NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

ILOS

At the end of the lecture the students should :

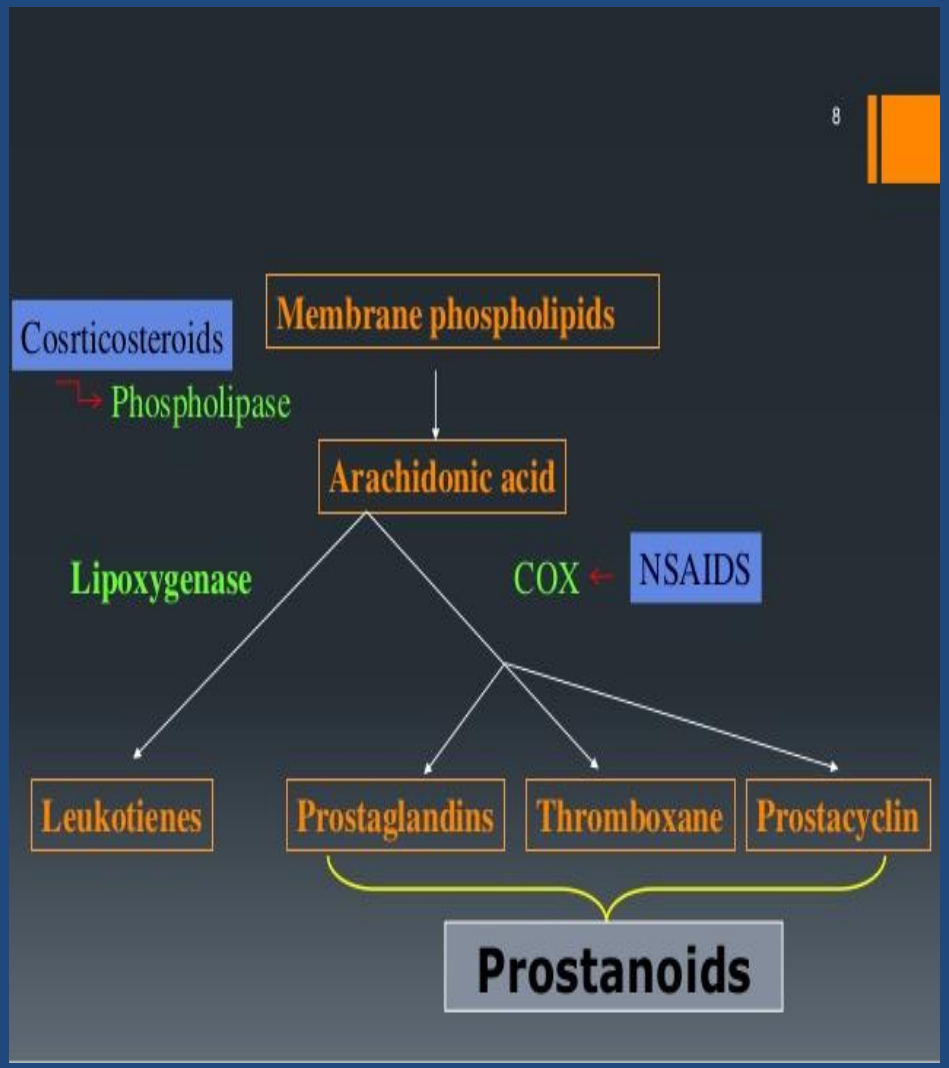
- Define NSAIDs
- Specify the general mechanism of actions
- Classify this group of drugs
- Describe the general pharmacological actions
- Enumerate the therapeutic uses
- Describe the general adverse effects
- Describe the general contraindications
- Know the difference between the selective & non-selective NSAIDs

Non-steroidal anti-inflammatory Drugs

- **NSAIDs** are group of drugs that share in common the capacity to induce:
- Analgesic effect.
- Antipyretic effect.
- Anti-inflammatory effect.

MECHANISM OF ACTION OF NSAIDS

- NSAIDs inhibit **cyclooxygenase (COX) enzymes** responsible for the production of prostaglandins (PGs) which promote **inflammation** necessary for healing, **pain** and **fever**.
- **As a consequence, ongoing inflammation, pain and fever are reduced by NSAIDs.**

