

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- "Non-steroidal" is used to
 - Distinguish from steroids
 - Which do not have a steroidal nucleus
- eicosanoids –
they possess
- Having anti inflammatory, analgesic and antipyretic effects

or

- Reduce pain , fever and inflammation
- Also called nonnarcotic, nonopioid or aspirin like

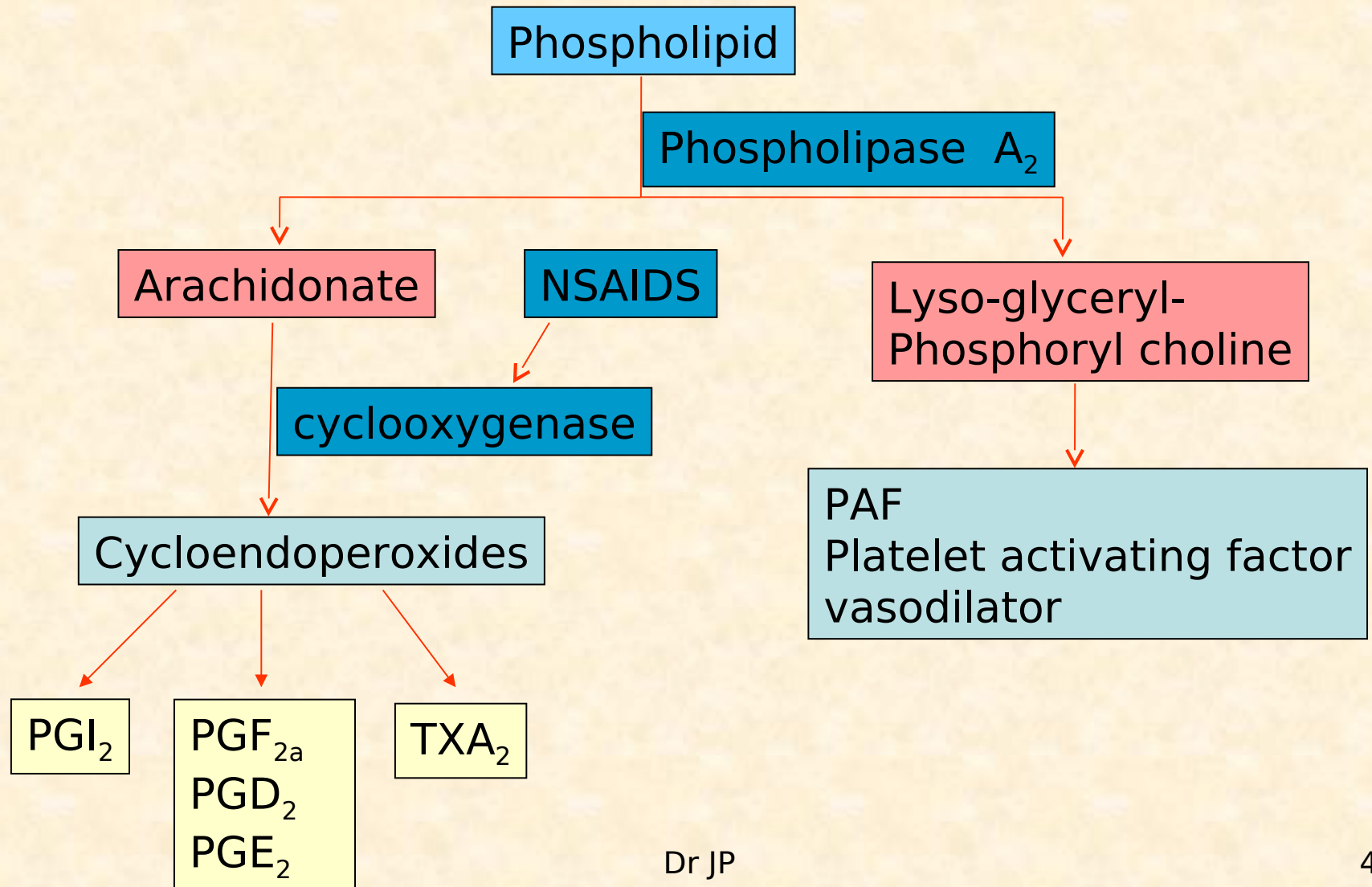
NSAIDs

- Compared to Morphine NSAIDS
 - Are weak analgesics
 - Do not depress CNS
 - Act primarily on
 - Peripheral pain mechanisms
 - CNS to raise pain threshold

NSAIDs

- Do not produce physical dependence
 - No abuse liability
- Most prominent members of this group
 - Aspirin
 - Ibuprofen and
 - Naproxen
 - Paracetamol (acetaminophen) has negligible anti-inflammatory activity, and is not a NSAID

