Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

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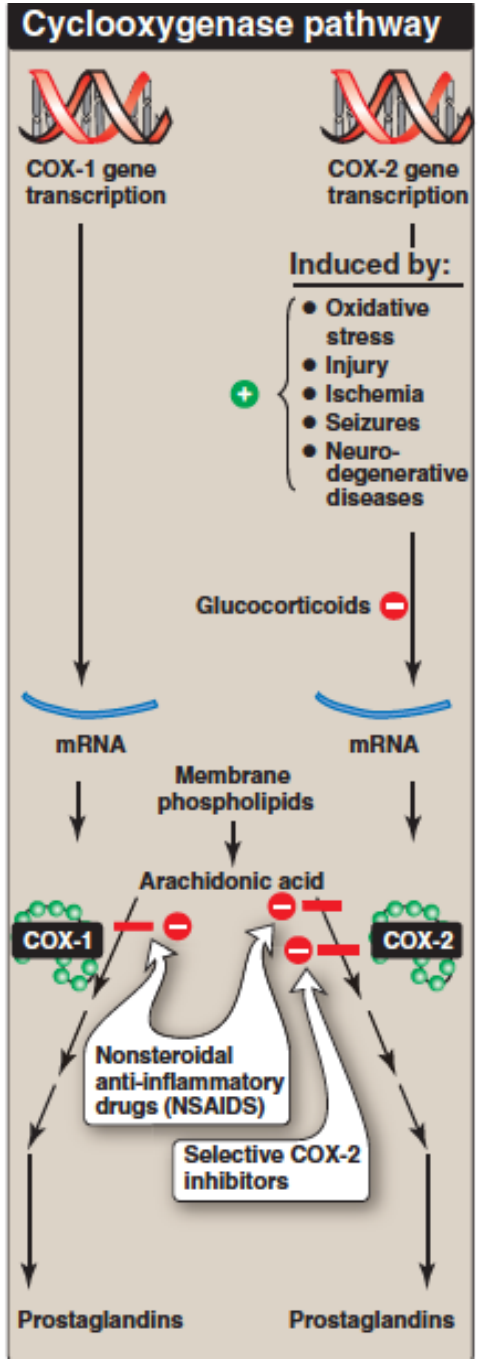
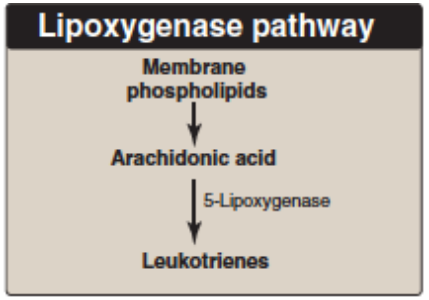
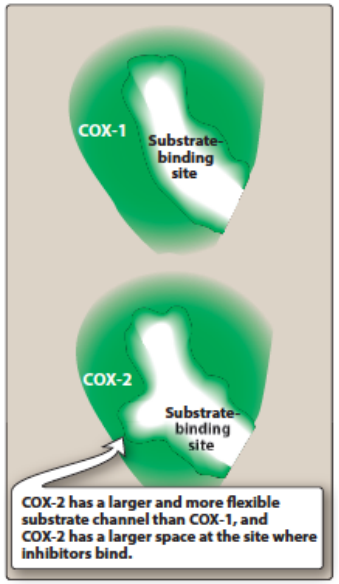
Figures and tables are originated from Lippincott's Pharmacology (6th Edition).

The NSAIDs act by inhibiting the synthesis of prostaglandins.