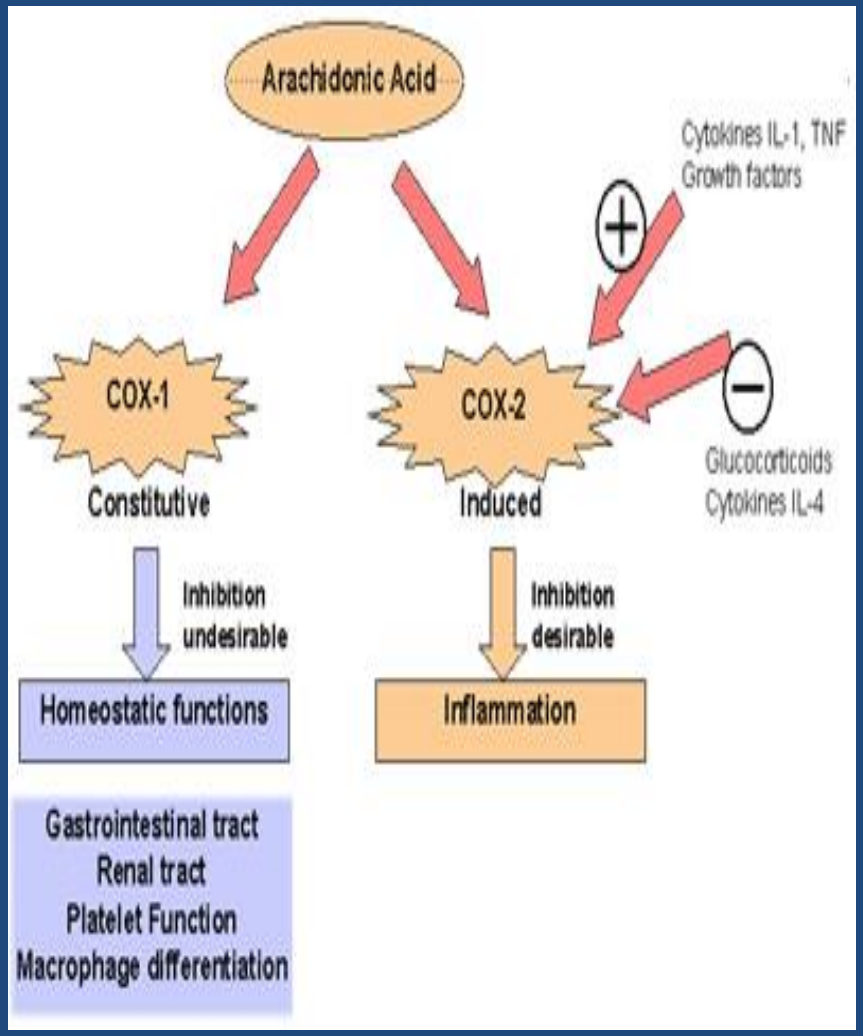


COX ISOFORMS

- **COX-1** produces PGs that support the blood clotting function of platelets; and protect the lining of the stomach from the damaging effects of acid. **NSAIDs which inhibit COX1 can cause ulcers in the stomach and promote bleeding.**

- **COX-2** is expressed at sites of inflammation and produces PGs that mediate inflammation and pain.

- **COX3 is** a new isozyme found in the brain , it is the target for **acetaminophen**.



CLASSIFICATION OF NSAIDS

Nonselective COX-1/COX-2 Inhibitors	Aspirin, Diclofenac
Selective COX-2 Inhibitors	Coxibs
Preferential COX2 inhibitors	Meloxicam
COX3 inhibitors	Paracetamol

