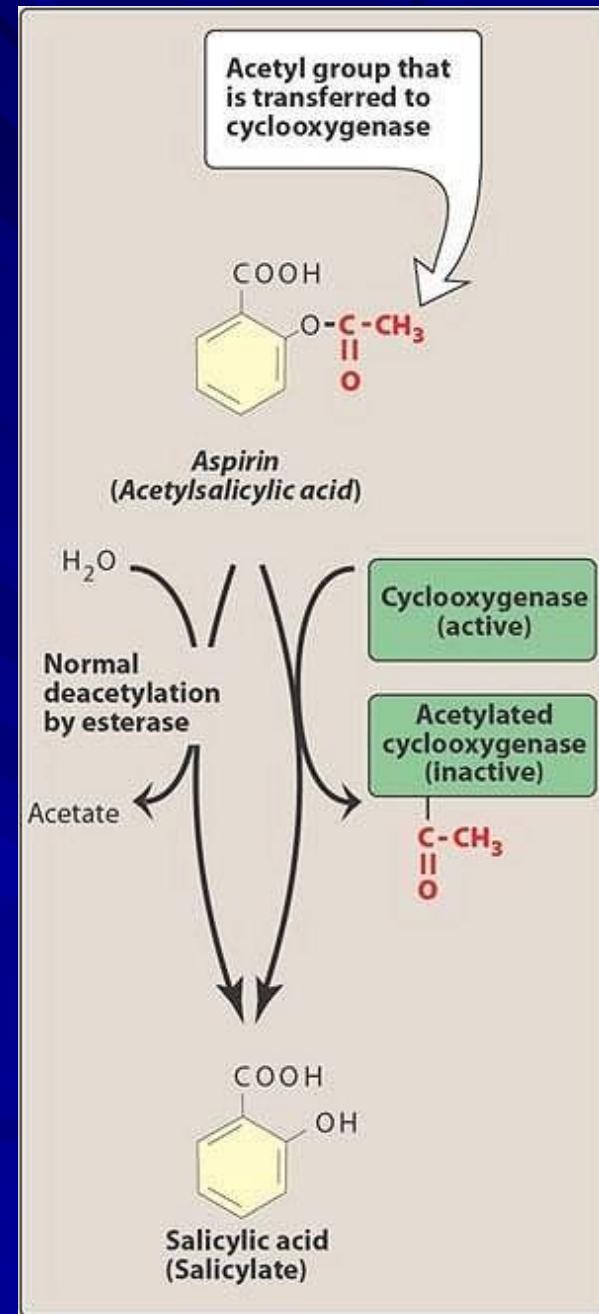
Mechanisms of Action of Aspirin

- It irreversibly inhibits platelet COX
- Antiplatelet effect lasts 8-10 days (the life of the platelet).
- In other tissues, synthesis of new COX replaces the inactivated enzyme so that a duration of action for ordinary doses is 6-12 hours

Pharmacokinetics

- Aspirin (acetylsalicylic acid; ASA)
- It irreversibly acetylates (inactivates) COX
- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic and analgesic effects.
- Salicylate, is reversible inhibitor of COX
- Elimination of salicylate is first order at low doses, with a half-life of 3-5 h, At high (anti-inflammatory) doses, half-life increases to 15 h or more and elimination becomes zero order.
- Alkalization of the urine increases the rate of excretion of free salicylate and its water-soluble conjugates

Metabolism of aspirin and acetylation of cyclooxygenase by aspirin



Clinical Uses of Aspirin

1. Decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis
2. Gout (anti inflammatory dose), rheumatic fever, osteoarthritis, and RA.
headache, arthralgia, and myalgia.
3. Long-term (5 years or longer) use of aspirin at low dosage reduce the incidence of colon cancer
4. Women at ***high risk*** of pre-eclampsia (75 mg of aspirin daily after 12 week of gestation)

Adverse Effects

- **Therapeutic anti-inflammatory** doses of aspirin cause gastric upset. Chronic use can result in gastric ulceration, upper gastrointestinal bleeding and renal effects, including acute failure
- **At higher doses** of aspirin, tinnitus, vertigo, hyperventilation and respiratory alkalosis
- **At very high doses** of aspirin, metabolic acidosis, dehydration, hyperthermia, collapse, coma and death.

