# NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

C.

#### **Abdul Waheed**

M.Pharm (Pharmacology)

Department of Pharmacology

Amity University, Noida

#### NSAIDs have following group of drugs

- Analgesic
- Antipyretic
- Antiinflammatory

### 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 derivative: phenylbutazone, Oxyphenbutazone

- B. Preferential COX-2 inhibitors
- Nimesulide, Meloxicam, Nabumeton.
- C. Selective COX-2 inhibitors
- Celecoxib, Etoricoxib, Parecoxib.
- D. Analgesic-antipyratics with poor antiinflammatory action
- 1. para aminophenol derivatives: Paracetamol
- 2. Pyrazolone derivative: Metamizol, Propiphenazone.
- 3. Benzoxazocine derivative: Nefopam

### Mechanism of action of NSAIDs

#### 1. Antiinflammatory effect

• due to the inhibition of the enzymes that produce prostaglandin H synthase (cyclooxygenase, or COX), which converts arachidonic acid to **prostaglandins**, and to **TXA2** and **prostacyclin**.

- Aspirin irreversibly inactivates COX-1 and COX-2 by acetylation of a specific serine residue.
- This distinguishes it from other NSAIDs, which reversibly inhibit COX-1 and COX-2.

#### 2. Analgesic effect

- A. The analgesic effect of NSAIDs is thought to be related to:
  - the peripheral inhibition of prostaglandin production
  - may also be due to the inhibition of pain stimuli at a subcortical site.
- B. NSAIDs prevent the potentiating action of prostaglandins on endogenous mediators of peripheral nerve stimulation (e.g., bradykinin).

#### 3. Antipyretic effect

- The antipyretic effect of NSAIDs is believed to be related to:
  - inhibition of production of prostaglandins induced by interleukin-1 (IL-1) and interleukin-6 (IL-6) in the hypothalamus
  - the "resetting" of the thermoregulatory system, leading to vasodilatation and increased heat loss.

# NSAIDs and Prostaglandin (PG) synthesis inhibition

- NSAIDs blocked PG generation.
- Prostaglandins, prostacyclin (PGI2), and thromboxane A2(TXA2) are produced from arachidonic acid by the enzyme cyclooxygenase.
- Cyclooxygenase (COX) exists in COX-1 and COX-2 isoforms.
- COX -3 has recently been identified

- Cyclooxygenase (COX) is found bound to the endoplasmatic reticulum. It exists in 3 isoforms:
- COX-1 (constitutive) acts in physiological conditions.
- COX-2 (inducible) is induced in inflammatory cells by pathological stimulus.
- COX-3 (in brain).

### Nonselective COX inhibitor

Salicylates

Aspirin:

• Aspirin is Acetylsalicylic acid converts to salicylic acid in body, responsible for action.



# PHARMACOLOGICAL ACTIONS

- 1. Analgesic, antipyretic, antiinflammatory actions:
- Aspirin is a weaker analgesic than morphine type drugs.
- Aspirin 600 mg < Codeine 60 mg < 6 mg Morphine</p>
- it effectively relieves inflammation, tissue injury, connective tissue and integumental pain, but is relatively ineffective in severe visceral and ischaemic pain.
- The analgesic action is mainly due to obtunding of peripheral pain receptors and prevention of PG-mediated sensitization of nerve endings.
- No sedation, subjective effects, tolerance or physical dependence is produced.
- Aspirin resets the hypothalamic thermostat and rapidly reduces fever by promoting heat loss, but does not decrease heat production.
- Antiinflammatory action is exerted at high doses (3-6 g/ day or 100 mg/kg/ day)

#### 2. Metabolic effects:

- significant only at antiinflammatory doses
- Cellular metabolism is increased, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation —> increased heat production.
- There is increased utilization of glucose —> blood sugar may decrease (especially in diabetics) and liver glycogen is depleted.
- 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:

- Effects are dose dependent.
- At antiinflammatory doses, respiration is stimulated by peripheral (increased C02 production) and central (increased sensitivity of respiratory centre to C02) actions.
- Hyperventilation is prominent in salicylate poisoning. Further rise in salicylate level causes respiratory depression; death is due to respiratory failure.

