# CHAPTER 9

# ANTI-INFLAMMATORY & GOUT DRUGS

**[1]Prof. Dr. SATISH KUMAR SHARMA**

[1]Professor, Glocal School of pharmacy, Glocal University Saharanpur- (U.P)

**Ch.Id:-ASU/NSP/EB/HOP/2022/Ch-09**

**DOI:** https://doi.org/10.52458/9789391842529.nsp2022.eb.asu.ch9

## ASPIRIN

Aspirin and other nonsteroidal anti-inflammatory drugs are organic acids with a low molecular weight. They all stop the production of prostaglandins. They reduce the production of free radicals and superoxide, and they may interact with adenylyl cyclase to change the concentration of cAMP in the cell. For the majority of articular and musculoskeletal disorders, aspirin is the drug of choice. It also serves as a benchmark against which all anti-inflammatory drugs are measured.

Pharmacokinetics: The stomach and upper small intestine absorb the salicylates quickly. The stomach's acidic environment keeps a large portion of the salicylate in nonionized form, which aids absorption. However, the drug has the potential to harm the mucosal barrier. Aspirin is absorbed as is, and esterases in tissue and blood rapidly hydrolyze it to acetic acid and salicylate. Albumin binds to salicylate. Although some salicylate from food and aspirin hydrolysis is excreted unchanged, the majority is converted to water-soluble conjugates that are quickly cleared by the kidney. The rate of excretion of free salicylate is increased when the urine is alkalinized.

**Pharmacodynamics**

Aspirin inhibits the enzyme cyclooxygenase in an irreversible manner, lowering the production of prostaglandins and thromboxane A2, but not of leukotrienes. Anti-inflammatory Effects: Aspirin interferes with the chemical mediators of the kallikrein system in addition to reducing the synthesis of eicosanoid mediators.

Aspirin inhibits granulocyte adhesion to damaged vasculature, stabilises lysosomes, and prevents polymorphonuclear leukocytes and macrophages from migrating into the inflammatory site.

Analgesic Effects: Aspirin works best for pain that is mild to moderate in intensity. Aspirin relieves muscle, vascular, and dental pain, as well as postpartum conditions, arthritis, and bursitis. Aspirin works peripherally by reducing inflammation, but it also inhibits pain stimuli at a subcortical level.

Antipyretic EffectsAspirin lowers body temperature. The decrease in temperature is due to increased heat dissipation caused by superficial blood vessel vasodilation.

Antipyresis is often accompanied by excessive sweating. Aspirin inhibits the production of prostaglandins induced by pyrogens and the central nervous system's response to interleukin-1.

*ISBN- 978-93-91842-52-9* 

Platelet Effects: By inhibiting thromboxane synthesis, aspirin prevents platelet aggregation. Aspirin prevents platelet aggregation for up to 8 days because its action is irreversible (until new platelets are formed).

**Clinical Uses**

Analgesic, antipyretics, and anti-inflammatory effects**:** Aspirin is one of the most commonly used drugs to treat mild to moderate pain from a variety of sources. In the treatment of severe visceral pain, aspirin is ineffective (acute abdomen, renal colic, pericarditis, or myocardial infarction). For the treatment of cancer pain, it and other NSAIDs have been combined with opioid analgesics. Rheumatoid arthritis, rheumatic fever, and other inflammatory joint diseases are treated with this drug.

Inhibition of platelet aggregation: In men, aspirin has been shown to help prevent transient ischemic attacks and unstable angina. In coronary artery bypass grafts, it lowers the risk of thrombosis. It may also help to prevent myocardial infarction.

**Adverse Effects**

Gastrointestinal Effects: The most serious side effect is stomach upset (intolerance). Gastritis caused by aspirin could be caused by the undissolved tablet irritating the gastric mucosa, nonionized salicylate absorption in the stomach, or inhibition of protective prostaglandins.

Central Nervous System Effects: Patients taking higher doses may experience "salicylism" tinnitus, decreased hearing, and vertigo, which can be reversed by lowering the dosage. Salicylates in higher doses cause hyperpnea by acting directly on the medulla. As a result of the increased ventilation, respiratory alkalosis may occur at toxic levels. Acidosis develops later as salicylic acid derivatives accumulate and the respiratory centre becomes depressed.

Other Adverse Effects: Low daily doses of aspirin usually raise serum uric acid levels, whereas doses exceeding 4 g daily lower uric acid levels below 2.5 mg/dL. In patients with underlying renal disease, salicylates may cause a reversible decrease in glomerular filtration rate. Because it can cause Raye syndrome in children with viral upper respiratory tract infections, asprin is not recommended.

Newer Nonsteroidal Anti-Inflammatory Drugs

The biosynthesis of prostaglandins is inhibited by the newer NSAIDs. They also inhibit chemotaxis, suppress interleukin-1 production, and disrupt calcium-mediated intracellular events. These are cyclooxygenase inhibitors that are reversible.