Alprostadil
Lubiprostane
Misoprostol
PGF2alpha analogs
PGI2 analogs





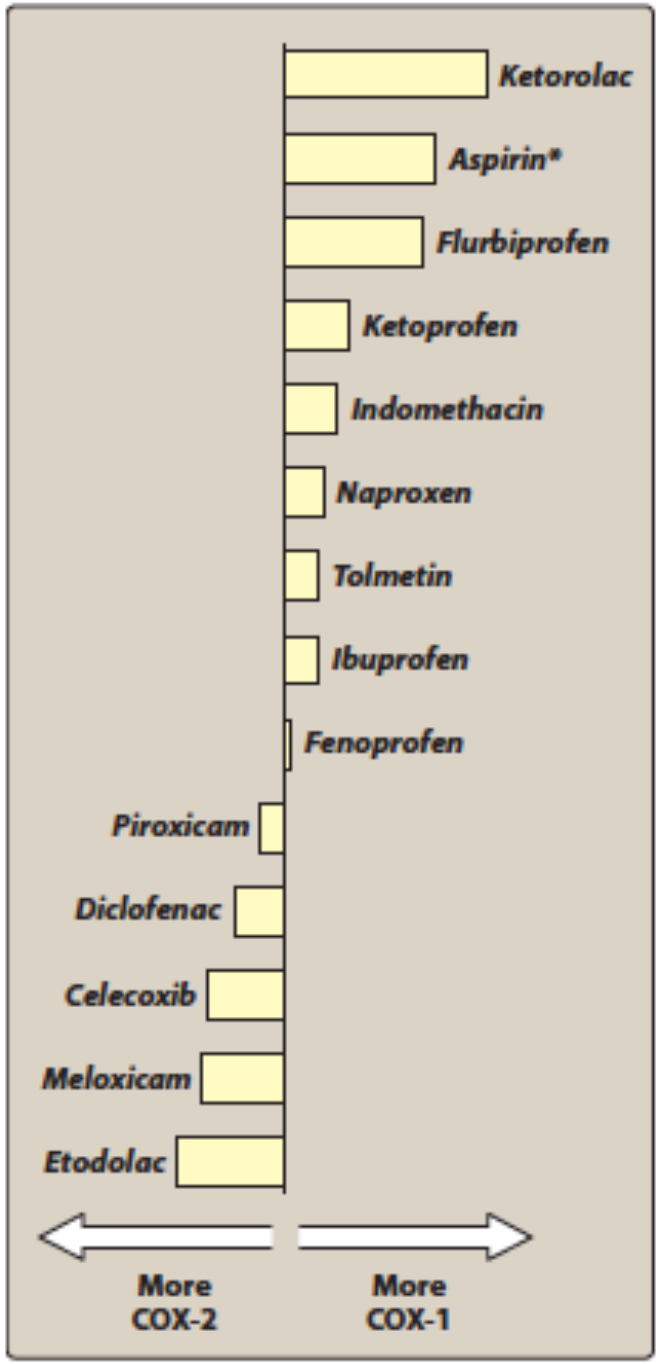


NSAIDs

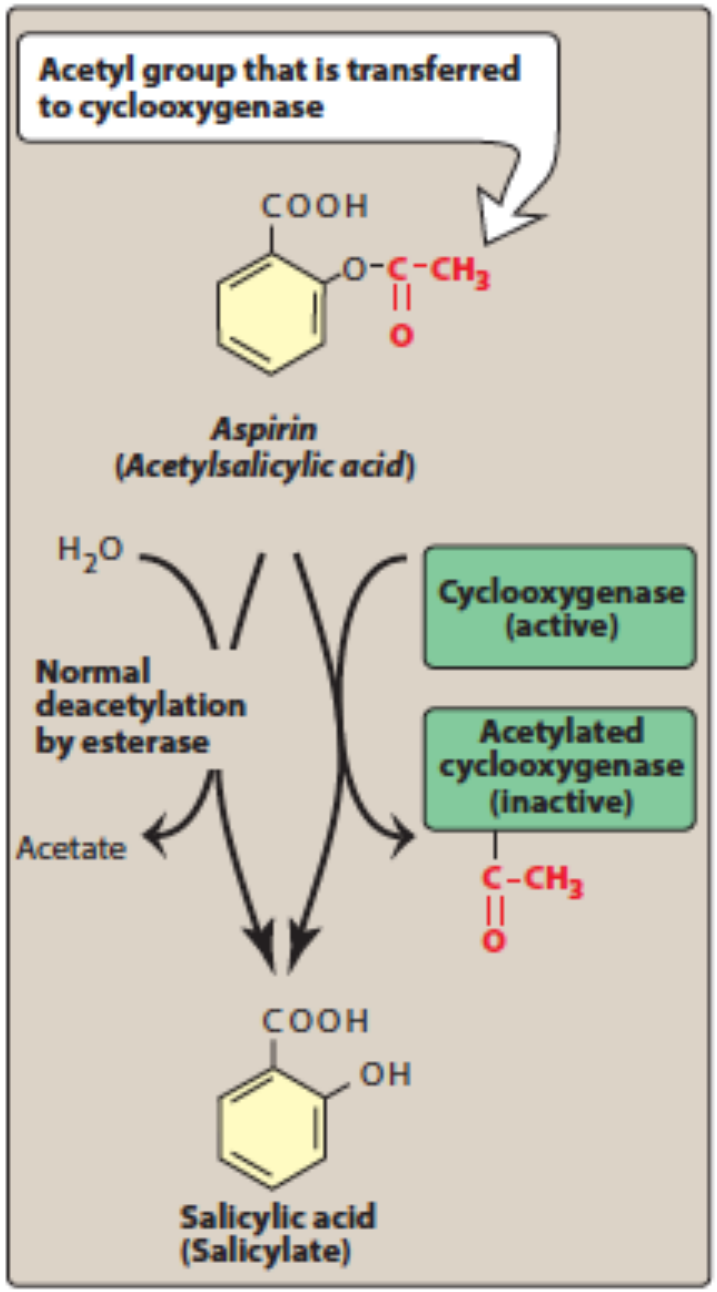
Aspirin BAYER, BUFFERIN, ECOTRIN
Celecoxib CELEBREX
Diclofenac CATAFLAM, FLECTOR, PENNSAID, VOLTAREN
Diflunisal DOLOBID
Etodolac
Fenoprofen NALFON
Flurbiprofen ANSAID
Ibuprofen ADVIL, MOTRIN
Indomethacin INDOCIN
Ketorolac ACULAR, ACUVAIL, TORADOL
Ketoprofen
Meclofenamate
Mefenamic acid PONSTEL
Meloxicam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

OTHER ANALGESICS

Acetaminophen (Paracetamol) OFIRMEV, TYLENOL



Aspirin



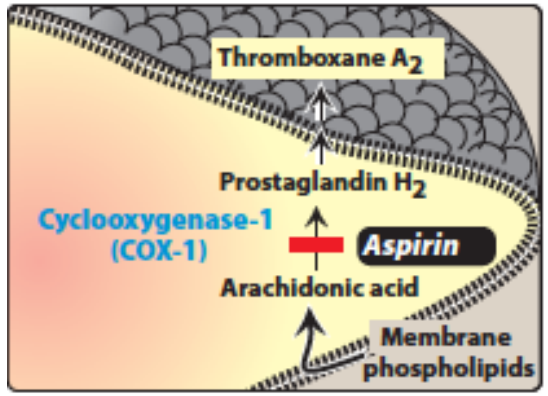
Aspirin exhibits antiinflammatory activity only at relatively high doses that are rarely used. At lower doses aspirin mediate the prevention of cardiovascular events such as stroke and myocardial infarction.
It is an irreversible inhibitor of COX activity.
All NSAIDs reduce inflammation (anti-inflammatory), pain (analgesic effect) and fever (antipyretic effect).

Therapeutic uses

- *Anti-inflammatory and analgesic uses:* Treatment of osteoarthritis, gout and romatoid arthritis. Also they can be used to treat common conditions like headache, arthralgia, myalgia and dysmenorrhea requiring analgesia.
- *Antipyretic uses:* Aspirin*, ibuprofen and naproxen may be used to treat fever.