#### 4. Acid-base and electrolyte balance:

- Antiinflammatory doses produce significant changes in the acid-base and electrolyte composition of body fluids.
- Initially, respiratory stimulation predominates and tends to wash out Co<sub>2</sub> despite increased production ....respiratory alkalosis, which is compensated by increased renal excretion of HCO<sub>3</sub>; (with accompanying Na+, K+ and water).
- Still higher doses cause respiratory depression with Co2 retention, while excess Co2 production continues.... respiratory acidosis .

#### 5. CVS:

- Aspirin has no direct effect in therapeutic doses.
- Larger doses increase cardiac output to meet increased peripheral O2 demand and causes direct vasodilatation.
- Toxic doses depress, vasomotor centre: BP may fall. Because of increased cardiac work as well as Na+ and water retention,
- CHF may be precipitated in patients with low cardiac reserve.

#### 6. GIT:

- Aspirin and released salicylic acid irritate gastric mucosa, cause epigastric distress, nausea and vomiting.
- It also stimulates CTZ.
- 7. Urate excretion:
- Aspirin in high dose reduces renal tubular excretion of urate

#### 8. 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.
- long-term intake of large dose decreases synthesis of clotting factors in liver and predisposes to bleeding; can be prevented by prophylactic vit K therapy.

### Pharmacokinetics

- Aspirin is absorbed from the stomach and small intestines.
- Its poor water solubility is the limiting factor in absorption: microfining the drug particles and inclusion of an alkali (solubility is more at higher pH) enhances absorption.
- Aspirin is rapidly deacetylated in the gut wall, liver, plasma and other tissues to release salicylic acid which is the major circulating and active form.
- It slowly enters brain but freely crosses placenta.
- The metabolites are excreted by glomerular filtration as well as tubular secretion.

### **Uses of Aspirin**

- As analgesic (300 to 600 mg during 6 to 8 h) for headache, backache, pulled muscle, toothache, neuralgias.
- As antipyretic in fever of any origin in the same doses as for analglesia. However, *paracetamol and metamizole are safer*, and generally preferred.
- Acute rheumatic fever. Aspirin is the first drug of choice. Other drugs substitute Aspirin only when it fails or in severe cases. Antirheumatic doses are 75 to 100 mg/kg/24 h (resp. 4–6 g daily) in the first weeks.
- Rheumatoid arthritis. Aspirin a dose of 3 to 5 g/24 h *after meal* is effective in most cases. Since large doses of Aspirin are poorly tolerated for a long time, the new NSAIDs (diclofenac, ibuprofen, etc.) in depot form are preferred.

- Aspirin therapy in children with rheumatoid arthritis has been found to raise serum concentration transaminases, indicating liver damage. Most cases are asymptomatic but it is potentially dangerous.
- An association between salicylate therapy and "Reye's syndrome", a rare form of hepatic encephalopathy seen in children, having viral infection (varicella, influenza), has been noted.
- Aspirin should not be given to children under 15years unless specifically indicated, e.g. for juvenile arthritis (paracetamol is preferred).
- Postmyocardial infarction and poststroke patients: By inhibiting platelet aggregation in low doses (100 mg daily) Aspirin decreases the incidence of reinfarction.

#### Symptoms of Aspirin overdose

Restlessness Irritability Excessive and unorganized talking Fear or nervousness Dizziness Confusion Abnormally excited mood Hallucinations Drowsiness Loss of consciousness

*Systemic:* Fever Double vision

—Uncontrollable shaking Seizures

> Burning throat pain

-Vomiting Pain

> -Decreased urination<sub>22</sub>

### Adverse effects

- 1. Gastrointestinal effects
  - most common adverse effects of high-dose aspirin use (70% of patients):
    - nausea
    - vomiting
    - diarrhea or constipation
    - dyspepsia (impaired digestion)
    - epigastric pain
    - bleeding, and ulceration (primarily gastric).

- These gastrointestinal effects are thought to be due to:
  - 1. direct chemical effect on gastric cells or
  - 2. decrease in the production and cytoprotective activity of prostaglandins, which leads to gastric tissue susceptibility to damage by hydrochloric acid.

