NSAIDS EPIDEMIOLOGY

NSAIDs amounts 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 and perforation

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

ILOS

To focus on the general mechanism of action of NSAIDs

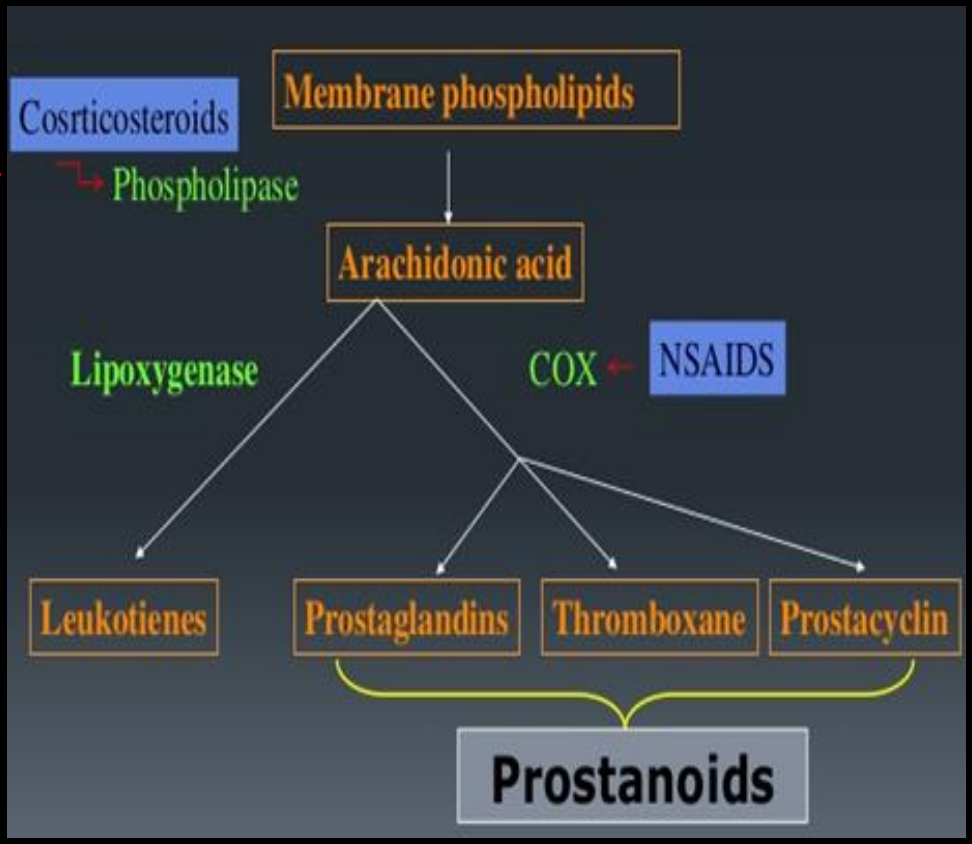
To outline the common pharmacodynamic effects and ADRs of NSAIDs

To classify NSAIDs on basis of their specifity to COX enzyme

To detail on the phramacokinetic properties and pharmacodynamic effects of **selected** NSAIDs

