# PHARMACOLOGY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS.

**Nonsteroidal anti-inflammatory drugs** NSAIDs are a class of medications used to treat pain, fever, and other inflammatory processes. This activity describes the indications, mechanism of action, administration, adverse effects, contraindications, monitoring, and important points for providers regarding NSAIDs.

NSAIDs are a drug class 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.

**Indications for NSAIDS include the following:**

Inflammatory conditions

Chronic joint disease

Musculoskeletal pain

Headache

Menstrual pain

Dental pain

Postoperative mild to moderate pain

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

**I. Non-selective COX-1,2 inhibitors:**

1. Salicylates: Acetylsalicylic acid, sodium salicylate, salicylic acid, Methyl salicylate, phenyl salicylate, mesalazine, diflunisal
2. Para-aminophenol derivatives: acetaminophen (paracetamol)
3. Pyrazolone derivatives: aminopyrine, methamisole (analgin), propiphenazone, Phenylbutazone, oxyphenbutazone
4. Phenylpropionic acid derivatives: (profenes) ibuprofen, naproxen, fenbufen, Thiaprofen, ketoprofen, phenoprofen.
5. Phenylacetic acid derivatives: Diclofenac sodium, Nabumetone, phenclofenac
6. Indoleacetic acid derivatives: Indometacin, Tolmetin, Ketorolac, Sulindac
7. Phenamic acid derivatives: Mephenamic acid, Fluphenamic acid, Tolphenamic acid,

8. Oxycams: Piroxicam, Tenoxicam, Procuazone, Azapropazone

**II. COX-2 inhibitors:**

1. COX-2 selective inhibitors: Celecoxib, Valdecoxib, Etherecoxib Rofecoxib
2. Non-selective COX-2 inhibitors: Nimesulide, Meloxicam, Etodolac

**III. Drugs of different groups:**

1. Gold drugs: crizanol, auranofin, myocrysin
2. Bee venom preparations: apizatron, virapin, ungapevin, apifor, apitoxin
3. Drugs based on snake venom: vipraxin, nayaxin, viprosal, nizvisal, nazatox
4. Various anti-inflammatory agents: dimethyl sulfoxide (dimethoxide), bischofit

Topical NSAIDs are also available for use in acute tenosynovitis, ankle sprains, and soft tissue injuries

**Mechanism of action of NSAIDs:**

Membrane phospholipids are initially converted to arachidonic acid by phospholipase $A_2$ as a result of inflammation and tissue damage. Arachidonic acid is then either converted to the prostaglandins via the COX pathway or alternatively converted to leukotrienes by the enzyme lipoxygenase (Figure 1). The type of prostaglandin produced depends on the specific tissue.