- The gastrointestinal effects may contraindicate **aspirin** use in patients with an active ulcer.
- Aspirin may be taken with prostaglandins to reduce gastric damage.
- Decrease gastric irritation by:
  - Substitution of enteric-coated or timed-release preparations, or
  - the use of **nonacetylated salicylates**, may decrease gastric irritation.

- 2. Hypersensitivity (intolerance)
- Hypersensitivity is relatively uncommon with the use of aspirin (0.3% of patients); hypersensitivity results in:
  - rash
  - bronchospasm
  - rhinitis
  - Edema, or
  - an anaphylactic reaction with shock, which may be life threatening.
- The incidence of intolerance is highest in patients with asthma, nasal polyps, recurrent rhinitis, or urticaria.
- Aspirin should be avoided in such patients.

- Cross-hypersensitivity may exist:
  - to other NSAIDs
  - to the yellow dye tartrazine, which is used in many pharmaceutical preparations.
- Hypersensitivity is not associated with:
  - sodium salicylate or
  - magnesium salicylate.

- The use of aspirin and other salicylates to control fever during viral infections (influenza and chickenpox) in children and adolescents is associated with an increased incidence of Reye's syndrome, an illness characterized by vomiting, hepatic disturbances, and encephalopathy that has a 35% mortality rate.
- Acetaminophen is recommended as a substitute for children with fever of unknown etiology.

### Miscellaneous adverse effects and

### contraindications

- May decrease the glomerular filtration rate, particularly in patients with renal insufficiency.
- Occasionally produce mild hepatitis
- Prolong bleeding time.
- Aspirin irreversibly inhibits platelet COX-1 and COX-2 and, thereby, TXA2 production, suppressing platelet adhesion and aggregation.
- The use of salicylates is contraindicated in patients with bleeding disorders
- Salicylates are not recommended during pregnancy; they may induce:
  - postpartum hemorrhage
  - premature closure of the fetal ductus arteriosus.

# Drug interactions

Drugs	Result
Diuretics	Decrease diuresis
Beta-blockers	Decrease antihypertensive effect
ACE inhibitors	Decrease antihypertensive effect
Anticoagulants	Increase of GI bleeding
Sulfonylurea	Increase hypoglycemic risk
Cyclosporine	Increase nephrotoxicity
GCS	Increase of GI bleeding
Alcohol	Increase of GI bleeding

# PROPIONIC ACID DERIVATIVES

- Ibuprofen was the first member
- The analgesic, antipyretic and antiinflammatory efficacy is rated somewhat lower than high dose of aspirin.
- All inhibit PG synthesis, naproxen being the most potent; but their *in vitro* potency tor this action does not closely parallel *in vitro* antiinflammatory potency.
- Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

#### • Ibuprofen:

- In doses of 2.4 g daily it is equivalent to 4 g of Aspirin in antiinflammatory effect.
- Oral ibuprofen is often prescribed *in lower doses* (< 2.4 g/d), at which it *has analgesic but not antiinflammatory efficacy*. It is available in low dose forms under several trade names (e. g. *Nurofen<sup>®</sup> film-tabl. 400 mg*).
- A topical cream preparation is absorbed into fascia and muscle. A liquid gel preparation of ibuprofen provides prompt relief in postsurgical dental pain.
- In comparison with indometacin, ibuprofen decreases urine output less and also causes less fluid retention.
- It is effective in closing ductus arteriosus in preterm infants, with much the same efficacy as indometacin.

- Flurbiprofen:
- Its (S)(-) enantiomer inhibits COX nonselectively, but it has been shown in rat tissue to also affect TNF-α and NO synthesis.
- Hepatic metabolism is extensive. It does demonstrate enterohepatic circulation.
- The efficacy of flurbiprofen at dosages of 200–400 mg/d is comparable to that of Aspirin and other NSAIDs for patients with rheumatoid arthritis, gout, and osteoarthritis.
- Flurbiprofen i.v. is effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat.

### Adverse effect

- Ibuprofen and all its congeners are better tolerated than aspirin.
- Side effects are milder and their incidence is lower.
- Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects.
- Gastric erosion and occult blood loss are rare.
- CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression.
- Rashes, itching and other hypersensitivity phenomena are infrequent.
- They are not to be prescribed to pregnant woman and should be avoided in peptic ulcer patient.

