Non-steroidal anti-inflammatory drugs (NSAIDs) and Steriods in Dentistry

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications that reduce pain, fever, and inflammation. They are widely used to treat a variety of conditions, including headaches, muscle aches, arthritis, and menstrual cramps. NSAIDs work by inhibiting **cyclooxygenase (COX) enzymes**, which produce prostaglandins, molecules that contribute to pain and inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs) and steroids are both used in dentistry to manage pain and inflammation, but they work through different mechanisms and have different side effects. NSAIDs, like ibuprofen, reduce inflammation and pain by inhibiting the production of prostaglandins, while steroids, like dexamethasone, reduce inflammation by inhibiting phospholipase A2 and reducing the production of inflammatory mediators. Understanding the differences and potential side effects of these drugs is crucial for dentists to ensure patient safety and effective pain management.

Indications

NSAIDs are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and used as opioid-sparing agents in certain acute trauma cases. They can be divided into classical non-selective NSAIDs and the newer COX-2 selective inhibitors.

NSAIDs are typically divided into groups based on their chemical structure and selectivity:

A- Non-selective NSAIDs

Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2.

- Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin

B- **COX-2 Selective NSAIDs**

However, COX-2 selective NSAIDs (ex. celecoxib) only target COX-2 and therefore have a different side effect profile.

- Celecoxib
- Rofecoxib
- Valdecoxib

Nonsteroidal Anti-inflammatory Drugs

1. Salicylic acid (aspirin).

2. Propionic acid (ibuprofen, fenoprofen, flurbiprofen, ketoprofen, naproxen).

3. Acetic acid (diclofenac, etodolac, indomethacin, tolmetin).

4. Enolic acid (meloxicam, piroxicam) 5.Fenamates (mefenamic acid) 6.Selective COX-2 inhibitor (celecoxib).

Mechanism of Action

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids. Specifically, thromboxanes play a role in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus, and play a role in anti-nociception.

There are two cyclooxygenase isoenzymes, COX-1 and COX-2. COX-1 gets constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. COX-2 is not constitutively expressed in the body; and instead, it inducibly expresses during an inflammatory response. Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (ex. celecoxib) only target COX-2 and therefore have a different side effect profile. Importantly, because COX-1 is the prime mediator for ensuring gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2 selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.

1- Anti-inflammatory actions

a- NSAIDs suppress the signs and symptoms of inflammation as pain, swelling and increased blood flow (vasodilatation) but there is no evidence that they alter the course or progress of the underlying chronic disease itself or induce remission because they do not have direct effect on cytokine/chemokine release, leukocyte migration, lysosomal enzyme release and toxic oxygen radical production, which contribute to tissue damage in chronic inflammatory conditions such as rheumatoid arthritis, vasculitis and nephritis.

b- NSAIDs Inhibit inflammation and immune response induced by prostaglandins (those mainly derived from COX-2).

2. Analgesic effects

The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders.. Mechanisms include the following:

a- Peripheral action: inhibition of PGE2 which is thought to sensitize nerve endings to the action of bradykinin and histamine released locally by the inflammatory process.

b- Central action: inhibit PGs formation in the spinal cord; prostaglandins in the spinal cord facilitate pain transmission from afferent pain fibers to relay neurons in the dorsal horn.

3. Antipyretic action

a- 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 an endogenous fever-producing agent (pyrogen), such as cytokines, is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation.

b- The NSAIDs lower body temperature by inhibiting PGE2 synthesis and resetting the "thermostat" back toward normal by dilatation of superficial blood vessels and stimulation of sweating.

4. Antiplatelet action of aspirin

5. Several NSAIDs (including aspirin) reduce the incidence of colon cancer when taken chronically for 5 years or longer.

Pharmacokinetics of NSAIDs:

- Nearly all NSAIDs are weak organic acids. 丨 All are well-absorbed from GIT; food does not affect drug bioavailability.

- Most of them highly protein bound especially to albumin.

- Most of the NSAIDs are highly metabolized, some by phase I (oxidative reactions) followed by phase II (conjugation reactions) and others by direct phase II reactions alone.

- While renal excretion is the most important route for final elimination, nearly all undergo varying degree of biliary excretion.

- NSAIDs with short half-lives differ from drugs with longer half-lives in that they stay in tissues (e.g. in the joints) longer than their half-lives.

