NSAIDS EPIDEMIOLOGY

NSAIDs account for 3.8% of all prescriptions

A significant quantity is sold over the counter (OTC)

Use increases with age

90% of all NSAIDs prescriptions are issued to patients at ages over 65 years

NSAIDs is the most prominent risk for gastric ulceration, hemorrhage & perforation

The prevalence of NSAID-induced ulcers is 10% to 30% .

ILOS

To focus on the general mechanism of action of NSAIDs

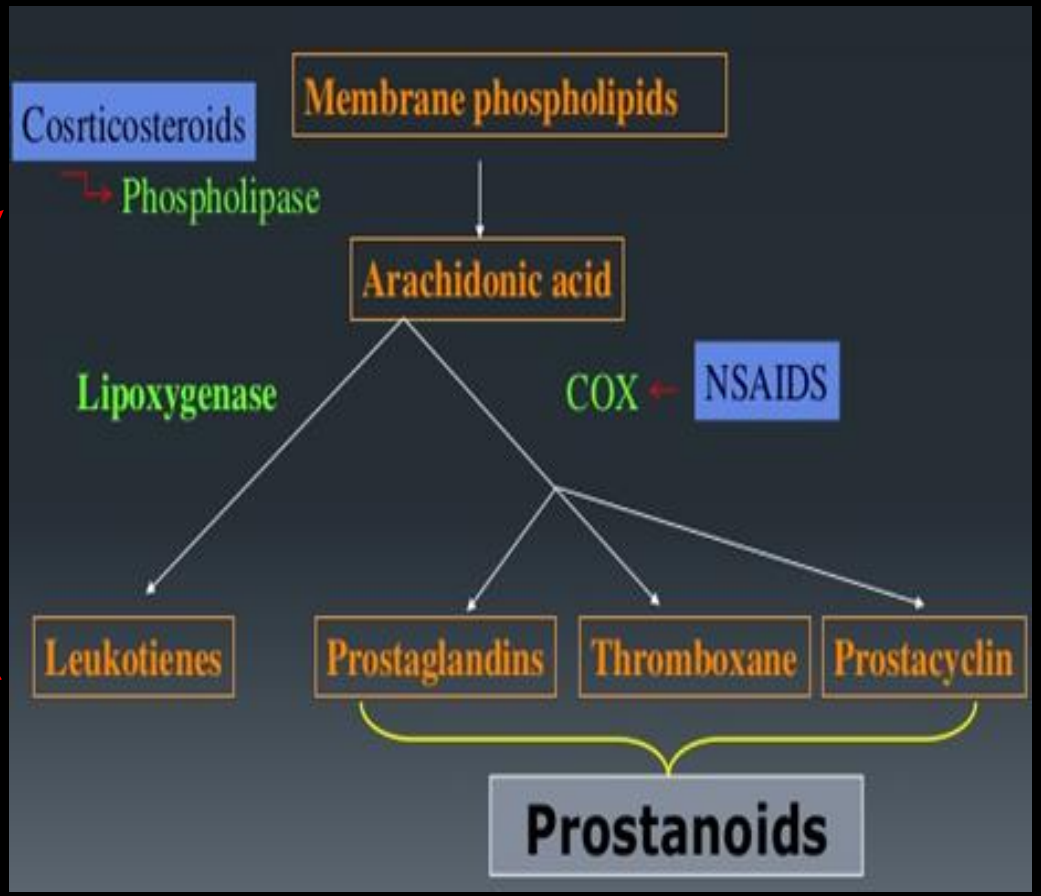
To classify NSAIDs on basis of their specificity to COX isoenzymes

To outline the common pharmacodynamic effects & ADRs of NSAIDs

To detail on the pharmacokinetic properties & pharmacodynamic effects of **selected** NSAIDs.

