Anti-inflammatory drugs (Part-1)

Inflammation- Definition:

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides.

However, inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA). The prognosis of RA results in joint damage and erosions, functional disability, pain, and reduced quality of life. Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain and halting or slowing disease progression.

Inflammatory process consequences:

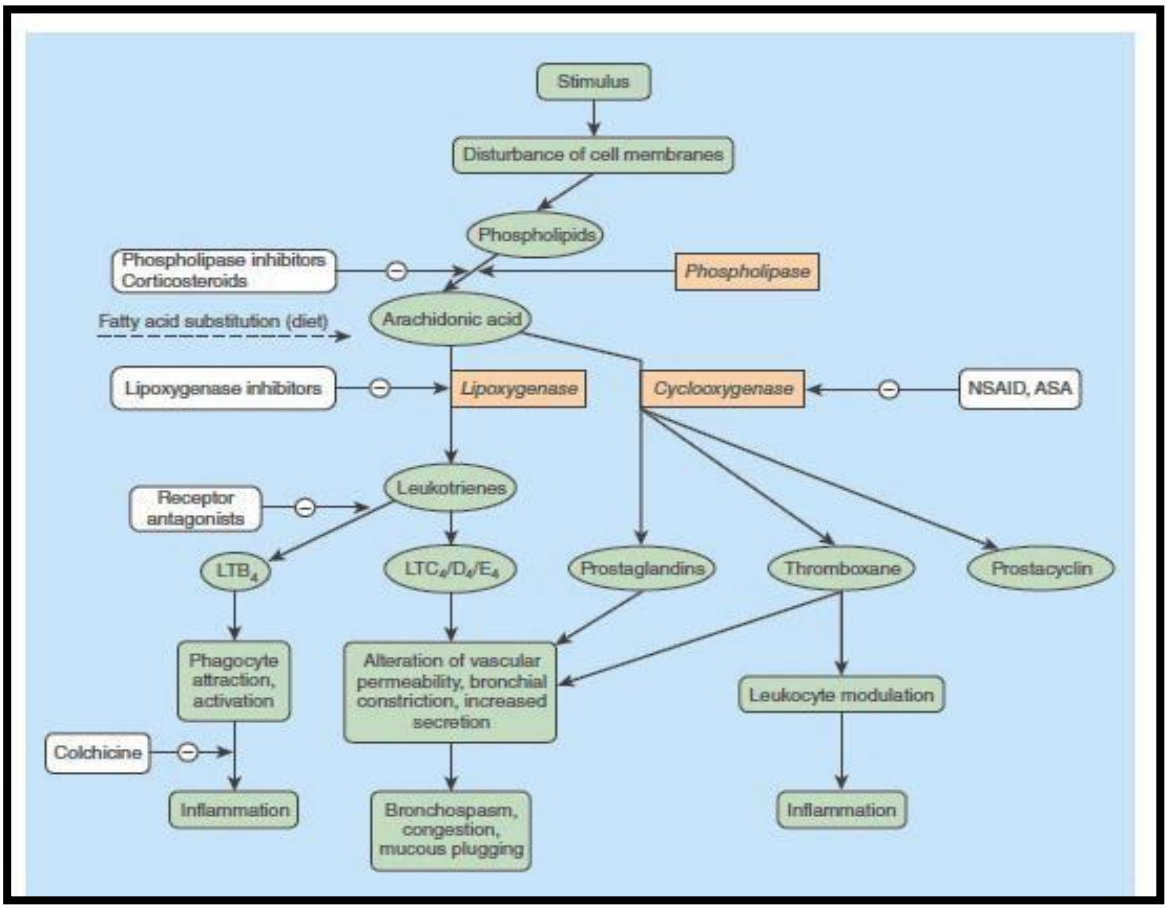

Figure1: Prostanoid mediators derived from arachidonic acid and sites of drug action. ASA, acetylsalicylic acid (aspirin); LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of Salicylic acid (aspirin), Propionic acid (ibuprofen, fenoprofen, flurbiprofen, ketoprofen, naproxen), Acetic acid (diclofenac, etodolac, indomethacin, tolmetin), Enolic acid (meloxicam, piroxicam), Fenamates (mefenamic acid), And the selective COX-2 inhibitor (celecoxib).

- ✓ They act primarily by inhibiting the cyclooxygenase (COX) enzymes that catalyse the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.
- ✓ Differences in the safety and efficacy of the NSAIDs may be explained by relative selectivity for the COX-1 or COX-2 enzyme. Inhibition of COX-2 is thought to lead to the anti-inflammatory and analgesic actions of NSAIDs, whereas inhibition of COX-1 is responsible for the prevention of cardiovascular events and most adverse events.

Aspirin and other NSAIDs

Aspirin is now rarely used as an anti-inflammatory medication as it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It is used more frequently at lower doses to prevent cardiovascular events such as stroke and myocardial infarction (MI). Aspirin is often differentiated from other NSAIDs since it is an irreversible inhibitor of COX activity.