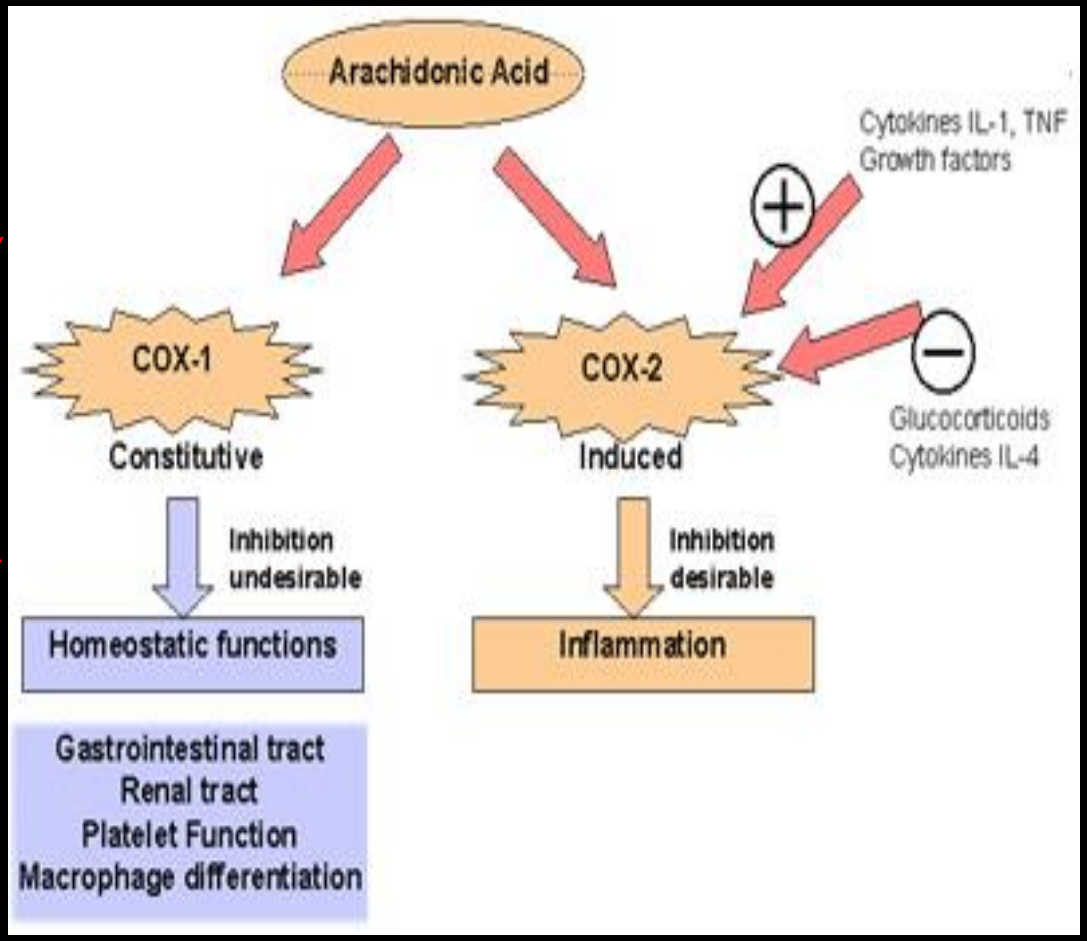
MECHANISM OF ACTION OF NSAIDS

NSAIDs inhibit cyclo oxygenase enzyme



COX ISOFORMS

COX3 is found in the brain



CLASSIFICATION OF NSAIDS

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

PGS

Nociceptors at nerve endings

PAIN

Inflammatory factors

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NSAIDs

Bradykinin
Histamine

PHARMACODYNAMIC EFFECTS

1-ANALGESIC

2-ANTIPYRETIC

Pyrogens

PGs

Thermoregulatory centre

Set point↑

Heat production↑
Heat dissipation↓

Fever

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NSAIDs

3-ANTI-INFLAMMATORY

NSAIDs

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PGs

Inflammatory factors

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Symptoms of inflammation

Bradykinin
Histamine
Serotonin

Red , Heat , Swelling, Pain

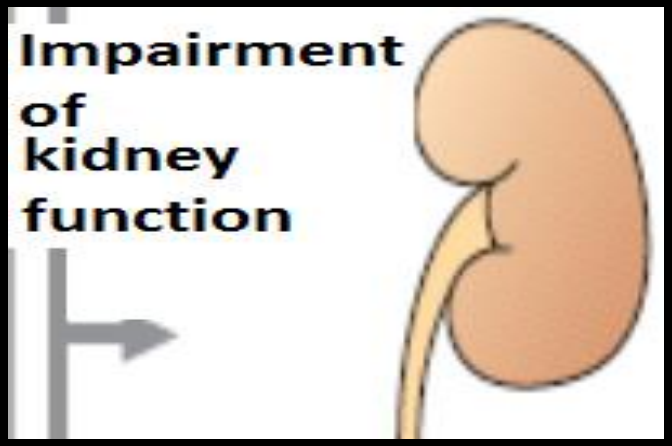
CLINICAL USES

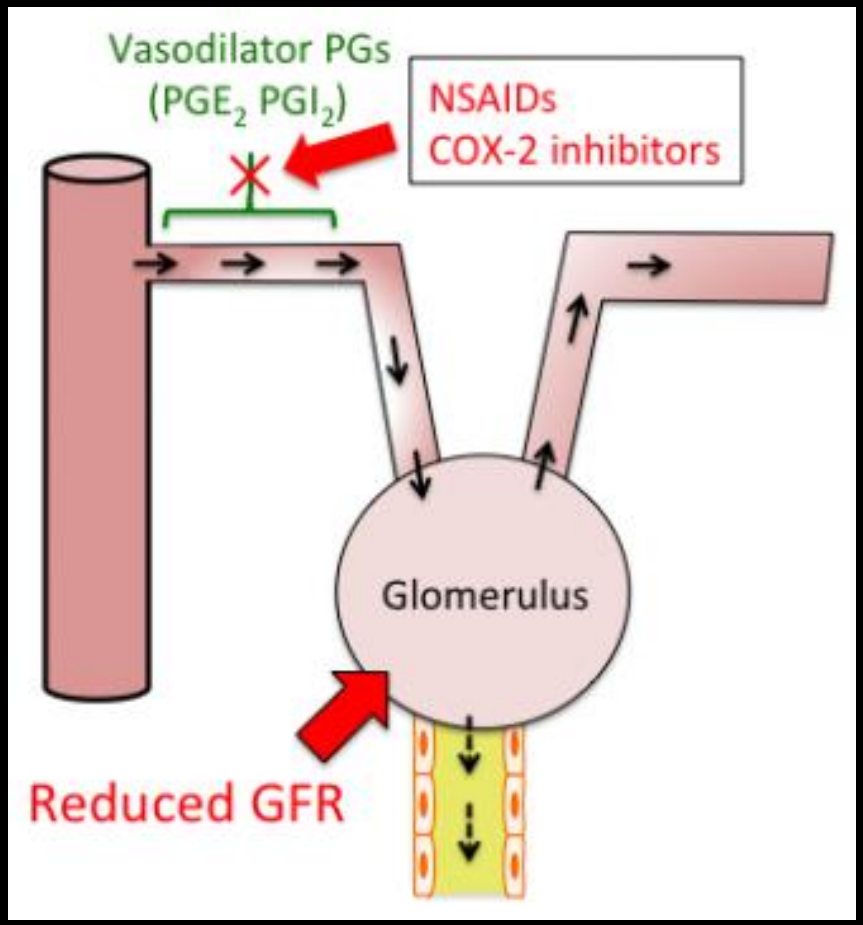
- Fever
- Headache, Migraine, Dental pain, Dysmenorrhea
- Common cold
- Rheumatoid arthritis / myositis

