Anti-inflammatory, Antipyretic, and Analgesic Agents

Prof. Omar Shaheen

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.

Inflammatory mechanism:

- WBC activation leads to stimulation of **T lymphocytes**, which recruit and activate monocytes and macrophages.
- These cells secrete proinflammatory **cytokines**, including tumor **necrosis factor (TNF)-α** and **interleukin (IL)-1**
- In addition to T lymphocyte activation, **B lymphocytes** are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation.

Progression in inflammatory reactions

- Inflammatory defensive reactions cause :
- progressive tissue injury, resulting in joint damage and erosions
- Functional disability
- Pain
- Reduced quality of life.

Anti-inflammatory agents include:

- nonsteroidal anti-inflammatory drugs (NSAIDs), *celecoxib*, *acetaminophen*, and
- disease-modifying antirheumatic drugs (DMARDs).
- Additionally, agents used for the treatment of gout

DRUGS FOR RHEUMATOID ARTHRITIS

Abatacept ORENCIA
Adalimumab HUMIRA
Certolizumab CIMZIA
Etanercept ENBREL
Golimumab SIMPONI
Hydroxychloroquine PLAQUENIL
Infliximab INFLECTRA, REMICADE, RENFLEXIS
Leflunomide ARAVA
Methotrexate OTREXUP, TREXALL
Rituximab RITUXAN
Sarilumab KEVZARA
Sulfasalazine AZULFIDINE
Tocilizumab ACTEMRA
Tofacitinib XELJANZ

DRUGS FOR GOUT

Allopurinol ZYLOPRIM
Colchicine COLCRYS
Febuxostat ULORIC
Pegloticase KRYSTEXXA
Probenecid GENERIC ONLY

Nonsteroidal Antiinflammatory Drugs

- Nonsteroidal antiinflammatory drugs (NSAIDs) are analgesic, antipyretic, and anti-inflammatory drugs, thus named to distinguish them from the glucocorticosteroids, which also possess anti-inflammatory
- properties. This class of drugs includes some commonly used over-the-counter agents, as well as many prescription-only agents.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs

Aspirin BAYER, BUFFERIN, ECOTRIN
Celecoxib CELEBREX
Diclofenac FLECTOR, PENNSAID, VOLTAREN
Diflunisal GENERIC ONLY
Etodolac GENERIC ONLY
Fenoprofen NALFON
Flurbiprofen GENERIC ONLY
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac ACULAR, ACUVAIL
Ketoprofen GENERIC ONLY
Meclofenamate GENERIC ONLY
Mefenamic acid PONSTEL
Meloxicam MOBIC
Methyl salicylate WINTERGREEN OIL
Nabumetone GENERIC ONLY
Naproxen ALEVE, ANAPROX, NAPROSYN
Oxaprozin DAYPRO
Piroxicam FELDENE
Salsalate GENERIC ONLY
Sulindac GENERIC ONLY
Tolmetin GENERIC ONLY

OTHER ANALGESICS

Acetaminophen (Paracetamol) OFIRMEV, TYLENOL

Nonsteroidal Antiinflammatory Drugs

- Mechanism of action
- — *Antiinflammatory:* 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 antiinflammatory effects of aspirin and the other NSAIDs.

Nonsteroidal Antiinflammatory Drugs

- Mechanism of action
- — Aspirin inhibits the cyclooxygenase enzymes by acetylating a single serine residue. This
- is an irreversible covalent modification that inactivates both COX-1 and COX-2. Other
- NSAIDs are competitive inhibitors of the cyclooxygenases.
- — *Analgesic:* NSAID analgesic effects occur as a result of decreased prostaglandin formation.
- — *Antipyretic:* Antipyretic effects are the result of decreasing prostaglandins in the temperature control center in the hypothalamus

NSAID 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
- — Aspirin is also used for the treatment and prophylaxis of thrombosis (low doses). It is widely
- used to prevent myocardial infarction (MI), stroke, and peripheral vascular thrombosis. It
- is also used after angioplasty, placement of stents, or bypass surgery to prevent thrombosis and re-stenosis.

NSAID-Side effects

- Many of the adverse effects of aspirin and the other NSAIDs result from inhibition of COX-1 (**Fig. 33.2**). 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 may be worsened with concomitant use of ethanol and selective serotonin reuptake inhibitors (SSRIs).
- — Bronchospasm in NSAID-sensitive asthmatics

Nonsteroidal Antiinflammatory Drug–induced bronchospasm

- A significant proportion of adults with asthma experience bronchospasm after taking aspirin and other nonsteroidal antiinflammator drugs (NSAIDs). This can be serious and sometimes fatal.
- Aspirin and other NSAIDs 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.