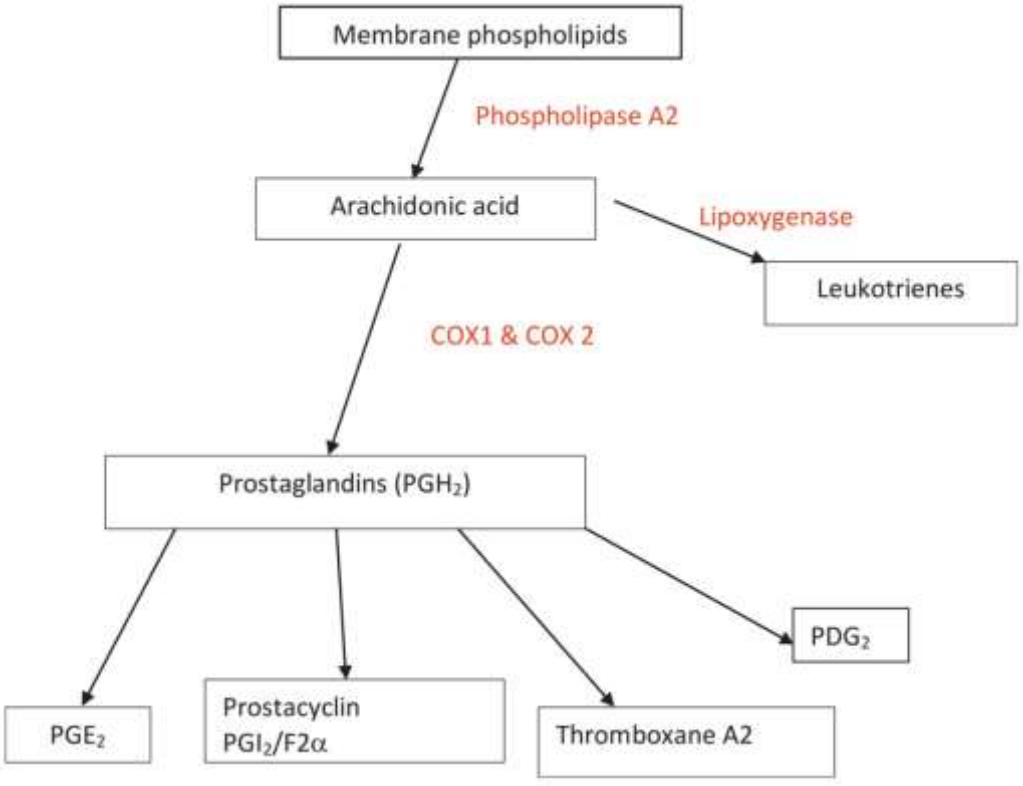

Figure 1. Arachidonic acid pathway showing production of prostaglandins from membrane phospholipids. The leukotriene pathway is responsible to the group of patients with NSAIDs–sensitive asthma.

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). 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. 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. 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. NSAIDs cause a reduction in their synthesis and therefore analgesia. COX 3 is found within the central nervous system and is believed to be the site of action of paracetamol; the exact nature of the isoenzyme is unclear at this time.

| Prostaglandin Subtype | Function |
|---|---|
| $PGE_2$ | Sensitise nerve endings to bradykinin, increase body temperature, vasodilation, gastroprotection |
| $PGF2_\alpha$ | Bronchoconstriction, uterine contractions |
| $PGD_2$ | Bronchoconstriction |
| $PGI_2$ (prostacyclin) | Vasodilatation (vasoconstriction in pulmonary epithelium), decreased platelet aggregation, gastroprotection |
| $TXA_2$ | Platelet aggregation, vasoconstriction |

A wide variety of NSAIDs are available with different degrees of inhibition of COX-1 and COX-2. Their degree of each isoenzyme inhibition determines their side-effect profile.

**Pharmacokinetic properties**

The majority of NSAIDS are administered orally, with the exceptions of ketorolac and parecoxib (intravenous administration) and diclofenac (oral, intravenous, and per rectum administration). They are weak organic acids and are therefore absorbed rapidly in the stomach and small intestine. The stomach has a lower pH than the small intestine and therefore, more drug is in the more

absorbable unionised form; however, the main source of absorption is the small intestine due to its larger surface area. NSAIDs have a high bioavailability due to limited first-pass hepatic metabolism. They are highly protein-bound molecules and as a result can displace other protein-bound medications leading to increased free drug concentrations and increased risk of adverse events (eg, displacement of warfarin from albumin leading to an increased risk of bleeding). Bioconversion is mostly hepatic with metabolites excreted in the urine.

**Adverse effects of NSAIDs**

NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

**Gastric adverse effects** are likely due to the inhibition of COX-1, preventing the creation of prostaglandins that protect the gastric mucosa. The damage is more likely in a patient that has a prior history of peptic ulcers. Since it is COX-1 specific, the use of COX-2 selective NSAIDs is a lower-risk alternative.

**Renal adverse effects** are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamics. In a patient with normal renal function, inhibition of prostaglandin synthesis does not pose a large problem; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur include acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/ interstitial nephritis.

**Cardiovascular adverse effects** can also be increased with NSAID use; these include MI, thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.

**Respiratory adverse effects** Up to 10% of patients with asthma have disease which is exacerbated by NSAIDs.[5,6] A proposed mechanism of action is that inhibition of arachidonic acid metabolism by COX leads to an increase in production of leukotrienes. Leukotrienes have direct bronchoconstrictor actions. **.** Anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.

**Hepatic adverse effects** are less common; NSAID-associated risk of hepatotoxicity (raised aminotransferase levels) is not very common, and liver-related hospitalization is very rare. Among the various NSAIDs, Diclofenac has a higher rate of hepatotoxic effects.

**Hematologic adverse effects** are possible, particularly with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.), and in some perioperative cases.