- combinations of two NSAIDs should generally be avoided, not only because they increase the risk of GI and other side effects but also because they sometimes have adverse interactions.

- For example, aspirin and other salicylates displace some NSAIDs (e.g., ketorolac) from plasma proteins and thereby increase their serum levels significantly.

Administration

Most commonly, NSAIDs are available as oral tablets. According to the package insert, the dosage for the most common over-the-counter NSAIDs are as follows:

- Ibuprofen: for 200 mg tablets, 1 to 2 tablets every 4 to 6 hours while symptoms persist. The daily limit for ibuprofen is 1200 mg.
- Aspirin regular strength: 325 mg tablets, 1 to 2 tablets every 4 hours, or 3 tablets every 6 hours. The daily limit for aspirin is 4000 mg.
- Naproxen sodium: for 220 mg tablets, 1 to 2 tablets every 8 to 12 hours. The daily limit for naproxen sodium is 660 mg**.**

Topical NSAIDs are also available (diclofenac sodium 1.5% topical solution, diclofenac hydroxyethyl pyrrolidine 1.3% patch, and diclofenac sodium gel 1%). They are most useful for treating pain due to soft-tissue injuries and osteoarthritis.

Specific NSAIDs can also be administered parenterally; for example, intravenous ibuprofen is available, given as a 30-minute infusion; this can be used as a non-opioid analgesic to manage pain and can also reduce fever. Trials have shown that using intravenous ibuprofen and morphine in postoperative adult patients can lower the total use of morphine. For treating pyrexia, an initial 400mg dose then 400 or 100 to 200 mg every 4 to 6 hours as needed. For the treatment of pain, 400 to 800 mg, every 6 hours as needed, is the recommended dose regimen. Ketorolac is also available for parenteral administration.

Adverse Effects

1- Gastric adverse effects: These are the most common mainly dyspepsia to bleeding.

- Normally, production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2a stimulate 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.
- NSAIDs should be taken with food or fluids to diminish Gl upset. If NSAIDs are used in patients at high risk for GI events, proton pump inhibitors, with misoprostol (PGE1 analogue) or H2 receptor blockers to prevent NSAID induced ulcers.

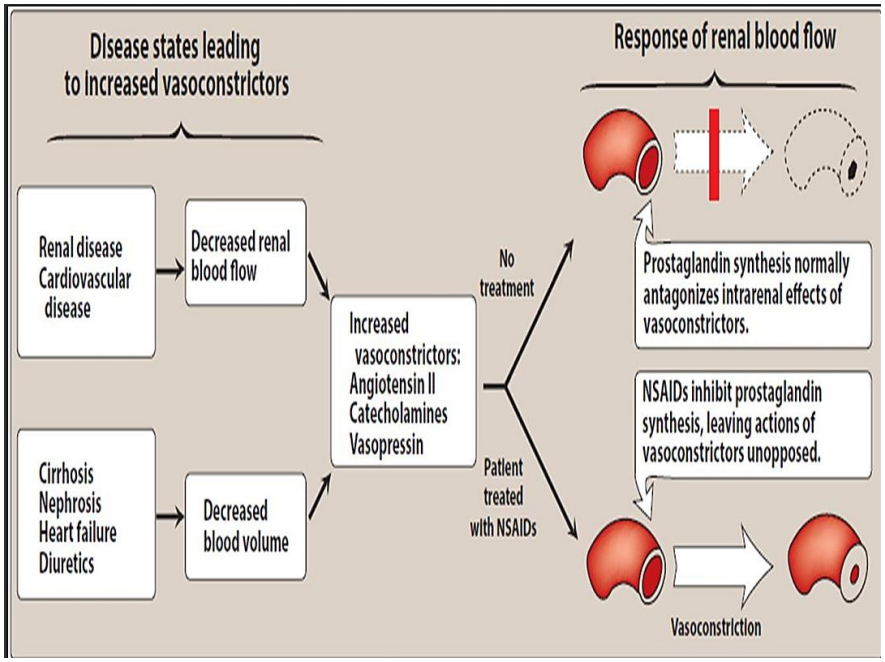
2- Adverse renal effects:

- Therapeutic dose in healthy individuals have little effects, but higher doses in susceptible patients (patients with history of heart failure or renal disease) may cause acute renal insufficiency which is reversible on stopping the drug.

- Nephrotoxicity is due, in part, to interference with the autoregulation of renal blood flow, which is modulated by prostaglandins(PGE2 and PGI2).

- Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients. These effects can diminish the beneficial effects of antihypertensive medications.

- Chronic NSAIDs consumption can cause analgesic nephropathy characterized by chronic nephritis and renal papillary necrosis.



3- Increased risk of bleeding (antiplatelet effect) and cardiovascular events:

- Aspirin inhibits COX-1-mediated formation of TXA2 and reduces platelet aggregation for the lifetime of the platelet (3-7 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 to reduce the risk of bleeding.

- Cardiac effects: 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.

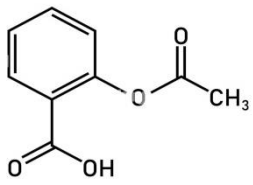
- Use of NSAIDs, other than aspirin, is discouraged in patients with established cardiovascular disease. Naproxen may be the least likely to be harmful.

4. Other unwanted effects:

- Rash are common idiosyncratic reaction of NSAIDs (especially mefenamic acid and sulindac). These rashes include: mild erythematous, urticarial and photosensitivity reaction.
- CNS effects, bone marrow disturbances
- liver disorders(Paracetamol overdose causes liver failure).
- Hypersensitivity reactions and aspirin-sensitive asthma in 15% of patients exposed to the drugs as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations.
- Pregnancy: Most NSAIDs are pregnancy risk category C in the first two trimesters. They should be used in pregnancy only if benefits outweigh risks to the developing fetus.
- [Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided because of the risk of premature closure of the ductus arteriosus.

Aspirin

- Acetylsalicylic acid (aspirin) is the prototype of traditional NSAIDs and was officially approved by the FDA in 1939.
- It is used more frequently at lower doses to prevent cardiovascular events(anti-platelet effect) such as stroke and MI.



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Mechanism of action

- Aspirin is a weak organic acid that irreversibly bind and inactivates COX-1.
- other NSAIDs are reversible inhibitors of COX (this is the basis for aspirin's long-lasting effects on platelets).
- The salicylates exhibit analgesic activity at lower doses. Only at higher doses 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.

Pharmacokinetics of aspirin:

- Part of aspirin is absorbed through the stomach, but most of the absorption occurs in the ileum.
- Aspirin rapidly (within 30 minutes) deacetylated by esterases in the body producing salicylate, which has the anti-inflammatory, antipyretic, and analgesic effects.
- Approximately 25% of salicylate is oxidized; some other conjugated with glucuronide or sulfate before excretion, and about 25% is excreted unchanged in urine, the rate of excretion being higher in alkaline urine.
- Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in first-order elimination and a serum half-life of 3.5 hours. With excessive doses (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, leading to a half-life of 15 hours or more.
- The duration of action of aspirin is not related to plasma half-life because it's irreversible inhibitor of COX.

Adverse effects:

1- Gastric upset (intolerance), GI bleeding, gastric and duodenal ulcers.

2- Increased risk of bleeding (antiplatelet effect).

3- Hepatotoxicity

4- Asthma exacerbation , rashes.

5- Renal toxicity rarely Reye's syndrome: Aspirin given during viral infections has been associated with an incidence of Reye's syndrome, which is rare but often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children. So children should be given paracetamol instead of aspirin.

Toxicity

- **Mild salicylate toxicity** is called salicylism and is characterized by nausea, vomiting, marked hyperventilation(as salicylates uncouple oxidative phosphorylation, which leads to elevated CO2 and increased respiration), headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).
- **High doses** cause Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure.
- Children are particularly prone to salicylate intoxication; ingestion of as little as 10 g of aspirin can be fatal.

Treatment of poisoning:

- measurement of serum salicylate concentrations and of pH to determine the best form of therapy.
- In mild cases, symptomatic treatment is usually sufficient.
- Increasing the urinary pH (alkalization using intravenous sodium bicarbonate) enhances the elimination of salicylate.
- In serious cases, mandatory measures include the intravenous administration of fluid, dialysis (hemodialysis or peritoneal dialysis).

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.
- Low doses of aspirin can reduce urate excretion, therefore should be avoided in patient with gout.

A- Diflunisal

- Diflunisal, a fluorinated derivative of salicylic acid which is more potent than that of aspirin in anti-inflammatory effect
- lacks antipyretic effect due to poor CNS penetration.
- Diflunisal is used in cases of pain due to arthritis.) It has low tendency to cause GI and antiplatelet side effects.