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

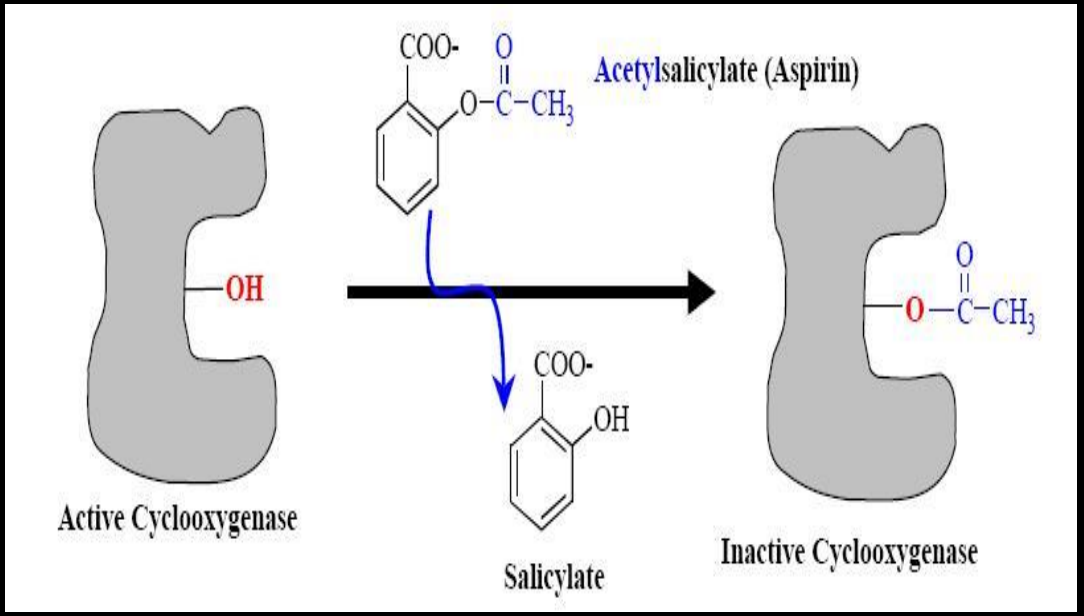
NON SELECTIVE COX INHIBITORS

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

NON SELECTIVE COX INHIBITORS

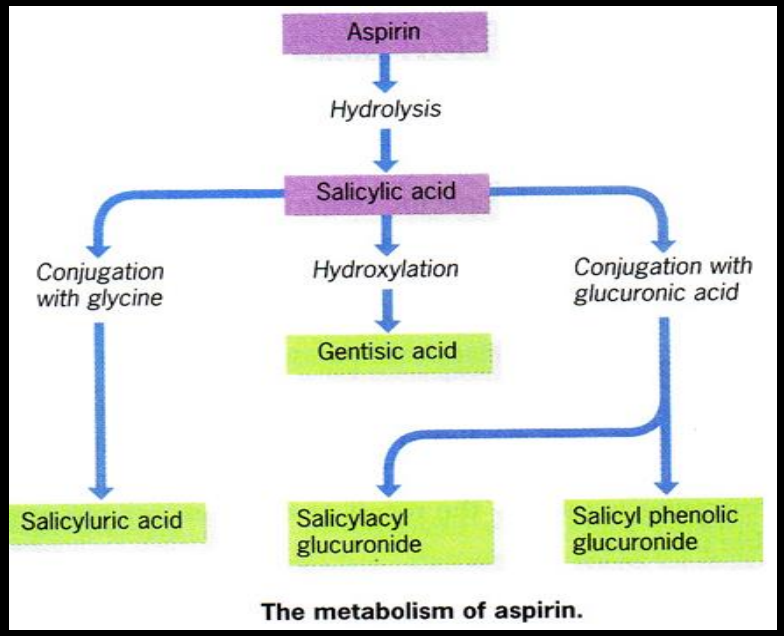
MECHANISM OF ACTION

Aspirin inhibits COX irreversibly



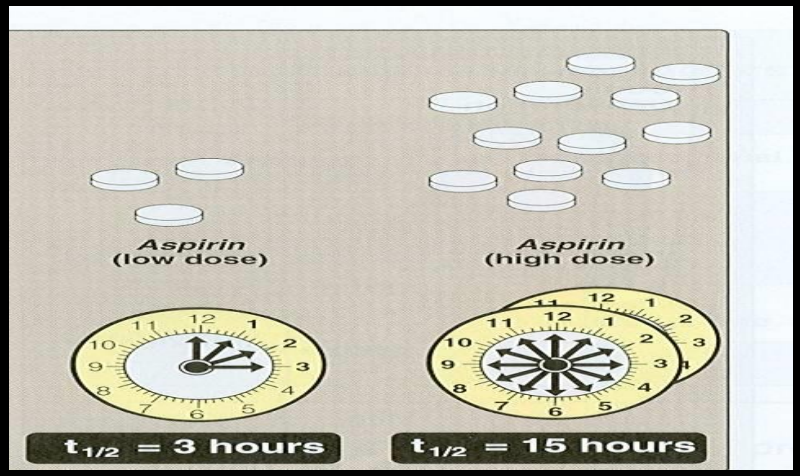
PHARMACOKINETICS

Metabolized by hydrolysis and then conjugation



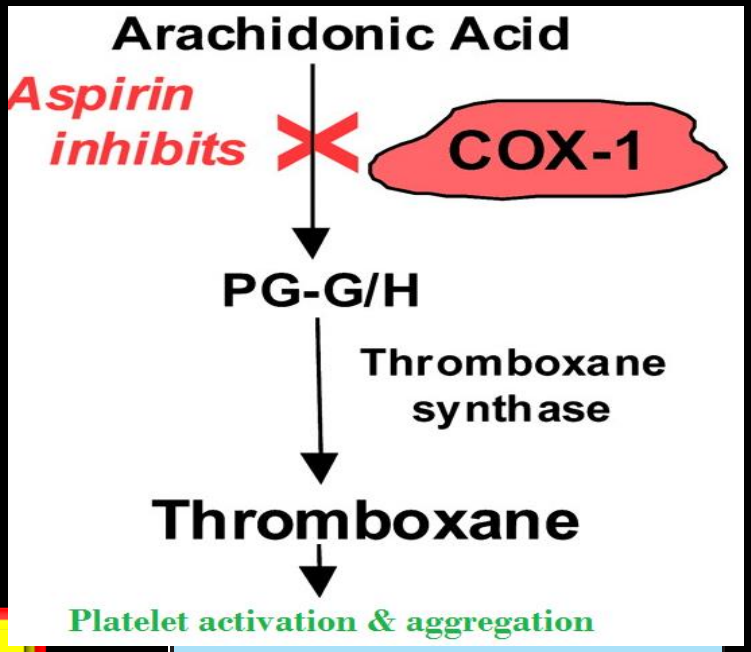
The metabolism of aspirin.