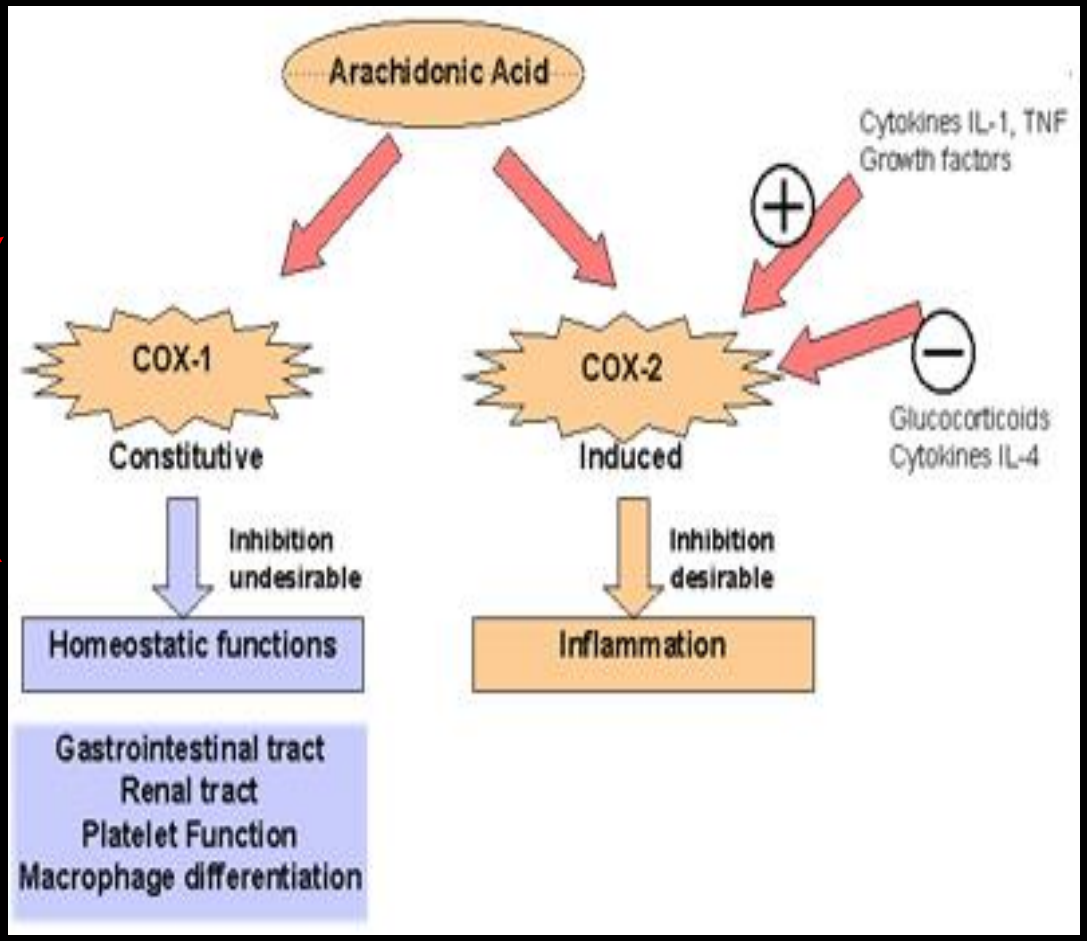
MECHANISM OF ACTION OF NSAIDS

NSAIDs inhibit cyclo oxygenase enzyme



COX ISOFORMS

COX3 is found in the brain



CLASSIFICATION OF NSAIDS

Nonselective COX-1/COX-2 Inhibitors	Aspirin, Diclofenac Ibuprofen, naproxen
Selective COX-2 Inhibitors	Coxibs
Preferential COX-2 inhibitors	Meloxicam
COX-3 inhibitors	Paracetamol

