NSAID Analgesics

ـ عبدالله میثاق

PAIN AND ANALGESICS OVERVIEW

1. NATURE OF PAIN

- Complex, subjective experience.
- Acts as a warning signal for tissue damage.

2. ANALGESCS VS. ANESTHESIA

ANALGESICS

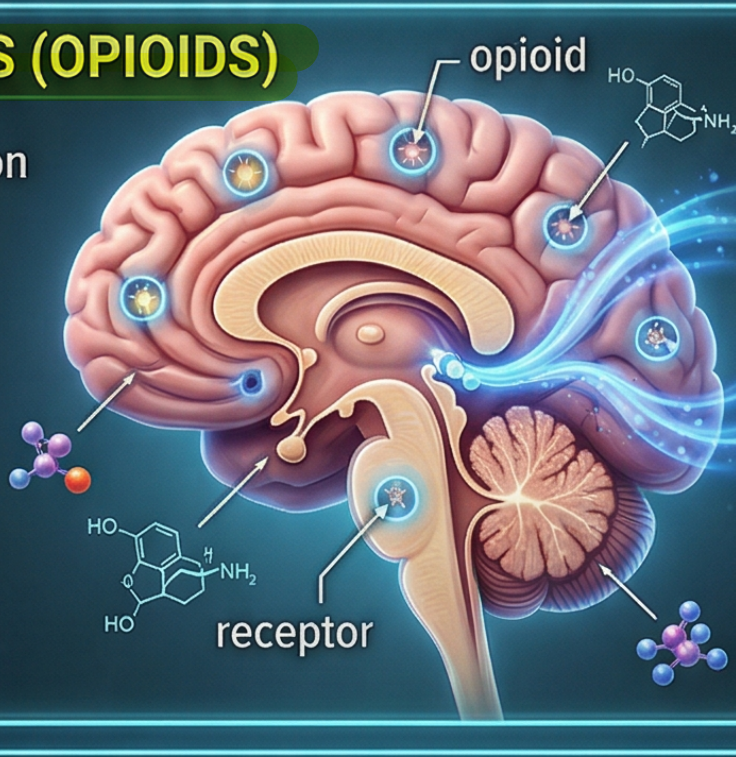
- Relieve pain selectively
- Do not block nerve impulses
- Do not alter consciousness

ANESTHESIA

- Total loss of sensation
- Total loss of consciousness

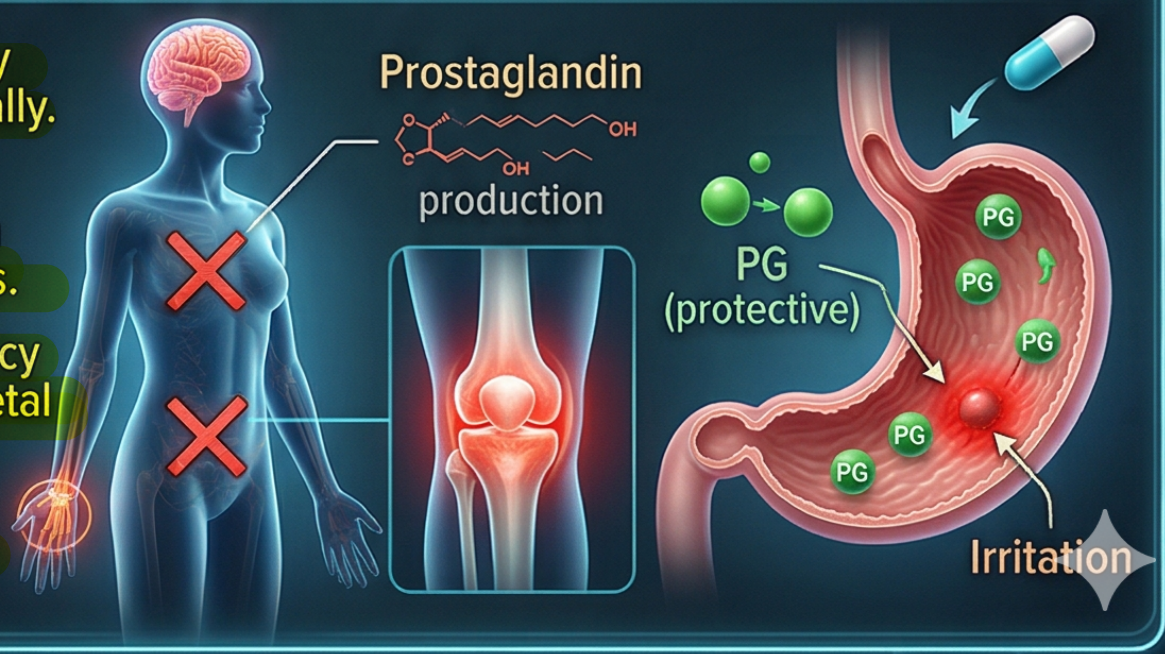
3. NARCOTICS (OPIOIDS)

- Work centrally on specific CNS receptors.
- Strong efficacy for any pain.
- Dangers of Tolerance and Dependence.



4. NON-NARCOTICS (NSAIDs)

- Work centrally and peripherally.
- Inhibit prostaglandin (PG) synthesis.
- Weaker efficacy (musculoskeletal pain).
- Dangers of GI irritation.



1. Pain and Analgesics Overview تحذيري

- Pain is a complex, subjective experience that acts as a warning signal for tissue damage.
- Analgesics relieve pain selectively without blocking nerve impulses or altering consciousness.
- Anesthesia, in contrast, involves a total loss of sensation and consciousness.
- **Narcotics (Opioids):** Work centrally on specific CNS receptors, have strong efficacy for any pain, but carry dangers of tolerance and dependence.
- **Non-Narcotics (NSAIDs):** Work centrally and peripherally by inhibiting prostaglandin (PG) synthesis, have weaker efficacy for musculoskeletal pain, but carry dangers of GI irritation.