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



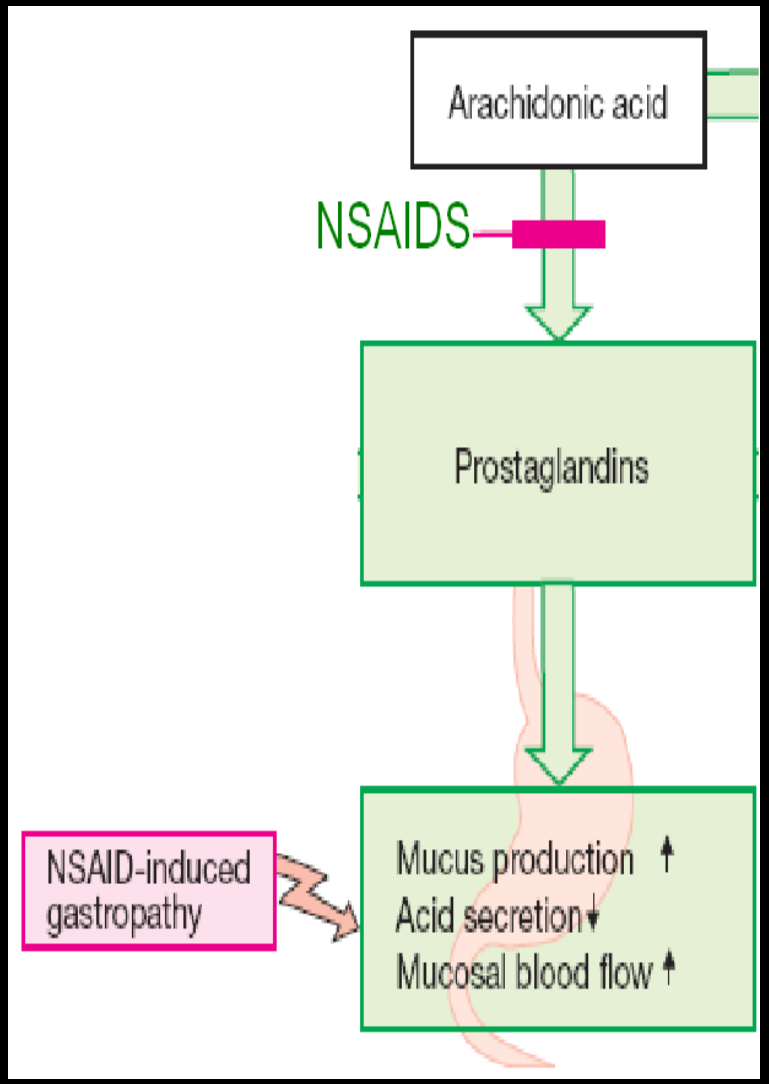
CLINICAL USES

- 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



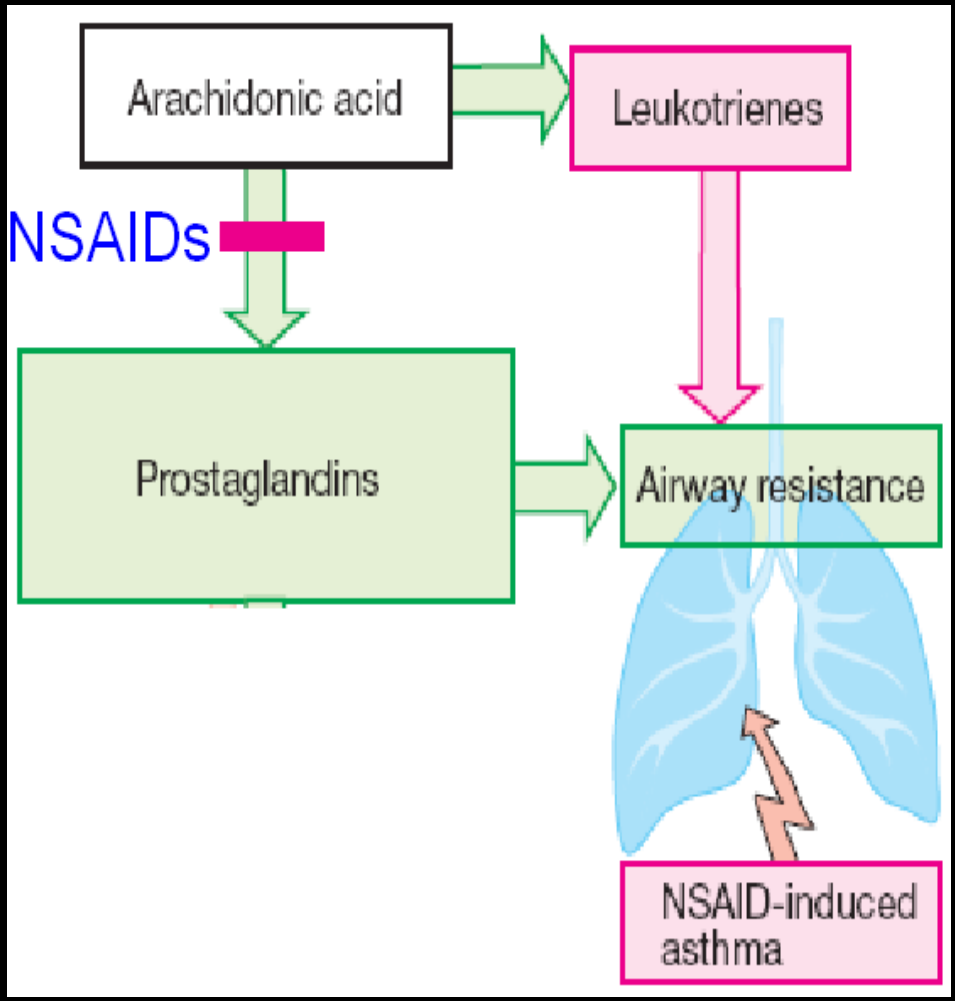
ADRS AT CLINICAL DOSES

- 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