  **Aspirin should be avoided in patients less than 20 years old with viral infections such as varicella or influenza, to prevent Reye syndrome.*

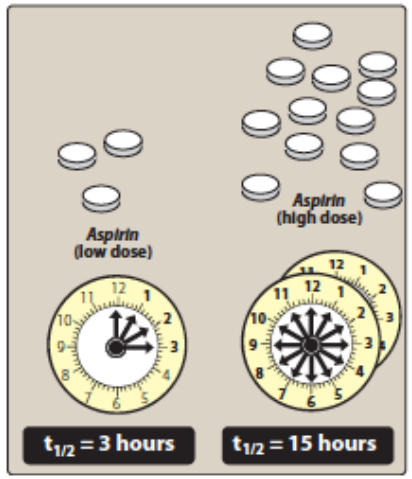
- *Cardiovascular applications:* Inhibition of platelet aggregation. Low-dose (80-100mg) aspirin inhibits COX-1-mediated production of TXA2 and subsequent vasocontraction and platelet aggregation. As aspirin irreversibly inhibits COX-1, the antiplatelet effects persist for the life of the platelet. Chronic use of low doses 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.



- *External applications:* Salicylic acid is used topically to treat acne, corns, calluses and warts.

Pharmacokinetics

After oral administration, aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate. Unionized salicylates are passively absorbed mostly from the upper small intestine (higher pH is requested for better dissolution).



Salicylate is secreted into the urine and can affect uric acid excretion. At the low doses of aspirin (<2mg/day), uric acid secretion is decreased, whereas at high doses, uric acid secretion may be unchanged or increased. Therefore, aspirin is avoided in gout or in patients taking probenecid.

Most NSAIDs are well-absorbed after oral administration. The majority of the group are metabolized by the liver to their inactive metabolites with exceptions like nabumetone and sulindac which have active metabolites. Elimiation of the active drug and metabolites is primarily via urine.

Adverse effects

«At the lowest effective dose for the shortest duration possible»

- Gastrointestinal: The most common adverse effects of NSAIDs are GI-related, ranging from dyspepsia to bleeding. Agents that inhibit COX-1 reduce beneficial levels of PGI2, PGE2 and PGF2alpha, 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. If the patient has a high risk for GI events, PPI or misoprostol should be used combined.

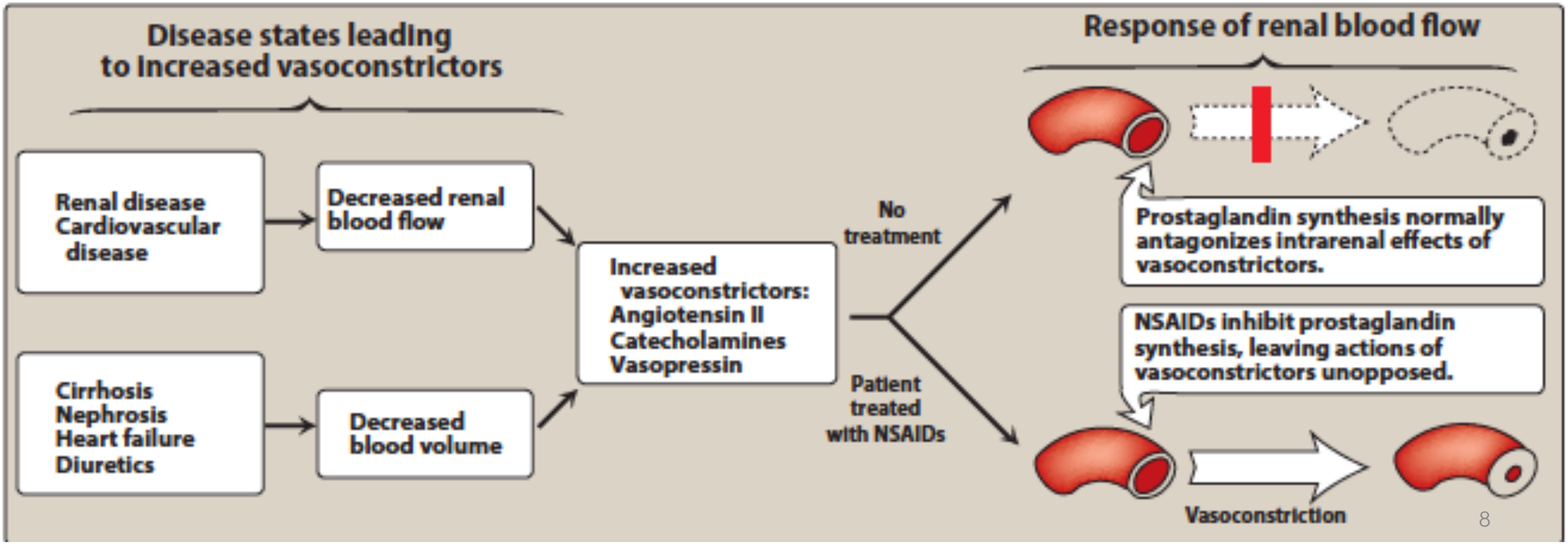
- Increased risk of bleeding: Aspirin irreversibly inhibits COX-1-mediated TXA2 formation, while other NSAIDs reversibly inhibit the production of TXA2. Because of the decrease in TXA2 production, platelet aggregation is reduced, producing an antiplatelet effect with a prolonged bleeding time.

