Non-steroidal Anti-inflammatory Drugs

I. **Classification:**

1. salicylates as aspirin
2. Non-steroidal anti-inflammatory drugs:
   a. non-selective: ibuprofen, diclofenac sodium, indometacin, piroxicam, meloxicam, sulindac
   b. selective COX2 inhibitors: celecoxib, rofecoxib, etoricoxib
3. Paracetamol

All NSAIDs act by the same mechanism and they have three main actions including anti-inflammatory, analgesic and antipyretic.

I. Mechanism of action of NSAIDs:

They all act by inhibiting the cyclooxygenase enzyme (COX) and this inhibit the oxidation of arachidonic acid

1. Anti-inflammatory action: occurs mainly due to inhibition of prostaglandins that mediate inflammatory responses as vasodilatation, oedema, and pain. The NSAIDs suppress the pain, swelling and increased blood flow associated with inflammation, but they have little or no action on the underlying disease process. These effects mainly due to inhibition of PGE2 and prostacyclin
2. Analgesic action: NSAIDs are effective in mild to moderate pain, especially that arising from inflammation or tissue damage. This is due to decrease in prostaglandins peripherally in the inflamed tissue. They may also have a central analgesic effect possibly in the spinal cord.

3. Antipyretic action: This is due to reduction of prostaglandins production in the hypothalamus (temperature regulating center). Bacterial toxins produce fever by releasing phylogenic substances from macrophage. NSAIDs do not affect the normal body temperature

II. Adverse effects of NSIDs:

Prostaglandins are important in gastric cytoprotection, platelets aggregation; renal vascular auto regulation and induction of labor.

Common adverse reaction to the NSAIDs

1. gastrointestinal disturbances: are the commonest adverse effects. These occur mainly from inhibition of gastric COX-1. These include, gastric discomfort, dyspepsia, diarrhea, nausea and vomiting and gastric ulceration and bleeding. Serious haemorrhage or perforation can occur. The prostaglandin analogue misoprostol can reduce gastric damage produced by these drugs. The gastrointestinal disturbances occur less common with selective Cox-2 inhibitors.
2. Skin reactions: skin rash which is idiosynchratic is common especially with mefenamic acid and sulindac. Serious and fatal skin reaction may occur
3. Adverse renal effects: may cause reversible renal insufficiency in susceptible patients. This is due to the inhibition of prostaglandins (PGE2 and PGI2), which involved in maintenance of renal blood flow. Chronic ingestion of NSADs can cause analgesic nephropathy characterized by nephritis and renal papillary necrosis.
4. Other unwanted effects include bone marrow suppression, liver disorders, aggravation of bronchial asthma

III. Drugs

A. Aspirin and Salicylates:

1. Mechanism of action:

Aspirin (salicylic acid) and salicylates act by irreversibly inhibiting cyclooxygenase enzyme.

2. Pharmacokinetics of salicylates:

Oral salicylates are rapidly absorbed from the upper intestine and the stomach with a peak serum level occurs in 1 hour. Absorption depends on gastric pH, gastric emptying time. Following absorption, aspirin is rapidly distributed to various body tissues. Aspirin undergoes rapid hydrolysis in the body. Aspirin is 80-90% bound to plasma proteins, especially albumin. It is metabolized by the liver and then excreted by the kidneys. The half-life is dependent on the dose and range from 2-3 hours in antiplatelets dose to 12 hours in the anti-inflammatory dose.

3. **Clinical uses of salicylates:**

a. analgesic in mild to moderate pain in a dose of 300-1000 mg every 4-6 hours
b. anti-inflammatory as in arthritis in an average dose of 3-4g/day
c. cardioprotection; this is due to irreversible inhibition of platelets aggregation, usually is small doses that inhibit thromboxane but not prostacyclin
d. local effect in GIT for the treatment of ulcerative colitis as meselamine (5-aminosalicylic acid)
e. local keratolytic effect which is useful in the treatment of warts, corns and fungal infections.