PGS

Nociceptors at nerve endings

PAIN

Inflammatory factors

-

+

NSAIDs

Bradykinin
Histamine

PHARMACODYNAMIC EFFECTS

1-ANALGESIC

2-ANTIPYRETIC

Pyrogens

PGs

Thermoregulatory centre

Set point↑

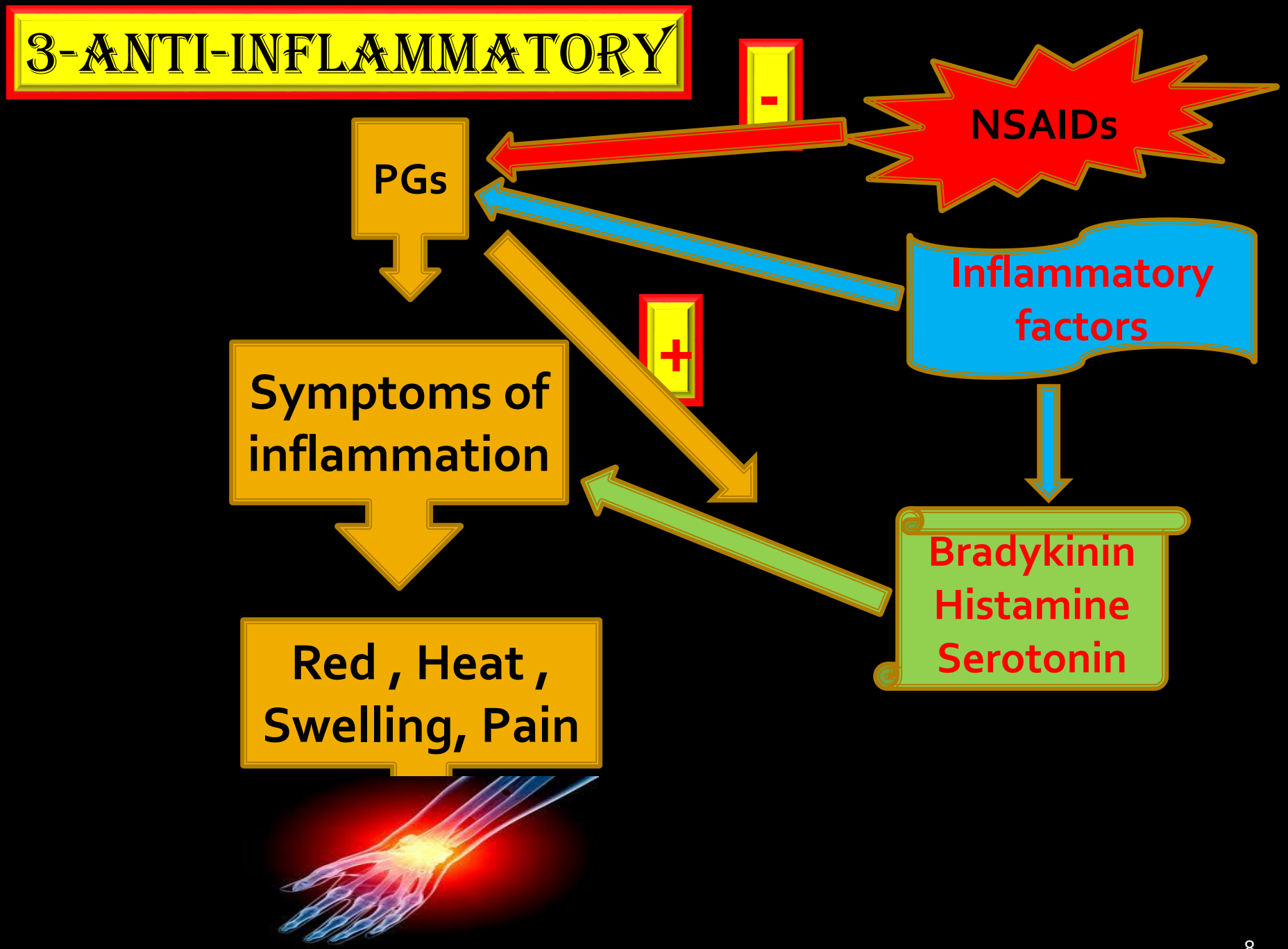
Heat production↑
Heat dissipation↓

Fever

-

NSAIDs

3-ANTI-INFLAMMATORY



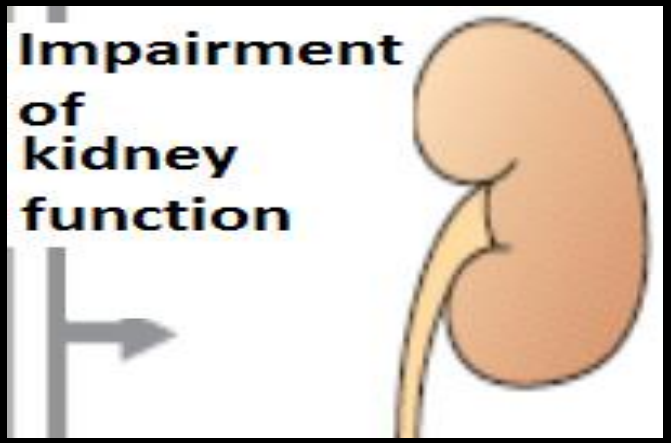
CLINICAL USES

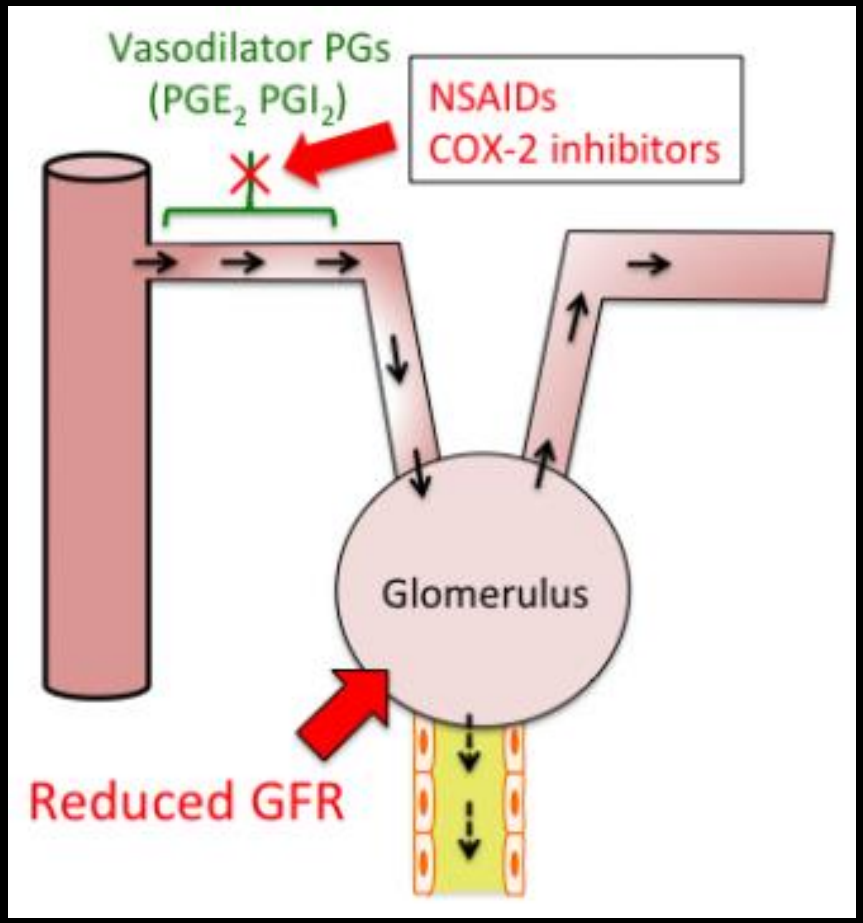
- Fever
- Headache, Migraine, Dental pain, Dysmenorrhea
- Common cold
- Rheumatoid arthritis / myositis

ADRS

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

ADRS





NSAIDs cause hemodynamically-mediated acute renal failure

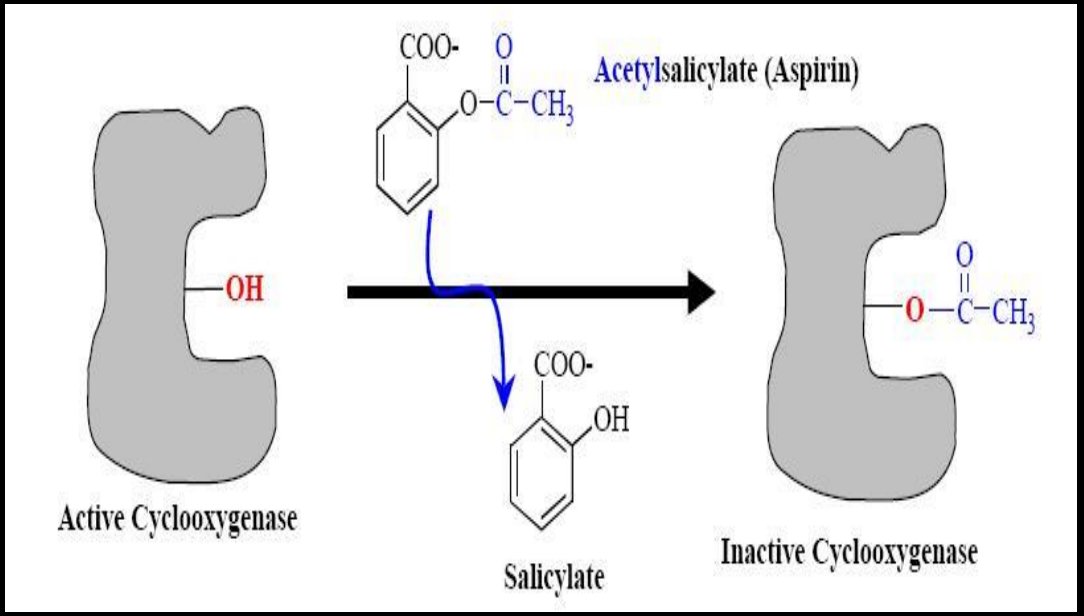
NON SELECTIVE COX INHIBITORS

- Aspirin
- Diclofenac
- Ibuprofen
- Ketoprofen
- Naproxen
- Piroxicam
- Indomethacin

