Non-steroidal anti-inflammatory drugs(NSAIDs)

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Non-steroidal anti-inflammatory drugs

- **Non-steroidal anti-inflammatory drugs**: are members of a therapeutic drug class which reduces pain, decreases inflammation, decreases fever, and prevents blood clots. Side effects depend on the specific drug, its dose and duration of use, but largely include an increased risk of gastrointestinal ulcers and bleeds,
- Usually abbreviated to **NSAID**s.
- Are drugs with analgesic, antipyretic and anti-inflammatory effects - they reduce pain, fever and inflammation.
- The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action.(Eicosanoids are signaling molecules made by the enzymatic or non-enzymatic oxidation of arachidonic acid or other polyunsaturated fatty acids (PUFAs) that are, similar to arachidonic acid, 20 carbon units in length.)
- As analgesics, NSAIDs are unusual in that they are non-narcotic

- **NSAIDs**
- Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature.
- They're often used to relieve symptoms of:
- headaches
- painful periods
- colds and flu
- coronavirus (COVID-19)
- conditions such as arthritis that can cause long-term pain
- Although NSAIDs are commonly used, they're not suitable for everyone and can sometimes cause side effects.
- They are also called
- – Non narcotic
- – Non opioid
- – Aspirin like analgesics
- They act primarily on peripheral pain mechanisms but also in CNS to raise pain threshold
- These drugs are chemically diverse, but most are organic acids.

What Are NSAIDs?

- Nonsteroidal anti-inflammatory drugs, or NSAIDs are the most prescribed medications for treating conditions such as arthritis. Most people are familiar with over-the-counter, nonprescription NSAIDs, such as aspirin, ibuprofen, and naproxen.
- NSAIDs are more than just pain relievers. They also help reduce inflammation and lower fevers. They prevent blood from clotting, which is good in some cases but not so beneficial in others.

Kinetics of NSAIDs / Absorption

- The NSAIDs share similar absorption properties as all NSAIDs are highly lipophilic substances.
- Absorption occurs throughout the gastrointestinal tract, but particularly in the stomach of monogastric animals, the pH is normally more acidic than plasma pH.
- An acidic environment promotes the absorption of NSAIDs which, as weak acids, are less ionized in gastric juice and therefore absorbed by the mechanism of ionic or diffusion trapping.
- Most NSAIDs are given as oral tablets or capsules; others are given by injection to avoid gastric irritation.

Kinetics of NSAIDs / Distribution

- The most significant aspect of NSAIDs distribution is plasma-protein binding which is high (>95%) for most NSAIDs, although salicylate is an exception, with binding of ~50%.
- The major plasma protein component is albumin. The high degree of protein binding limits renal excretion of most NSAIDs. High plasma-protein binding may also limit the distribution of NSAIDs from plasma to body fluids and tissues.
- However, this does not necessarily limit and may even enhance therapeutic efficacy in acute inflammation because protein leaks from the vascular component into inflamed tissues and because drug concentrations in inflammatory exudates commonly exceed those in plasma. Protein binding does limit penetration into fluids such as milk.
- Flunixin and phenylbutazone have concentrations in milk that are ~1% of the plasma levels, corresponding approximately to the nonbound plasma concentration.

Kinetics of NSAIDs / Metabolism

- Knowledge of the mechanism of action of NSAIDs, as competitive inhibitors for arachidonic acid binding to COX, provides a good tool to predict whether NSAID metabolites are active or not.
- Generally, phase-I metabolism of NSAIDs produces more polar products.
- These polar metabolites are not efficient COX inhibitors because they lack the lipophilic properties to compete with arachidonic acid and prevent its binding to COX .
- Accordingly, it is easy to conclude that most of the NSAIDs are metabolized into inactive products, which is the case in reality.

Kinetics of NSAIDs / Excretion

- NSAIDs are mostly excreted as phase-II glucouronides and in a few cases as sulfate conjugates.
- In addition, small percentages of NSAIDs are excreted unchanged in urine. If the drug is excreted unchanged, its rate of excretion is expected to increase if the drug is coadministered with agents that render the urine pH alkaline such as the antacids aluminum hydroxide and milk of magnesia .