2. Adverse effects:

a. GIT, nausea, vomiting, dyspepsia and peptic ulceration, which may lead to gastric bleeding. This is due to inhibition of COX1 in the gastric

mucosa. The gastric effect can be reduced by the use of misoprostol or other antiulcer drugs

b. liver toxicity, especially at high doses, with increase in liver enzymes
c. effect on uric acid, low doses decrease uric acid excretion and lead to hyperuricemia, while high doses increase uric excretion, lower the blood levels and cause uricosuria
d. increase bleeding tendency due to platelets aggregation inhibition, salicylates may also potentiate the effect of anticoagulants
e. respiratory system: Salicylates increase O2 consumption and CO2 production due to uncoupling of oxidative phosphorylation, the increase CO2 stimulates respiration. Salicylates can also stimulate the respiratory centers directly
f. Reye syndrome: when aspirin given in viral infection in children was found to be associated with "Reye" syndrome which consists of hepatitis and cerebral edema and is often fatal
g. in toxic doses salicylates cause "salicylism" characterized by dizziness, tinnitus, deafness, nausea and vomiting. Salicylates in toxic doses also cause respiratory stimulation which lead to hyperventilation, hyperthermia, hyperglycemia and glucosuria.

B. Individual Non-steroidal anti-inflammatory Drugs

1. Non-Selective Cox inhibitors

a. Indometacin (indomethacin)

Is an indole derivative which is a more potent non-selective inhibitor of COX than aspirin, it also inhibits the motility of polymorphonuclear leukocytes. It has both

analgesic and anti-inflammatory activities. It is estimated to be 20 times more potent than aspirin.

It is used for the closure of patent ductus arteriosus in premature infants, it is also used in ankylosing spondylitis.

High incidence of adverse effect limits its use as a long term analgesic drug .

Adverse effects include GI disturbances, which can be fatal, hepatitis, pancreatitis, headache, dizziness, vertigo and mental confusion. Bone marrow suppression with neutropenia and a plastic anemia

b. Diclofenac Sodium

Diclofenac is a phenylacetic acid derivative, it is one of the most commonly used NSAID. It has analgesic anti-inflammatory and antipyretic actions. Diclofenac absorbed well when given orally with a short half-life of about 2 hours. It is metabolized by the liver.

Diclofenac is useful for the long term management of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. It is available as tablets, injection and cream or gel for topical application.

Adverse effect mainly on the GIT, elevation of liver enzymes

c. Ibuprofen

Ibuprofen Is also a commonly used NSAID , it is a propionic acid derivative, and it is a non-selective COX inhibitor.

Absorbed rapidly when given orally and metabolized by the liver, with a half-life of about 2 hours. Used in chronic inflammatory conditions and also antipyretic as alternative to aspirin especially in children.

Adverse effects on the GIT is probably less than with aspirin, it also cause dizziness, burring of vision , skin rash

d. Naproxen

Is non-selective COX inhibitor, useful in inflammatory condition, dysmenorrhea, and acute gout. Absorbed well when given orally. Naproxen can be absorbed following rectal administration, has a variable half-life of about 14 hours, it is excreted almost entirely in the urine. It is 99% bound to plasma proteins.

e. Piroxicam

Is an oxicam derivative, a nonselective COX inhibitor and in addition, it inhibits activation of neutrophils independently, so it has an additional mechanism of action. It is well absorbed after oral administration and undergoes enterohepatic circulation. piroxicam is 90% bound to plasma proteins. Has long half-life, so can be given once daily. Is useful in osteoarthritis and rheumatoid arthritis, but less suitable for acute analgesia except for gout

f. Meloxicam

Is useful in osteoarthritis, has less gastric damage than other drugs, inhibits COX2 more than COX1

g. Sulindac

Is a derivative of indometacin, it is a pro-drug converted inside the body to sulphide, which COX inhibitor, it is about half potent as indometacin. Sulidac absorbed well when given orally metabolized by the liver into active sulphide, it is highly protein bound. It is useful in osteoarthritis, rheumatoid arthritis ankylosing spondylitis and acute gout.

Adverse effects similar to indometacin, but with lower incidence.

h. Ketorolac

Is a potent analgesic, but has moderate anti-inflammatory effects. Its use is limited to the short term(5 days) treatment of pain as it can be given im, iv and

orally. It has a rapid onset and a short duration of action. It is useful in postoperative pain. Topical ophthalmic form is useful in the treatment of allergic conjunctivitis.