NON SELECTIVE COX INHIBITORS

MECHANISM OF ACTION

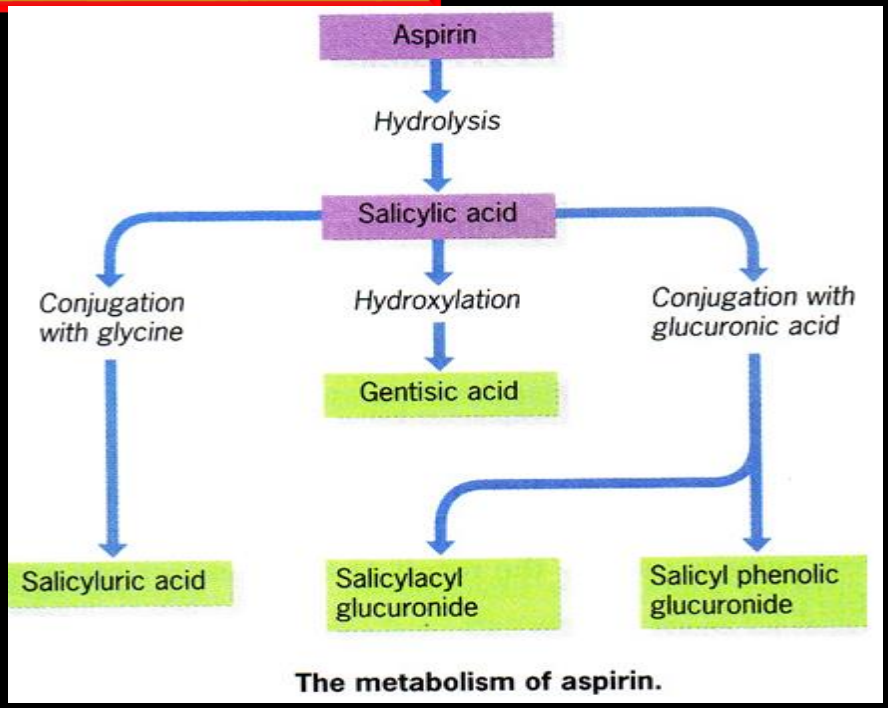
Aspirin inhibits COX irreversibly



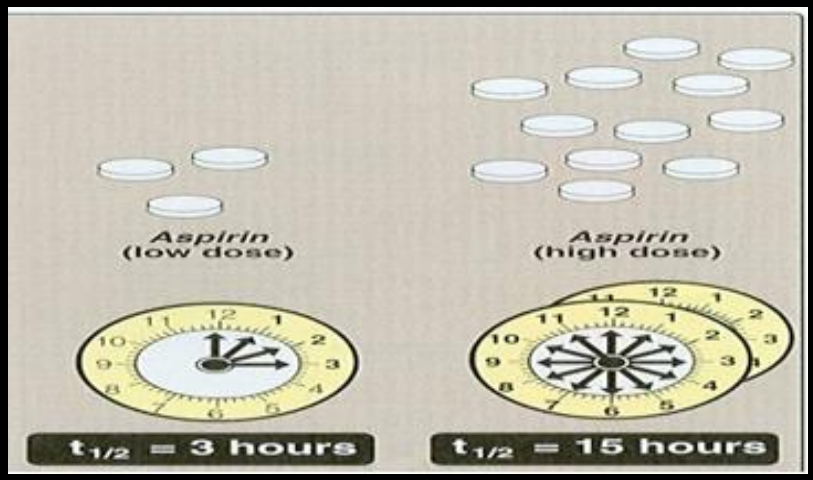
PHARMACOKINETICS

Metabolized by hydrolysis & then conjugation

Why a high dose has a long plasma half- life?



The metabolism of aspirin.



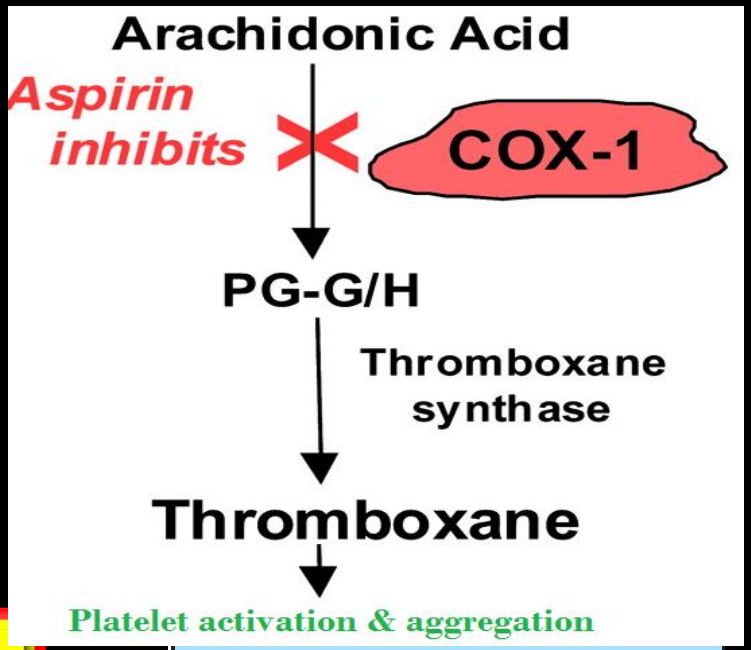
CLINICAL USES

Acute rheumatic fever

Reducing the risk of myocardial infarction (cardioprotective)