Non steroidal anti-inflammatory drugs

- Types of NSAIDS:

1. Non-selective COX inhibitors (COX 1,2,3)
2. Selective COX-2 inhibitors (Celecoxib, Rofecoxib)
3. COX-3 inhibitors : paracetamol (not anti-inflammatory). Why?

❖**Mechanism of action of NSAIDS** They inhibit cyclo-oxygenase enzyme ►▼Prostaglandins ► ▼Fever, pain, Inflammation.

1. Antipyretic action: decrease set point of heat regulatory centre in hypothalamus, increase sweating

The anti-inflammatory actions of NSAIDS

- Due to reduction of PGE2 and PGI2 that participate in the inflammatory process .
- Stabilize lysosomes
- Inhibit granulocyte adherence to damaged vasculature
- Inhibit migration of macrophages to the inflammatory sites
- Inhibit Kinin-Kallikrein system

Shared Adverse effects of NSAIDS

- GIT side effects: Dyspepsia, Gastric ulceration
- Disturbances of renal function: (Analgesic abuse nephropathy) due to decreased vasodilatory PGs
- Hypersensitivity: e.g. aspirin induced asthma
- Bleeding tendency
- Displacing other drugs from plasma proteins
- Salt and water retention and hyperkalemia
- May prolong pregnancy and spontaneous labor

Indications

- Pain and inflammation in rheumatic diseases
- Musculoskeletal disorders
- Post-operative analgesia
- Acute Gout
- Migraine
- Dysmenorrhoea
- Fever and pain in children (including post-immunization pyrexia)
- Pyrexia
- Dental pain
- Less well-defined conditions of back pain and soft-tissue disorders

What are NSAIDs and how do they work?

- Prostaglandins are a family of chemicals that are produced by the cells of the body and have several important functions.
- They promote inflammation that is necessary for healing, but also results in **pain**, and **fever**.
- Support the blood clotting function of platelets.
- And protect the lining of the stomach from the damaging effects of acid.