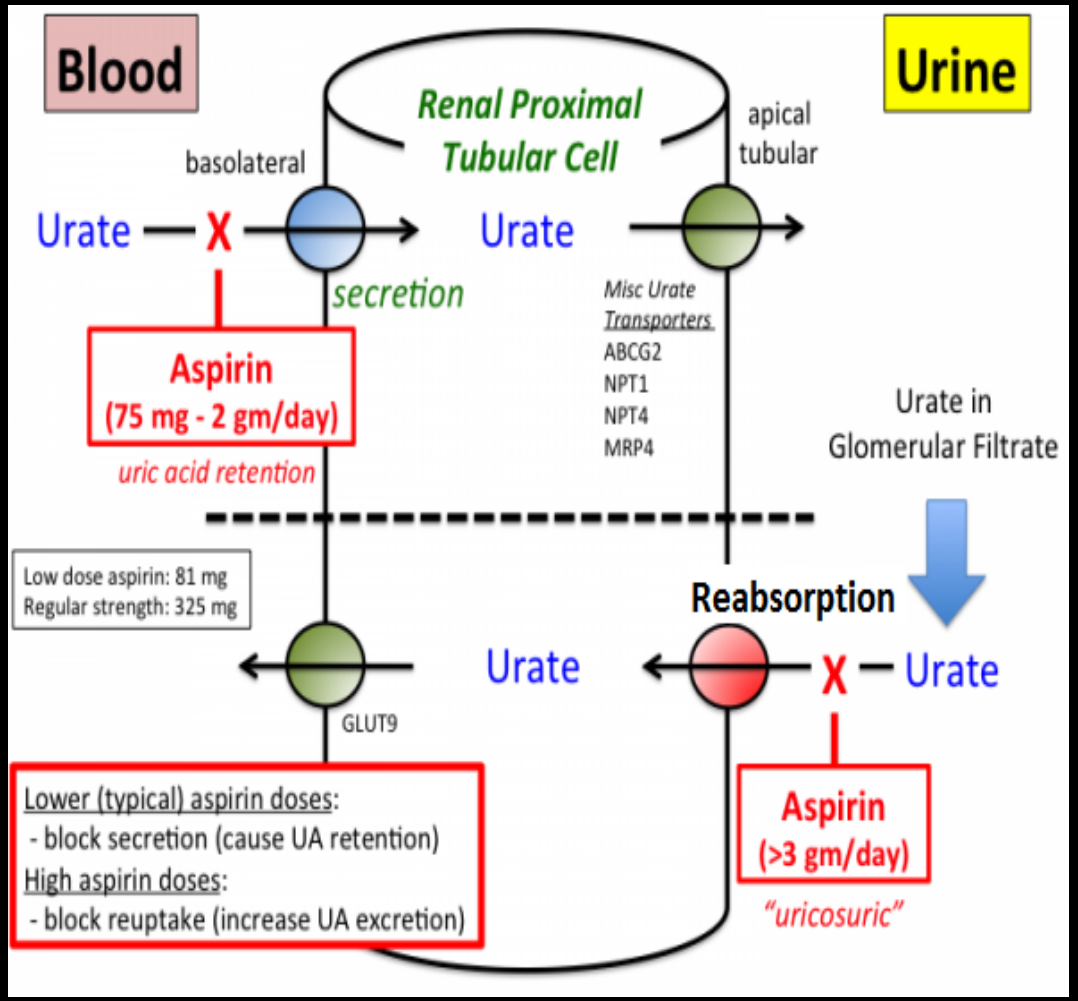
Salicylism (ringing of ear , vertigo)

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)

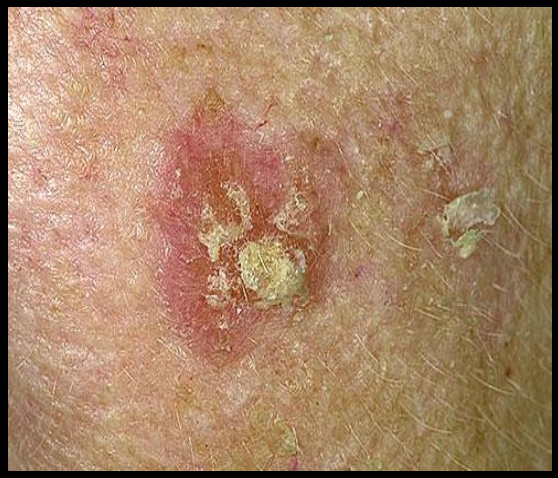
PREPARATIONS

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.