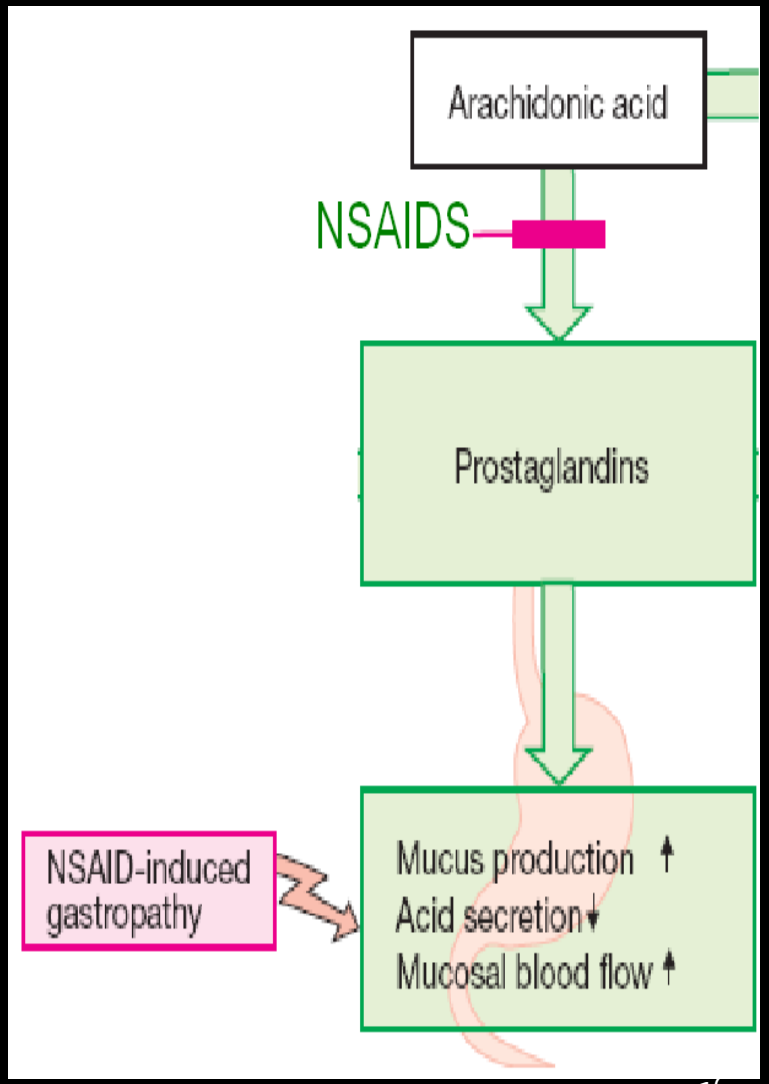
Prevention of pre-eclampsia

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



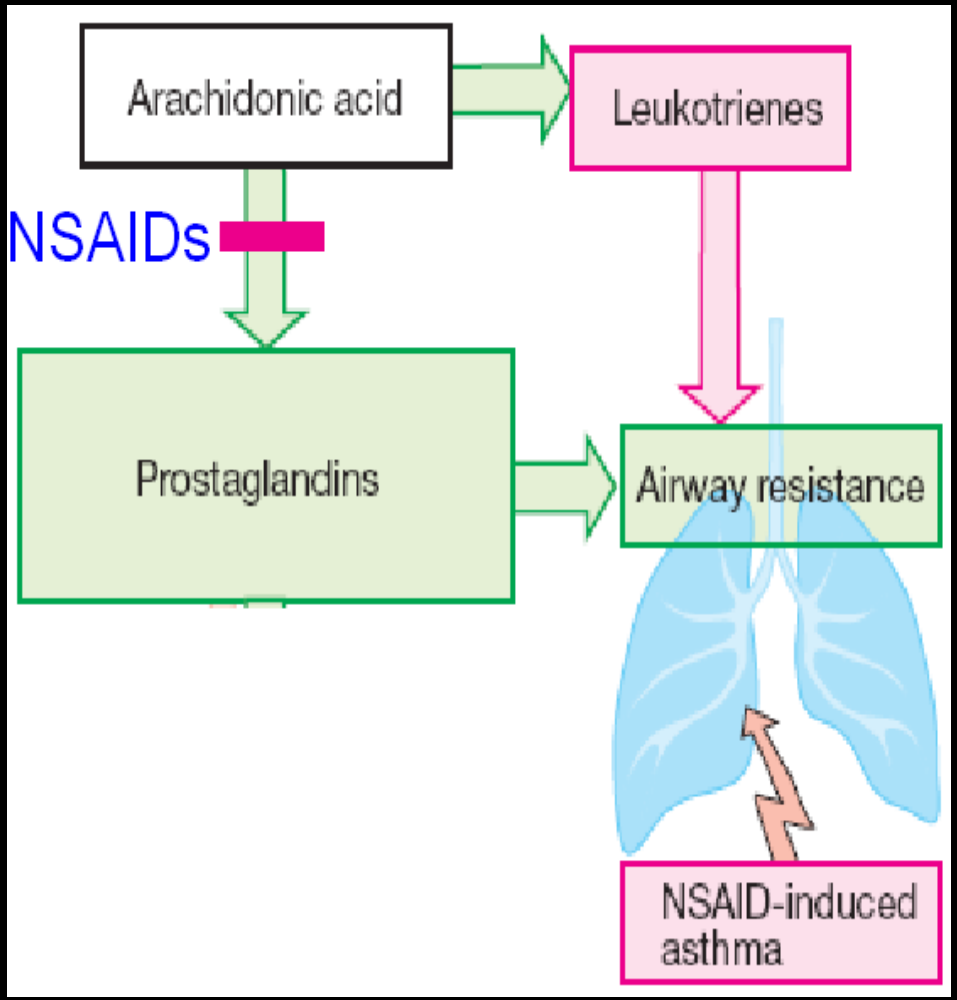
ADRS AT CLINICAL DOSES

- Hypersensitivity
- Acute Gouty arthritis
- Reye's syndrome
- Impaired haemostasis
- GIT side effects, dyspepsia, nausea, vomiting
- Mucosal damage→ hemorrhage



ADRS AT CLINICAL DOSES

- Bronchospasm in aspirin- sensitive asthmatics



ADRS AT OVERDOSE

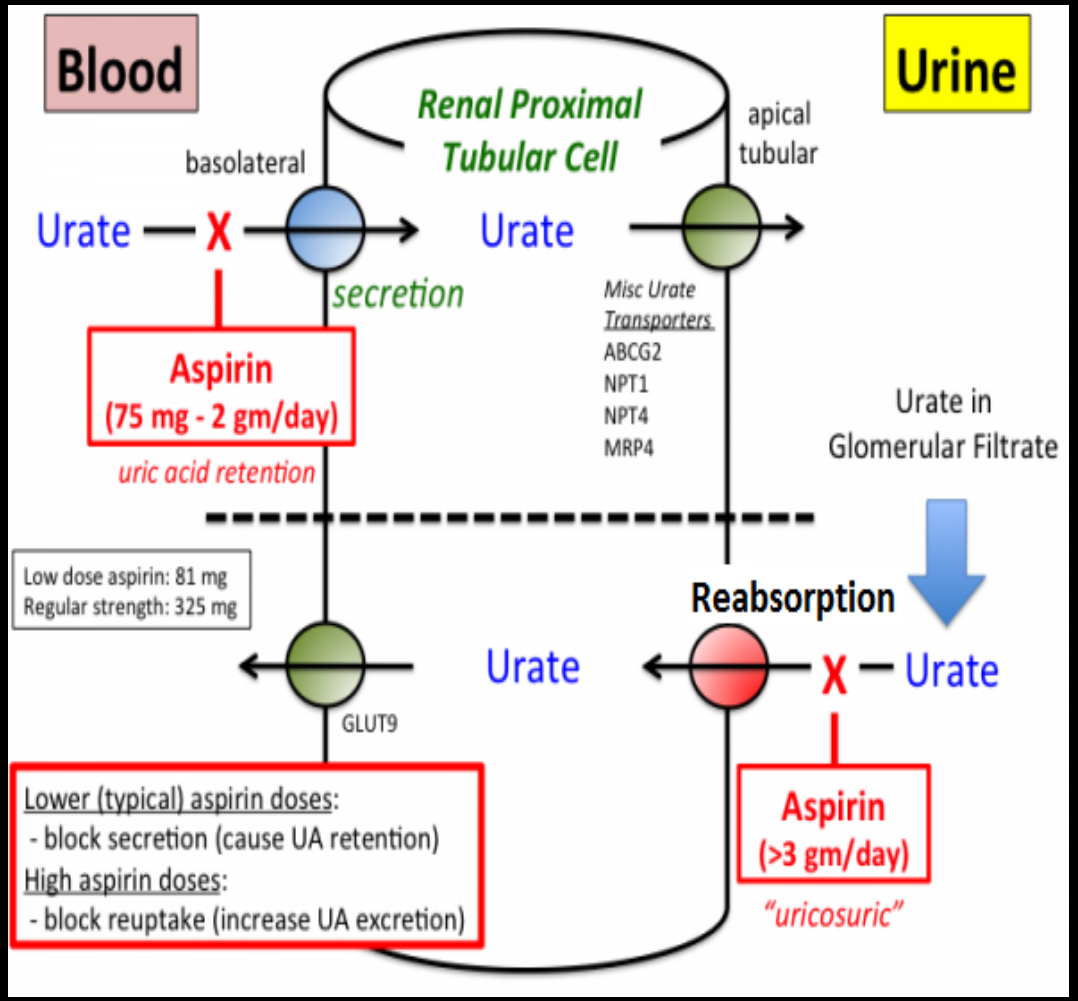
Salicylism (ringing of ear , vertigo)