Mediators derived from Phospholipids and their Actions



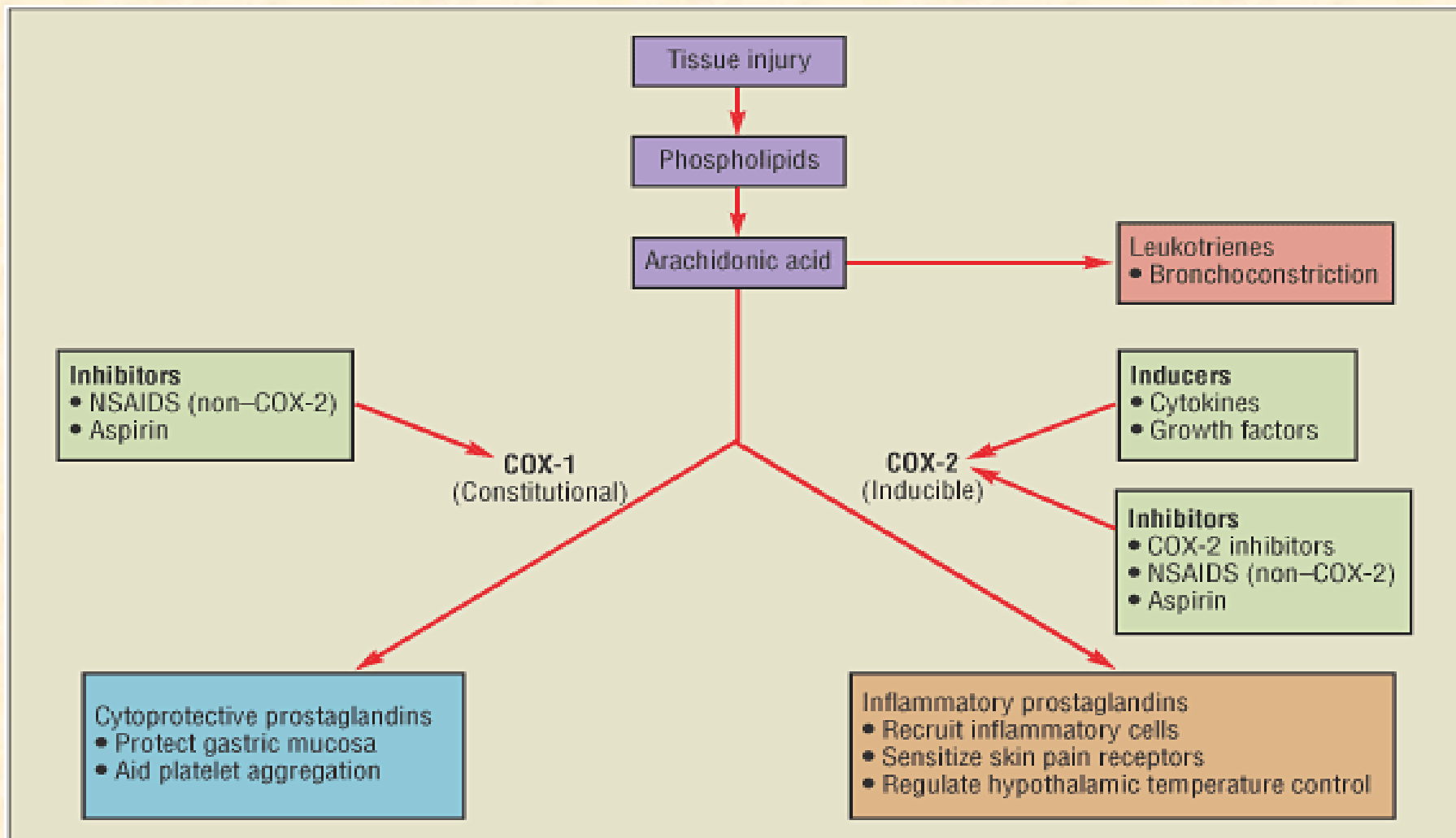


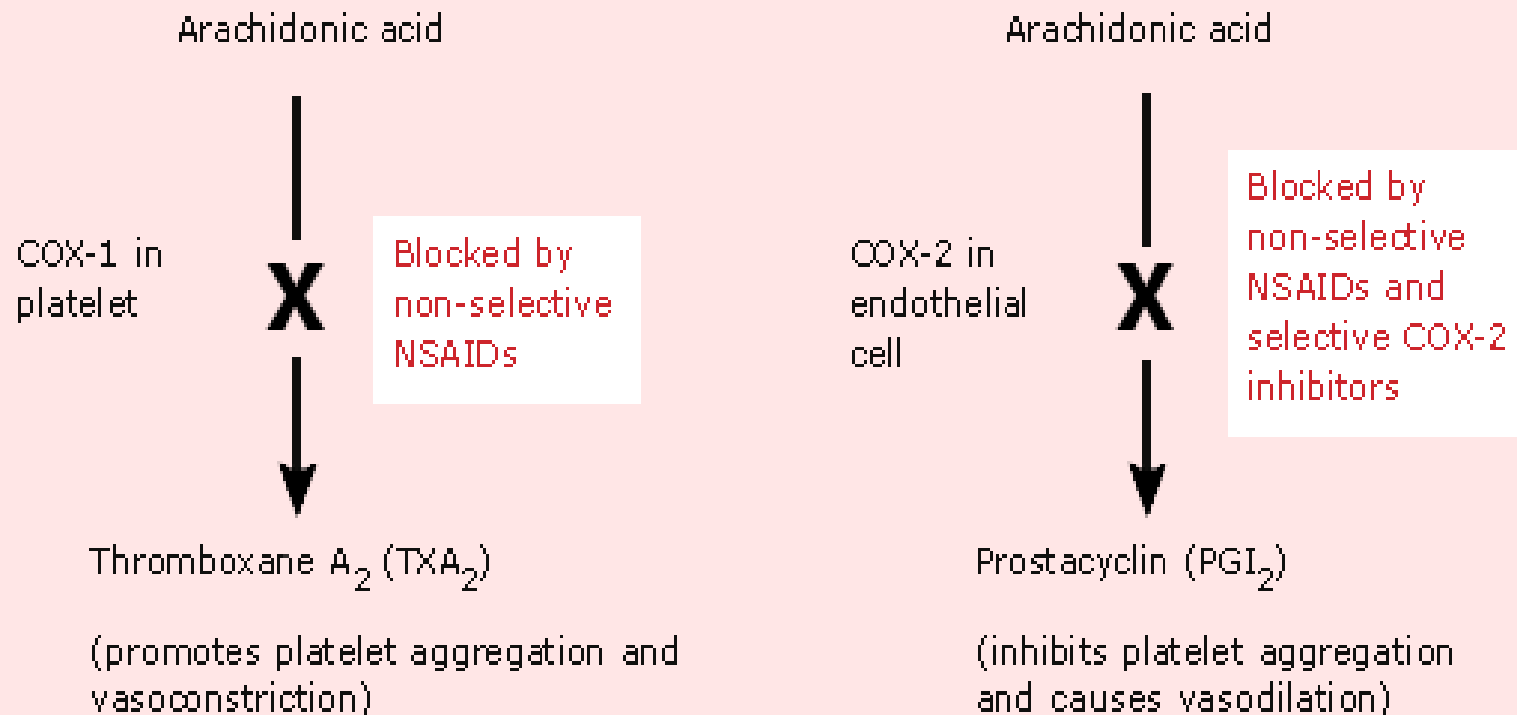
FIGURE 1. Algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclooxygenase enzymes (COX-1 and COX-2).

NSAIDs

- Non-selective inhibitors of the enzyme
 - **Cyclooxygenase inhibiting both Isoenzymes**
 - (COX-1) –constitutive
Present in platelets, stomach and kidney
 - (COX-2) – Inducible by cytokinins and Endotoxins at site of inflammation of joints
- Prostaglandins act as messenger molecules in inflammation process
- A newly discovered COX-3 ^{Dr JB} may also have some