Mechanism of action

Aspirin is a weak organic acid that irreversibly acetylates and, thus, inactivates COX. The other NSAIDs are reversible inhibitors of COX. NSAIDs, including aspirin, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect). However, not all NSAIDs are equally effective in each of these actions.

a. Anti-inflammatory actions

Inhibition of COX diminishes the formation of prostaglandins (PGs) and, thus, modulates aspects of inflammation mediated by prostaglandins. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.

b. Analgesic action

PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE2 synthesis, the sensation of pain can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs.

c. Antipyretic action

The NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release and resetting the "thermostat" back toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation through peripheral vasodilation and sweating. NSAIDs do not affect normal body temperature.

Therapeutic uses

a. Anti-inflammatory and analgesic use

NSAIDs are used in the treatment of osteoarthritis, RA, and common conditions requiring analgesia (e.g: headache, arthralgia, myalgia, and dysmenorrhea). Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized. The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity. For example, two 325-mg aspirin tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

b. **Antipyretic uses:** Aspirin, ibuprofen, and naproxen may be used to treat fever. Aspirin should be avoided in patients less than 19 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome—a syndrome that can cause fulminating hepatitis with cerebral oedema, often leading to death.

c. **Cardiovascular applications:** Aspirin irreversibly inhibits COX-1–mediated production of TXA2, thereby reducing TXA2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events. The antiplatelet effects persist for the life of the platelet. Low doses of aspirin (75 to 162 mg—commonly 81 mg) are used prophylactically to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a history of previous MI, TIA, or stroke.

d. **External applications:** Salicylic acid is used topically to treat acne, corn, and warts. Methyl salicylate ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs. Diclofenac is available in topical formulations (gel or solution) for the treatment of osteoarthritis in the knees or hands. In addition, ocular formulations of ketorolac are approved for the management of seasonal allergic conjunctivitis and inflammation and pain related to ocular surgery.

Pharmacokinetics Aspirin and other NSAIDs

- Most of the salicylates cross both the BBB and the placenta and are absorbed through intact skin (especially methyl salicylate).
- Salicylate is secreted into the urine and can affect uric acid excretion. Therefore, aspirin should be avoided in gout, if possible, or in patients taking probenecid.
- Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example sulindac) have active metabolites. The excretion of active drugs and metabolites is primarily via the urine.

Adverse events:

Because of the adverse event profile, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a. **Gastrointestinal:** These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding.

- Normally, the production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2α stimulate the synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these PGs, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration.
- Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity).
- NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients at high risk for GI events, proton pump inhibitors should be used concomitantly to prevent NSAID-induced ulcers.

b. Increased risk of bleeding (antiplatelet effect)

As described above, aspirin inhibits COX-1–mediated formation of TXA2 and reduces platelet aggregation for the lifetime of the platelet (3 to 7 days). Platelet aggregation is the first step in thrombus formation and the antiplatelet effect of aspirin results in a prolonged bleeding time. For this reason, aspirin is often withheld for at least 1 week before surgery.

- NSAIDs other than aspirin are not utilized for their antiplatelet effect but can still prolong bleeding time, especially when combined with anticoagulants.
- Concomitant use of NSAIDs and aspirin can prevent aspirin from binding to COX.
- Patients who take aspirin for cardioprotection should avoid concomitant NSAID use if possible or take aspirin at least 30 minutes before the NSAID.

c. Renal effects

NSAIDs prevent the synthesis of PGE2 and PGI2, PGs that are responsible for maintaining renal blood flow. Decreased synthesis of PGs can result in the retention of sodium and water and may cause oedema. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications. In susceptible patients, NSAIDs have led to acute kidney injury.

d. Cardiac effects: Agents such as aspirin, with a very high degree of COX-1 selectivity at low doses, have a cardiovascular protective effect thought to be due to a reduction in the production of TXA2. Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI2 production mediated by COX-2. An increased risk for cardiovascular events, including MI and stroke, has been associated with all NSAIDs except aspirin.

All NSAIDs carry a boxed warning regarding the increased risk for cardiovascular events. The use of NSAIDs, other than aspirin, is discouraged in patients with established cardiovascular disease. For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, naproxen may be the least likely to be harmful.

e. Other adverse effects: NSAIDs are inhibitors of COXs and, therefore, inhibit the synthesis of PGs but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations. Central nervous system (CNS) adverse events, such as headache, tinnitus, and dizziness, may occur. Approximately 15% of patients taking aspirin experience hypersensitivity reactions. Symptoms of a true allergy include urticaria, bronchoconstriction, and angioedema. Patients with severe hypersensitivity to aspirin should avoid using NSAIDs.

f. Drug interactions: Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in an increased concentration of free salicylate. Alternatively, aspirin can displace other highly protein-bound drugs, such as warfarin or phenytoin resulting in higher free concentrations of these agents.

g. Toxicity: Mild salicylate toxicity is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result. Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication; ingestion of as little as 10 g of aspirin can be fatal.

h. Pregnancy: NSAIDs should be used in pregnancy only if benefits outweigh risks to the developing foetus. Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy. In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.