### Pharmacokinetic and interactions

- Well absorbed orally.
- Highly bounded to the plasma protein (90-99%).
- Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided.
- Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.
- All propionic acid derivatives enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile.

### Uses

- Ibuprofen is used as a simple analgesic, and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea. In which the action is clearly due to PG synthesis inhibition.
- It is available as an over-the-court drug.
- Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders.
- They are indicated in soft tissue injuries, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

### Anthranilic acid derivative

#### • Mephenamic acid:

- An analgesic, antipyretic and weaker antiinflammatory drug, which inhibits COX as well as antagonises certain actions of PGs.
- Mephenamic acid exerts peripheral as well central analgesic action.

#### • Adverse effects:

- Diarrhoea is the most important dose-related side effect. Epigastric distress is complained, but gut bleeding is not significant.
- Skin rashes, dizziness and other CNS manifestations have occurred.
- Haemolytic anaemia is a rare but serious complication.
- Pharmacokinetics:
- Oral absorption is slow but almost complete. It is highly bound to plasma proteins-displacement interactions can occur; partly metabolized and excreted in urine as well as bile. Plasma t1/2 is 2-4 hours.
- Uses:
- Mephenamic acid is indicated primarily as analgesic in muscle, joint and soft tissue pain where strong antiinflammatory action is not needed. It is quite effective in dysmenorrhoea. It may be useful in some cases of rheumatoid and osteoarthritis but has no distinct advantage.

### Aryl-acetic acid derivatives

#### • Diclofenac:

- An analgesic-antipyretic antiinflammatory drug, similar in efficacy to naproxen. It inhibits PG synthesis and is somewhatCOX-2 selective. The antiplatelet action is short lasting. Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.
- Adverse effects of diclofenac are generally mild epigastric pain, nausea, headache, dizziness, rashes. Gastric ulceration and bleeding are less common. Reversible elevation of serum aminotransferases has been reported more commonly; kidney damage is rare.
- A preparation combining diclofenac and misoprostol (PGE<sub>1</sub>) decreases upper GI ulceration but may result in diarrhoea.
- Diclofenac is among the most extensively used NSAID; employed in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, toothache, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions-affords quick relief of pain and wound edema.

#### • Aceclofenac:

• A somewhat COX-2 selective congener of diclofenac having similar properties. Enhancement of glycosaminoglycan synthesis may confer chondroprotective property.

# Oxicam derivatives

- Piroxicam:
- It is a long-acting potent NSAID with antiinflammatory potency similar to indomethacin and good analgesic-antipyretic action.
- It is a reversible inhibitor of COX; lowers PG concentration in synovial fluid and inhibits platelet aggregation-prolonging bleeding time.
- In addition, it decreases the production of IgM rheumatoid factor and leucocyte chemotaxis.

#### Pharmacokinetics:

- It is rapidly and completely absorbed
- 99% plasma protein bound;
- Largely metabolized in liver by hydroxylation and glucuronide conjugation;
- Excreted in urine and bile;
- Plasma t1/2 is long nearly 2 days.
- Adverse effects:
- The g.i. side effects are more than ibuprofen, but it is better tolerated and less ulcerogenic than indomethacin or phenylbutazone; causes less faecal blood loss than aspirin. Rashes and pruritus are seen in < 1% patients. Edema and reversible azotaemia have been observed.
- Tenoxicam:
- A congener of piroxicam with similar properties and uses.

# Pyrrolo-pyrrole derivative

- Ketorolac:
- A novel NSAID with potent analgesic and modest antiinflammatory activity.
- In postoperative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects.
- it inhibits PG synthesis and relieves pain by a peripheral mechanism.
- rapidly absorbed after oral and i.m. administration.
- It is highly plasma protein bound and 60% excreted unchanged in urine.
- Major metabolic pathway is glucuronidation.
- plasma t1/2 is 5-7 hours.