The majority of these medications are well absorbed. The majority of NSAIDs are highly metabolised, with some going through phase I and II mechanisms and others going through direct glucuronidation (phase II) alone. While renal excretion is the most important, all undergo biliary excretion and reabsorption to varying degrees (enterohepatic circulation). All NSAIDs are highly protein-bound, with albumin being the most common.

**Ibuprofen**

Ibuprofen is metabolised extensively in the liver, and only a small amount is excreted unchanged. Gastrointestinal irritation and bleeding are common, but not as common as with aspirin. Rashes, pruritus, tinnitus, dizziness, headache, and fluid retention have all been reported in addition to the gastrointestinal symptoms. Agranulocytosis and aplastic anaemia are two rare hematologic side effects. Acute renal failure, interstitial nephritis, and nephrotic syndrome are all kidney effects that occur very rarely.

**Diclofenac**

Diclofenac is an anti-inflammatory, analgesic, and antipyretic drug that inhibits cyclooxygenase. Following oral administration, the drug is rapidly absorbed and has a half-life of 1-2 hours. In the synovial fluid, it builds up. The cyclooxygenase inhibitory potency of diclofenac is higher than that of naproxen. The medication is used to treat chronic inflammatory conditions like rheumatoid arthritis and osteoarthritis, as well as acute musculoskeletal pain. Gastric ulceration, gastrointestinal distress, and occult gastrointestinal bleeding are some of the side effects.

**Sulindac**

Sulindac is a prodrug. Its active metabolite is, an acetic acid derivative like diclofenac. Only effective after liver enzymes convert it to a sulphide, which is excreted in bile and then reabsorbed from the intestine.Enterohepatic cycling extends the time of action from 12 to 16 hours. The indications and side effects are the same as with other NSAIDs. Stevens-Johnson epidermal necrolysis syndrome, thrombocytopenia, agranulocytosis, and nephrotic syndrome have all been reported as more severe reactions. Sulindac, like diclofenac, has the potential to cause an increase in serum aminotransferase; it is also linked to cholestatic liver damage.

**Mefenamic Acid**

Another fenamate, mefenamic acid, has analgesic properties but is probably less effective as an anti-inflammatory agent than aspirin and is clearly more toxic.

*ISBN- 978-93-91842-52-9* 

**Piroxicam**

It is rapidly absorbed in the stomach and upper small intestine, reaching an 80 percent peak plasma concentration in just one hour. Twenty percent of patients experience gastrointestinal symptoms. Dizziness, tinnitus, headache, and rash are some of the other side effects.

**Nimesulide:** It is a new NSAID that is rapidly and almost completely absorbed after oral administration. Plasma proteins are strongly bound. It is a weak prostaglandin synthesis inhibitor. Nimesulide has the advantage of causing less gastric irritation than other NSAIDs.

**Rofecoxib:** Rofecoxib is a COX-2 inhibitor that is highly selective and specific. By inhibiting cyclooxygenase-2, it prevents prostaglandin synthesis. It is approximately 90% bound to plasma proteins. Nausea, dyspepsia, epigastric discomfort, heartburn, diarrhoea, and fluid retention are the most common side effects.

It is mainly useful in osteoarthritis, acute pain like dental pain & primary dysmenorrhoea.

## NSAIDS FOR SPECIAL INDICATIONS

**Indomethacin**

Indomethacin is slightly more toxic than aspirin, but it is more effective in some situations. Indomethacin is well absorbed and highly bound to plasma proteins after oral administration. The liver is responsible for metabolism, and unchanged drugs and inactive metabolites are excreted in the bile and urine.

Clinical Uses: pericarditis and pleurisy treatment, acute gouty arthritis and ankylosing spondylitis, pericarditis and pleurisy.

Adverse Effects: Abdominal pain, diarrhoea, gastrointestinal haemorrhage, and pancreatitis are all possible gastrointestinal side effects. Dizziness, confusion, and depression have all been linked to CNS effects. There have been reports of serious hematologic reactions such as thrombocytopenia and aplastic anaemia.

Acetaminophen

Acetaminophen is a phenacetin active metabolite that has analgesic properties. In peripheral tissues, it is a weak prostaglandin inhibitor with no anti-inflammatory properties.

*ISBN- 978-93-91842-52-9*

Pharmacokinetics: Acetaminophen is administered orally. The rate of gastric emptying influences absorption. Acetaminophen is partially metabolised by hepatic microsomal enzymes and is slightly bound to plasma proteins.

Indications: It's a good analgesic and antipyretic, but it doesn't have any anti-inflammatory properties. The medication is effective for mild to moderate pain, such as headaches, myalgia, and postpartum discomfort.

Adverse Effects: It's hepatotoxic (avoid if you have a history of liver disease) and causes hemolytic anaemia and methemoglobinemia.

## DRUGS USED IN GOUT

Gout is a genetic metabolic disease marked by recurrent attacks of acute arthritis caused by monosodium urate deposits in joints and cartilage. It's also possible that uric acid calculi form in the kidneys. High serum levels of uric acid, a poorly soluble substance that is the major end product of purine metabolism, are usually linked to gout.