THE INFLAMMATORY PATHWAYS

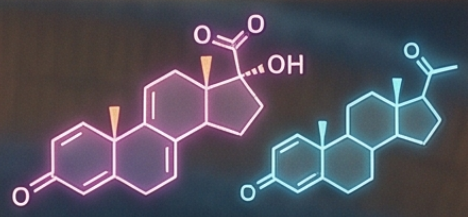
CELLULAR TRIGGER & INHIBITION

STIMULUS
(like an injury)

activates Phospholipase.

PHOSPHOLIPASE

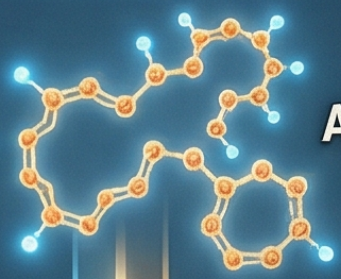
CORTICOSTEROIDS



CORTICOSTEROIDS inhibit phospholipase, shutting down the entire inflammation cascade early.

THE ARACHIDONIC ACID SPLIT

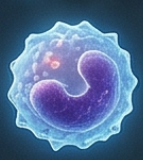
Phospholipase converts membrane phospholipids into Arachidonic acid



Arachidonic acid

THE LOX PATHWAY

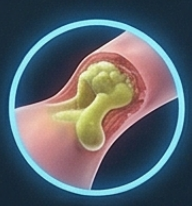
- Produces **Leukotrienes.**
  - **LTB4** attracts phagocytes to cause inflammation.



Phagocyte.

- **LTC4, LTD4, and LTE4** cause bronchospasm, mucous plugging, and altered vascular permeability.

Bronchiole constriction

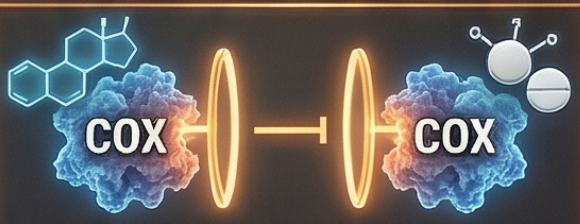


Mucus plug

Leaky capillary

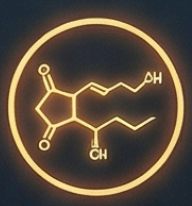
THE COX PATHWAY & INHIBITION

NSAIDs and Aspirin

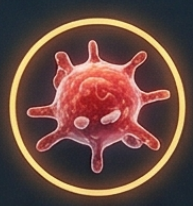


NSAIDs and **Aspirin** block this pathway.

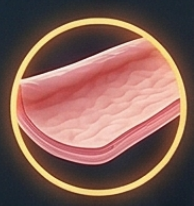
- Produces **Prostaglandins, Thromboxane**, and **Prostacyclin.**



Prostaglandins



Thromboxane



Prostacyclin

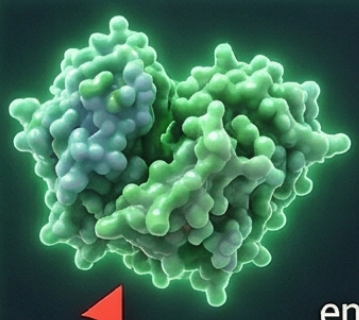
2. The Inflammatory Pathways

- A stimulus (like an injury) disturbs cell membranes, activating an enzyme called Phospholipase.
- Phospholipase converts membrane phospholipids into Arachidonic acid.
- **Corticosteroids** work by inhibiting phospholipase, shutting down the entire inflammation cascade early.
- Arachidonic acid splits into two pathways: Cyclooxygenase (COX) and Lipoxygenase (LOX).
- **The LOX Pathway:** Produces Leukotrienes. LTB4 attracts phagocytes to cause inflammation. LTC4, LTD4, and LTE4 cause bronchospasm, mucous plugging, and altered vascular permeability.
- **The COX Pathway:** Produces Prostaglandins, Thromboxane, and Prostacyclin. NSAIDs and Aspirin block this pathway.

COX ISOFORMS & NSAID EFFECTS

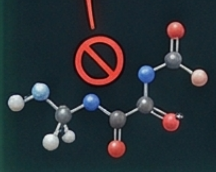
1. COX ISOFORMS: FUNCTION & DISTRIBUTION

COX-1 (Constitutive)

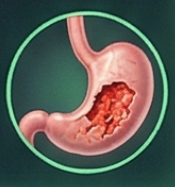


stomach
kidney
intestine
platelets
endothelium

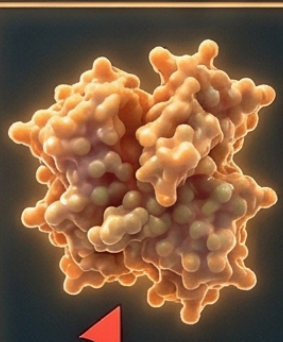
Produces PGE_2 (protects stomach acid), TxA_2 (platelet aggregation), PGI_2.



Inhibiting COX-1 causes GI toxicity.

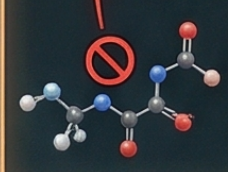


COX-2 (Inducible)

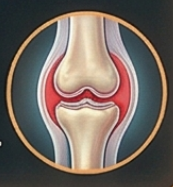


Induced by cytokines at inflammatory sites like macrophages and synoviocytes.