1-ANALGESIC

NSAIDs

Prostaglandins

PGE2 PGF2

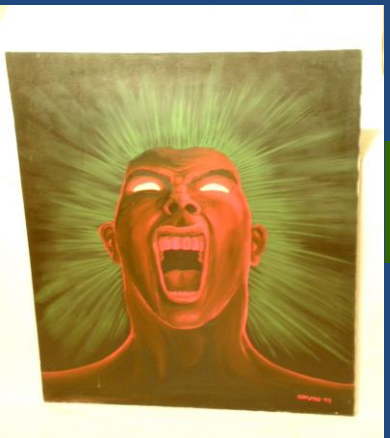
Factors

+

Bradykinin

Histamine

Nerve ending of pain



Pain

- **Block PGs production**
- **Sites of action:**

peripheral tissue

2-ANTIPYRETIC

Prostaglandins PGE2

Pyrogen

NSAIDs

Thermoregulatory center

- **Antipyretic Mechanism**

Block PGs production

Sites of action: CNS

Set point ↑

Heat production ↑
Heat dissipation ↓

Fever

3-Anti-inflammatory

NSAIDs

Prostaglandins

PGE2 , PGF2

Inflammatory factors

+

Bradykinin

Histamine

5-HT

Symptoms of inflammation

Red, swelling, Heat, pain

Block PGs production

- **Sites of action: peripheral tissues**

CLINICAL USES

Fever

Headache, Migraine,
Dental pain, Dysmenorrhea

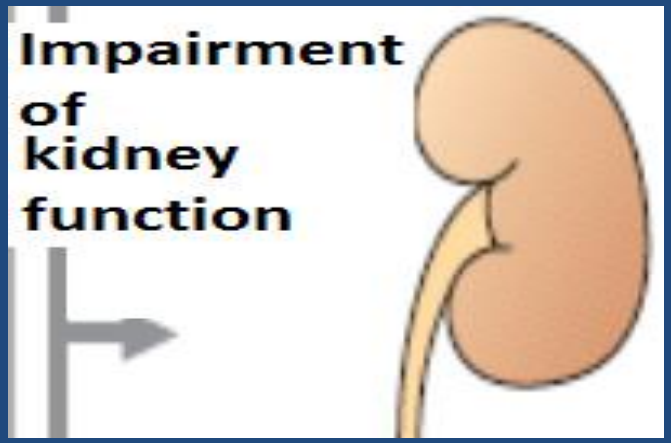
Common cold

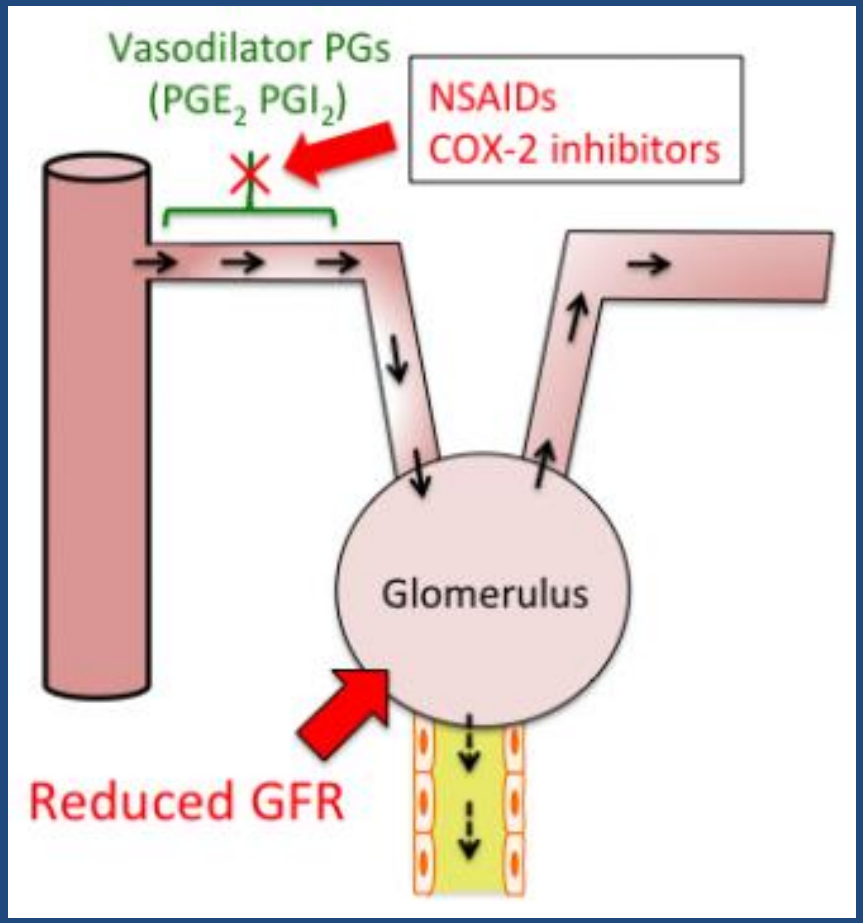
Rheumatoid arthritis /
myositis

ADRS

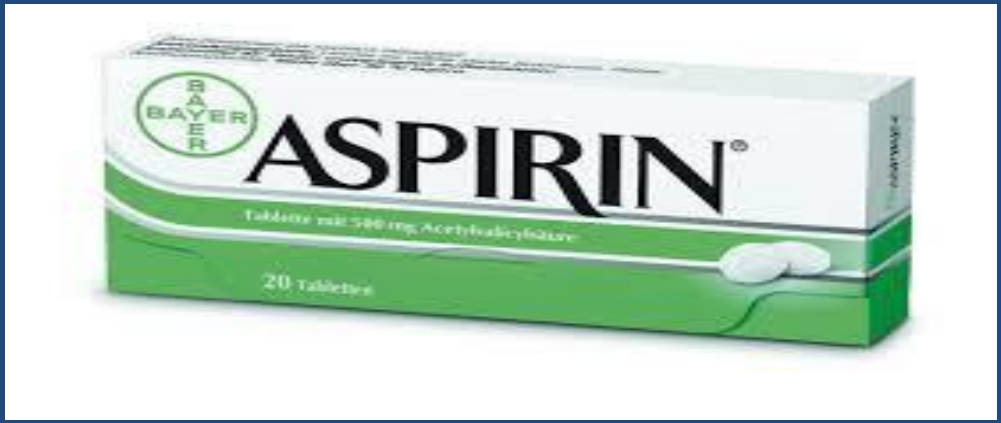
- GIT upsets (nausea, vomiting)
- GIT bleeding & ulceration
- Bleeding
- Hypersensitivity reactions
- Inhibition of uterine contraction
- Salt & water retention