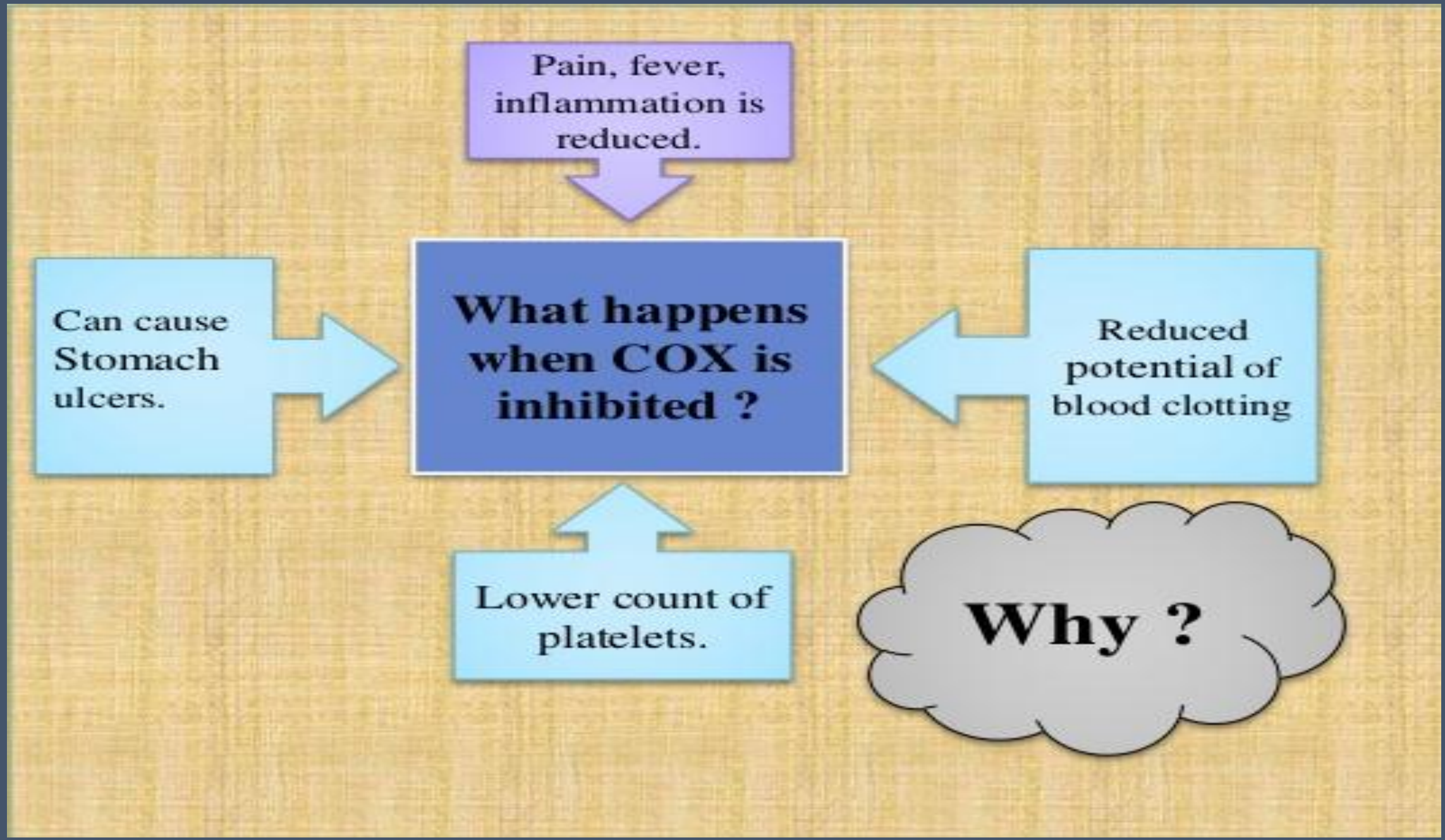
Pharmacokinetics

- NSAIDs are generally very similar:

- Lipid-soluble weak acids
- Nearly complete absorption from GI tract
- Topical formulations are available (diclofenac)
- IV formulations are available (ibuprofen)
- Minimal 1st-pass hepatic metabolism
- Highly protein-bound
- Small volume of distribution
- Metabolized by CYP3A and CYP2C and /or glucuronidation.
- Half-lives vary from < 2 to > 8 hours.
- Excreted renally

❑How does NSAIDS work ?

- It basically inhibits COX (Cyclooxygenase) enzyme.
- COX enzymes produce PROSTAGLADINS.
- Prostagladins are the active lipid compounds (eicosanoids).
- COX are of two types:


Pain, fever, inflammation is reduced.
Can cause Stomach ulcers.
What happens when COX is inhibited ?
Reduced potential of blood clotting
Lower count of platelets.
Why ?

MECHANISM OF ACTION

Analgesic	Antipyretic	Anti-Inflam.
• **Centrally** • inhibition of COX enzymes in CNS • **peripherally** • Anti-Inflammatory action	• **Centrally** inhibition of COX enzymes • in CNS • inhibition of interleukin-1	• **Peripherally** inhibition of COX enzymes • Antioxidant effect

(CONTINUE)