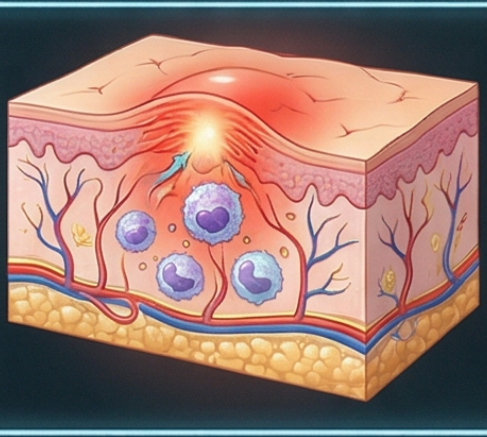
Produces inflammatory PGs, proteases, superoxide radicals.



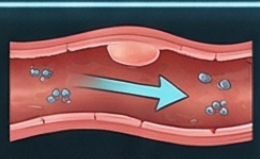
Inhibiting COX-2 provides anti-inflammatory relief.



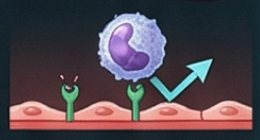
2. NSAID EFFECTS: ANTI-INFLAMMATORY ACTION



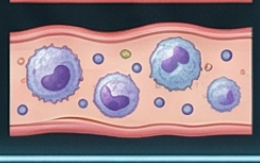
- NSAIDs decrease vasodilator PGs (PGE_2, PGI_2) to reduce edema.



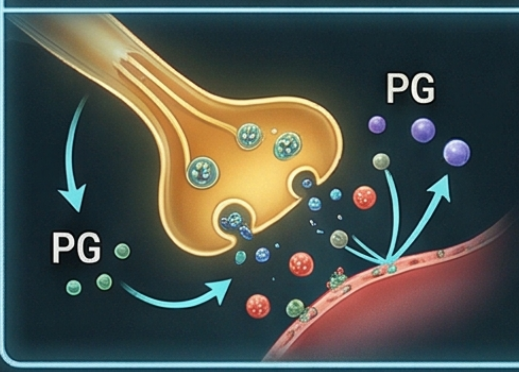
- Inhibit adhesion molecules so white blood cells cannot stick.



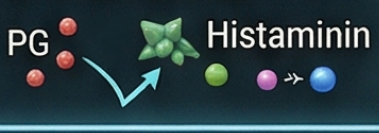
- Reduce the accumulation of inflammatory cells.



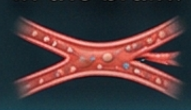
3. NSAID EFFECTS: ANALGESIC ACTION



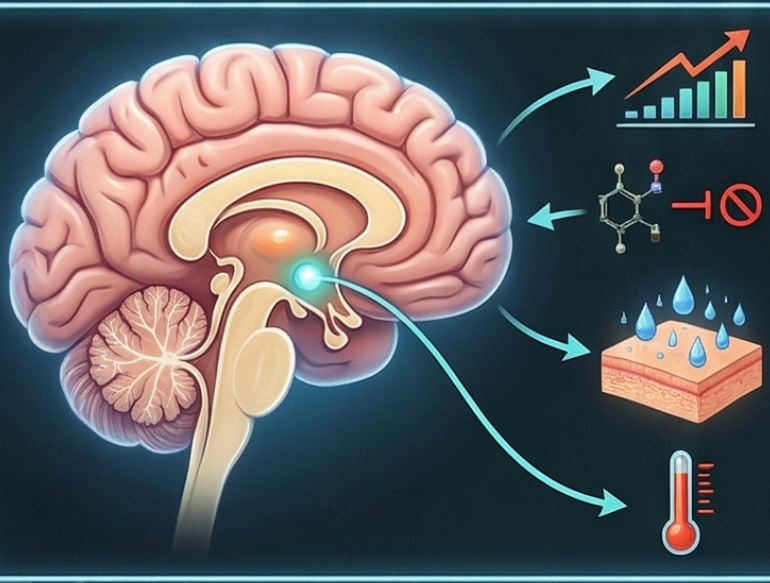
- Decreased PGs lower the sensitivity of pain nerves to bradykinin and histamine.



Headache Relief: NSAIDs decrease PG-mediated vasodilation in the brain.



4. NSAID EFFECTS: ANTIPYRETIC ACTION



- Fever happens when PGE_2 elevates the hypothalamus set-point.
- NSAIDs block PGE_2, resetting the set-point to normal.
- The body then cools down via sweating and peripheral vasodilation.

- NSAIDs do not lower normal body temperature.

3. COX Isoforms & NSAID Effects

- **COX-1 (Constitutive):** Always present in the stomach, kidney, intestine, platelets, and endothelium. It produces PGE2 (protects stomach acid), TxA2 (platelet aggregation), and PGI2. Inhibiting COX-1 causes GI toxicity.

- **COX-2 (Inducible):** Induced by cytokines at inflammatory sites like macrophages and synoviocytes. It produces inflammatory PGs, proteases, and superoxide radicals. Inhibiting COX-2 provides anti-inflammatory relief.

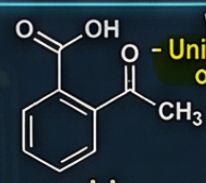
- **Anti-inflammatory Action:** NSAIDs decrease vasodilator PGs (PGE2, PGI2) to reduce edema, inhibit adhesion molecules so white blood cells cannot stick, and reduce the accumulation of inflammatory cells.

- **Analgesic Action:** Decreased PGs lower the sensitivity of pain nerves to bradykinin and histamine. Headache relief occurs because NSAIDs decrease PG-mediated vasodilation in the brain.

- **Antipyretic Action:** Fever happens when PGE2 elevates the hypothalamus set-point. NSAIDs block PGE2, resetting the set-point to normal. The body then cools down via sweating and peripheral vasodilation. NSAIDs do not lower normal body temperature.

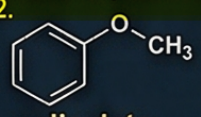
4. ASPIRIN
(THE PROTOTYPE NSAID)

1 MECHANISM



Weak organic acid.
- Unique, irreversible (permanent) inactivation of COX-1 and COX-2.