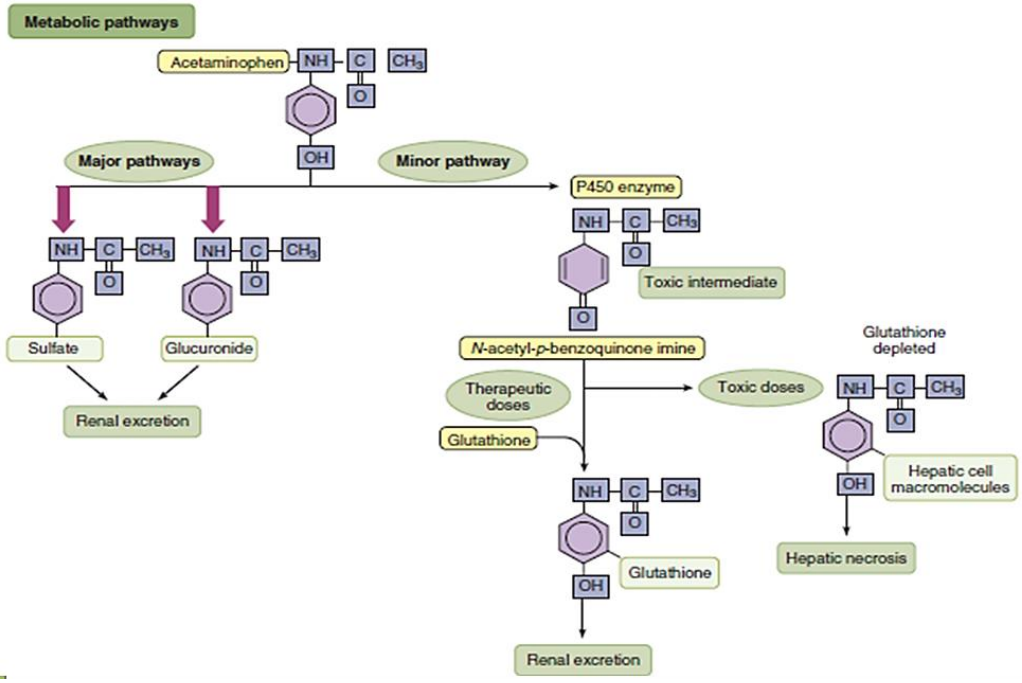
B- Acetaminophen (Paracetamol):

- One of the most commonly used drugs.
- Mechanism: inhibits PG 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. It is not considered as NSAID.
- It does not affect platelet function or increase bleeding time.

Pharmacokinetics:

- Paracetamol given orally and is well absorbed, peak concentration occur within 30-60 minutes.
- The plasma half-life of therapeutic dose is 2-4 hours, but with toxic doses it may be extended to 4-8 hours.

- Paracetamol is inactivated in the liver, being conjugated to give inactive glucuronide or sulfate. A portion of paracetamol is hydroxylated to form N acetyl-p-benzoquinoneimine(NAPQI) , a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups.
- At normal doses of acetaminophen, the N-acetyl-p-benzoquinoneimine, reacts with the sulfhydryl group of glutathione, forming a nontoxic substance.
- Acetaminophen and its metabolites are excreted in the urine.
- The drug is also available in intravenous and rectal formulations.



Adverse effects:

1- With normal therapeutic doses, paracetamol is virtually free of any significant adverse effects.

2- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.

3- With large doses of paracetamol {acute ingestion of more than 150–200 mg/kg (children) or 7 g total (adults) is considered potentially toxic}, the available glutathione in the liver becomes depleted, and N-acetyl-p benzoquinoneimine reacts with the sulfhydryl groups of hepatic proteins, causing hepatic necrosis which is a very serious and potentially life threatening condition.

4- Administration of I.V. N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within 10 hours of the overdose.

Propionic acid derivatives

- **Ibuprofen** was the first in this class of agents. It has been followed by **naproxen**, **fenoprofen** , **ketoprofen**, **flurbiprofen** , and **oxaprozin**.
- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity.
- These drugs are among the most widely used NSAIDs for pain and inflammation caused by trauma, infection, autoimmune disorders, neoplasms, joint degeneration, and arthritic disorders.
- Ibuprofen is used IV to close a patent ductus arteriosus (PDA) in preterm infants.
- It has also topical cream preparation for musculoskeletal pain and a liquid gel preparation for postsurgical dental pain.
- ketoprofen has also been reported to stabilize lysosomal membranes and antagonize the action of bradykinin.
- Flurbiprofen is also available in a topical ophthalmic formulation, intravenous preparation for perioperative minor analgesia and lozenge form for sore throat.
- The most common adverse effects are GI, ranging from dyspepsia to bleeding. CNS side effects such as headache, tinnitus, and dizziness, have also been reported.

