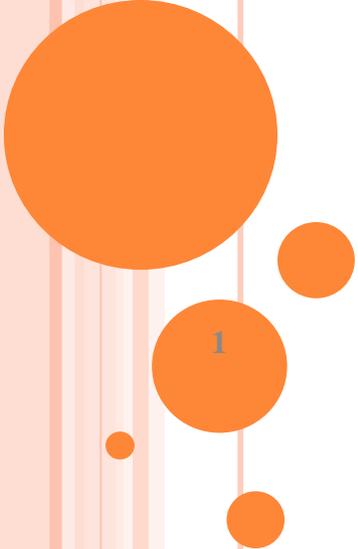


NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)



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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

- The term "nonsteroidal" is used to distinguish these drugs from steroids, which have a similar eicosanoid-depressing, anti-inflammatory action.
- NSAIDs are non-narcotic, non-opioid, aspirin-like analgesics.
- Most currently available NSAIDs act by inhibiting the prostaglandin (PG) synthase enzymes.
- Most NSAIDs are competitive, reversible, active site inhibitors of the COX enzymes. Aspirin inhibits them irreversibly.

CLASSIFICATION

Nonselective COX inhibitors (traditional NSAIDs)

Salicylates	Propionic acid derivatives	Fenamate	Enolic acid derivatives	Acetic acid derivatives	Pyrazolone derivatives
Aspirin	Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen	Mephennamic acid.	Piroxicam, Tenoxicam	Ketorolac, Indomethacin, Nabumetone	Phenylbutazone, Oxyphenbutazone

Preferential COX-2 inhibitors	Selective COX-2 inhibitors	Analgesic-antipyretics with poor Antiinflammatory action
Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac	Celecoxib, Etoricoxib, Parecoxib.	<p>1. Paraaminophenol derivative: Paracetamol (Acetaminophen).</p> <p>2. Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone.</p> <p>3. Benzoxazine derivative: Nefopam.</p>

MECHANISM OF ACTION (MOA)

Cyclooxygenase Inhibition

Aspirin and NSAIDs inhibit the COX enzymes and PG production.

There are two forms of COX, COX-1 and COX-2.

- COX-1, expressed constitutively in most cells, is the dominant source of prostanoids for housekeeping functions.
- COX-2 is the more important source of prostanoid formation in inflammation.
 - ❖ induced by cytokines, shear stress, and tumor promoters.

Membrane Phospholipids

Phospholipase A2



Arachidonic Acid

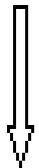
Lipoxygenase

Leukotrienes

Physiological
Regulation Performed
by COX-1

*Non-Selective Cox
Inhibitors*

Inflammatory
response by newly
expressed COX-2



*Cox-2
Selective
NSAID's*



PGE_2

PGI_2

TXA_2

GI
Protection

GI
Protection
Platelet Function
Regulation of
blood flow
Kidney Function

Platelet function
Regulation of
blood flow

PGE_2 PGI_2 TXA_2
Other Chemical
Mediators

Inflammation
Pain
Fever

COX1

- *Expressed in all tissues
- *constitutive
- *COX-1 products (PGE₂, PGI₂) are involved in normal cellular processes in stomach, platelets and kidney

COX2

- *Selectively expressed in renal, brain & endothelium, fetus
- COX-2 products (PG) are induced by various mediators of inflammation, interleukin, superoxide radicals, cytokines and endotoxins mainly in inflamed areas and cause more pain and inflammation
- Constitutive in brain and kidney
- Inducible in macula densa in response to salt restriction
- *Does not affect platelet aggregation

MOA CONTD...

Irreversible Cyclooxygenase Inhibition by Aspirin

- Aspirin covalently modifies COX-1 and COX-2, irreversibly inhibiting COX activity.
- The duration of aspirin's effects is related to the turnover rate of COXs in different target tissues.
- The importance of enzyme turnover in recovery from aspirin action is most notable in platelets.
- Platelets being anucleate have a markedly limited capacity for protein synthesis.
 - Inhibition of platelet COX-1–dependent TxA₂ formation is cumulative with repeated doses of aspirin.