Deacetylate

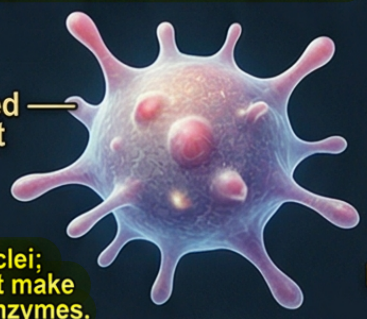


aspirin → salicylate

Salicylate covalently and irreversibly binds to the active sites of COX-1

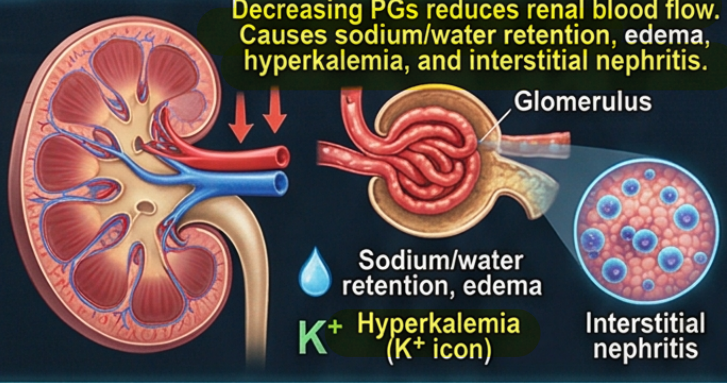
2 PLATELET EFFECTS

Low doses (81 mg daily) permanently block thromboxane. Bleeding time prolonged for platelet's 7-day lifespan.



3 KIDNEY EFFECTS

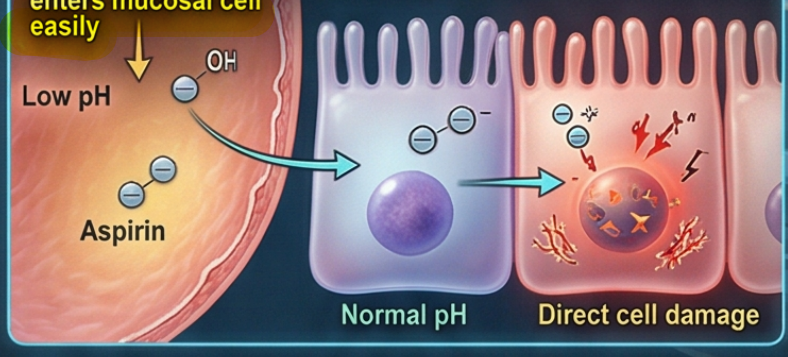
Decreasing PGs reduces renal blood flow. Causes sodium/water retention, edema, hyperkalemia, and interstitial nephritis.



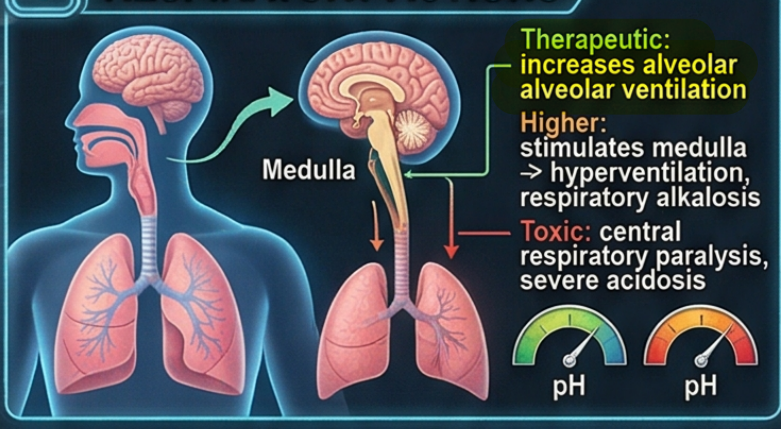
4 GI EFFECTS

Acidic stomach: uncharged aspirin enters mucosal cell easily

Normal pH cell: ionizes, becomes trapped, causes direct cell damage.



3 RESPIRATORY ACTIONS

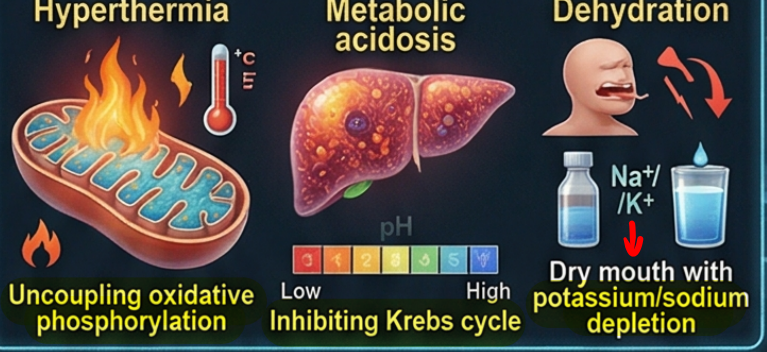


Therapeutic: increases alveolar alveolar ventilation

Higher: stimulates medulla -> hyperventilation, respiratory alkalosis

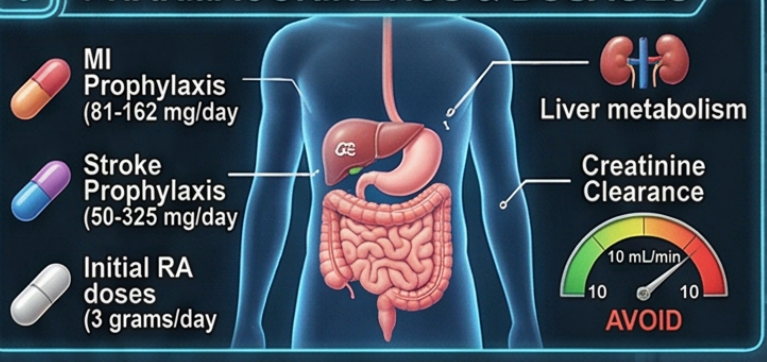
Toxic: central respiratory paralysis, severe acidosis