Other Adverse Effect of Aspirin

- Prolonged bleeding time
- * Contraindicated in hemophilic patient
- * Aspirin should not be taken for at least 1 week prior to surgery
- Hypersensitivity nasal polyps ,urticaria, bronchoconstriction & angioedema
- Reye's syndrome (rapid liver degeneration and encephalopathy) in Children with viral infections (avoided in children and teenagers) (<15 years) with chickenpox or influenza

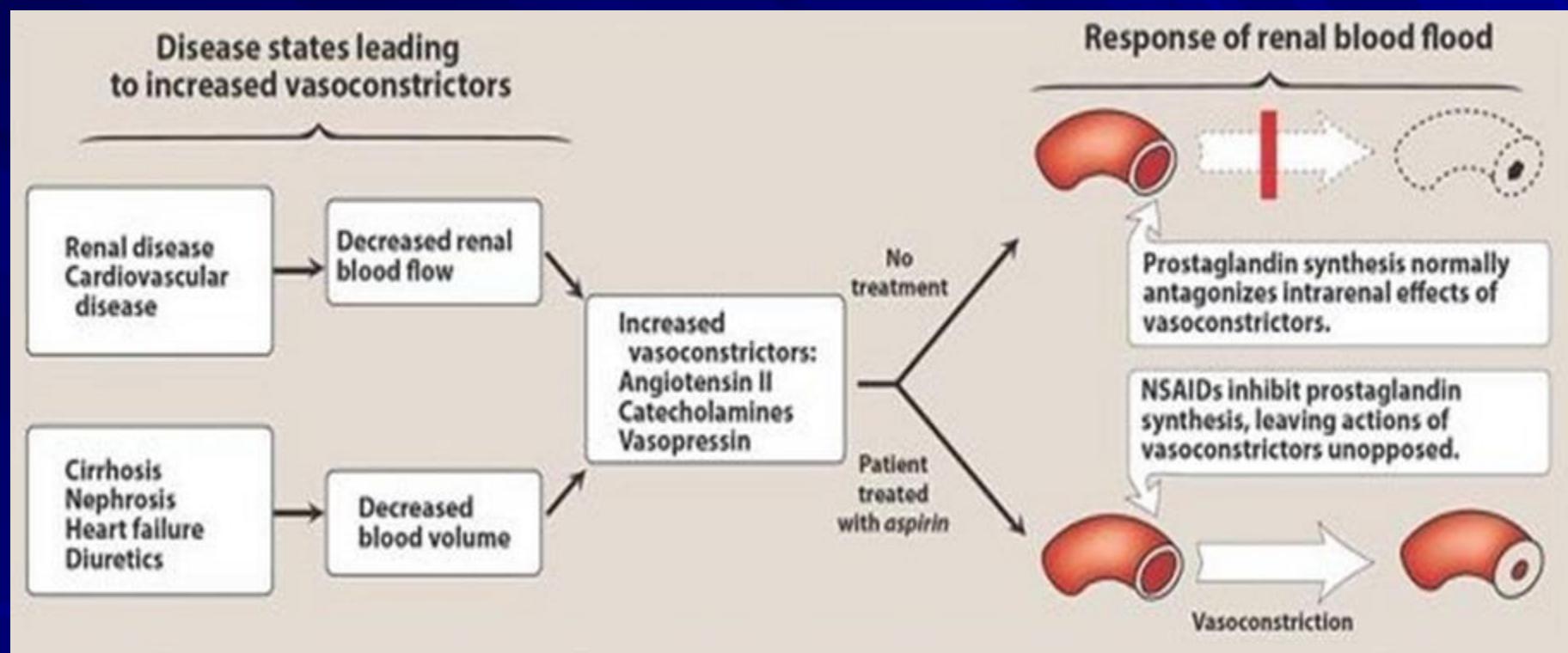
Aspirin is Classified as FDA Pregnancy

- Category C risk during Trimesters 1 and 2
- Category D during Trimester 3.

Note: Aspirin should be avoided during pregnancy and in breast-feeding

*indicated only for Women at *high risk* of pre-eclampsia

Renal Effect of Aspirin Inhibition of Prostaglandin Synthesis.



Drug Interactions

- Ketorolac and aspirin, increased platelet aggregation inhibition
- live varicella virus vaccination
- Warfarin, phenytoin, or valproic acid(Aspirin displace these drug from there protein-binding)
- Probenecid or sulfinpyrazone, because these agents cause increased renal excretion of uric acid whereas aspirin (<2g/day) cause reduced clearance of uric acid.