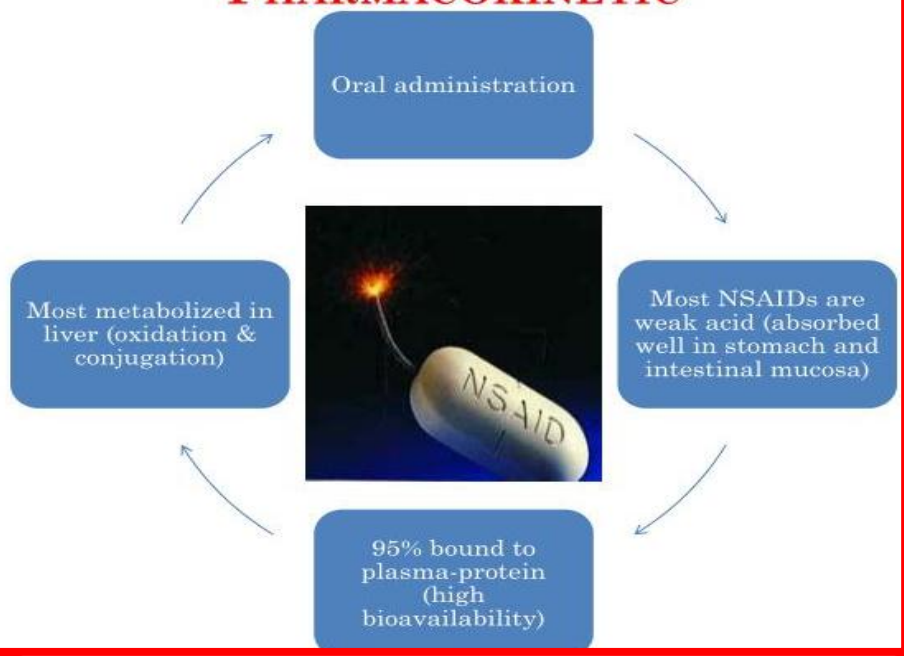
Effect on platelets

• Inhibit platelet aggregation through inhibition the synthesis of TXA_2 (inhibit cox-1)

ANALGESIC

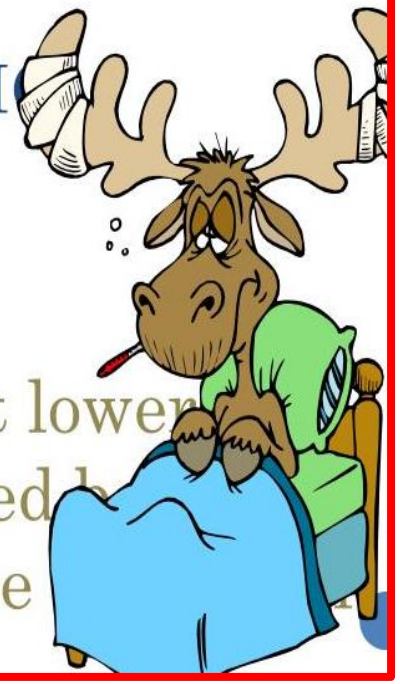
Drug that relieve pain.

PHARMACOKINETIC



ANTIPYRETIC

Drug that lower elevated b temperature



Mode of action

- Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both :
  - The cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes.
  - Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A_2).
  - Prostaglandins act (among other things) as messenger molecules in the process of inflammation.
  - This mechanism of action was elucidated by John Vane, who later received a Nobel Prize for his work.
  - A newly discovered COX-3 may also have some role.

Prostaglandins

- Prostaglandins are produced within the body's cells by the enzyme cyclooxygenase (COX).
- There are two COX enzymes, COX-1 and COX-2.
- Both enzymes produce prostaglandins that promote inflammation, **pain**, and **fever**.
- However, only COX-1 produces prostaglandins that support platelets and protect the stomach.
- Nonsteroidal anti-inflammatory **drugs** (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body.
- As a consequence, ongoing inflammation, pain, and fever are reduced.
- Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

NSAIDs: Mechanism of Action

- NSAIDs: Mechanism of Action Analgesia - treatment of headaches and pain • Block the undesirable effects of prostaglandins, which cause headaches

- NSAIDs: Mechanism of Action Antipyretic: reduce fever • Inhibit prostaglandin E2 within the area of the brain that controls temperature

- NSAIDs: Mechanism of Action Relief of inflammation • Inhibit the leukotriene pathway, the prostaglandin pathway, or both

NSAIDs

Six structurally related groups:

- Acetic acids
- Carboxylic acids
- Propionic acids
- Enolic acids
- Fenamic acids
- Nonacidic compounds

NSAIDs: Acetic Acid

- diclofenac sodium (Voltaren)
- diclofenac potassium (Cataflam)
- etodolac (Lodine)
- indomethacin (Indocin)
- sulindac (Clinoril)
- tolmetin (Tolectin)