RENAL ADRS



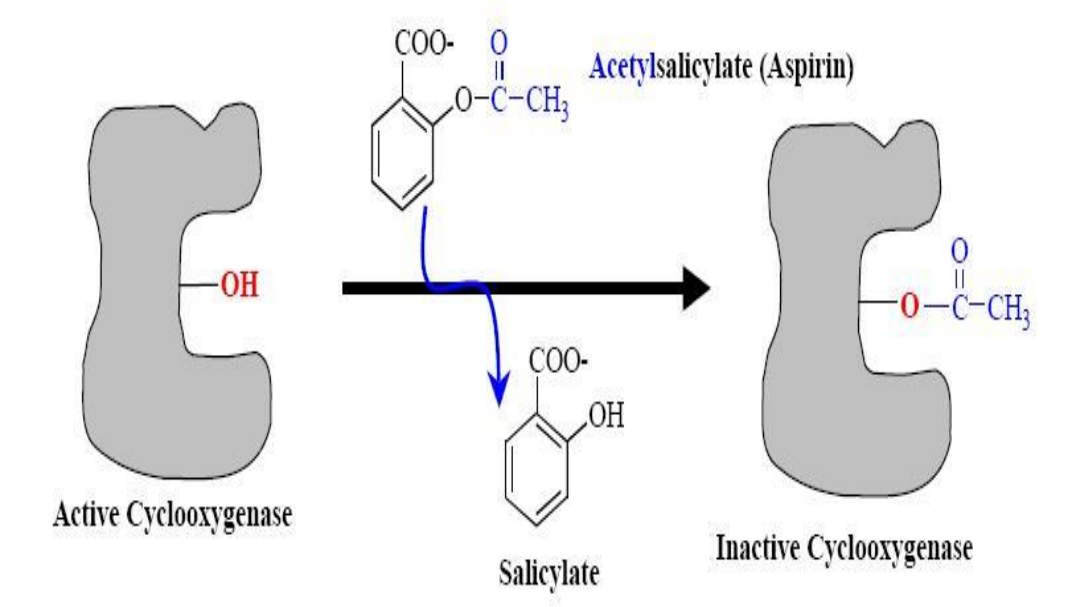


NSAIDs cause hemodynamically-mediated acute renal failure



MECHAISM OF ACTION

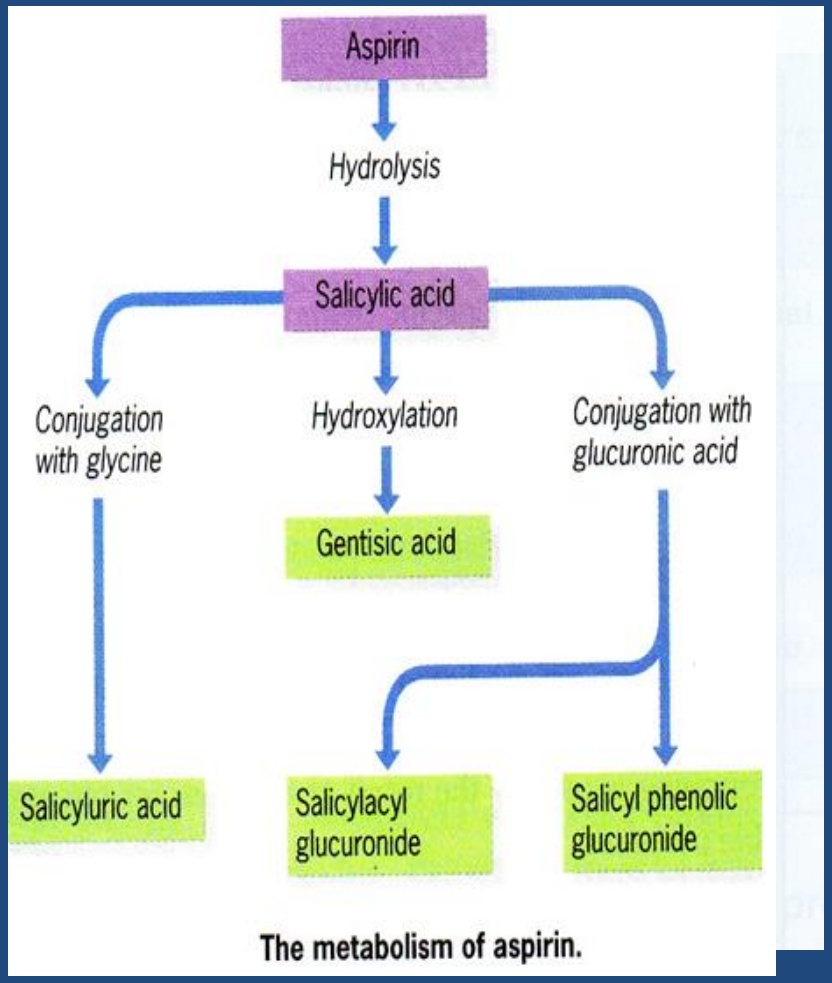
Aspirin inhibits COX irreversibly



PHARMACOKINETICS

Metabolized by hydrolysis and then conjugation

Higher dose of aspirin has a long plasma half- life



The metabolism of aspirin.

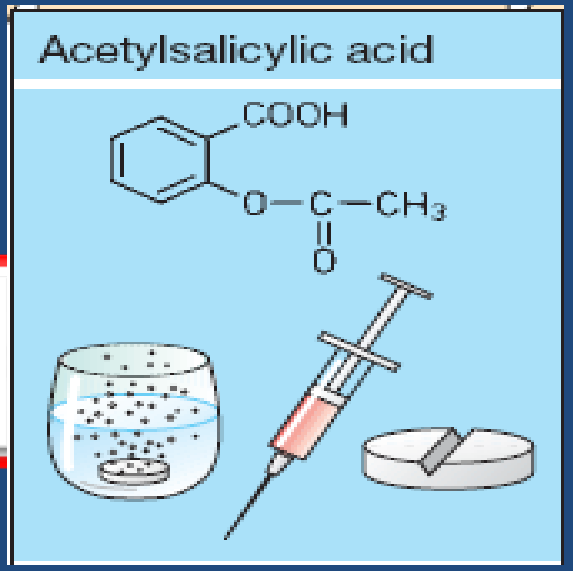
CLINICAL USES

Acute rheumatic fever

Reducing the risk of myocardial infarction (cardioprotective)