MOA CONTD...

Selective Inhibition of Cyclooxygenase-2

- Constitutively expressed COX-1 is the predominant source of cytoprotective PGs formed by the GI epithelium.
- COX-2 is source of PG formation in inflammation and cancer.
- Selective inhibitors of COX-2 were developed based on the hypothesis
 - they would afford efficacy similar to tNSAIDs with better GI tolerability.

Features of nonselective COX inhibitors and selective COX-2 inhibitors

<u>Action</u>	Nonselective COX inhibitors	Selective/COX-2 inhibitors
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	-
5. Gastric mucosal damage	+	-
6. Renal salt/water retention	+	+
7. Delay/prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	-

MOA CONTD...

An anti-inflammatory action: the decrease in prostaglandin E₂ and prostacyclin reduces vasodilatation and, indirectly, oedema.

An analgesic action: decreased prostaglandin generation means less sensitisation of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-hydroxytryptamine.

An antipyretic action: endogenous pyrogens elevate the hypothalamic set point for temperature causing fever.

THERAPEUTIC USES

Three main therapeutic effects of all NSAIDs, including selective COX-2 inhibitors are:

- **anti-inflammatory effect:** modification of the inflammatory reaction
 - **Acetaminophen, which is antipyretic and analgesic is largely devoid of anti-inflammatory activity.**
- **analgesic effect:** reduction of certain types of (especially inflammatory) pain
- **antipyretic effect:** lowering of body temperature when this is raised in disease (i.e. fever).

THERAPEUTIC USES

- **Fetal Circulatory System:** Indomethacin and ibuprofen have been used in neonates to close the inappropriately patent ductus arteriosus.
- **Cardioprotection:** Aspirin reduces the risk of serious vascular events in high risk patients.
 - Irreversible acetylation of platelet COX → inhibition of platelet function until sufficient numbers of newplatelets are released.
 - Permanent and complete suppression of platelet COX-1–dependent TxA2 formation → cardioprotective effect of aspirin.

INDICATIONS FOR NSAIDS

- Pyrexia
- Mild to moderate pain
- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout
- Dysmenorrhoea
- Metastatic bone pain
- Headache & Migraine
- Postoperative pain
- Injury
- PDA (Patent Ductus Arteriosus)

OTHER CLINICAL USES

○ **Systemic Mastocytosis:**

- In patients with systemic mastocytosis, PGD₂, released from mast cells in large amounts is the major mediator of severe episodes of flushing, vasodilation, and hypotension.
- This PGD₂ effect is resistant to antihistamines.
- The addition of aspirin or ketoprofen provides relief.

○ **Niacin Intolerability:** Aspirin inhibits PGD₂ mediated flushing by niacin.

○ **Bartter Syndrome:**

- Caused by mutations in a Na⁺-K⁺-2Cl⁻ co-transporter.
- Treatment with indomethacin, combined with potassium repletion and spironolactone, is associated with improvement in the biochemical derangements and symptoms.

ADVERSE EFFECTS OF NSAIDs

Gastrointestinal:

- Abdominal pain
- Nausea
- Diarrhea
- Anorexia
- Gastric erosions/ulcers
- Anemia
- GI hemorrhage

Platelets:

- Inhibited platelet activation
- Propensity for bruising
- Increased risk of hemorrhage

ADVERSE EFFECTS OF NSAIDs

Renal:

- Salt and water retention
- Edema, worsening of renal function in renal/cardiac and cirrhotic patients
- Decreased effectiveness of antihypertensive medications
- Decreased effectiveness of diuretic medications
- Decreased urate excretion (especially with aspirin)
- Hyperkalemia

Cardiovascular:

- Closure of ductus arteriosus
- Myocardial infarction*
- Stroke*
- Thrombosis*

*** With the exception
of low-dose aspirin**

ADVERSE EFFECTS OF NSAIDs

CNS:

- Headache
- Vertigo
- Dizziness
- Confusion
- Hyperventilation (salicylates)

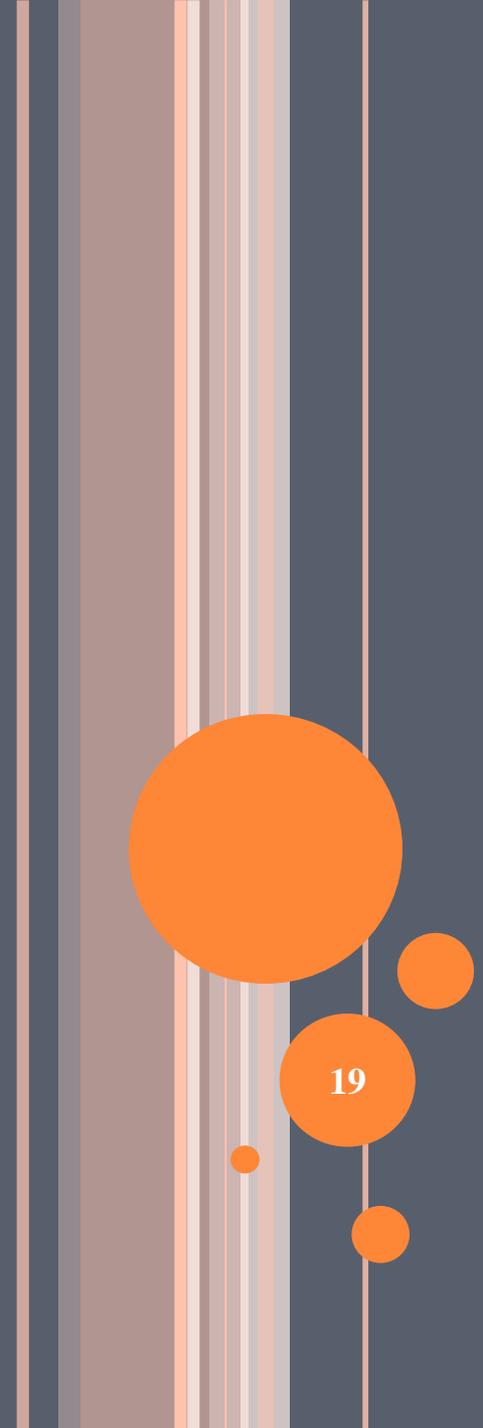
Uterus:

- Prolongation of gestation
- Inhibition of labor

ADVERSE EFFECTS OF NSAIDs

Hypersensitivity:

- Vasomotor rhinitis
- Angioneurotic edema
- Asthma
- Urticaria
- Flushing
- Hypotension
- Shock



ASPRIN & SOME OTHER IMPORTANT NSAIDs

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ASPIRIN

Actions-

- reduces inflammation
- antiinflammatory action is exerted at high doses (3–6 g/day or 100 mg/kg/ day).
- analgesic(0.3–1.5 g/day) for inflammatory pain
- antipyretic (i.e. reduces raised temperature)
- At low doses (40-325mg) it acts as antiplatelet drug

MOA- Irreversibly inactivating both cyclo-oxygenase (COX-1 and COX-2).

Abs/Distrb/Elim- Given orally. Half-life only 30min – rapid hydrolysis to salicylate but effects last longer because the COX has been inactivated and new enzyme must be produced.

USES

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

USES

6. By inhibiting platelet aggregation aspirin lowers the incidence of reinfarction in Postmyocardial infarction and poststroke patients.
- Aspirin 6–1000 mg/day reduces the incidence of myocardial infarction (MI)
 - ‘New onset’ or ‘sudden worsening’ angina is associated with high infarction rate & can be reduced to half by 100–150 mg aspirin per day for 12 weeks.
 - Aspirin reduces ‘transient ischaemic attacks’ and lowers incidence of stroke in such patients

ADVERSE EFFECTS

Gastrointestinal disturbances, especially gastric bleeding.