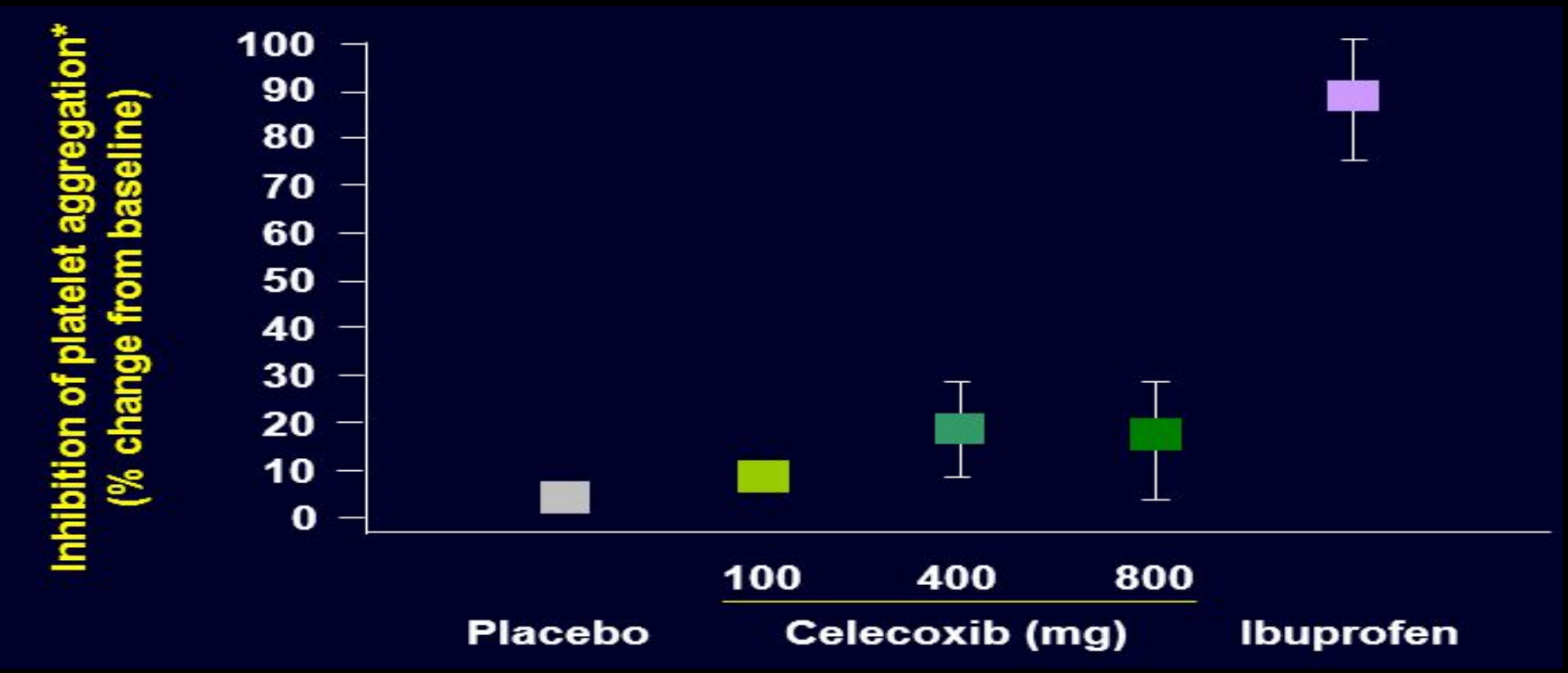
Intramuscular preparations

SELECTIVE COX-2 INHIBITORS

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

Withdraw because of risk of myocardial infarction & stroke

SELECTIVE COX-2 INHIBITORS



- No effect on platelet aggregation (COX-1)