  Aspirin is not given at least 1 week prior to surgery.

Adverse effects

«At the lowest effective dose for the shortest duration possible»

- Actions on the kidney: Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema. These effects can also mitigate the beneficial effects of antihypertensive medications.



Adverse effects

«At the lowest effective dose for the shortest duration possible»

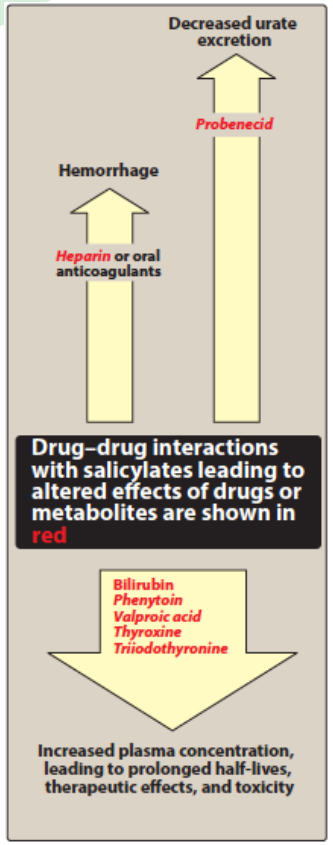
- Cardiac effects: Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events. Use of NSAIDs, other than aspirin is discouraged in patients with established cardiovascular disease. Naproxen appears to be the least likely to be harmful.

- NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotrien production and increase the risk of exacerbations of asthma.

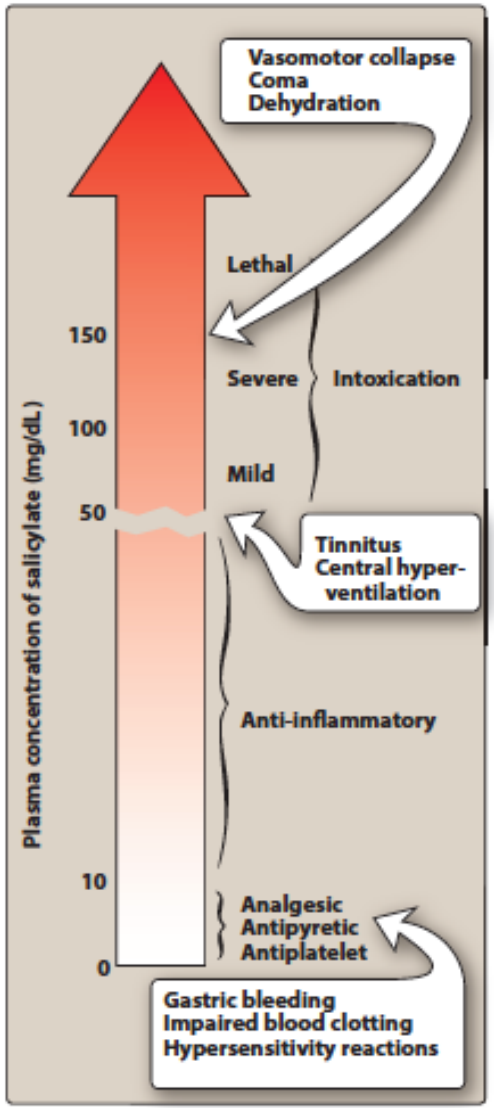
- Adverse effects associated with central nervous system like headache, tinnitus and dizziness may be seen.