Prevention of pre-eclampsia

Chronic use of small doses ,
reduce the incidence of colon cancer



ADRS AT CLINICAL DOSES

Hypersensitivity bronchospasm, rhinitis, conjunctivitis, urticaria

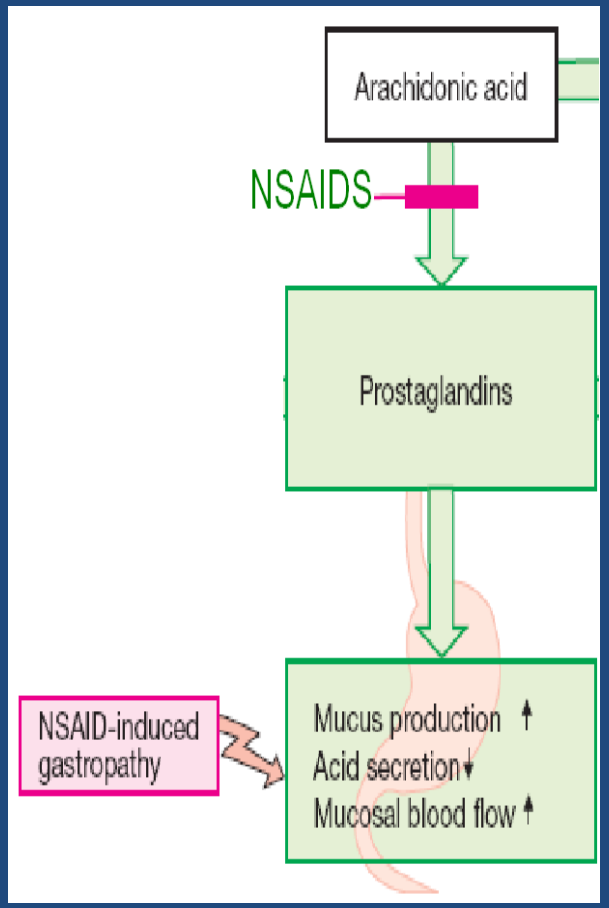
Acute gouty arthritis (low doses)