- In high dosage can cause 'salicylism' (tinnitus, vertigo, reduced hearing); allergic reactions occasionally; renal toxicity rarely.
- Can cause the potentially fatal Reye's syndrome (encephalopathy & liver disorder) in children after a viral infection.
- At therapeutic dose it can cause hyperuricemia.
- Prolongs bleeding time.

PRECAUTIONS AND CONTRAINDICATIONS

- Aspirin is C/I in patients who are sensitive to it and in peptic ulcer, bleeding tendencies, in children suffering from chicken pox or influenza.
- Liver disease: can cause hepatic necrosis.
- It should be avoided in diabetics, in those with low cardiac reserve or frank CHF and in juvenile rheumatoid arthritis.
- Aspirin should be stopped 1 week before elective surgery.
- Pregnancy & lactation
- G-6PD deficiency

ASPIRIN TOXICITY - TREATMENT

- **Decrease absorption** - activated charcoal, emetics, gastric lavage
- **Enhance excretion** - alkalinize urine, forced diuresis, hemodialysis
- **Supportive measures** - fluids, decrease temperature, bicarbonate, electrolytes, glucose, etc...

PARACETAMOL

Actions:

Paracetamol has potent analgesic and antipyretic actions but rather weaker anti inflammatory effects than other NSAIDs.

MOA:

Inhibition of COX-1, COX-2 and also the recently identified COX-3 which occurs predominantly in the CNS.

Absorption/Metabolism:

It is given orally and metabolised in the liver (half-life 2-4 hours).
Metabolized to N-acetyl paraaminobenzo quonimine (NAPQ) by microsomal enzyme.

Adverse Effects:

- Hepatotoxicity due to NPAQ
- Glutathione produced by liver detoxifies NPAQ
- Chronic alcoholics are predisposed to toxicity due to
 - Reduced glutathione
 - Alcohol induces production of NPAQ from acetaminophen.
- Antidote of choice is N - acetylcysteine

DICLOFENAC

- Diclofenac reduces inflammation , acts as an analgesic, reducing pain in conditions such as arthritis or acute injury.
- The action of one single dose is much longer (6 to 8 hours) than the very short half-life that the drug indicates.
- This could be partly because it persists for over 11 hours in synovial fluids.

Diclofenac is used for:

- musculoskeletal complaints: arthritis
 - rheumatoid arthritis
 - polymyositis,
 - osteoarthritis,
 - dental pain
 - ankylosing spondylitis
 - gout attacks
 - Pain management in kidney stones and gallstones.
- Additional indication is: acute migraines.

- Used commonly to treat : mild to moderate **post-operative** or **post-traumatic pain**, particularly when inflammation is also present.
- Is effective against: menstrual pain and endometriosis.

Propionic acid derivatives

- Naproxen, fenoprofen, ketoprofen, flurbiprofen and oxaprozin.

Mechanism of action:

- These drugs are reversible inhibitors of the cyclooxygenases, and thus, inhibit the synthesis of prostaglandins.

Uses:

- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity.
- Used in the chronic treatment of rheumatoid arthritis and osteoarthritis, because their gastrointestinal effects are generally less intense than that of aspirin.

IBUPROFEN

- Ibuprofen is a NSAID originally marketed as Brufen.
- It is used for relief of symptoms of
Arthritis
Primary dysmenorrhea,
Fever

As an analgesic, especially where there is an inflammatory component.

- Ibuprofen is known to have an antiplatelet effect, though it is relatively mild and short-lived when compared with aspirin or other better-known antiplatelet drugs.
- Ibuprofen is a *core* medicine in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic healthcare system.

MEFENAMIC ACID

- Used to treat pain, including menstrual pain. It is typically prescribed for oral administration.
- Decreases inflammation (swelling) and uterine contractions by inhibiting prostaglandin synthesis.
- Used for perimenstrual migraine headache prophylaxis, with treatment starting 2 days prior to the onset of flow or 1 day prior to the expected onset of the headache and continuing for the duration of menstruation.