Diflunisal

- Although diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate.
- Clearance depends on renal function & hepatic metabolism

Clinical Uses

- In rheumatoid arthritis
- Pain control in Cancer with bone metastases
- Pain control in dental (third molar) surgery.
- A 2% diflunisal oral ointment is clinically useful analgesic for painful oral lesions.

Propionic Acid Derivatives

Ibuprofen

Flurbiprofen

Enoprofen

Naproxen

Ibuprofen

- It has analgesic effect in doses (<2400 mg/d)
- It has anti-inflammatory effect in doses of 2400 mg/d, equivalent to anti-inflammatory effect of 4 g of aspirin
- Ibuprofen is effective in closing patent ductus arteriosus in preterm infants (oral & IV) with the same efficacy and safety as indomethacin.
- Well absorbed by topical cream & liquid gel
- In addition to common adverse effects, rare hematologic effects include agranulocytosis and aplastic anemia.

Contraindication of Ibuprofen

- In individuals who have allergy to Aspirin or have reactivity to Aspirin (nasal polyps, angioedema and bronchospastic reactivity)
- Aseptic meningitis (particularly in patients with systemic lupus erythematosus)

Flurbiprofen

- More complex mechanism of action than other NSAIDs.
- Affect tumor necrosis factor- α (TNF- α) and nitric oxide synthesis.
- Topical ophthalmic formulation for inhibition of intraoperative miosis
- Flurbiprofen intravenously is effective for perioperative analgesia in minor ear, neck and nose surgery
- Lozenge form for sore throat.
- Adverse effect profile is similar to that of other NSAIDs in most ways, flurbiprofen is also rarely associated with cogwheel rigidity, ataxia, tremor and myoclonus

Naproxen

- It is effective for the usual rheumatologic indications
- It is available in a slow release formulation, oral suspension, topical preparation and an ophthalmic solution are also available.

Adverse Effects

- The common adverse effects, rare cases of allergic pneumonitis, leukocytoclastic vasculitis and pseudoporphyria.

Oxicam Derivatives

Piroxicam (nonselective COX inhibitor)

Meloxicam (preferentially selective COX-2 inhibitor)

Piroxicam

- Piroxicam, an oxicam is a nonselective COX inhibitor
- Its long half-life ,once-daily dosing
- Piroxicam can be used for the usual rheumatic indications.
- Dosages higher than 20 mg/d increase peptic ulcer and bleeding
- This risk is 9.5 times higher with piroxicam than with other NSAIDs

Meloxicam

- Meloxicam is related to piroxicam
- preferentially inhibits COX-2 over COX-1
- Meloxicam considered “preferentially” selective (at its lowest therapeutic dose of 7.5 mg/d) rather than “highly” selective as celecoxib
- It is associated with fewer clinical GI symptoms and complications than piroxicam
- Meloxicam inhibit synthesis of thromboxane A₂, even at supratherapeutic doses, its blockade of thromboxane A₂ does not reach levels that result in decreased in vivo platelet function

Fenamates

Mefenamic, Meclofenamate

- Have no advantages over other NSAIDs as anti-inflammatory agents.
- Mefenamic acid relieve pain in primary dysmenorrhea

Side Effects:

- Diarrhea, can be severe, and they are associated with inflammation of the bowel.
- Hemolytic anemia

Indomethacin

- It is an indole derivative
- It is a potent nonselective COX inhibitor and inhibit phospholipase A and C, reduce neutrophil migration and decrease T-cell and B-cell proliferation.
- It has been used to accelerate closure of patent ductus arteriosus
- Indomethacin also used for other conditions, including, juvenile rheumatoid arthritis, pleurisy, nephrotic syndrome and diabetes insipidus.
- An ophthalmic preparation for conjunctival inflammation and to reduce pain after traumatic corneal abrasion.
- Oral rinse for Gingival inflammation

Side Effects of Indomethacin

- In addition to the common side effects of NSAIDs
- The GI effects may include pancreatitis.
- Serious hematologic reactions
- Headache is experienced by 15-25% of patients and may be associated with dizziness, confusion, and depression, hallucinations
- Renal papillary necrosis.

