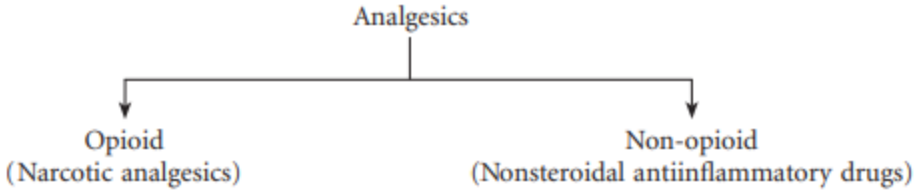
Analgesics

Analgesics are drugs that relieve pain without significantly altering consciousness. They relieve pain without affecting its cause.



Nonsteroidal Anti-inflammatory Drugs (NSAIDs):

- ✓ NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities.
- ✓ They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.
- ✓ Note: Differences in 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 prevention of cardiovascular events and most adverse events.

Aspirin:

Aspirin can be thought of as a traditional NSAID, but 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 cyclooxygenase activity.

Mechanism of action:

Aspirin is a weak organic acid that irreversibly inactivates cyclooxygenase. The other NSAIDs are reversible inhibitors of cyclooxygenase. The 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.

Actions of nonsteroidal anti-inflammatory drugs (NSAIDs):

a. Anti-inflammatory actions:

Inhibition of cyclooxygenase diminishes the formation of prostaglandins 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:

Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation.

The NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release, 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 have no effect on normal body temperature.

Therapeutic uses:

a. Anti-inflammatory and analgesic uses.

b. Antipyretic uses:

Aspirin, ibuprofen, and naproxen may be used to treat fever.

[Note: 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 edema, 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.

Chronic use of aspirin allows for continued inhibition as new platelets are generated. Aspirin is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.

d. External applications:

Salicylic acid is used topically to treat acne, corns, calluses, 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 treatment of osteoarthritis in the knees or hands.

In addition, ocular formulations of ketorolac are approved for management of seasonal allergic conjunctivitis and inflammation and pain related to ocular surgery.

Pharmacokinetics

-Aspirin:

- In low doses, elimination follows first-order kinetics and with high doses as the metabolizing enzymes get saturated, it switches over to zero-order kinetics. After this, an increase in salicylate dosage increases its plasma concentration disproportionately and severe toxicity can occur.

- Alkalinization of urine increases the rate of excretion of salicylates.
- Salicylate can affect uric acid excretion. Therefore, aspirin should be avoided in gout, if possible, or in patients taking probenecid.

- Other NSAIDs:

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, nabumetone and sulindac) have active metabolites. Excretion of active drug and metabolites is primarily via the urine.

Adverse Events:

a.GIT: Nausea, vomiting, dyspepsia, epigastric pain, acute gastritis, ulceration and GI bleeding.
Normally, production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, 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).
Ulcerogenic effect is the major drawback of NSAIDs, which is prevented/minimized by taking:
a. NSAIDs after food.
b. proton pump inhibitors/H2-blockers/misoprostol with NSAIDs.
c. buffered aspirin (preparation of aspirin with antacid).
d. selective COX-2 inhibitors.

b. Increased risk of bleeding (antiplatelet effect):
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 prior to 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 cyclooxygenase. Patients who take aspirin for cardioprotection should avoid concomitant NSAID use if possible or take aspirin at least 30 minutes prior to the NSAID.

c. Analgesic nephropathy: Slowly progressive renal failure may occur on chronic use of high doses of NSAIDs. Renal failure is usually reversible on stoppage of therapy but rarely, NSAIDs may cause irreversible renal damage.

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. 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.Hypersensitivity: It is relatively more common with aspirin. The manifestations are skin rashes, urticaria, rhinitis, bronchospasm, angioneurotic oedema and rarely anaphylactoid reaction. Bronchospasm (aspirin-induced asthma) is due to increased production of leukotrienes. Incidence of hypersensitivity is high in patients with asthma, nasal polyps, recurrent rhinitis or urticaria. Therefore, aspirin should be avoided in such patients.

F.In people with G6PD deficiency, administration of salicylates may cause **haemolytic anaemia**.