5 TOXICITY (SALICYLATE TOXICITY)

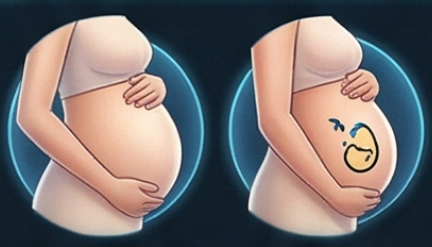


4 PASSIVE GI ABSORPTION [illegible]OKIN

6 PHARMACOKINETICS & DOSAGES



7 PREGNANCY & BREAST MILK

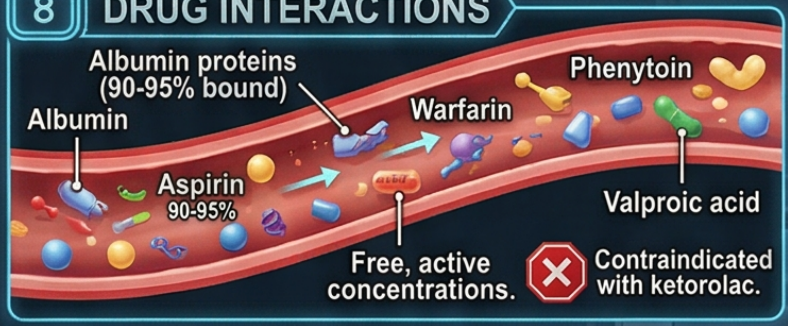


Excreted in breast milk.

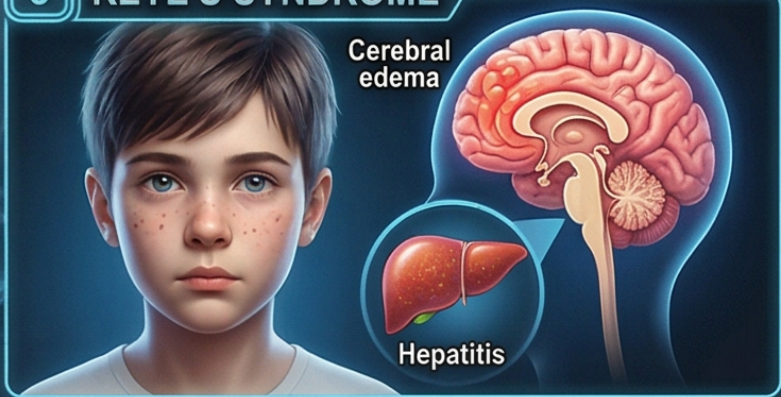
Trimester 1 & 2: Category C

Trimester 3: Category D

8 DRUG INTERACTIONS



9 REYE'S SYNDROME



10 REYE'S SYNDROME

FATAL DISEASE. NEVER GIVE TO CHILDREN/TEENAGERS WITH VIRAL INFECTIONS (e.g., CHICKENPOX).

4. Aspirin (The Prototype NSAID)

- **Mechanism:** Aspirin is a weak organic acid that uniquely and irreversibly (permanently) inactivates COX-1 and COX-2. It is rapidly deacetylated in the body into salicylate.

- **Platelet Effects:** Low doses (81 mg daily) permanently block thromboxane in platelets. Since platelets lack nuclei, they cannot make new enzymes, so bleeding time is prolonged for the platelet's 7-day lifespan.

- **Kidney Effects:** Decreasing PGs reduces renal blood flow, causing sodium/water ~~retention~~, edema, hyperkalemia, and interstitial nephritis.

- **GI Effects:** In the acidic stomach, aspirin is uncharged, easily enters mucosal cells, then ionizes (becomes negatively charged) in the normal pH of the cell, becoming trapped and causing direct cell damage.

- **Respiratory Actions:** Therapeutic doses increase alveolar ventilation. Higher doses stimulate the medulla causing hyperventilation and respiratory alkalosis. Toxic doses cause central respiratory paralysis and severe acidosis.

- **Toxicity:** Salicylate toxicity causes hyperthermia (uncoupling oxidative phosphorylation), metabolic acidosis (inhibiting Krebs cycle), and dehydration with potassium/sodium depletion.

- **Pharmacokinetics & Dosages:** Absorbed passively in the stomach/intestine. 81 to 162 mg/day for MI prophylaxis. 50 to 325 mg/day for stroke prophylaxis. 3 grams/day for initial rheumatoid arthritis doses. Metabolized by the liver and cleared by the kidneys. Avoid if creatinine clearance is under 10 mL/min.

- **Pregnancy:** FDA Category C in trimesters 1 and 2; Category D in trimester 3. Excreted in breast milk.

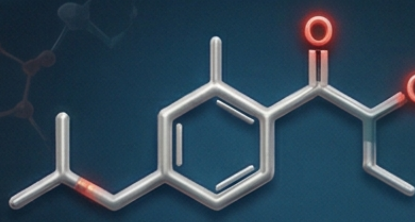
- **Drug Interactions:** Aspirin is 90-95% protein-bound to albumin. It can displace warfarin, phenytoin, and valproic acid, increasing their free, active concentrations in the blood. Contraindicated with ketorolac.

- **Reye's Syndrome:** A fatal disease causing cerebral edema and hepatitis. Never give aspirin to children or teenagers with viral infections like chickenpox.

5. OTHER REVERSIBLE NSAIDs

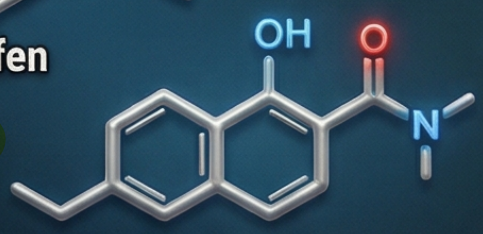
1 PROPIONIC ACID DERIVATIVES (Ibuprofen, Naproxen)

- Reversibly inhibit COX and bind totally to serum albumin.