- Adverse effects:
- Nausea, abdominal pain, dyspepsia, ulceration, loose stools, drowsiness, headache, dizziness, nervousness, pruritus, pain at injection site, rise in serum transaminase and fluid retention have been noted.
- Use:
- Ketorolac is frequently used in postoperative, dental and acute musculoskeletal pain: 15-30 mg i.m. or i.v. every 4-6 hours (max. 90 mg/day).
- It may also be used for renal colic, migraine and pain due to bony metastasis.
- Continuous use for more then 5 days is not recommended.

### Indole derivative

- Indomethacin:
- It is a potent antiinflammatory drug with prompt antipyretic action.
- Indomethacin relieves only inflammatory or tissue injury related pain.
- It is a highly potent inhibitor of PG synthesis and suppresses neutrophil motility.
- In toxic doses it uncouples oxidative phosphorylation (like aspirin).
- Pharmacokinetics:
- Indomethacin is well absorbed orally
- It is 90% bound to plasma proteins, partly metabolized in liver to inactive products and excreted by kidney.
- Plasma t1/2 is 2-5 hours.

#### • Adverse effect:

- A high incidence (up to 50%) of GI and CNS side effects is produced: GI bleeding, diarrhoea, frontal headache, mental confusion, etc.
- It is contraindicated in machinery operators,
- drivers, psychiatric patients, epileptics, kidney
- disease, pregnant women and in children.

### PREFERENTIAL COX-2 INHIBITORS

- Nimesulide:
- weak inhibitor of PG synthesis and COX-2 selectivity.
- Antiinflammatory action may be exerted by other mechanisms as well, e.g. reduced generation of superoxide by neutrophils, inhibition of PAF synthesis and TNFa release, free radical scavanging, inhibition of metalloproteinase activity in cartilage.
- The analgesic, antipyretic and antiinflammatory activity of nimesulide has been rated comparable to other NSAIDs.
- It has been used primarily for short-lasting painful inflammatory conditions like sports injuries, sinusitis and other ear-nose-throat disorders, dental surgery, bursitis, low backache, dysmenorrhoea, postoperative pain, osteoarthritis and for fever.

- Nimesulide is almost completely absorbed orally, 99% plasma protein bound, extensively metabolized and excreted mainly in urine with a t1/2 of 2-5 hours.
- Adverse effects of nimesulide are gastrointestinal (epigastralgia, heart burn, nausea, loose motions), dermatological (rash, pruritus) and central (somnolence, dizziness).

# **SELECTIVE COX-2 INHIBITORS**

- They 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.
- It has been concluded that selective COX-2 inhibitors should be used only in patients at high risk of peptic ulcer, perforation or bleeds. If selected, they should be administered in the lowest dose for the shortest period of time. Moreover, they should be avoided in patients with history of ischaemic heart disease/ hypertension/ cardiac failure/ cerebrovascular disease, who are predisposed to CV events.

#### Celecoxib:

- It exerts antiinflammatory, analgesic and antipyretic actions with low ulcerogenic potential. Comparative trials in rheumatoid arthritis have found it to be as effective as naproxen or diclofenac, without affecting COX-1 activity in gastroduodenal mucosa. Platelet aggregation in response to collagen exposure remained intact in celecoxib recipients and serum TXB2 levels were not reduced. Though tolerability of celecoxib is better than traditional NSAIDs, still abdominal pain, dyspepsia and mild diarrhoea are the common side effects. Rashes, edema and a small rise in BP have also been noted.
- Celecoxib is slowly absorbed, 97% plasma protein bound and metabolized primarily by CYP2C9 with a t1/2 of 10 hours. It is approved for use in osteo- and rheumatoid arthritis in a dose of 100-200 mg BD.

#### • Etoricoxib:

• This newer COX-2 inhibitor has the highest COX-2 selectivity. It is suitable for once-a-day treatment of osteo /rheumatoid / acute gouty arthritis, dysmenorrhoea, acute dental surgery pain and similar conditions, without affecting platelet function or damaging gastric mucosa. The t1/2 is 24 hours. Side effects are dry mouth, aphthous ulcers, taste disturbance and paresthesias.

#### • Parecoxib:

• It is a prodrug of valdecoxib suitable for injection, and to be used in postoperative or similar short-term pain, with efficacy similar to ketorolac.

Theather south