Drug interaction of Indomethacin

Probenecid prolongs indomethacin's half-life by inhibiting both renal and biliary clearance

Etodolac

- Acetic acid derivative
- Intermediate half-life
- Use of parenteral ketorolac is generally restricted to 72 h because of the risk of gastrointestinal and renal damage with longer administration.

Sulindac

- Sulindac is a sulfoxide prodrug
- Duration of action to 12–16 hours.

Indication of Sulindac

1. Rheumatic disease
2. Suppresses familial intestinal polyposis
3. Inhibit the development of colon, breast and prostate cancer in humans.

Adverse Reactions

- Stevens-Johnson syndrome, thrombocytopenia, agranulocytosis & nephrotic syndrome
- ↑serum aminotransferases, cholestatic liver damage

Diclofenac

- It is a phenylacetic acid derivative
- Gastrointestinal ulceration may occur less frequently than other NSAIDs.
- A preparation combining diclofenac and misoprostol decreases upper gastrointestinal ulceration but may result in diarrhea.
- Another combination of diclofenac and omeprazole was also effective in prevention of bleeding
- Renal adverse effects were common in high-risk patients.
- Elevation of serum aminotransferases occurs more commonly with this drug than with other NSAIDs.

- Diclofenac ophthalmic preparation can be used after intraocular lens implantation
- Topical gel effective for solar keratoses.
- Diclofenac is also available as rectal suppository, oral mouthwash and intramuscular preparation

Tolmetin

- Pyrrolealkanoic acid derivative
- Tolmetin is a nonselective COX inhibitor
- Short half-life (1–2 hours)
- It is not often used.
- It is ineffective (for unknown reasons) in the treatment of gout and it may cause (rarely) thrombocytopenic purpura.

Nabumetone

- Naphthylacetic acid prodrug
- Its half-life of more than 24, once-daily dosing
- It does undergo enterohepatic circulation
- Indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects.
- It may be less damaging to the stomach than some other NSAIDs when given at a dosage of 1000mg/d. Unfortunately, higher dosages (eg, 1500-2000mg/d) are often needed.
- Associated with pseudoporphyria and photosensitivity in some patients.

Selective COX-2 Inhibitors

- The efficacy of COX-2-selective drugs equals that of the older NSAIDs, less GI adverse effect
- Selective COX-2 inhibitors may increase the incidence of edema and hypertension.
- The selective COX-2 inhibitors do not affect platelet function at their usual doses.
- Same risk of renal damage as nonselective COX inhibitors, because COX-2 contributes to homeostatic renal effects.

Celecoxib

- It is a selective COX-2 inhibitor
- 10–20 times more selective for COX-2 than COX-1
- **Celecoxib is** cyclooxygenase-2 (COX-2)-selective inhibitors, less gastrointestinal toxicity but a higher incidence of cardiovascular thrombotic events than the nonselective drugs, Celecoxib may cause rashes (Probably because it is a sulfonamide).
- Celecoxib may potentiate the anticoagulant effects of warfarin (celecoxib and the active form of warfarin are metabolized via CYP2C9)
- Celecoxib is still available for use in patients with RA
- Celecoxib has a Food and Drug Administration initiated “black box” warning concerning cardiovascular risks

Pharmacokinetics

- Celecoxib is readily absorbed.
- Its half-life is about 11 hours; thus, the drug is usually taken once a day.
- Metabolized in the liver
- Excreted in the feces and urine.
- Celecoxib should be avoided in patients with severe hepatic and renal disease.

Note: The COX-2 inhibitors having a greater inhibitory effect on endothelial prostacyclin (PGI₂) formation than on platelet TXA₂ formation & this increase risk of arterial thrombosis because Prostacyclin promotes vasodilation and inhibits platelet aggregation, whereas TXA₂ has the opposite effects.

Contraindication of Celecoxib

- Allergic patient to sulfonamides, aspirin or nonselective NSAIDs
- In patients with chronic renal insufficiency, severe heart disease, volume depletion and/or hepatic failure.

Drug Interaction

- Enzyme Inhibitors such as fluconazole, fluvastatin, zafirlukast and may increase serum levels of celecoxib.
- Celecoxib It is enzyme Inhibitors, elevated levels of some b-blockers, antidepressants and antipsychotic drugs.

➤ **Rofecoxib and Valdecoxib**, were withdrawn from the market because of their association with increased cardiovascular thrombotic events.