Ibuprofen

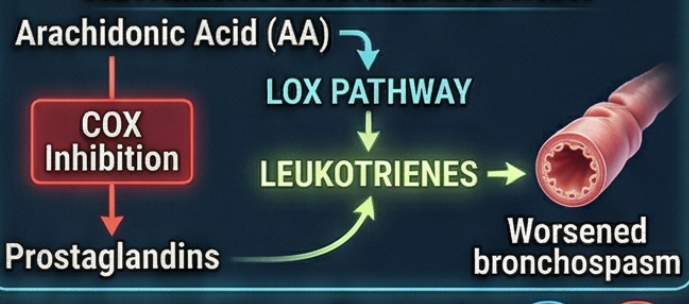
- Ibuprofen max dose: 3200mg/day.



Naproxen

- Ibuprofen max dose:

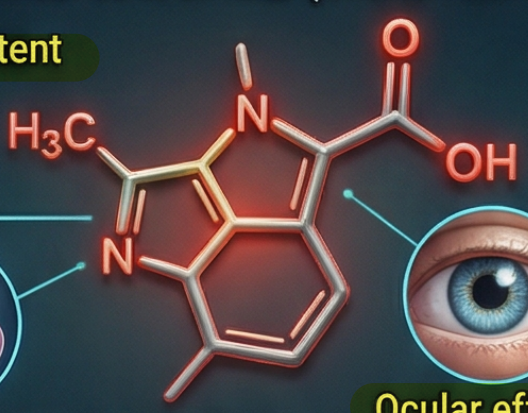
ASTHMATIC CONTRAINDICATION



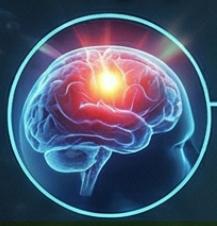
- Naproxen carries cardiovascular and GI bleeding risks.

2 ACETIC ACID DERIVATIVES (Indomethacin, Diclofenac, Sulindac)

- Indomethacin is very potent but **highly toxic.**



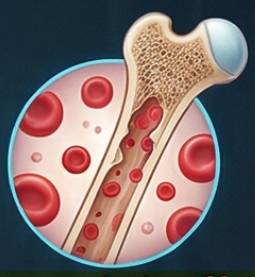
Indomethacin



Severe frontal headaches in 25-50% patients

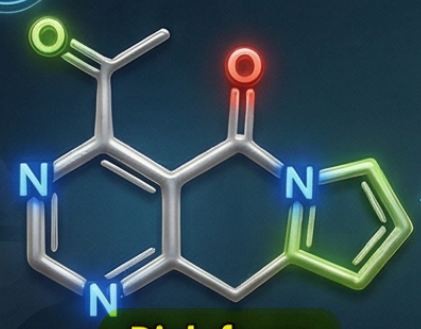
Vertigo

Ocular effects (corneal deposits)



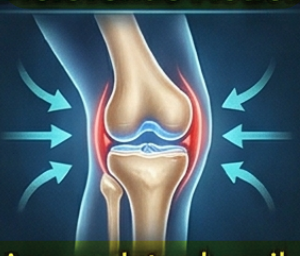
Hematopoietic effects (leukopenia, aplastic anemia)

3 HETEROARYL ACETIC ACIDS (Diclofenac, Ketorolac)



Diclofenac

Diclofenac Action

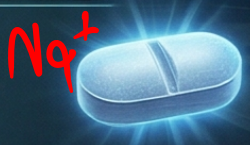


Accumulates heavily in synovial fluid.

- Excellent for joint inflammation.

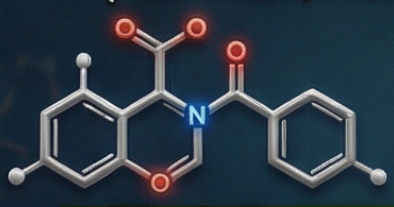
Formulations

Diclofenac Potassium (Prompt release)

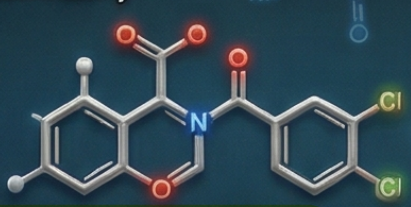


Diclofenac Sodium (Delayed release)

4 OXICAM DERIVATIVES (Piroxicam, Meloxicam)



Piroxicam

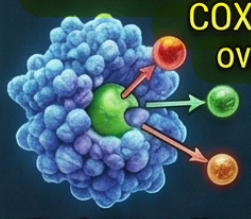


Meloxicam

- Long half-lives allow once-daily administration.

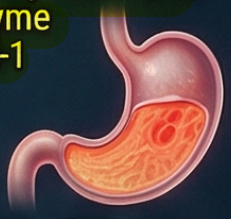
Meloxicam GI Effect

Meloxicam preferentially binds a 3D COX-2 enzyme over COX-1



Preferentially binds COX-2

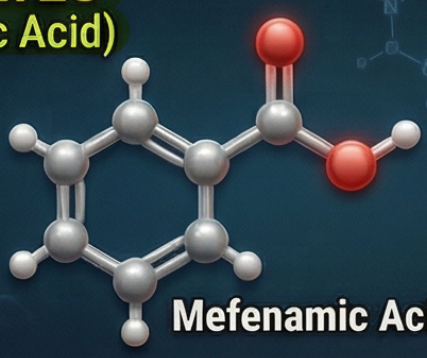
VS



Less GI irritation at lower doses

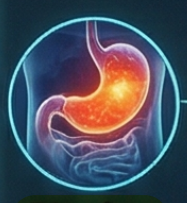
5 FENAMATES (Mefenamic Acid)

- No major advantages.