**Bone Healing** There is a theoretical risk that NSAIDs, in particular COX-2 inhibitors, reduce bone-healing rates and increase the incidence of nonunion of fractures. After a fracture there is an increased production of prostaglandins as part of the inflammatory response, which increases local blood flow.[3] It is hypothesised that blocking this mechanism is detrimental to bone healing; however, there is currently no high-quality scientific evidence to confirm this.

NSAIDs are **contraindicated in patients:**

- ✓ With NSAID hypersensitivity or salicylate hypersensitivity, as well as in patients who have experienced an allergic reaction (urticaria, asthma, etc.) after taking NSAIDs
- ✓ Who have undergone coronary artery bypass graft surgery
- ✓ During the third trimester of pregnancy
- ✓ Childs till 12 year old (except Kawasaki deasese)

**DRUG INTERACTIONS**

Angiotensin-converting enzyme (ACE) inhibitors act, at least partly, by preventing the breakdown of kinins that stimulate PG production. Thus, NSAIDs might attenuate the effectiveness of ACE inhibitors by blocking the production of vasodilator and natriuretic PGs.

Due to hyperkalemia, the combination of NSAIDs and ACE inhibitors also can produce marked bradycardia leading to syncope, especially in the elderly and in patients with hypertension, diabetes mellitus, or ischemic heart disease.

Corticosteroids and SSRIs may increase the frequency or severity of GI complications when combined with NSAIDs.

NSAIDs may augment the risk of bleeding in patients receiving warfarin both because almost all tNSAIDs suppress normal platelet function temporarily during the dosing interval and because some NSAIDs also increase warfarin levels by interfering with its metabolism; thus, concurrent administration should be avoided.

Many NSAIDs are highly bound to plasma proteins and thus may displace other drugs from their binding sites. Such interactions can occur in patients given salicylates or other NSAIDs together with warfarin, sulfonylurea hypoglycemic agents, or methotrexate; the dosage of such agents may require adjustment to prevent toxicity.

Patients taking lithium should be monitored because certain NSAIDs (e.g., piroxicam) can reduce the renal excretion of this drug and lead to toxicity, while others can decrease lithium levels (e.g., sulindac).

## SALICYLIC ACID DERIVATIVES

Acetylsalicylic acid, sodium salicylate, salicylic acid, Methyl salicylate, phenyl salicylate, mesalazine, diflunisal

**Acetylsalicylic Acid (ASA; Aspirin)** Causes inhibition of COX1 and COX
**Actions are dose-dependent:**

- ***Antiplatelet*** aggregation – low dose, the basis for post-MI prophylaxis and to reduce the risk of recurrent TIAs (75-300mg)
- ***Analgesia and antipyresis-*** Moderate dose 500 mg
- ***Antiinflammatory***- High doses more 500mg
- ***Uric acid elimination***: Low to moderate doses: ↓ tubular secretion → hyperuricemia º High doses: ↓ tubular reabsorption → uricosuria

**– Acid-base and electrolyte balance**
Dose-dependent actions:

- **High therapeutic**: mild uncoupling of oxidative phosphorylation →↑ respiration →↓ pCO2→respiratory alkalosis→ renal compensation →↑ HCO3– elimination →compensated respiratory alkalosis (pH = normal, ↓ HCO3−, ↓ pCO2)
  In adults, this can be a stable condition; in children →↑ toxicity.
  **- Toxic doses:** inhibits respiratory center →↓ respiration →↑ pCO2→respiratory acidosis (↓ pH, ↓ HCO3–, normalization of pCO2) plus inhibition of Krebs cycle and severe uncoupling of oxidative phosphorylation (↓ ATP) →metabolic acidosis, hyperthermia, and hypokalemia (↓ K+).

**Adverse effects:**
Gastrointestinal irritation: gastritis, ulcers, bleeding
Salicylism: tinnitus, vertigo, ↓ hearing—often first signs of toxicity
Bronchoconstriction: exacerbation of asthma
Hypersensitivity, especially the "triad" of asthma, nasal polyps, rhinitis
Reye syndrome: encephalopathy
↑ bleeding time (antiplatelet)

Chronic use: associated with renal dysfunction

**Drug interactions:** ethanol (↑ gastrointestinal bleeding), warfarin (↑ effects), and uricosurics (↓ effects)

**• Aspirin overdose and management:**

– Extensions of the toxic actions described above, plus at high doses vasomotor collapse occurs, with both respiratory and renal failure.

