Anti-inflammatory, Antipyretic, and Analgesic Agents

- ✓ Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. It's the body's effort to inactivate invading organisms, remove irritants, and set the stage for tissue repair.
- ✓ **Inflammatory mechanism:** WBC activation leads to stimulation of T-lymphocytes, which recruit monocytes and macrophages. These cells secrete proinflammatory cytokines, including TNF-α and IL-1. B-lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation.
- ✓ **Progression in inflammatory reactions cause:** progressive tissue injury (resulting in joint damage and erosions), Functional disability, Pain, and Reduced quality of life.
- ✓ **Anti-inflammatory agents include:** nonsteroidal anti-inflammatory drugs (NSAIDs), celecoxib, acetaminophen, disease-modifying antirheumatic drugs (DMARDs), and agents used for the treatment of gout.

Nonsteroidal Anti-inflammatory Drugs: analgesic, antipyretic, and anti-inflammatory drugs. This class includes some commonly used over the-counter agents, as well as many prescription-only agents.

Mechanism of action:

- **Anti-inflammatory:** NSAIDs inhibit the cyclooxygenase enzymes COX-1 and COX-2. These enzymes catalyze the formation of prostaglandin H2, which is the precursor for prostaglandin, prostacyclin, and thromboxane synthesis.
  COX-1 is present in most tissues, and in the gastrointestinal (GI) tract it maintains the normal lining of the stomach. It is also involved in kidney and platelet function.
  COX-2 is induced by inflammation. COX-2 inhibition is thought to lead to the analgesic, antipyretic, and anti-inflammatory effects of NSAIDs.
- **Analgesic:** through decreased prostaglandin formation.
- **Antipyretic:** through decreasing prostaglandins in the temperature control center in the hypothalamus.

NSAIDs uses:

- Mild to moderate pain (e.g., dental, muscle, joint, and postoperative)
- Inflammation and accompanying pain associated with diseases, such as rheumatoid arthritis (high doses)
- Reduction of fever

NSAID-Side effects: Many result from inhibition of COX-1, these include:

- Acute renal failure
- Skin rash or hypersensitivity reactions, which require immediate discontinuation of the drug.
- Gastric distress, occult gastric bleeding, and acute hemorrhage. These effects are worsened with concomitant use of ethanol and selective serotonin reuptake inhibitors (SSRIs).
- Bronchospasm in NSAID-sensitive asthmatics.

Nonsteroidal anti-inflammatory Drug–induced bronchospasm

A significant proportion of adults with asthma experience bronchospasm after taking NSAIDs. This can be serious and sometimes fatal. They are therefore contraindicated in patients with asthma who have a history of hypersensitivity reactions and should be used with caution in all asthmatics.
*Acetaminophen can be used by asthmatics to treat mild to moderate pain.

NSAID-Contraindications:

Gastric ulcers (gastric irritation may aggravate ulcers), Asthma, Influenza-like illnesses in children or teenagers (up to 19 years of age); there is an increased risk of developing Reye syndrome in children with influenza or chickenpox, Pregnancy (third trimester); NSAIDs may cause premature closure of the ductus arteriosus.

The relative strength of the anti-inflammatory, analgesic, and antipyretic actions varies slightly among different NSAID agents. The major difference is in pharmacokinetics. Individual patients may show different therapeutic responses and adverse reactions to the different agents.

- **Fever and antipyretic drugs**

Fever is produced by endogenous pyrogens (e.g., IL-1) released by infective bacteria. These pyrogens act on the anterior hypothalamus to increase prostaglandin synthesis, which in turn stimulates the thermoregulatory center to reset the new set point to a higher temperature. Because body temperature is cooler than the new set point, body temperature increases (heat production and conservation of heat) until it stabilizes at the new, elevated set point temperature. After the fever breaks and the new set point returns to 37° C, the patient vasodilates and sweats to lose heat until body temperature returns to normal.

NSAIDs and acetaminophen are effective in suppressing fever because they inhibit cyclooxygenase and therefore prostaglandin synthesis. In doing so, they lower the set point temperature and will cause activation of the heat loss mechanisms. Steroids may also be used to reduce fever by blocking the release of arachidonic acid (the precursor of prostaglandins) from membrane phospholipids.

Salicylates:

Drug	Mechanism of action	Pharmacokinetics	Effects	Uses	Contraindications	Toxicity
Aspirin (Acetylsalicylic Acid)	inhibits the COX enzymes by acetylating a single serine residue; an irreversible covalent modification that inactivates both enzymes. Other NSAIDs are competitive inhibitors of the cyclooxygenases.	– Well absorbed (oral administration). – Rapidly metabolized by plasma esterases to salicylic acid and acetic acid. – Salicylate ion is (80–90%) bound to plasma proteins. – Metabolism by conjugation in the liver – Metabolites are excreted in the urine.	**Cardiovascular:** at low doses, prevents thrombosis (inhibits platelets' COX-1). No effect on blood pressure. **Blood:** increased bleeding time (inhibition of platelet aggregation) **Kidney:** no nephrotoxicity **Liver:** dose-dependent alterations in liver function *These changes usually are subclinical and reversible.	analgesic, anti-inflammatory, and antipyretic actions, also, for the treatment and prophylaxis of thrombosis. Widely used to prevent myocardial infarction, and stroke. Used after angioplasty, placement of stents, or bypass surgery to prevent thrombosis and re-stenosis.	– Influenza-like illnesses or chickenpox in children or teenagers. – Asthma and nasal polyps. – Bleeding disorders such as hemophilia. – Alcohol use (3 or more drinks/day) or peptic ulcer. – Decreased hepatic function.	– Acute toxicity (Reye syndrome) and is life-threatening. – Progressively leads to tinnitus, hyperventilation, respiratory alkalosis, fever, metabolic acidosis, shock, coma, and death. – Treatment is gastric lavage for acute cases, alkaline diuresis with sodium bicarbonate to increase excretion, and supportive measures.