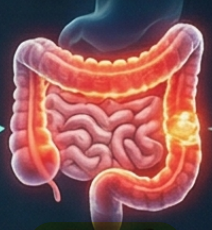


Mefenamic Acid

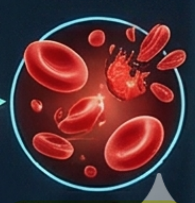
Severe Side Effects



Diarrhea



Bowel inflammation



Hemolytic anemia

5. Other Reversible NSAIDs

- **Propionic Acid Derivatives (Ibuprofen, Naproxen):** Reversibly inhibit COX and bind totally to serum albumin. Ibuprofen max dose is 3200mg/day. Contraindicated in asthmatics because blocking COX pushes arachidonic acid into the LOX pathway, producing leukotrienes that worsen bronchospasm. Naproxen carries cardiovascular and GI bleeding risks.

- **Acetic Acid Derivatives (Indomethacin, Diclofenac, Sulindac):** Indomethacin is very potent but highly toxic, causing severe frontal headaches in 25-50% of patients, vertigo, ocular effects (corneal deposits), and hematopoietic effects (leukopenia, aplastic anemia).

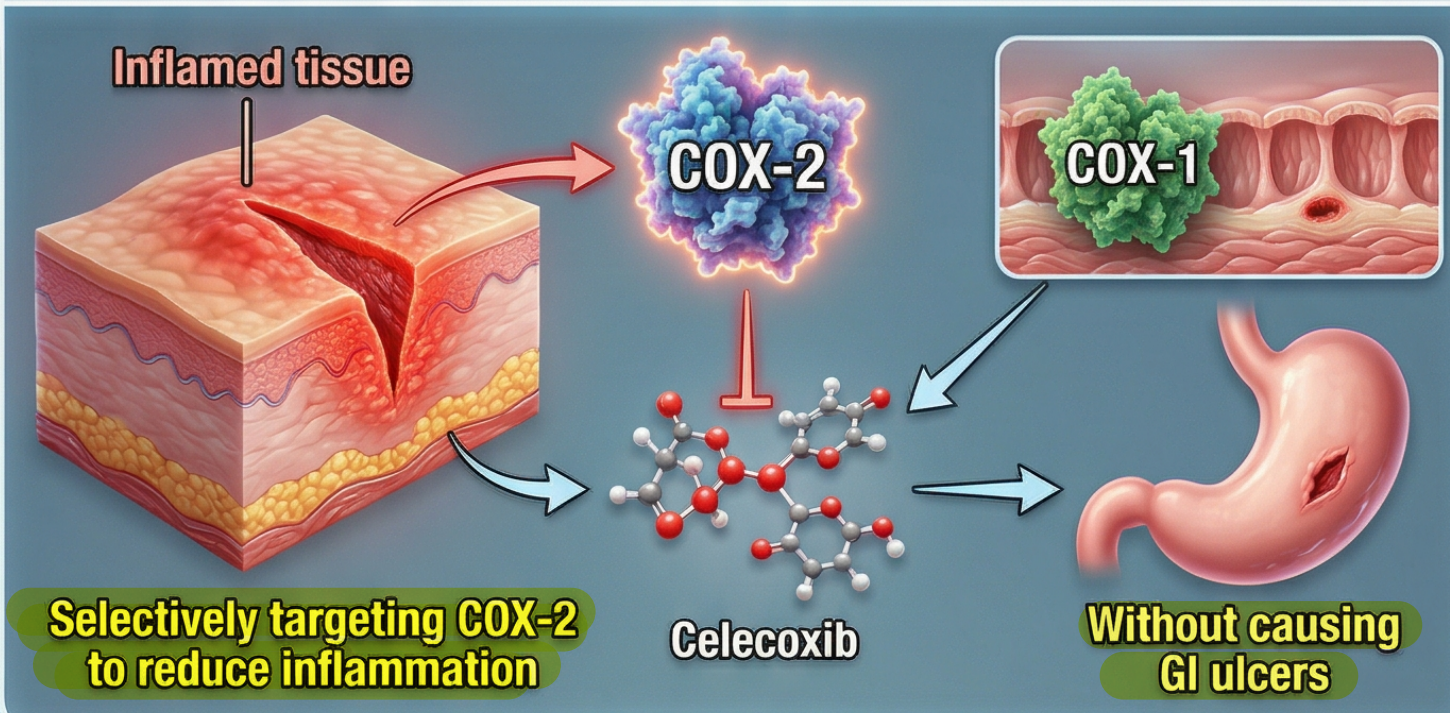
- **Heteroaryl Acetic Acids (Diclofenac, Ketorolac):** Diclofenac accumulates heavily in synovial fluid, making it excellent for joint inflammation. Diclofenac potassium is prompt release; Diclofenac sodium is delayed release.

- **Oxicam Derivatives (Piroxicam, Meloxicam):** Have long half-lives allowing once-daily administration. Meloxicam preferentially binds COX-2, showing less GI irritation at lower doses.

- **Fenamates (Mefenamic Acid):** No major advantages, but severe side effects include diarrhea, bowel inflammation, and hemolytic anemia.