GENERAL ADRS

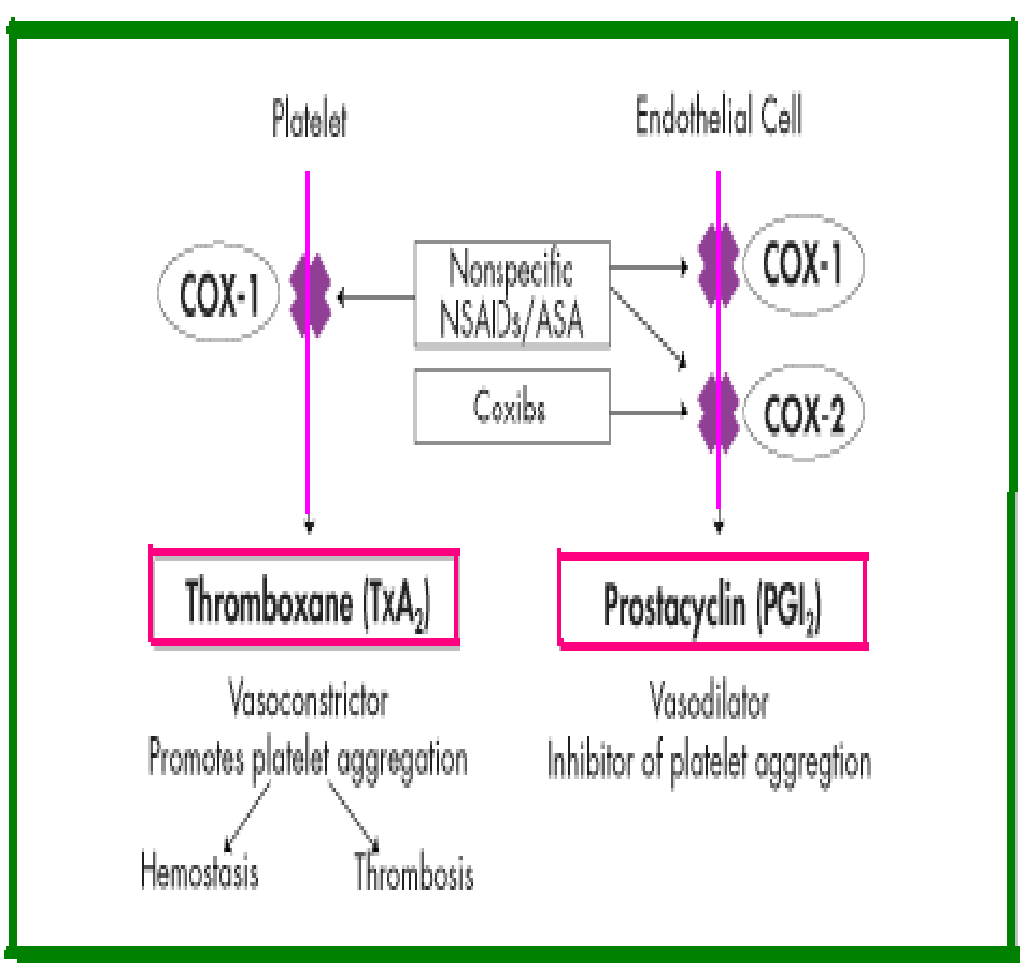
Renal toxicity

Dyspepsia & heartburn

Allergy

Cardiovascular (do not offer the cardioprotective effects of non-selective group).