Fever and antipyretic drugs

- Fever is produced by endogenous pyrogens (e.g., interleukin-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.

Fever and antipyretic drugs (cont.)

- 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.
- Aspirin (and other 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.

NSAID-Contraindications

- Gastric ulcers (gastric irritation may aggravate ulcers)
- Asthma (NSAIDs can induce bronchospasm in asthmatics)
- 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 antiinflammatory, 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.

Salicylates (Aspirin (Acetylsalicylic Acid))

- **Pharmacokinetics**
- — Well absorbed following oral administration
- — Rapidly metabolized by plasma esterases to salicylic acid and acetic acid
- — Salicylate ion is highly bound (80–90%) to plasma proteins
- — Conjugation in the liver is the primary route of metabolism.
- — Metabolites are excreted in the urine.
- **Effects**
- — *Cardiovascular system:* at low doses, aspirin inhibits platelet COX-1 and prevents thrombosis.
- Aspirin does not affect blood pressure.
- — *Blood:* increased bleeding time due to inhibition of platelet aggregation
- — *Kidney:* no nephrotoxicity
- — *Liver:* there may be dose-dependent alterations in liver function with salicylate use. These
- changes usually are subclinical and reversible.

Salicylates

- **Contraindications/Precautions**
- Influenza-like illnesses or chickenpox in children or teenagers (up to 19 years of age), as there is an increased risk of developing Reye syndrome.
- Asthma and nasal polyps, as there is an increased likelihood of hypersensitivity reaction
- Bleeding disorders such as hemophilia, as aspirin may increase bleeding
- Alcohol use (three or more drinks/day) or peptic ulcer, as there is an increased risk of GI bleeding
- — Decreased hepatic function
- **Toxicity**
- — Acute toxicity may occur in children and teenagers (Reye syndrome) and is life-threatening.
- — Overdose 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

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

Indomethacin

- Mechanism of action. Similar to aspirin.
- Uses
- — Indomethacin has been the agent of choice for gout; however, there is no evidence it is superior to other NSAIDs for acute gout.
- — To accelerate closure of patent ductus arteriosus

Indomethacin

- **side effects.**
- — The most frequent central nervous system (CNS) effect (indeed, the most common side effect) is severe frontal headache, occurring in 25 to 50% of patients who take the drug for long periods. Dizziness, vertigo, lightheadedness, and mental confusion may occur. Seizures have been reported, as have severe depression, psychosis, hallucinations, and suicide.
- — GI complaints are common and can be serious. Diarrhea may occur and sometimes is associated
- with ulcerative lesions of the bowel. Acute pancreatitis has been reported, as have rare but potentially fatal cases of hepatitis.
- — Neutropenia, thrombocytopenia, and, rarely, aplastic anemia
- *Note:* Most adverse effects are dose-related.

Indomethacin

- Contraindications
- — Underlying peptic ulcer disease
- *Note:* Caution is advised when administering indomethacin 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 summarizes other NSAIDs.

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 Inhibitor Celecoxib

- **Mechanism of action**. Celecoxib is a selective COX-2 inhibitor and as such inhibits the production of vascular prostaglandins, which are inhibitors of platelet aggregation and vasodilators.
- Unlike the nonselective NSAIDS, which inhibit both COX-1 and COX-2, 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. However, 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 maintain the normal lining of the stomach.
- **Side effects**. Adverse cardiovascular and cerebrovascular events are more likely due to the prothrombotic state.

- *Note*: 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

- Acetaminophen is excluded from the NSAID group of drugs because it does not have significant antiinflammatory activity, although it is analgesic and antipyretic.
- Mechanism of action. Acetaminophen is a weak inhibitor of cyclooxygenases. Its mechanism of action is not well understood.
- Pharmacokinetics
- — Well absorbed following oral administration
- — The primary route of metabolism is conjugation in the liver.
- — Elimination is by filtration and active proximal tubular secretion into the urine.

Acetaminophen

- Effects
- — *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
- — Acetaminophen has no significant antiinflammatory properties, which may be accounted for by the fact that it has greater activity against CNS cyclooxygenases than those in the periphery.

Acetaminophen

- Uses
- — Mild to moderate pain and pyrexia in patients for whom aspirin is contraindicated
- — Analgesic of choice in pregnancy
- *Note:* Acetaminophen does not cause Reye syndrome and may be used in children.

Acetaminophen

- **Toxicity**.
- Acetaminophen has a high therapeutic index, requiring ≥ 6 g to be ingested for toxicity to occur. Hepatotoxicity is the most serious toxic effect, which is caused by the 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 acetaminophen 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 may conjugate directly with NAPQI by serving as a glutathione substitute (only effective within 10 to 24 hours of overdose).