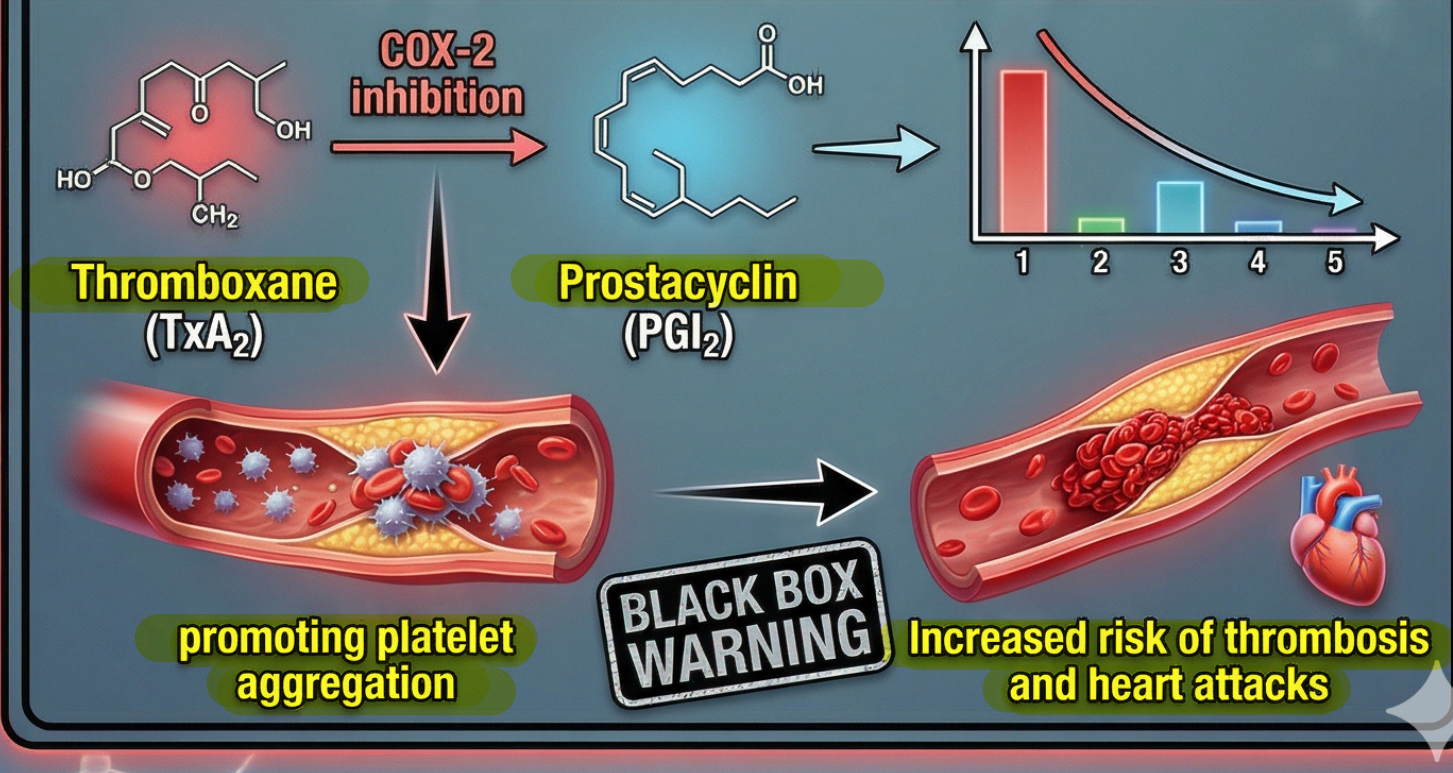
6. SELECTIVE COX-2 INHIBITORS

1. CELECOXIB DEVELOPMENT



2. RISKS & WITHDRAWALS

3. BLACK BOX WARNING MECHANISM



6. Selective COX-2 Inhibitors

- **Celecoxib:** Developed to reduce inflammation without GI ulcers by selectively targeting COX-2.
- **Risks:** May increase edema and hypertension. Rofecoxib was withdrawn due to fatal thromboembolic events.
- **Black Box Warning:** Celecoxib carries a black box warning because it imbalances thromboxane and prostacyclin production, promoting platelet aggregation and increasing the risk of thrombosis and heart attacks.

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7. ACETAMINOPHEN (PARACETAMOL)

1. MECHANISM OF ACTION

- Inhibits **PG synthesis** primarily in the CNS.

PG → PG synthesis block

Strong **antipyretic** (reduces fever)

analgesic (pain relief)

- Weak peripheral anti-inflammatory effects.

2. SAFETY PROFILE

Platelet function

normal clotting and bleeding time

Time

no alteration

- Does not affect platelet function or increase bleeding time.

Drug of choice for children with viral infections to avoid **Reye's syndrome**.

3. TOXICITY & OVERDOSE MECHANISM

Normal Doses
(Liver Conjugation)

- Small portion forms toxic metabolite (N-acetylbenzoiminoquinone), neutralized by glutathione.

Non-toxic metabolites

N-acetylbenzoiminoquinone

Glutathione

Overdose
(Glutathione Depletion)

- An overdose depletes glutathione, causing toxic buildup that leads to fatal hepatic necrosis.

Glutathione

0 Glutathione

Fatal hepatic necrosis

4. DOSING & ANTIDOTE

4g/day
MAX SAFE DOSE

Max safe dose is **4g/day**.

ACETYLCYSTEINE
Acetylcysteine

- Antidote for overdose: **Acetylcysteine**
- Scavenges free radicals
- Must be given within **8-12 hours** to prevent liver death

vs

7. Acetaminophen (Paracetamol)

- **Mechanism:** Inhibits PG synthesis primarily in the CNS, giving it strong antipyretic and analgesic properties but weak peripheral anti-inflammatory effects.

- **Safety:** Does not affect platelet function or increase bleeding time. It is the drug of choice for children with viral infections to avoid Reye's syndrome.

- **Toxicity and Overdose:** Normal doses are conjugated safely in the liver. A small portion forms a toxic metabolite (N-acetylbenzoiminoquinone), which is neutralized by glutathione. An overdose depletes glutathione, causing toxic buildup that leads to fatal hepatic necrosis.

- **Dosing and Antidote:** Max safe dose is 4g/day. The antidote for overdose is Acetylcysteine, which scavenges free radicals and must be given within 8-12 hours to prevent liver death.