Gout treatment aims to relieve acute gout attacks while also preventing recurrent gout attacks and urate lithiasis. Synoviocytes phagocytoze urea crystals, which then release prostaglandins, lysosomal enzymes, and interleukin-1. Polymorphonuclear leukocytes migrate into the joint space, attracted by these chemotactic mediators, amplifying the ongoing inflammatory process. More mononuclear phagocytes (macrophages) appear in the later stages of the attack, ingest the urate crystals, and release more inflammatory mediators.

Colchicine

Colchicine is easily absorbed when taken by mouth. The drug's metabolites are excreted in the intestine and urine.

Colchicine significantly reduces gouty arthritis pain and inflammation without affecting urate metabolism or excretion or having any other analgesic effects. Colchicine works to reduce inflammation by preventing leukocyte migration and phagocytosis. It also stops leukotriene B4 forming.

Indications: Colchicine is a drug that is used to treat acute gouty arthritis inflammation.

Adverse Effects: Colchicine frequently causes diarrhoea and can also cause nausea, vomiting, and stomach pain. Colchicine can cause hair loss, bone marrow depression, peripheral neuritis, and myopathy in rare cases. Burning throat pain, bloody

diarrhoea, shock, hematuria, and oliguria are all symptoms of acute intoxication after ingesting large (nontherapeutic) doses of the alkaloid.

**NSAIDS in Gout**

Urate crystal phagocytosis is inhibited by indomethacin and other NSAIDs. Indomethacin can be used as a first-line treatment for gout or as a backup if colchicine fails or causes too much discomfort. The most common treatment for acute gout today is indomethacin. Except for aspirin, all other NSAIDs can be used to treat acute gouty attacks.

Uricosuric Agents

Probenecid and sulfinpyrazone are uricosuric drugs that are used to reduce the amount of urate in the body in patients with tophaceous gout or those who have more frequent gout attacks. To avoid the formation of uric acid calculi in a patient who excretes a large amount of uric acid, uricosuric agents should be avoided. Uricosuric drugs are organic acids that act on the renal tubule's anionic transport sites.

Pharmacokinetics: Probenecid is reabsorbed completely by the renal tubules and metabolised slowly. The kidneys quickly excrete sulfinpyrazone or its active hydroxylated derivative. It has a similar effect to probenecid after oral administration.

Pharmacodynamics: The glomerulus filters uric acid freely. It is reabsorbed and secreted in the middle segment of the proximal tubule, just like many other weak acids. The uricosuric drugs probenecid and sulfinpyrazone, as well as high doses of aspirin, affect these active transport sites, reducing net uric acid reabsorption in the proximal tubule. Aspirin should not be used for analgesia in gout patients because it causes net retention of uric acid by inhibiting the secretory transporter in small doses.

Indications: If several acute attacks of gouty arthritis have occurred, evidence of tophi appears, or plasma levels of uric acid in gout patients are so high that tissue damage is almost inevitable, uricosuric therapy should be started.

Adverse Effects: Both drugs irritate the gastrointestinal tract, but sulfinpyrazone is more active. Although probenecid is more likely to cause allergic dermatitis, either compound can cause a rash. The use of probenecid has caused nephrotic syndrome. Aplastic anaemia can be caused by both sulfinpyrazone and probenecid.

Allopurinol

Reduce uric acid synthesis by inhibiting xanthine oxidase with allopurinol as an alternative to increasing uric acid excretion in the treatment of gout.

After oral administration, allopurinol is absorbed. Allopurinol, like uric acid, is metabolised by xanthine oxidase. Alloxanthine, the resulting compound, retains its ability to inhibit xanthine oxidase and has a long action time.

Pharmacodynamics: Purines are not a significant source of uric acid in the diet. Purine is synthesised in the body from amino acids, formate, and carbon dioxide in significant amounts. Purine ribonucleotides that are not incorporated into nucleic acids or that are derived from nucleic acid degradation are converted to xanthine or hypoxanthine and oxidised to uric acid. Allopurinol inhibits this last step, resulting in a decrease in plasma urate levels and a reduction in the size of the urate pool, as well as an increase in the more soluble xanthine and hypoxanthine.

**Indications**

- for recurrent renal stones
- When serum urate levels are grossly elevated.
- in patients with renal functional impairment;
- in chronic tophaceous gout

Adverse effects- Gastrointestinal intolerance, including nausea, vomiting, and diarrhoea, is a possible side effect. There may be peripheral neuritis and necrotizing vasculitis, as well as bone marrow element depression. There have been reports of hepatic toxicity and interstitial nephritis.

**Questions**

a) Explain what is pharmacokinetics of iron?
b) Describe the different types of iron formulations and their side effects?
c) Describe the mechanism of action and effect of folic acid and vit $B_{12}$ ?
d) Mention theeffects and adverse reaction of oral anticoagulants and heparin?
e) Explain the role of aspirin as an antiplatelet agent?

*ISBN- 978-93-91842-52-9* 