- Aspirin may induce hypersensitivity reactions including urticaria, bronchoconstriction and angioedema. Fatal anaphylactic shock is rare.

Drug interactions and toxicity



Aspirin can displace other highly protein-bound drugs such as warfarin, phenytoin or valproic acid resulting in higher free concentrations of these agents.



Salicylism is the mild form of salicylate intoxication which is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness and tinnitus.

Severe salicylate intoxication: restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis and death.

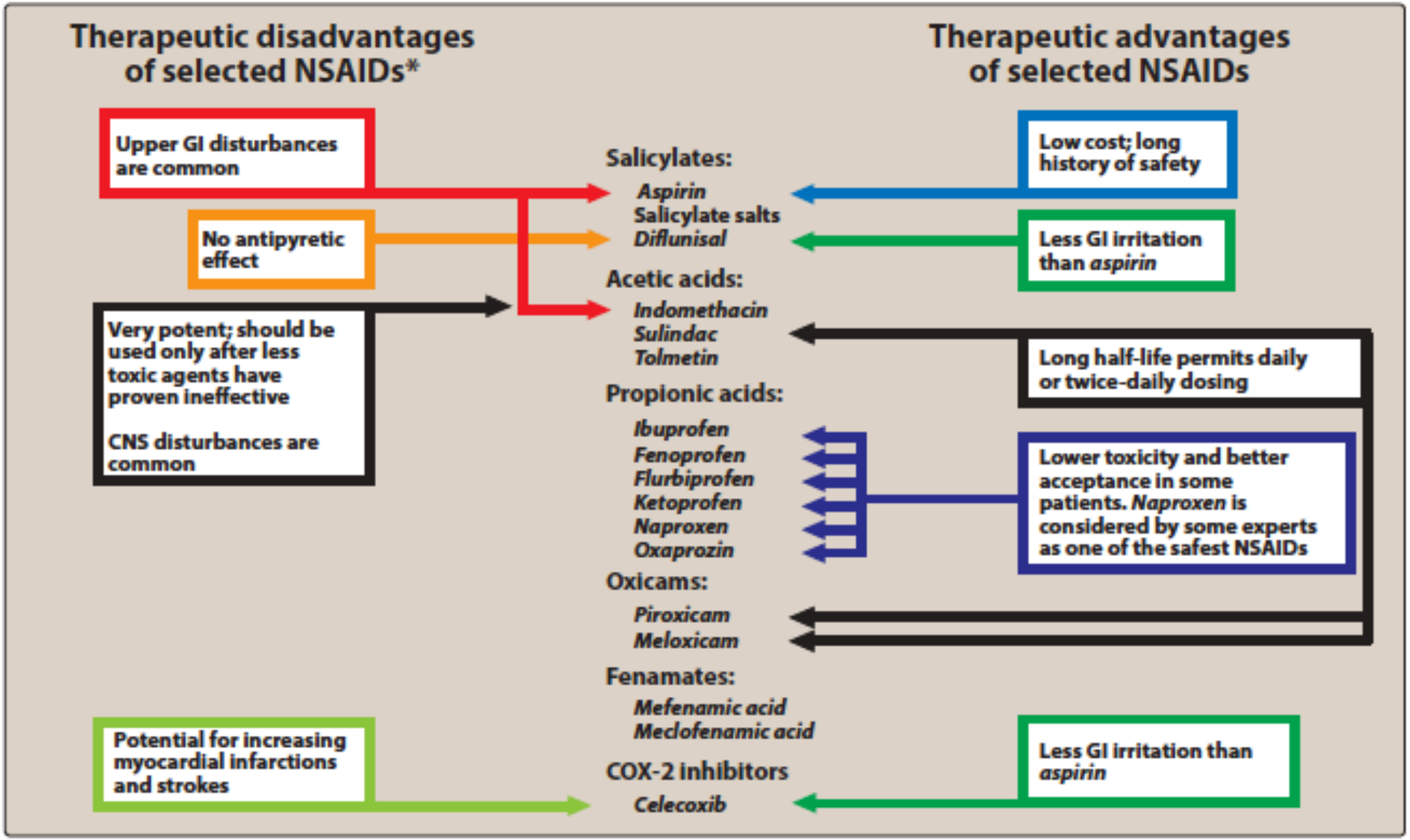
Celecoxib

A selective COX-2 inhibitor. The inhibition of COX-2 is reversible.

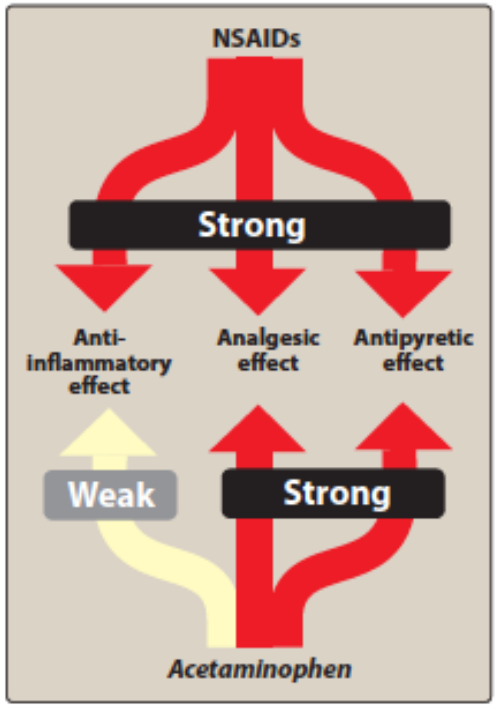
Therapeutic uses: Celecoxib is approved for the treatment of romatoid arthritis, osteoarthritis and acute mild to moderate pain.

Pharmacokinetics: Celecoxib is readily absorbed after oral administration. It is extensively metabolized in the liver by CYP2C9 and is excreted in feces and urine. The half-life is about 11 hours and the drug may be dosed once or twice Daily.

Adverse effects: Headache, dyspepsia, diarrhea and abdominal pain. Like other NSAIDs, the drug has a similar risk for cardiovascular events.


Therapeutic disadvantages of selected NSAIDs*
Therapeutic advantages of selected NSAIDs
Upper GI disturbances are common
No antipyretic effect
Very potent; should be used only after less toxic agents have proven ineffective