– No specific antidote. Management includes gastric lavage (+/− activated charcoal) plus ventilatory support and symptomatic management of acid-base and electrolyte imbalance, and the hyperthermia and resulting dehydration. Increased urine volume and its alkalinization facilitate salicylate renal elimination.

## Para-aminophenol derivatives: acetaminophen (paracetamol)

**Paracetamol (acetaminophene)**

Phenacetin, a toxic prodrug that is metabolized to acetaminophen, is still available in some other countries.

**Mechanism of action:** Causes inhibition of COX-3 in the CNS
antipyretic – analgesic, very weak anti-inflammatory effect (does not affect the periphery)
**Pharmacological actions:** Acetaminophen is an analgesic and antipyretic agent; it lacks antiinflammatory or antiplatelet effects.
*Unlike ASA*, paracetamol is not an acid, does not bind with plasma proteins, does not compete with oral anticoagulants (it binds to blood proteins), does not inhibit lactic acid secretion, does not affect prothrombin synthesis, does not have anti-inflammatory effect.
**Pharmacokinetics and Clinical Use**: Acetaminophen is effective for the same indications as intermediate dose aspirin. Acetaminophen is therefore useful as an aspirin substitute, especially in children with viral infections and in those with any type of aspirin intolerance. Acetaminophen is well absorbed orally and metabolized in the liver. Its half-life, which is 2–3 h in persons with normal hepatic function, is unaffected by renal disease.

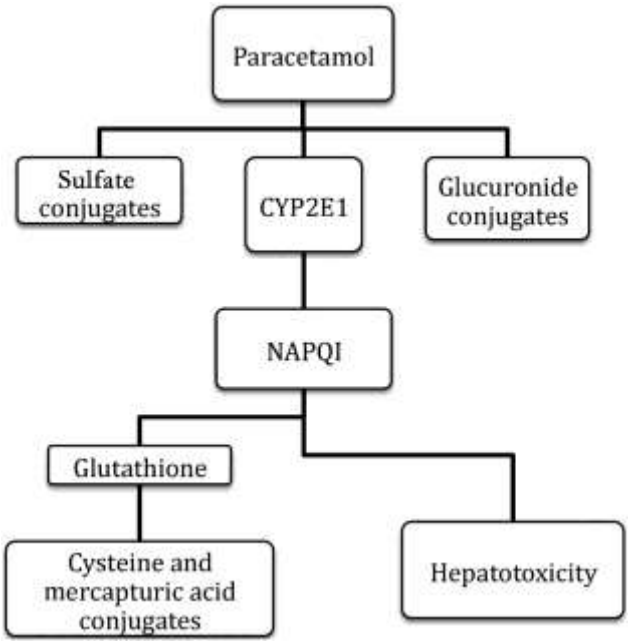


Figura 2 Acetamenophene metabolism

**Pharmacokinetic and toxicity:** At therapeutic doses, 90 percent of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine. One-half of the remaining acetaminophen is excreted unchanged in the urine and one-half is metabolized via the hepatic cytochrome

P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) mixed function oxidase pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is hepatotoxic. With normal doses (blue arrows), NAPQI is rapidly conjugated to hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine. With toxic doses (red arrow), the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes. Once glutathione stores are depleted, NAPQI begins to accumulate and hepatic injury ensues. Prompt administration of acetylcysteine, a sulfhydryl donor, may be lifesaving after an overdose. People who regularly consume 3 or more alcoholic drinks per day are at increased risk of acetaminophen-induced hepatotoxicity

- **PYRAZOLONE DERIVATIVES: AMINOPYRINE, METHAMISOLE (ANALGIN), PROPIPHENAZONE, PHENYLBUTAZONE, OXYPHENBUTAZONE**

This group of drugs includes phenylbutazone, metamizole, oxyphenbutazone, antipyrine, aminopyrine, and dipyrone; These drugs were used clinically for many years but have essentially been abandoned because of their propensity to cause irreversible ***agranulocytosis***