NSAIDs: Carboxylic Acids

Acetylated

- aspirin (ASA)
- choline magnesium salicylate (Trilisate)
- diflunisal (Dolobid)

Nonacetylated

- salicylamide
- salsalate (Disalcid)
- sodium salicylate

NSAIDs: Propionic Acids

- fenoprofen (Nalfon)
- flurbiprofen (Ansaid)
- ibuprofen (Motrin, others)
- ketoprofen (Orudis)
- ketorolac (Toradol)
- naproxen (Naprosyn)
- oxaprozin (Daypro)

NSAIDs: Other Agents

Enolic acids

- phenylbutazone (Butazolidin)
- piroxicam (Feldene)

Fenamic acids

- meclofenamic acid (Meclomen)
- mefenamic acid (Ponstel)

Nonacidic compounds

- nabumetone (Relafen)

NSAIDs: Other Agents

COX-2 Inhibitors

- celecoxib (Celebrex)
- rofecoxib (Vioxx)

NSAIDs: Drug Effects

- Analgesic (mild to moderate)
- Antigout
- Antiinflammatory
- Antipyretic
- Relief of vascular headaches
- Platelet inhibition (ASA)

NSAIDs: Therapeutic Uses

- Relief of mild to moderate pain
- Acute gout
- Various bone, joint, and muscle pain
- Osteoarthritis
- Rheumatoid arthritis
- Juvenile rheumatoid arthritis
- Dysmenorrhea
- Fever

Who can take NSAIDs?

➢Most people can take NSAIDs, but some people need to be careful about taking them.

It's a good idea to ask a pharmacist or doctor for advice before taking an NSAID if you:

- are over 65 years of age
- are pregnant or trying for a baby
- are breastfeeding
- have asthma
- have had an allergic reaction to NSAIDs in the past
- have had stomach ulcers in the past
- have any problems with your heart, liver, kidneys, blood pressure, circulation or bowels
- are taking other medicines
- are looking for medicine for a child under 16 (do not give any medicine that contains aspirin to children under 16)

Contraindications

- **NSAIDs may be used with caution by people with the following conditions**:
- Irritable bowel syndrome (IB)
- Persons who are over age 50, and who have a family history of gastrointestinal (GI) problems.
- Persons who have had previous gastrointestinal problems from NSAID use.

- **NSAIDs should usually be avoided by people with the following conditions:**
- Peptic ulcer or stomach bleeding.
- Uncontrolled hypertension.
- Kidney disease.
- People that suffer with inflammatory bowel disease (Crohn's disease or ulcerative colitis).

Table: Comparison of NSAIDs

Class	Mechanism of action	Clinical use	Side effects
Reversible NSAIDs (e.g., ibuprofen, ketorolac, indomethacin)	•Reversibly inhibit COX-1 and COX-2 •Decreased prostaglandin and thromboxane A_2 (TXA_2) synthesis	•Analgesic •Antipyretic •Antiinflammatory •Closure of patent ductus arteriosus (PDA)	•Gastric ulcers and GI bleeding •AKI •Interstitial nephritis •Renal papillary necrosis •Aspirin: • Reye syndrome in children with a viral infection • Asthma-like symptoms in patients with nasal polyps or atopy • Tinnitus • Mixed respiratory alkalosis–metabolic acidosis
Aspirin	•Irreversibly inhibits COX-1 and COX-2 •Decreased prostaglandin and TXA_2 synthesis	•Low dose (< 300 mg/day): antiplatelet •Medium dose (300–2400 mg/day): analgesic and antipyretic •High dose (2400–4000 mg/day): antiinflammatory	
COX-2 inhibitors (e.g., celecoxib)	•Selectively inhibit COX-2 •Decreased prostaglandin synthesis •Spared platelets and TXA_2 synthesis	•Rheumatoid arthritis •Osteoarthritis	•Increased risk of thrombosis: • Deep venous thrombosis • Pulmonary embolism •Acute MI •Sulfa allergy

THANK YOU