CNS disturbances are common
Potential for increasing myocardial infarctions and strokes
Salicylates:
Aspirin
Salicylate salts
Diflunisal
Acetic acids:
Indomethacin
Sulindac
Tolmetin
Propionic acids:
Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin
Oxicams:
Piroxicam
Meloxicam
Fenamates:
Mefenamic acid
Meclofenamic acid
COX-2 inhibitors
Celecoxib
Low cost; long history of safety
Less GI irritation than aspirin
Long half-life permits daily or twice-daily dosing
Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs
Less GI irritation than aspirin

Acetaminophen



Inhibits prostaglandin synthesis in the CNS which explains the mechanism of its antipyretic and analgesic properties. It has less effect on COX in peripheral tissues which accounts for its weak anti-inflammatory activity.
Acetaminophen does not affect platelet function. It is not considered as a member of NSAIDs.

Therapeutic uses:
Acetaminophen is an alternative to analgesic and antipyretic effects of NSAIDs

- for those patients with gastric risks
- in those whom a prolongation of bleeding time is not desirable
- those who do not require the anti-inflammatory action of NSAIDs.

It is the analgesic/antipyretic of choice for children with viral infections or chickenpox.

At therapeutic doses, acetaminophen is free of significant adverse effects. With large doses, hepatic necrosis, a very 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.