**Metamizole** is a strong analgesic and antipyretic with spasmolytic (antispasmodic) properties. It has weak anti-inflammatory properties. Metamizole can lead to agranulocytosis, a life-threatening side effect where a patient's neutrophil count falls below 500 cells per microliter. It has been shown that metamizole-induced agranulocytosis is caused by the development of drug-dependent anti-neutrophil antibodies requiring covalent binding of neutrophils to metamizole and its metabolites.[2]

- **PHENYLPROPIONIC ACID DERIVATIVES: (PROFENES) IBUPROFEN, NAPROXEN, FENBUFEN, THIAPROFEN, KETOPROFEN, PHENOPROFEN.**

**Ibuprofen,** the most commonly used NSAID, was the first member of the propionic acid class of NSAIDs.

Mechanism of Action. Propionic acid derivatives are nonselective COX inhibitors with the effects and side effects common to other tNSAIDs.

**Ibuprofen** has analgesic, antipyretic, anti-inflammatory properties. Weaker than other phenylpropionic acid derivatives.Stimulates synthesis of ***endogenous interferon*** (immunomodulating effect). Induced patent ductus arteriosus closure.

Naproxen is the longest acting than ibuprophen. Propionic acid derivatives are approved for use in the symptomatic treatment of rheumatoid arthritis and

osteoarthritis. Some also are approved for pain, ankylosing spondylitis, acute gouty arthritis, tendinitis, bursitis, and migraine and for primary dysmenorrhea. Small clinical studies suggest that the propionic acid derivatives are comparable in efficacy to aspirin for the control of the signs and symptoms of rheumatoid arthritis and osteoarthritis, perhaps with improved tolerability.

## ACETIC ACID DERIVATIVES

**INDOMETHACIN** is indicated for the treatment of moderate to severe rheumatoid arthritis, osteoarthritis, and acute gouty arthritis; ankylosing spondylitis; and acute painful shoulder. Although indomethacin is still used clinically, mainly as a steroid-sparing agent, toxicity and the availability of safer alternatives have limited its use. Indomethacin is available in an injectable form for the ***closure of patent ductus arteriosu***s.

**Mechanism of Action**. Indomethacin is a more potent nonselective inhibitor of the COXs than is aspirin; it also inhibits the motility of polymorphonuclear leukocytes, depresses the biosynthesis of mucopolysaccharides, and may have a direct, COX-independent vasoconstrictor effect. Indomethacin has prominent anti-Inflammatory and analgesic–antipyretic properties similar to those of the salicylates.

**Absorption, Distribution, and Elimination**. Oral indomethacin has excellent bioavailability. Peak concentrations occur 1-2 hours after dosing.

**Adverse Effects and Drug Interactions.** GI adverse events, diarrhea may occur and sometimes is associated with ulcerative lesions of the bowel, acute pancreatitis.The most frequent CNS effect is severe frontal headache. Dizziness, vertigo, light-headedness, and mental confusion may occur, Seizures have been reporteds. Hematopoietic reactions include neutropenia, thrombocytopenia, and rarely aplastic anemia. Indomethacin antagonizes the natriuretic and anti-hypertensive effects of furosemide and thiazide diuretics and blunts the anti-hypertensive effect of β-receptor antagonists, AT1-receptor antagonists, and ACE inhibitors**.**

**SULINDAC** is a congener of indomethacin, which was developed in an attempt to find a less toxic but effective alternative

**Mechanism of Action.** Sulindac is a ***prodrug*** and appears to be either inactive or relatively weak in vitro. The active sulfide metabolite is >500 times more potent than sulindac as an inhibitor of COX but less than half as potent as indomethacin

**Therapeutic Uses.** Sulindac has been used mainly for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendonitis, bursitis, acute painful shoulder, and the pain of acute gout A use proposed for sulindac is to prevent ***colon cancer*** in patients with familial adenomatous polyposis

**Ketorolac**

Ketorolac, a heteroaryl acetic acid derivative, is a potent analgesic but only a moderately effective anti-Inflammatory drug.

**Therapeutic Uses**. The use of ketorolac is limited to ≤5 days for acute pain requiring opioid-level analgesia and can be administered intramuscularly, intravenously, or orally.

## PHENYLACETIC ACID DERIVATIVES: DICLOFENAC SODIUM, NABUMETONE, PHENCLOFENAC

**Diclofenac**

Diclofenac, a phenylacetic acid derivative, is among the most commonly used NSAIDs. Administration: oral, transdermal, topical (gel; ophthalmic drops, others) or oral .