Reye's syndrome

Impaired haemostasis

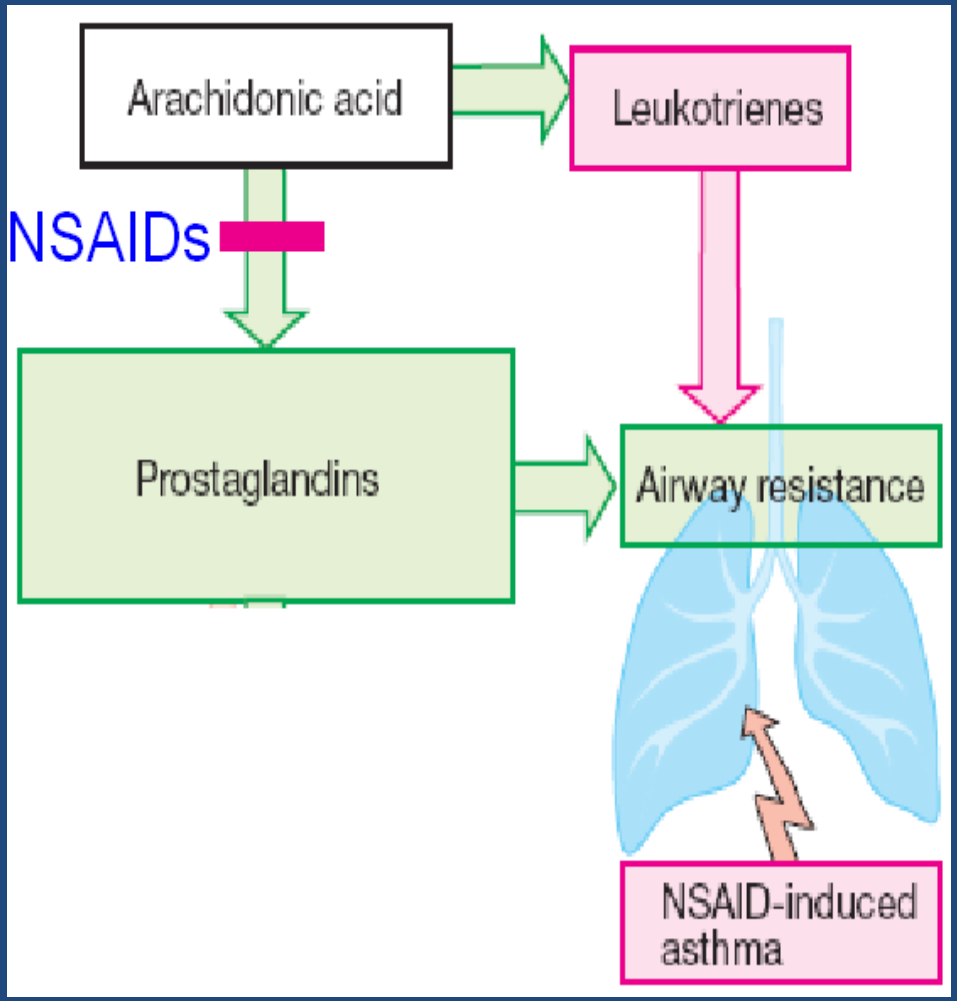
GIT side effects, dyspepsia, N, V

Mucosal damage→ hemorrhage



ADRS

Bronchospasm in aspirin- sensitive asthmatics



ADRS AT OVERDOSE

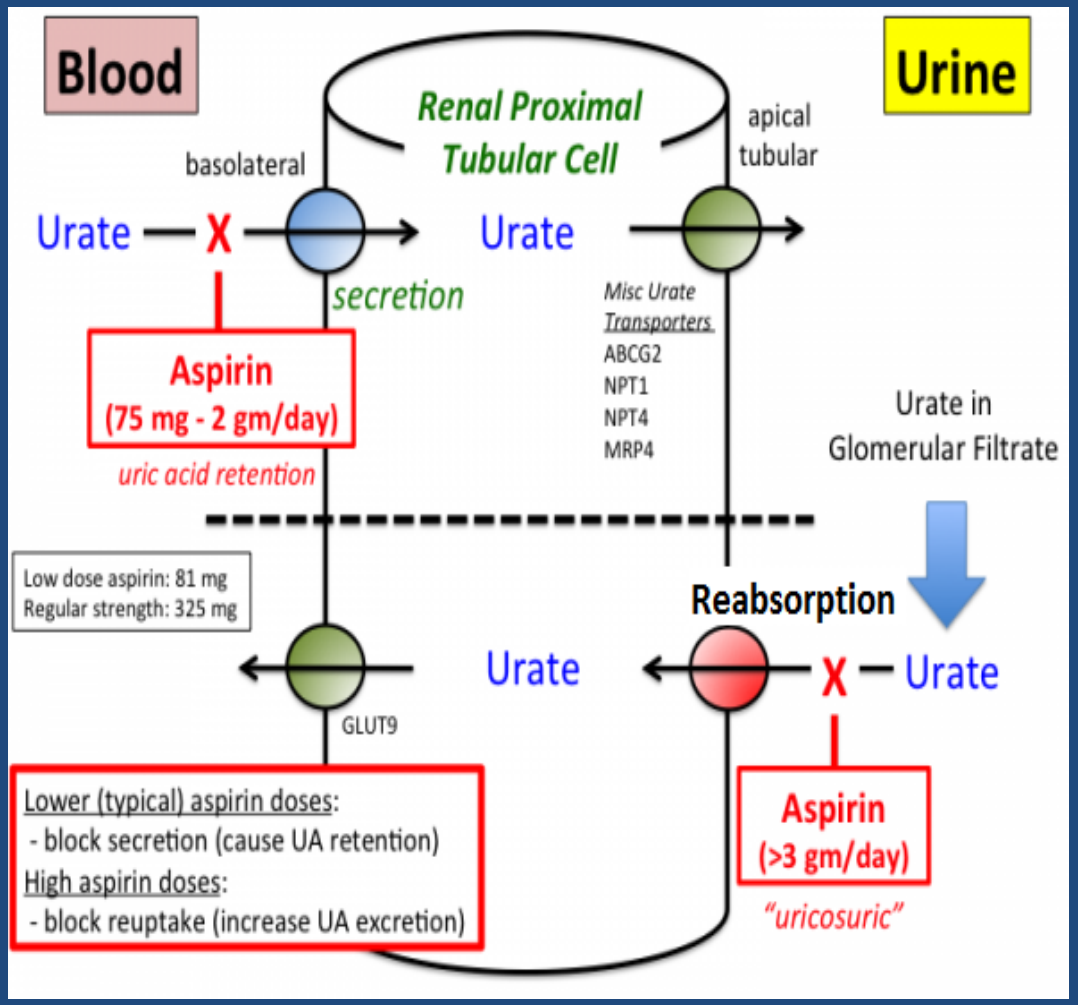
Salicylism (ringing of ear , vertigo)

Hyperthermia

Gastric ulceration & bleeding

CONTRAINDICATIONS

- Peptic ulcer
- Pregnancy
- Hemophilic patients
- Patients taking anticoagulants
- Children with viral infections
- Gout (small doses)



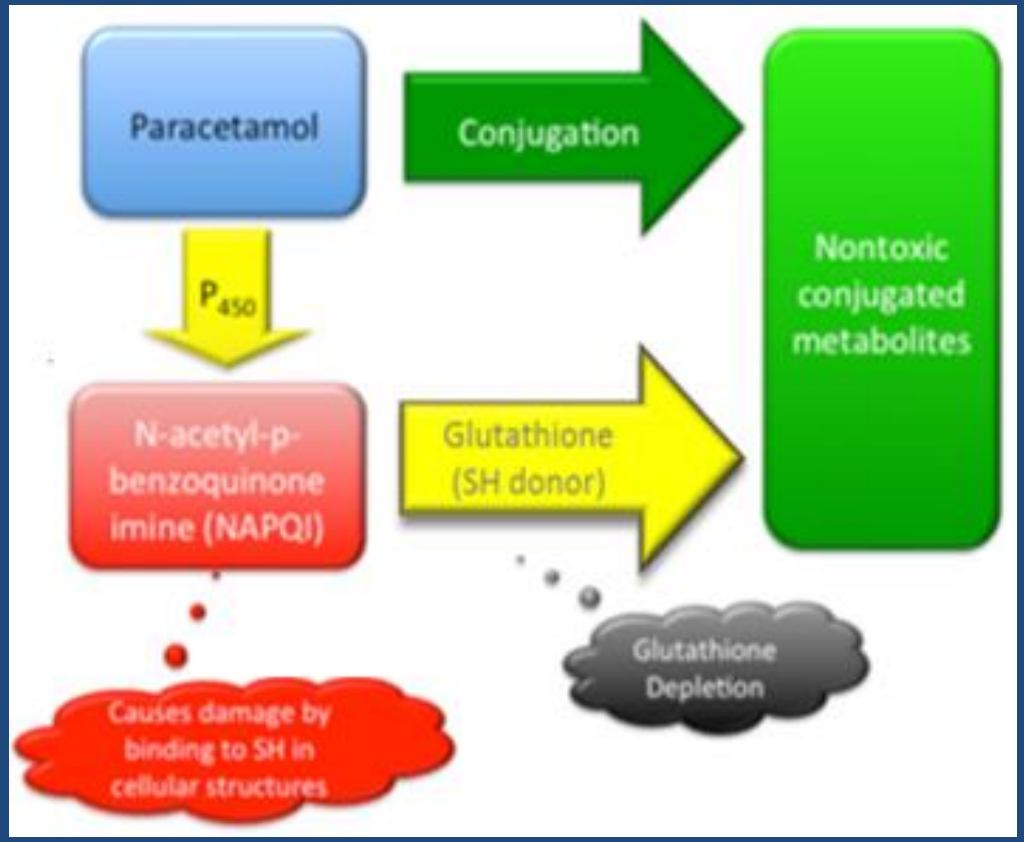
Paracetamol

Weak anti-inflammatory effect

Given orally , well absorbed.