- Since hepatic metabolism plays a significant role in mefenamic acid elimination, patients with known liver deficiency may be prescribed lower doses.
- Kidney deficiency may also cause accumulation of the drug and its metabolites in the excretory system. Therefore patients suffering from renal conditions should not be prescribed mefenamic acid.

INDOMETHACIN

- Indomethacin, is a potent nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation.
- Probenecid prolongs indomethacin's half-life by inhibiting both renal and biliary clearance.

Clinical Uses:

- Gout and ankylosing spondylitis. In addition, it has been used to treat patent ductus arteriosus.

Clinical Uses:

- An ophthalmic preparation for conjunctival inflammation to reduce pain after traumatic corneal abrasion.
- Gingival inflammation is reduced after administration of indomethacin oral rinse.
- Epidural injections produce a degree of pain relief similar to that achieved with methylprednisolone in post laminectomy syndrome.

KETOROLAC

- Ketorolac is an NSAID promoted for systemic use mainly as an analgesic, not as an antiinflammatory drug (though it has typical NSAID properties).
- Rapidly absorbed after oral and i.m. administration.
- It is most often given intramuscularly or intravenously, but an oral dose formulation is available.
- Highly plasma protein bound and 60% excreted unchanged in urine.
- T_{1/2} is 5-7 hours.

- The drug has been used successfully to replace morphine in some situations involving mild to moderate postsurgical pain.
- When used with an opioid, it may decrease the opioid requirement by 25–50%.
- An ophthalmic preparation is available for anti-inflammatory applications.
- Toxicities are similar to those of other NSAIDs, although renal toxicity may be more common with chronic use.

PIROXICAM

- Piroxicam, an oxicam is a nonselective COX inhibitor but at high concentrations also inhibits polymorphonuclear leukocyte migration, decreases IgM rheumatoid factor and inhibits lymphocyte function.
- Suitable for use as long-term antiinflammatory drug in rheumatoid and osteo-arthritis, ankylosing spondylitis.
- Toxicity includes gastrointestinal symptoms (20% of patients), dizziness, tinnitus, headache, and rash.
- When piroxicam is used in dosages higher than 20 mg/d, an increased incidence of peptic ulcer and bleeding is encountered.

INDOMETHACIN

- Inhibits $PLPA_2$ and possesses immunosuppressive property
- Indicated in Bartter's syndrome

MEFANAMIC ACID

- possesses PG receptor antagonistic and $PLPA_2$ inhibitory activity.
- Useful in dysmenorrhoea.
- **Piroxicam** and **Tenoxicam** are longest acting NSAIDs due to enterohepatic circulation.
- **Nefopam** does not inhibit PG synthesis but relieves traumatic, post-op and musculoskeletal pain.

COX-2 SELECTIVE INHIBITORS

- These drugs have advantage of **very little GI toxicity**.
- **Renal toxicity** is similar to traditional NSAIDs and **chances of thrombosis** (acute MI and stroke) are increased on prolonged use.
- Celecoxib, rofecoxib and valdecoxib are sulphonamide derivatives (can cause hypersensitivity reactions)
- Etoricoxib is longest acting and requires hepatic function monitoring during its use.
- Lumiracoxib is a newer cox 2 inhibitor that has more activity in the acidic medium.

COX-2 SELECTIVE INHIBITORS

- COX-2 inhibitors have been recommended mainly for treatment of osteoarthritis and rheumatoid arthritis.
- Other indications include primary familial adenomatous polyposis, dysmenorrhea, acute gouty arthritis & acute musculoskeletal pain.
- Currently, 3 selective COX-2 inhibitors (also called coxibs) Celecoxib, Etoricoxib and Parecoxib are available in India.
 - **Rofecoxib and valdecoxib were withdrawn due to increased risk of thrombotic disorders like myocardial infarction.**

THANK YOU