Acetic acid derivatives

- Indomethacin is one of the most potent inhibitors of COX. It may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T-cell and B-cell proliferation.
- Because of its greater tendency to cause adverse effects, this drug is usually reserved for the management of moderate to severe acute inflammatory conditions. It is also used to treat infants with a patent ductus arteriosus.

Adverse effects of indomethacin include:

1- GIT: gastric discomfort, dyspepsia, abdominal pain, diarrhea, hemorrhage, pancreatitis..
2- CNS: Headache (15-25%), dizziness, confusion, depression, and rarely psychosis
3- Hematology: thrombocytopenia, aplastic anemia.
4- Renal papillary necrosis.

A- Diclofenac

- has preferential activity on COX-2 (similar to celecoxib).
- It is approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis.

- It is available in a number of preparations, including immediate-release, extended-release, a transdermal patch , and a new formulation for topical administration (Voltaren Gel),intramuscular injection, rectal suppository and ophthalmic preparation.
- It is more potent than indomethacin or naproxen.

B- Sulindac is an inactive prodrug that is closely related to indomethacin. It is noted for having a renal-sparing effect such that moderate doses alter renal prostaglandin production less than with other NSAIDs.

C- Ketorolac is a potent analgesic but has moderate anti-inflammatory effects. It is used parenterally for the treatment of postoperative pain as it produces analgesia comparable to that of morphine, but for only a short duration. Also it is used topically for allergic conjunctivitis.

D- Etodolac has effects similar to those of the other NSAIDs. GI problems are less common.

E- Nabumetone is one of the few non-acidic NSAIDs, it is a ketone prodrug indicated for the treatment of RA and osteoarthritis and is associated with a low incidence of adverse effects.

Enolic acid derivatives

- Piroxicam and meloxicam are used to treat RA, ankylosing spondylitis, and osteoarthritis.
- They have long half-lives, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- Meloxicam inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than piroxicam.

Fenamates

Mefenamic acid and **meclofenamate** are commonly used for their analgesic action. They may cause rashes, diarrhea or bowel inflammation.

Selective COX-2 inhibitors

The selective COX-2 inhibitors are a group of drugs (known as coxibs) that provide potent anti-inflammatory activity without causing significant GI toxicity.

- **Celecoxib** , the first selective COX-2 inhibitor to be marketed, was soon followed by the release of rofecoxib. The latter drug was withdrawn from the market because of the relative increase risk of confirmed cardiovascular events(e.g., heart attack and stroke).

 Etoricoxib , another highly selective COX-2 inhibitor with claimed to have stronger analgesic efficacy than celecoxib. It is suitable for once-a-day therapy for various arthritis conditions, ankylosing spondylitis, surgical pain, etc.

- As compared to others in this group, etoricoxib shows very low GI-related side effects.

 Parecoxib is one of the selective COX-2 inhibitors.

 Valdecoxib has been modified suitably as a prodrug which is suitable for injection after demethylation. Therefore, it can be used for postoperative conditions by intravenous or intramuscular routes.

- Valdecoxib has been reported to cause severe skin reactions and parecoxib injection shares such risk due to its active metabolite conversion into valdecoxib.

A- Celecoxib

 It is more selective for inhibition of COX-2 than of COX-1 (about 10–20 times).

 It is approved for treatment of RA, osteoarthritis, and acute mild to moderate pain.

 Recent studies show that NSAIDs including celecoxib can delay or slow the progress of Alzheimer disease.

 In addition, celecoxib is found to be more effective than nonselective COX inhibitors in protecting against colon carcinogenesis.

Pharmacokinetics: Celecoxib is readily absorbed, reaching a peak concentration in about 3 hours.

 It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in the feces and urine.

 The half-life is about 11 hours, and the drug may be dosed once or twice daily.

Adverse effects:

1- Most common : headache, dyspepsia, diarrhea, and abdominal pain.