Hyperthermia

Gastric ulceration & bleeding

CONTRAINDICATIONS

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



NON SELECTIVE COX INHIBITORS

CLINICAL USES

- Analgesic
- Antipyretic
- Anti-inflammatory
- Acute gouty arthritis
- Locally to prevent post- operative ophthalmic inflammation (solution)

PREPARATIONS

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

Diclofenac with omeprazole to prevent recurrent bleeding

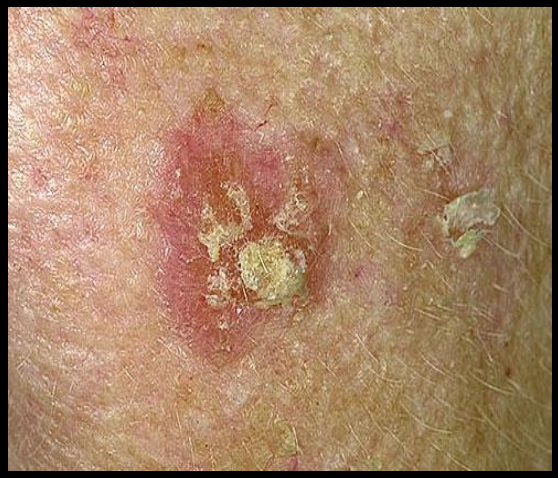
0.1% ophthalmic preparation for postoperative ophthalmic inflammation

A topical gel 3% for solar keratoses

Rectal suppository as analgesic

Oral mouth wash

IM preparations for pain & fever.



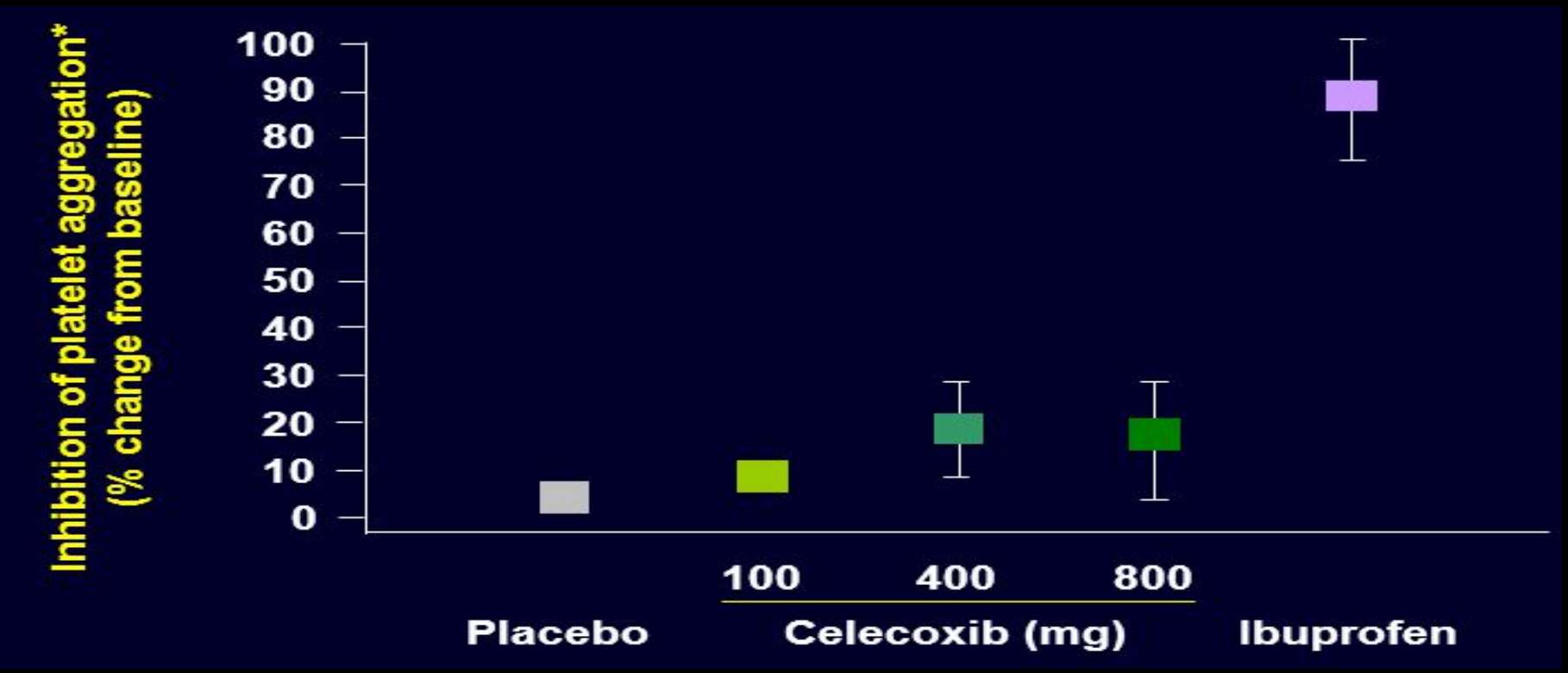
SELECTIVE COX-2 INHIBITORS:

coxibs

- Celecoxib
- Etoricoxib
- Paracoxib
- Lumiracoxib
- Rofecoxib
- Valdecoxib

Withdrawn because of risk of myocardial infarction & stroke

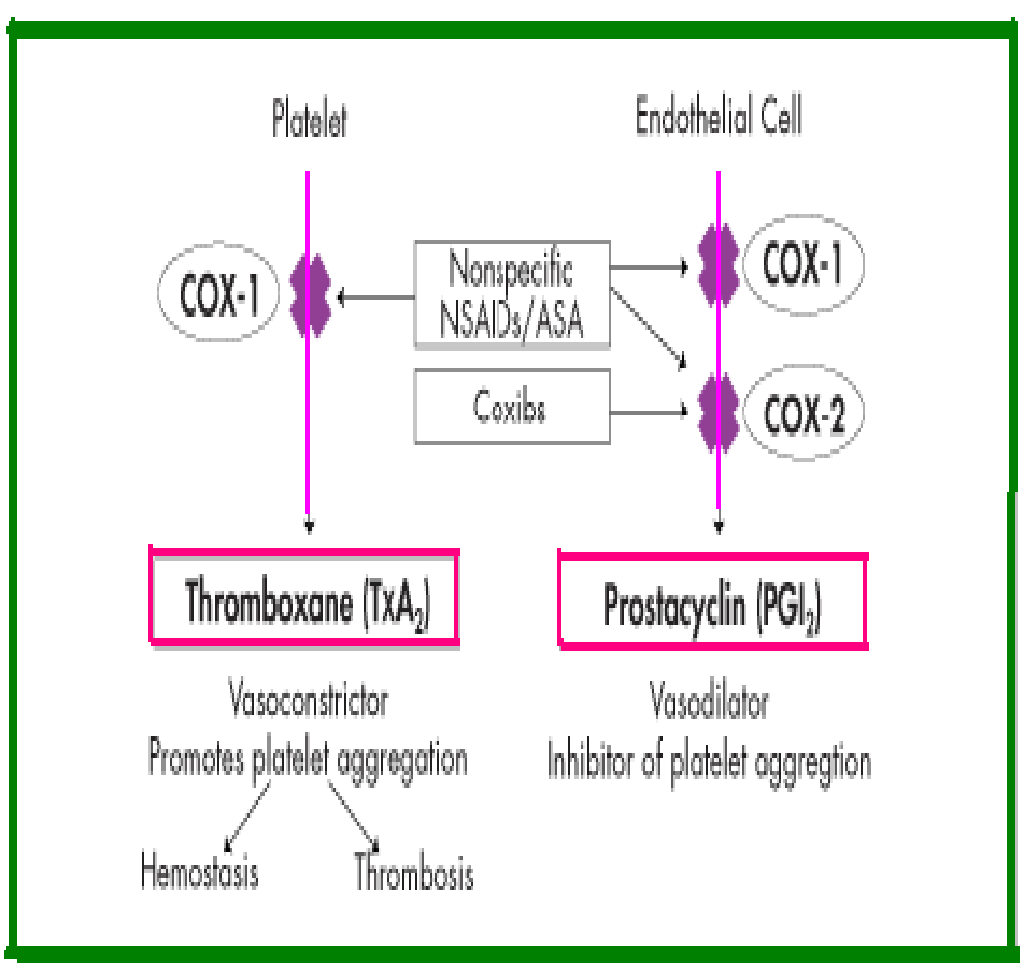
SELECTIVE COX-2 INHIBITORS



- No effect on platelet aggregation (COX-1)

GENERAL ADRS

- Renal toxicity
- Dyspepsia & heartburn
- Allergy
- Cardiovascular (do not offer the cardioprotective effects of non-selective group)
- Should not be given to a patient with CV disease



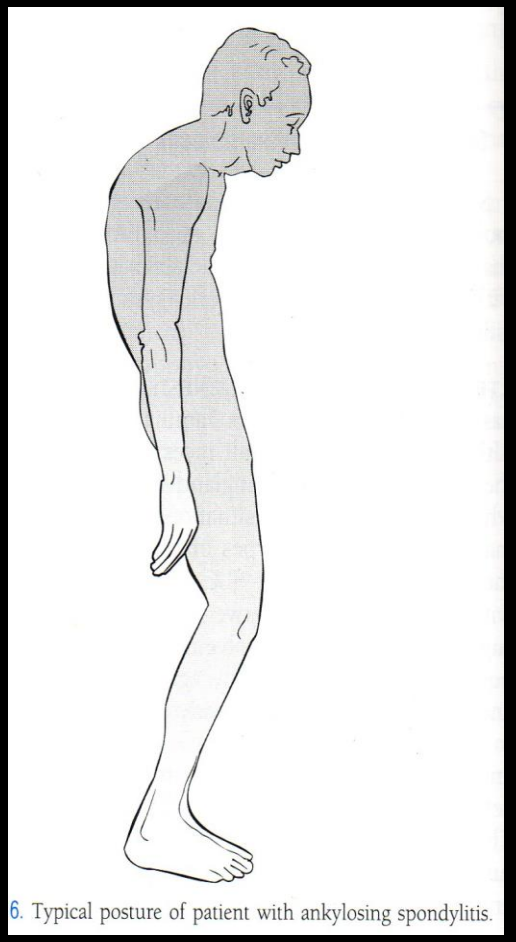
GENERAL CLINICAL USES

Short-term use in postoperative patients

Acute gouty arthritis

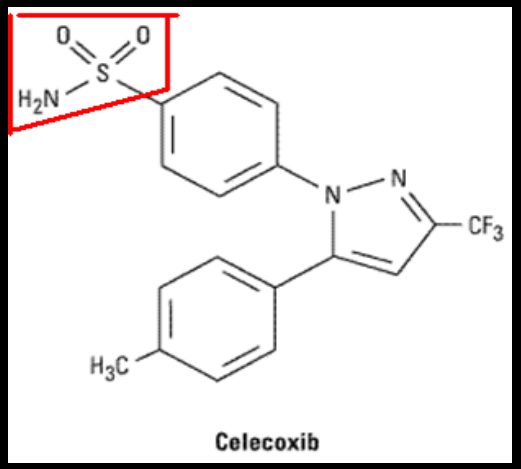
Acute musculoskeletal pain

Ankylosing spondylitis



6. Typical posture of patient with ankylosing spondylitis.

SELECTIVE COX-2 INHIBITORS



Half-life 11 hours

Food decrease its absorption

Highly bound to plasma proteins

Contraindicated in patients allergic to sulphonamides.