Salicylic Acid Salts and Derivatives:

Drug	Mechanism of action	Pharmacokinetics	Uses	Side effects
(Mesalamine, Olsalazine, and Sulfasalazin)	Do not irreversibly inhibit COX enzymes and much less effective than aspirin as COX inhibitors. They also do not inhibit platelet aggregation.	These agents are taken orally or rectally.	– Ulcerative colitis (local effect on the GI tract). – Crohn disease. – Rheumatoid arthritis (sulfasalazine).	Less frequent and minor compared with aspirin.

Other NSAIDS:

Drug	Mechanism of action	Uses	Side effects	Contraindications
Indomethacin	Similar to aspirin.	– Agent of choice for gout; but there is no evidence it is superior to other NSAIDs for acute gout. – To accelerate closure of patent ductus arteriosus	– Most frequent CNS effect is severe frontal headache, in 25-50% of patients who take the drug for long periods. – Dizziness, vertigo, lightheadedness, and mental confusion may occur. – Seizures, depression, psychosis, hallucinations, and suicide. – GI complaints are common and can be serious. Diarrhea and it's sometimes associated with ulcerative lesions of the bowel. Acute pancreatitis and rarely but potentially fatal cases of hepatitis. – Neutropenia, thrombocytopenia, and, rarely, aplastic anemia. – Most adverse effects are dose related.	– Underlying peptic ulcer disease. – Caution when administering to elderly patients or to those with underlying epilepsy, psychiatric disorders, or Parkinson disease because they are at greater risk for the development of serious CNS adverse effects.

Table 33.1 ► Summary of Other NSAIDs

Drugs	Comments
Diclofenac, etodolac, ketorolac, sulindac, tolmetin	These NSAIDs have greater potency against COX-2, have some COX-2 selectivity, and have less antiinflammatory activity than other NSAIDs
	They are similar to indomethacin
Ibuprofen, fenoprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin	Propionic acid derivatives that differ mainly in pharmacokinetics.
Piroxicam, meloxicam	Major advantage is long duration of action
Nabumetone	Unique structure but similar activity to other NSAIDs

COX-2 selective inhibitors:

Drug	Mechanism of action	Side effects
Celecoxib	Inhibits production of vascular prostaglandins, which are inhibitors of platelet aggregation and vasodilators. Unlike the nonselective NSAIDS, celecoxib does not reduce the endogenous production of thromboxane A2, a potent activator of platelet aggregation and a vasoconstrictor. Thus, inhibition of prostacyclin without inhibition of thromboxane A2 creates a prothrombotic state. The fact that it does not inhibit COX-1 leads to fewer GI side effects because it does not inhibit prostaglandins in the GI tract which maintains the normal lining.	Adverse cardiovascular and cerebrovascular events are more likely due to the prothrombotic state. Rofecoxib and valdecoxib have been withdrawn from the market because of the increased risk of cardiovascular events. Although celecoxib also carries such risks, it remains available, and its benefits (i.e., the reduced GI side effects) may outweigh the risks in properly selected and informed patients.

Other analgesic-antipyretic drugs:

Drug	Mechanism of action	Pharmacokinetics	Effects	Uses	Toxicity
Acetaminophen is excluded from the NSAID group of drugs because it does not have significant anti-inflammatory activity, although it is analgesic and antipyretic.	Acetaminophen is a weak inhibitor of cyclooxygenases. Its mechanism of action is not well understood.	Well absorbed (oral administration). Metabolism by conjugation in the liver. Elimination is by filtration and active proximal tubular secretion into the urine.	**Antipyretic effects:** comparable to aspirin **Analgesic effects:** comparable to aspirin **Cardiovascular system:** no effects at therapeutic doses. **Respiratory system:** no effects at therapeutic doses. **Blood:** no antiplatelet effects. No significant antiinflammatory properties (greater activity against CNS cyclooxygenases than those in the periphery)	Mild to moderate pain and pyrexia in patients for whom aspirin is contraindicated. Analgesic of choice in pregnancy. * Acetaminophen does not cause Reye syndrome and may be used in children.	– High therapeutic index, requiring ≥ 6 g to be ingested for toxicity to occur. – Hepatotoxicity is the most serious effect, caused by accumulation of N-acetyl-p-benzo-quinone imine (NAPQI), a toxic compound produced in small amounts during the metabolism of acetaminophen. Normally, it is immediately detoxified in the liver by conjugation with glutathione. In cases of overdose, glutathione may be depleted, and NAPQI may accumulate and damage the liver. – Concurrent ethanol use may worsen the hepatic effect. – Treat with acetylcysteine, which both replenish glutathione stores and conjugate directly with NAPQI, serving as a glutathione substitute (only effective within 10 to 24 hours of overdose).

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