**Mechanism of Action.** Diclofenac has analgesic, antipyretic, and anti-Inflammatory activities. Its potency is substantially greater than that of indomethacin, naproxen, or several other tNSAIDs. The selectivity of diclofenac for COX-2 resembles that of celecoxib. In addition, diclofenac appears to reduce intracellular concentrations of free AA in leukocytes, perhaps by altering its release or uptake.

**Therapeutic Uses.** Diclofenac is approved in the U.S. for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, pain, primary dysmenorrhea, and acute migraine.

**Nabumetone**

Nabumetone is the prodrug of 6-methoxy-2-naphthylacetic acid; thus it is a weak inhibitor of COX in vitro but a potent COX inhibitor in vivo.

**Therapeutic Uses.** Nabumetone is an anti-Inflammatory have indicated substantial efficacy in the treatment of rheumatoid arthritis and osteoarthritis, with a relatively low incidence of side effects. Nabumetone is absorbed rapidly and is converted in the liver to one or more active metabolites, principally 6methoxy-2-naphthylacetic acid, a potent nonselective inhibitor of COX. This metabolite, inactivated by O-demethylation in the liver, is then conjugated before excretion and is eliminated with a t1/2 of ~24 hours.

**Common Adverse Effects.** Nabumetone is associated with crampy lower abdominal pain and diarrhea, but the incidence of GI ulceration appears to be

lower than with other tNSAIDs. Other side effects include rash, headache, dizziness, heartburn, tinnitus, and pruritus.

**COMPARISONS OF NSAIDS WITH ASA (acetylsalicylic acid):**

**Analgesia:** ketorolac > ibuprofen/naproxen > ASA

**Gastrointestinal irritation:** < ASA, but still occurs (consider misoprostol)
Minimal effects on acid-base balance; no effects on uric acid elimination

**Allergy:** common, possible cross-hypersensitivity with ASA

**– Renal:** chronic use may cause nephritis, nephritic syndrome, acute failure (via ↓ formation of PGE2 and PGI2, which normally maintain GFR and RBF)

—does not occur with sulindac

• Specific toxicities:

– Indomethacin: thrombocytopenia, agranulocytosis, and > CNS effects

– Sulindac: Stevens-Johnson syndrome, hematotoxicity

**COX-2–SELECTIVE NSAIDS**

The first COX-2–selective NSAIDs were diaryl heterocyclic coxibs. Celecoxib is the only such compound still approved in the U.S. Etoricoxib is approved in several countries; rofecoxib and valdecoxib were withdrawn worldwide. .

**Therapeutic Uses.** All COX-2–selective NSAIDs have been shown to afford relief from postextraction dental pain and to afford dose-dependent relief from inflammation in osteoarthritis and rheumatoid arthritis. The European Medicines Agency advises that these medicines should not be used in patients with ischemic heart disease or stroke and that prescribers should exercise caution when using selective COX-2 inhibitors in patients with risk factors for heart disease such as

hypertension, hyperlipidemia, diabetes, smoking, or peripheral arterial disease. As for all NSAIDs, the agency advises the lowest effective dose for the shortest possible duration of treatment

## CELECOXIB

**Therapeutic Uses.** Compared with conventional NSAIDs, it is no more effective as an anti-inflammatory agent. Celecoxib is used for management of acute pain in adults, for the treatment of osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, and primary dysmenorrhea.

• Primary differences are:

– Less gastrointestinal toxicity

– Less antiplatelet action

- ✓ However, it may possibly exert prothrombotic effects via inhibition of endothelial cell function (MI and strokes).
- ✓ Cross-hypersensitivity between celecoxib and sulfonamides

## ROFECOXIB

**ROFECOXIB** was introduced in 1999. Details of its pharmaco-dynamics, pharmacokinetics, therapeutic efficacy, and toxicity have been reviewed. Rofecoxib showed a significant (2-fold) increase in the incidence of serious thromboembolic events ( COX-2 block lead to decrease in PGI12 –prostacyclin synthesis) in subjects receiving 25 mg of rofecoxib relative to placebo, rofecoxib was withdrawn from the market worldwide in 2004.