PREFERENTIAL COX-2 INHIBITORS

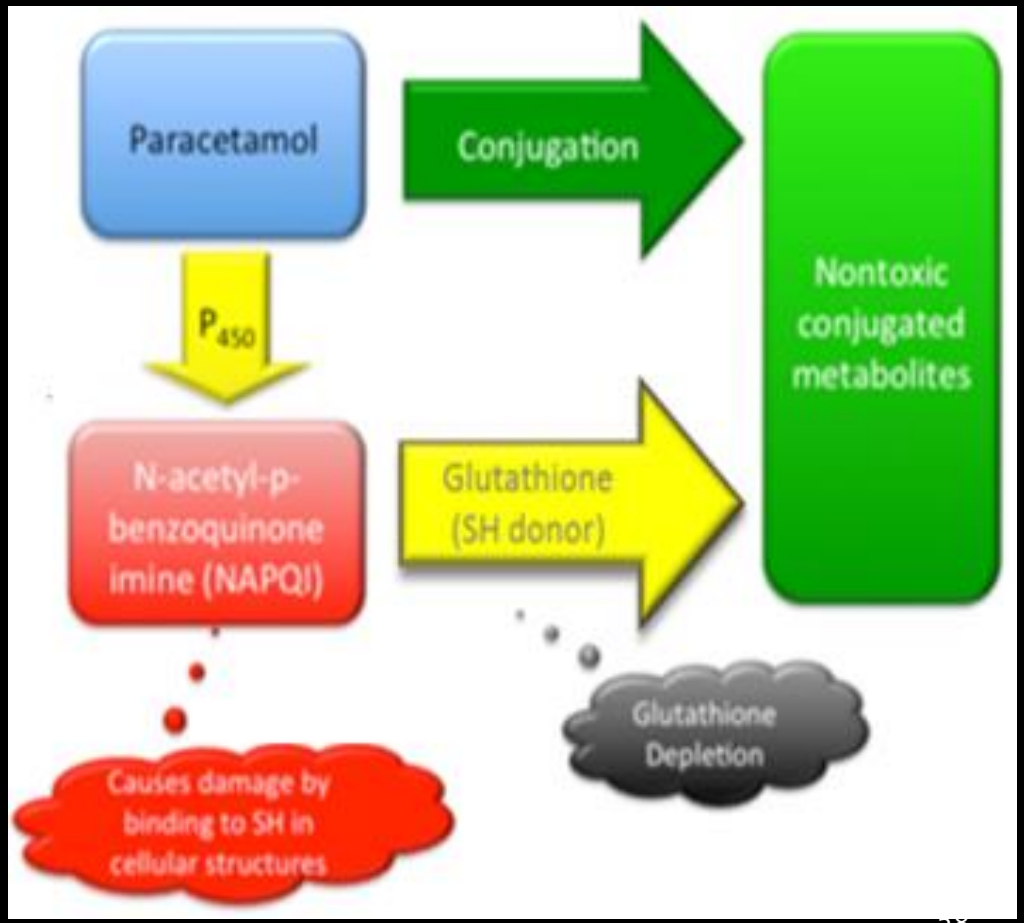
- Meloxicam, nimesulide, nambumetone
- Preferentially inhibits COX-2 over COX-1, particularly at low dose
- Associated with lower GIT symptoms & complains, compared to non –selective COX inhibitors
- $t_{1/2}$=20 hours
- Used for osteoarthritis & rheumatoid arthritis.

COX-3 INHIBITORS

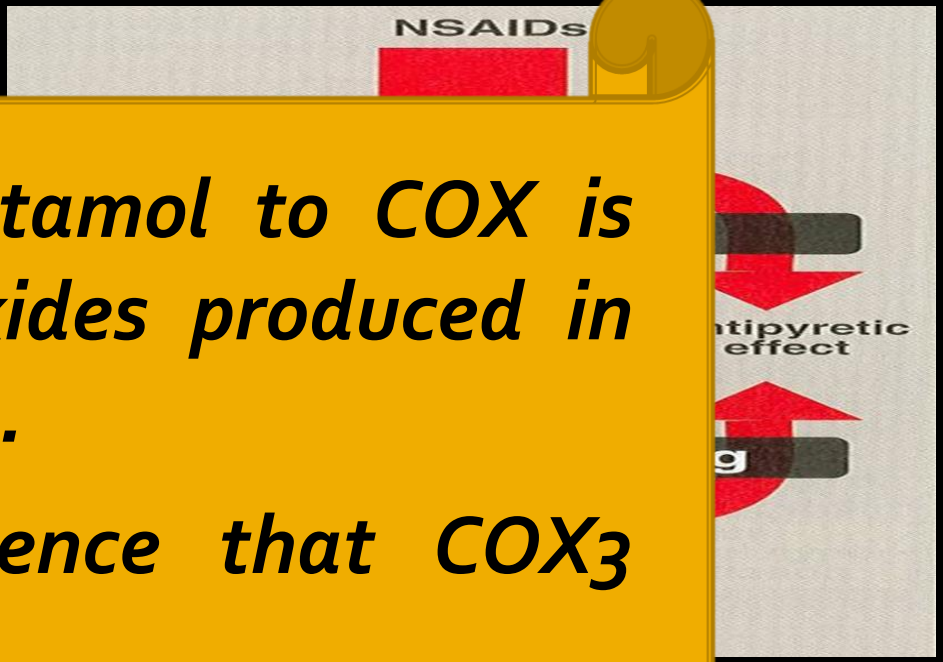
Given orally, well absorbed.

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

Metabolized by conjugation at therapeutic doses



COX-3 INHIBITORS



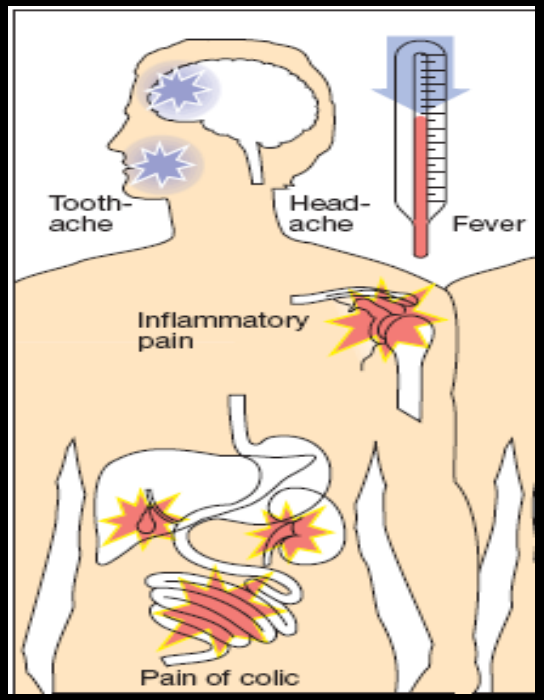
Binding of paracetamol to COX is <u>inhibited</u> by peroxides produced in inflammatory sites.

There is no evidence that COX3 exists in humans.

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 imine, which causes liver damage

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