Adverse effects include, GIT, dyspepsia, nausea, vomiting and gastric bleeding, also headache and dizziness.

i. Mefenamic acid

is a non-selective COX- inhibitors useful in the treatment of osteoarthritis, rheumatoid arthritis, postoperative pain dysmenorrhea and menorrhagia

Adverse effects include GI disturbances, skin rash, fatigue, hypotension and palpitation, glucose intolerance, hemolytic anemia and thrombocytopenia

2. Selective COX-2 inhibitors

These include the cyclic coxibs as celecoxib, etoricoxib, rofecoxib, parecoxib and lumeracoxib

They have high affinity for COX-2 than COX-1, they are effective in relieving pain and having anti-inflammatory effect, they have no effect on platelets aggregation

a. Celecoxib

Is selective reversible inhibitor of COX-2 enzyme, it does not inhibit platelets aggregation.

It is readily absorbed from the GIT with peak serum level in about 3 hours. Celecoxib is extensively metabolized by the liver and excreted in the urine and feces. The half-lifer is about 11 hours, and usually taken once daily. It is useful in osteoarthritis, rheumatoid arthritis, primary dysmenorrheal and pain relief .

Adverse effects include abdominal pain, diarrhea and dyspepsia with less incidence of peptic ulcer. It is contraindicated in patients allergic to sulphonamides. Kidney damage may occur and the drug should be avoided in patients with renal insufficiency. Celecoxib was found to increase the risk of myocardial infarction and stroke related to dose and underlying risk factors. The drug should be avoided in patients at risk of cardiovascular or cerebrovascular disease.

b. Parecoxib

Is selective COX-2 inhibitor which can be given by injection, it effective analgesic for the relief of moderate to severe postoperative pain.

Its rapidly (5 minutes) absorbed following intramuscular injection and converted to valdecoxib , the active metabolite of the drug. Valdecoxib is metabolized by the liver.

c. Etoricoxib

Is COX-2 selective. It is incompletely absorbed following oral administration with a half-life of about 20-26 hours. It is extensively metabolized by the liver and the dose needs to be adjusted in liver disease. Used in a single daily dose for the treatment of osteoarthritis, rheumatoid arthritis and gouty arthritis. Etoricoxib is also useful in dysmenorrhea and post-operative pain. Etoricoxib has less incidence of GIT adverse effect but can increase the incidence of stroke and myocardial infarction.

3. Paracetamol

Paracetamol (acetaminophine) has little or no anti-inflammatory activity

Mechanism of action

Paracetamol inhibits prostaglandins synthesis centrally in the brain. This explains its antipyretic and analgesic effects. Paracetamol has less effect on cyclooxygenase in the peripheral tissue, which explains its weak anti-inflammatory activity. Paracetamol also has no effect on platelets function.

Pharmacokinetics

Paracetamol is rapidly absorbed from the GIT. It undergoes first pass metabolism by the liver. Paracetamol is conjugated with glucuronide and sulfate the liver. A portion of paracetamol is hydroxylated to form N-acetylbenzoiminoquinone (NAPQI), which is highly reactive and toxic metabolite that can combine with the SH- group . At normal dose the toxic metabolite is combines with the SH- group of glutathione.

Clinical uses

Paracetamol is used as analgesic and antipyretic especially in patients with peptic ulcer or gastritis. It also has no effect of platelets function and no interaction with anticoagulant drugs.

It is also the antipyretic of choice in children with viral infection or chicken pox (aspirin may cause "Reyes" syndrome in children with viral infections).

Also paracetamol has no effect on uric acid excretion and can be used safely in patients with gout

Adverse effects

Paracetamol in normal therapeutic doses it is free of side effects, very rarely it causes skin rash and minor allergic reactions

Paracetamol overdose

Acute ingestion of paracetamol in high doses (> 7.5g) can result in toxicity. The main toxicity includes hepatic necrosis, renal tubular necrosis, hypoglycemia and

coma. The toxicity results from the accumulation of NAPQI which binds to macromolecules of the liver cells, this lead to enzyme inactivation and damage of the liver cells. Doses of 20-25 g are potentially toxic due to acute liver failure. The antidote for paracetamol toxicity is N-acetylcysteine which is a precursor of glutathione that help the inactivation of NAPI and reduce its toxicity