Should not be given to a patient with CV disease



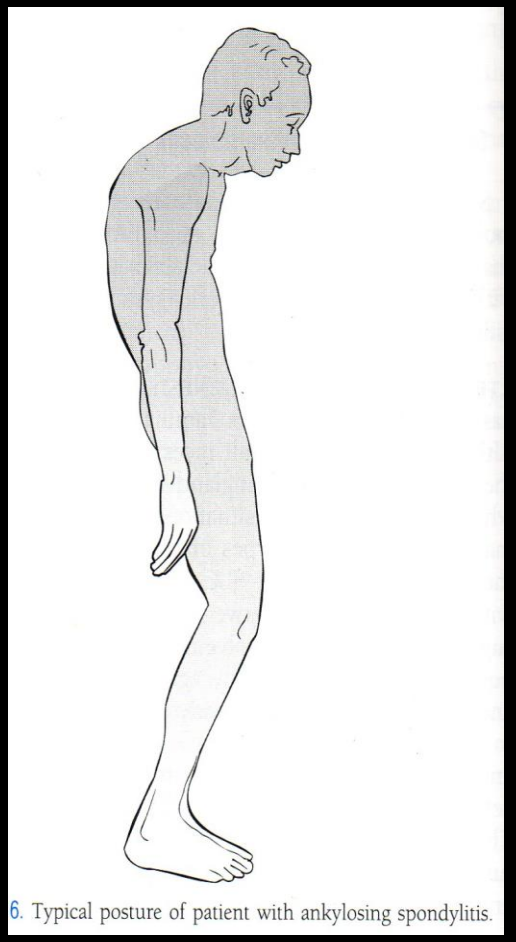
GENERAL CLINICAL USES

Short-term use in postoperative patients

Acute gouty arthritis

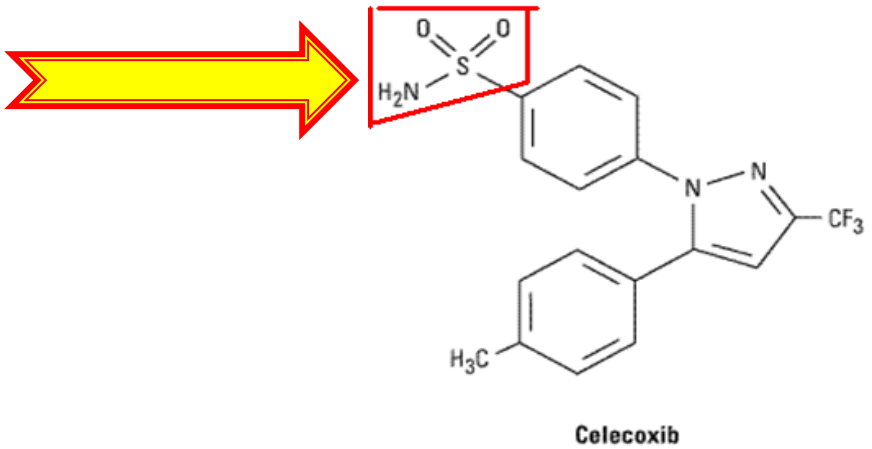
Acute musculoskeletal pain

Ankylosing spondylitis



6. Typical posture of patient with ankylosing spondylitis.

SELECTIVE COX-2 INHIBITORS



Celecoxib

Half-life 11 hours

Food decrease its absorption

Highly bound to plasma proteins

Contra indicated in patients allergic to sulphonamides

PREFERENTIAL COX-2 INHIBITORS

etone

- 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

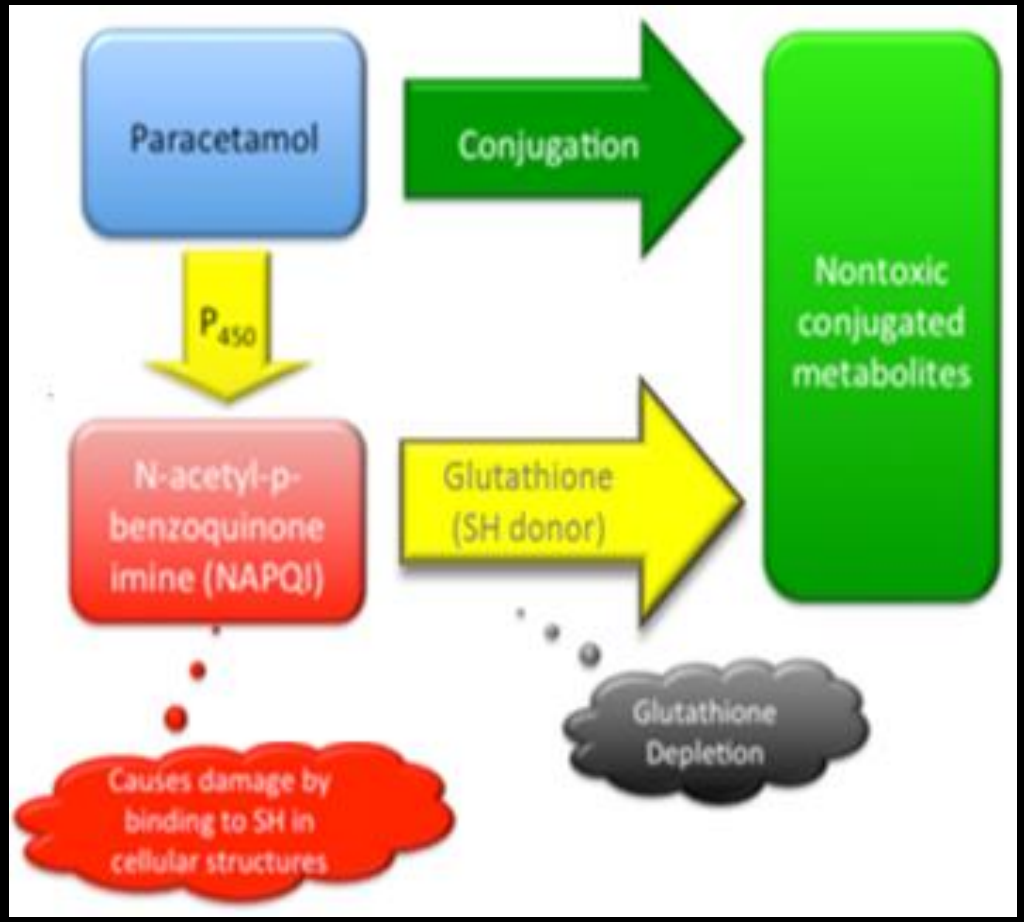
COX-3 INHIBITORS

Weak anti inflammatory effect

Given orally , well absorbed.

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

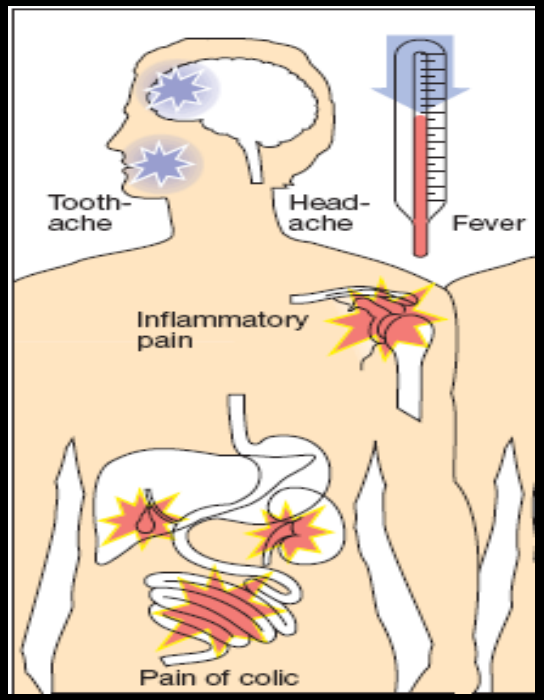
Metabolized by conjugation at therapeutic doses



CLINICAL USES

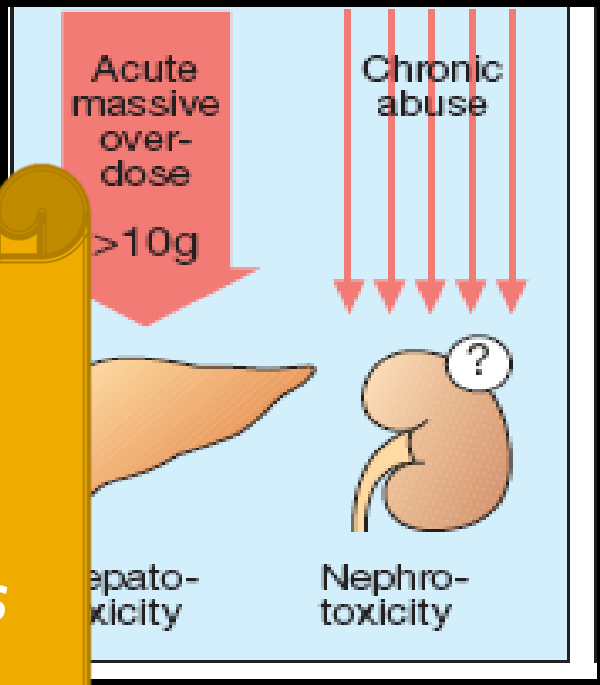
Commonly used analgesic antipyretic instead of aspirin in cases of:-

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



ADRS

Mainly on liver due to its active metabolite



Binding of paracetamol to COX is inhibited by peroxides produce in inflammatory sites.
There is no evidence that COX3 exists in humans.

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