$t_{1/2}$=2-4 h

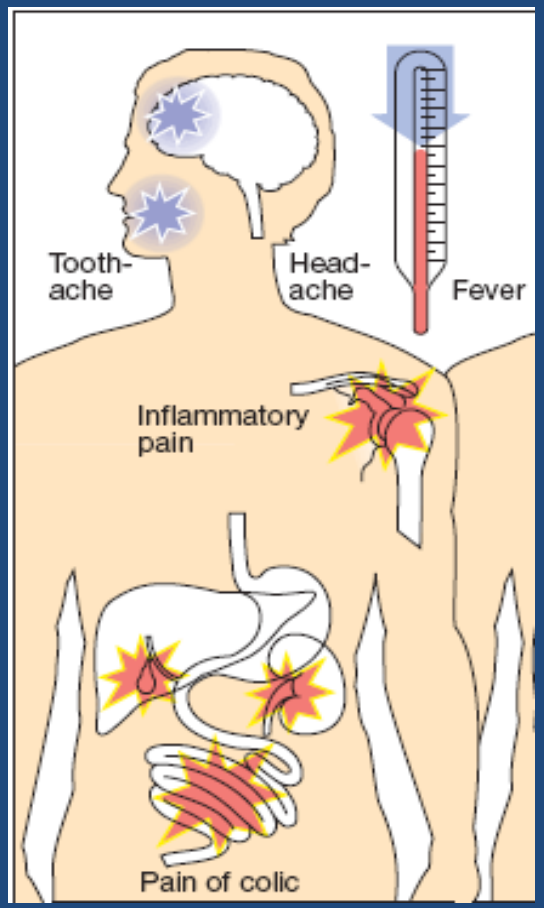
Metabolized by conjugation at therapeutic doses



CLINICAL USES

Commonly used analgesic antipyretic instead of aspirin in cases of:-

- Peptic or gastric ulcers
- Bleeding tendency
- Allergy to aspirin
- Viral infections in children
- Pregnancy

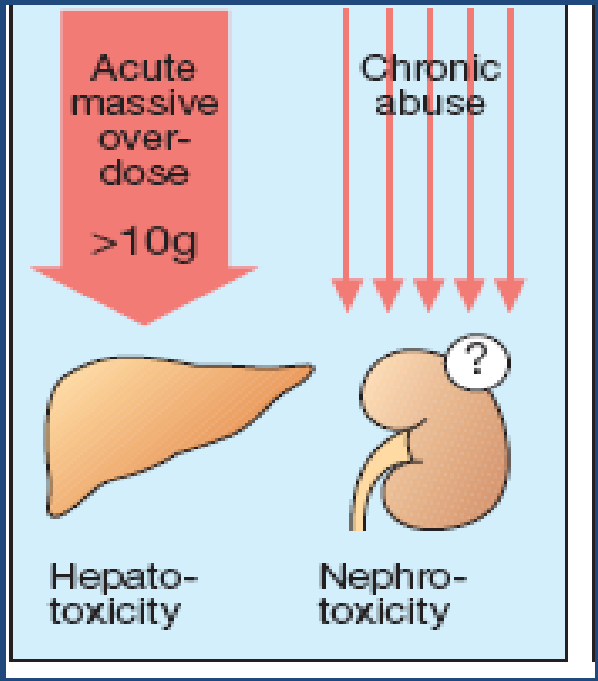


ADRS

Mainly on liver due to its active metabolite

Therapeutic doses elevate liver enzymes

In large doses it is metabolized into N- acetyl-p-benzoquinone, which causes liver damage



Treatment of toxicity of paracetamol is by **N-acetylcysteine** to neutralize the toxic metabolite

CLINICAL USES

- Analgesic
- Antipyretic
- Antiinflammatory
- Acute gouty arthritis
- Locally to prevent post-operative ophthalmic inflammation

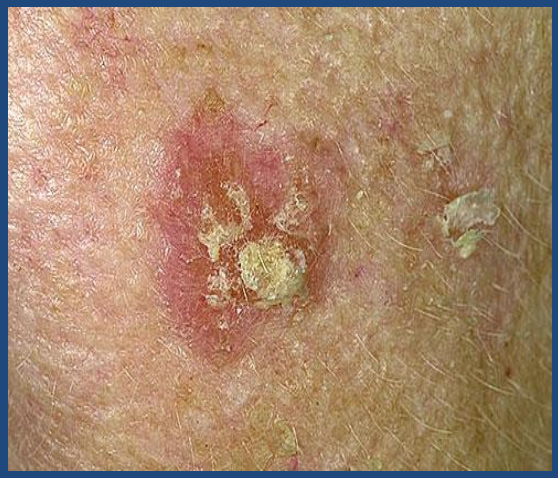
PREPARATIONS

Diclofenac with **misoprostol** decreases upper gastrointestinal ulceration , but result in diarrhea.

Diclofenac with **omeprazole** to prevent recurrent bleeding

0.1% ophthalmic preparation for postoperative ophthalmic inflammation.

A topical gel 3% for solar keratoses.