2- Celecoxib is associated with less GI bleeding and dyspepsia than other NSAIDs.

3- However, this benefit is lost when aspirin is added to celecoxib therapy.

4- Patients who are at high risk of ulcers and require aspirin for cardiovascular prevention should avoid the use of celecoxib.

5- It is contraindicated in patients who are allergic to sulfonamides(because it is a sulfa-NSAID).

6- Celecoxib should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure.

7- Inhibitors of CYP2C9, such as fluconazole, fluvastatin, and zafirlukast, may increase serum levels of celecoxib.

B- CHOICE OF NSAID

- All NSAIDs, including aspirin, are about equally efficacious with a few exceptions—tolmetin seems not to be effective for gout, and aspirin is less effective than other NSAIDs (eg, indomethacin) for ankylosing spondylitis.
- For patients with renal insufficiency, nonacetylated salicylates (salicylate, sodium salicylate, and salicyl salicylate which are effective anti-inflammatory drugs, but they do not inhibit platelet aggregation.) may be best.
- Diclofenac and sulindac are associated with more liver function test abnormalities than other NSAIDs.
- Selective COX-2 inhibitor celecoxib is probably safest for patients at high risk for GI bleeding but may have a higher risk of cardiovascular toxicity.
- The choice of NSAID thus requires a balance of efficacy, cost-effectiveness, safety, and numerous personal factors.

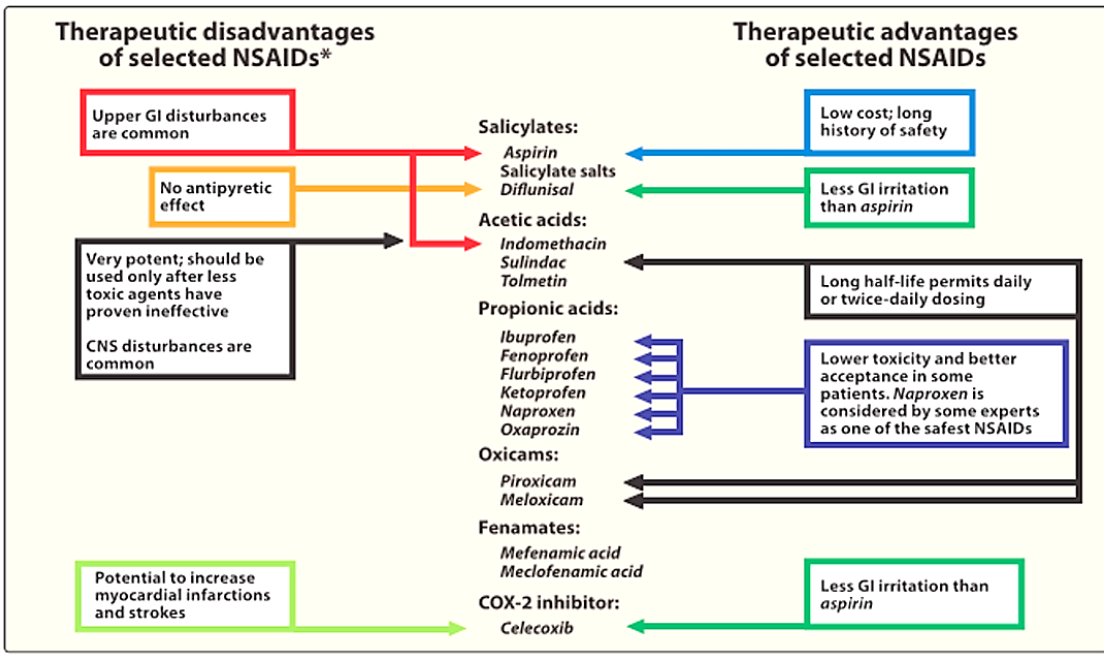


Figure 38.16
Summary of nonsteroidal anti-inflammatory agents (NSAIDs). *As a group, with the exception of *aspirin*, these drugs may have the potential to increase risk of myocardial infarction and stroke. GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2.

External applications of NSAIDs:

1- Salicylic acid is used topically to treat acne, corns, and warts.

2- Methyl salicylate ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs.

3- Diclofenac is available in topical formulations (gel or solution) for treatment of osteoarthritis in the knees or hands.

4- Ocular formulations of ketorolac are approved for management of seasonal allergic conjunctivitis, inflammation and pain related to ocular surgery.