G. Prolonged use of salicylates interferes with action of vitamin K in the liver decreased synthesis of clotting factors **(hypoprothrombinaemia)** predisposes to bleeding (can be treated by administration of vitamin K).

h. Reye's syndrome: Use of salicylates in children with viral infection may cause hepatic damage with fatty infiltration and encephalopathy—Reye's syndrome. Hence, salicylates are contraindicated in children with viral infection.

i.Pregnancy: These drugs inhibit PG synthesis, thereby delay onset of labour and increase chances of postpartum haemorrhage. In the newborn, inhibition of PG synthesis results in premature closure of the ductus arteriosus.

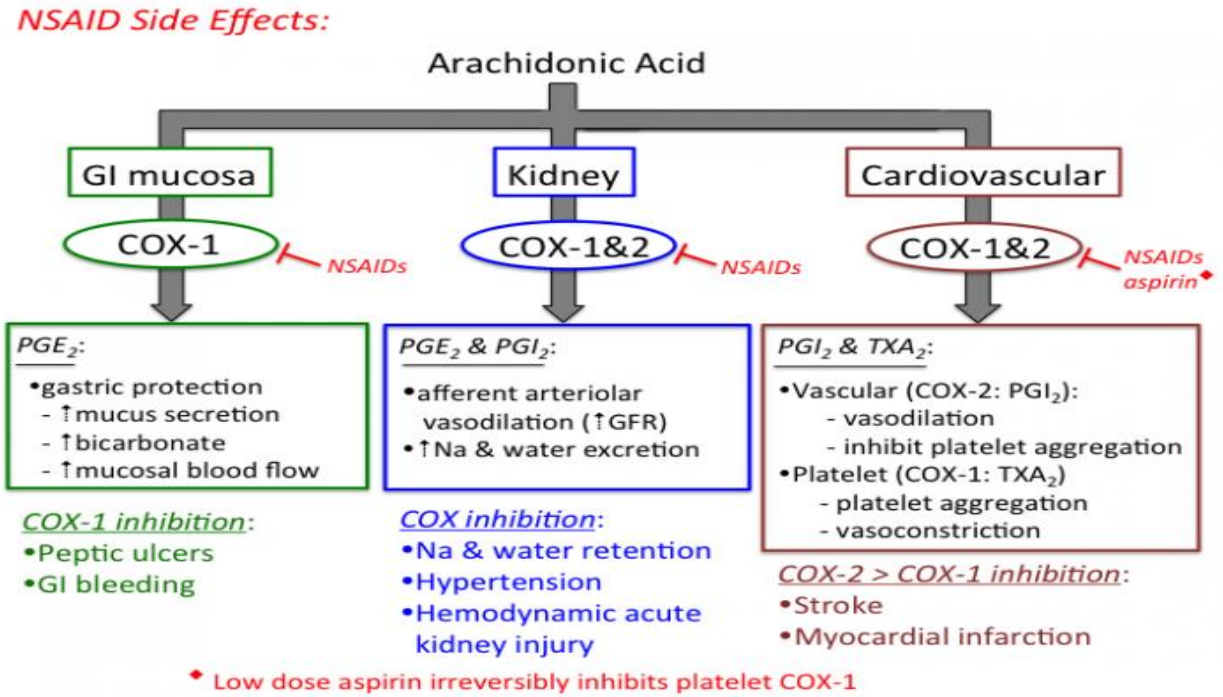
[Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.]

j.Drug interactions

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

k.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.



Celecoxib:

- Celecoxib, a selective COX-2 inhibitor.
- Unlike the inhibition of COX-1 by aspirin (which is irreversible), the inhibition of COX-2 is reversible.
- Celecoxib is approved for the treatment of RA, osteoarthritis, and acute pain.
- Celecoxib is readily absorbed after oral administration
- The drug may be dosed once or twice daily.
- Celecoxib should be avoided in patients with severe hepatic or renal disease.

Acetaminophen

- Acetaminophen inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity.
- Acetaminophen does not affect platelet function or increase bleeding time.
- It is not considered an NSAID.
- Acetaminophen is used for the treatment of fever and the relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs.
- Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).
- Acetaminophen is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism.
- It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione produced by the liver, forming a nontoxic substance.
- Acetaminophen and its metabolites are excreted in urine.
- The drug is also available in intravenous and rectal formulations.
- At normal therapeutic doses, acetaminophen has few significant adverse effects. With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins. Hepatic necrosis, a serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. [Note: N-acetylcysteine is an antidote in cases of overdose].
- Acetaminophen should be avoided in patients with severe hepatic impairment.