Rectal suppository as analgesic

Oral mouth wash

Intramuscular preparations

SELECTIVE COX-2 INHIBITORS

- Potent anti-inflammatory
- Antipyretic & analgesic
- Lower incidence of gastric upset
- No effect on platelet aggregation (COX-1)

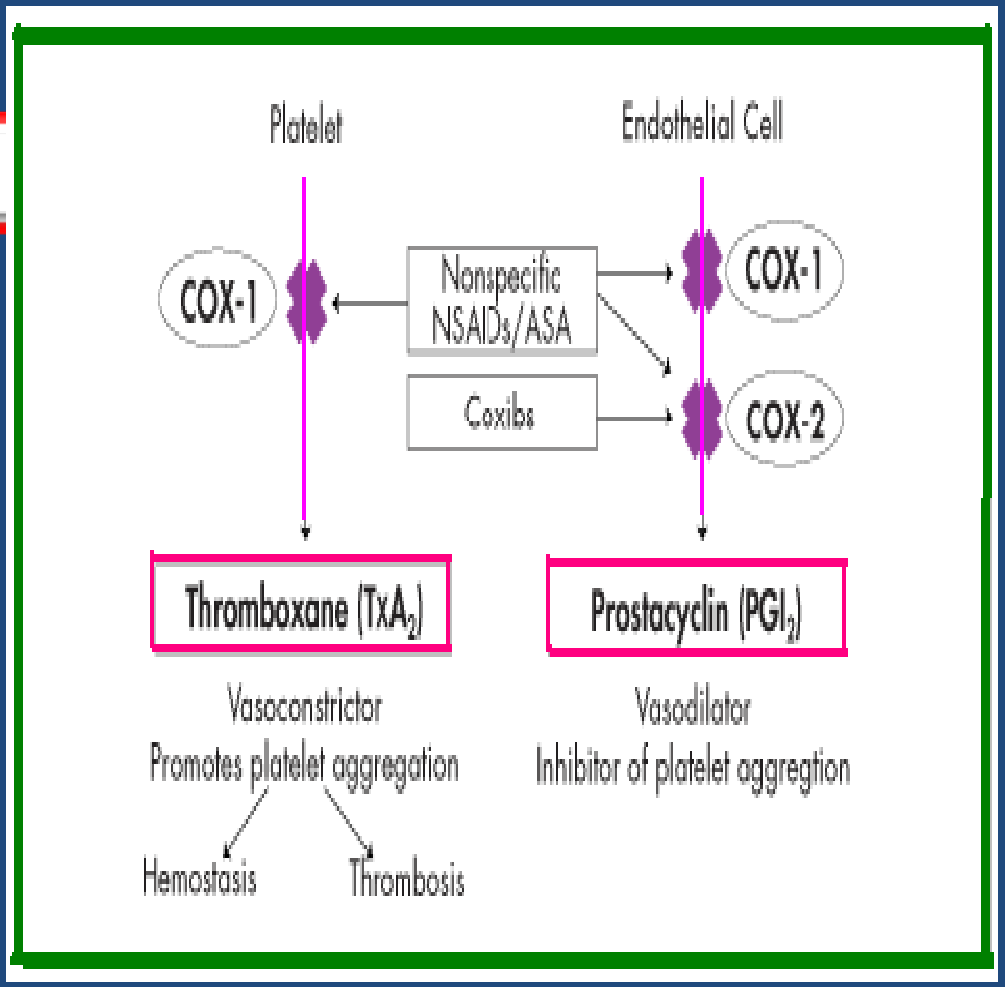
GENERAL ADRS

Renal toxicity

Dyspepsia & heartburn

Allergy

Cardiovascular (do not offer the cardio-protective effects of non-selective group



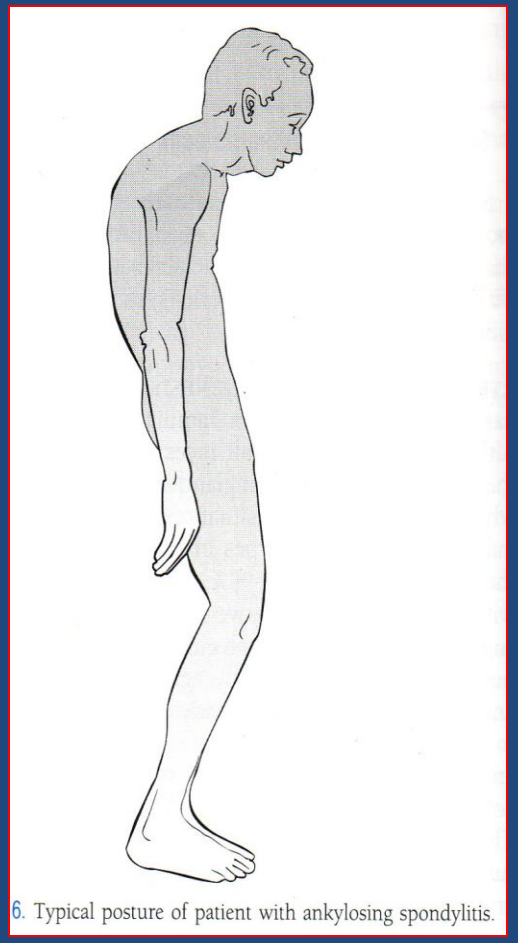
GENERAL CLINICAL USES

Short-term use in postoperative patients

Acute gouty arthritis

Acute musculoskeletal pain

Ankylosing spondylitis



6. Typical posture of patient with ankylosing spondylitis.

Half-life 11 hours

Food decrease its absorption

Highly bound to plasma proteins