Fig. 1

Mechanisms of action of non-steroidal anti-inflammatory drugs



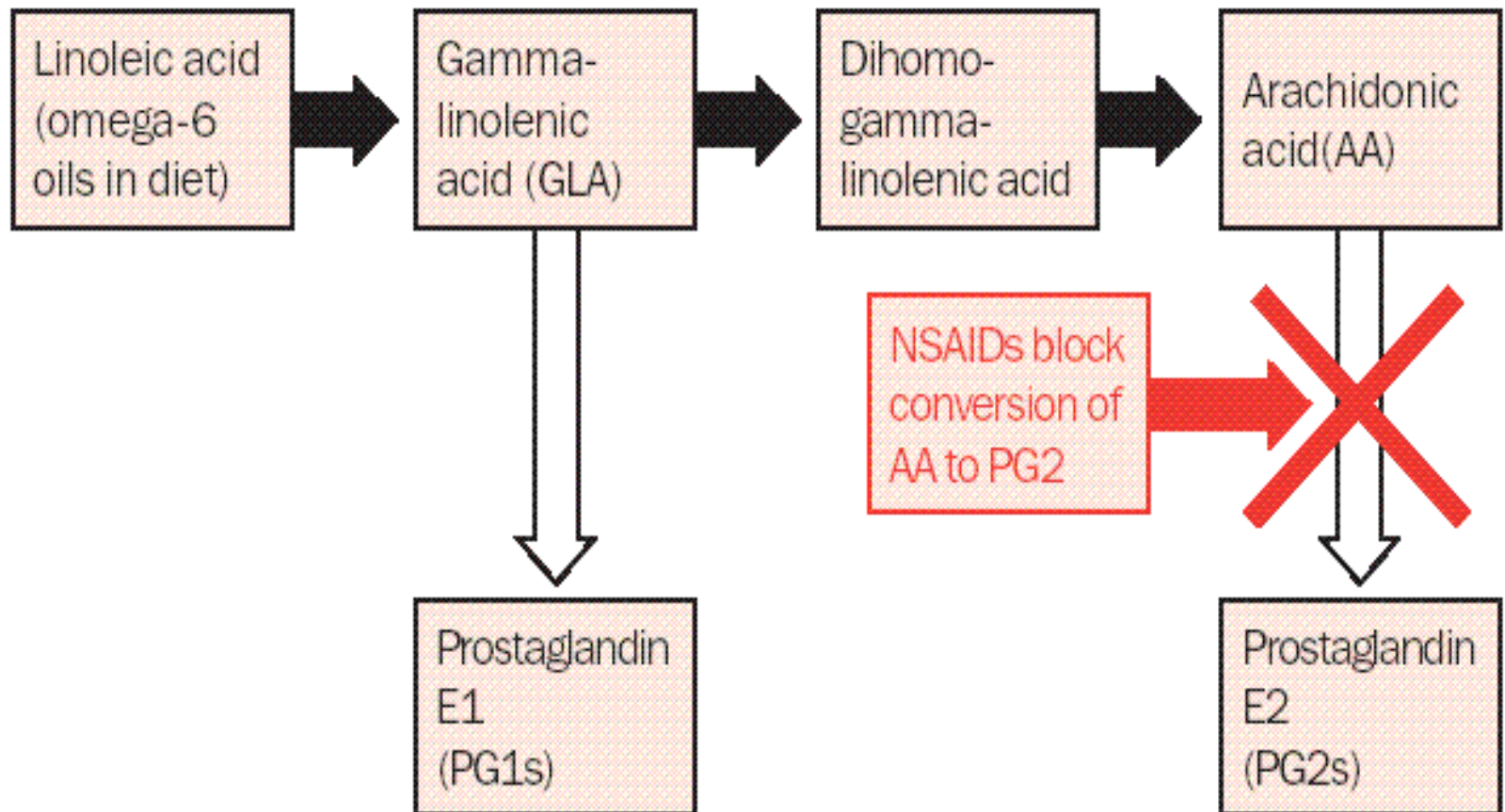
TXA₂ - Thromboxane

- Thrombotic
- Vasoconstrictor

PGI₂ - Prostacyclin

- Vasodilator
- Hyperalgesic
- Stops platelet aggregation

How NSAIDs block the inflammation process



Classification

- Nonselective COX inhibitors (conventional NSAID's)
 - **Salicylates** - Aspirin, sodium salicylate, diflunisal
 - **Pyrazolone** - Phenylbutazone, oxyphenbutazone
 - **Indole derivatives** - Indomethacin, sulindac
 - **Propionic acid derivatives** -Ibuprofen, naproxen, ketoprofen, lubiprofen
 - **Anthranilic acid derivatives** - Mephenamic acid
 - **Aryl- acetic acid derivatives** - Diclofenac

- **Preferential COX -2 inhibitors**

- Nimesulide, Meloxicam, Nabumetone

- **Selective COX -2 inhibitors**

- celecoxib, Rofecoxib, valdecoxib

- **Analgesic- antipyretic with poor anti inflammatory action**

- **Paraminaphenol derivatives** – Paracetamol

- **Pyrazolone derivatives** -

Metamizol(Dipyrone),

Propiphenazone

- **Benzoxazocine derivative** - Nefopam

Dr JP

NSAIDs Uses

- Indicated for the treatment of
 - Acute or chronic conditions
(where pain and inflammation are present)
 - Cancer and cardiovascular diseases
 - Postoperative pain
 - Mild-to-moderate pain
(due to inflammation and tissue injury)

NSAIDs Uses

- **Indicated for the symptomatic relief of**
 - Rheumatoid arthritis
 - Osteoarthritis
 - Inflammatory arthropathies
(ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
 - Acute gout
 - Dysmenorrhoea
 - Metastatic bone pain
 - Headache, and migraine
 - also given to just born infants whose ductus arteriosus is not closed ^{Dr JP} within 24 hours of birth¹²

NSAIDs

Common adverse reactions (ADRs)

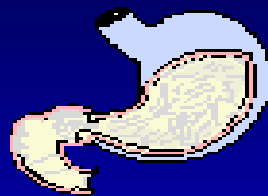
- Gastrointestinal (GI) effects
 - Ulcer perforation
 - Upper gastrointestinal bleeding and
 - Dyspepsia

Renal effects

- Platelet aggregation reduced therefore bleeding time increased (not to the same extent as aspirin)
- These effects are dose-dependent

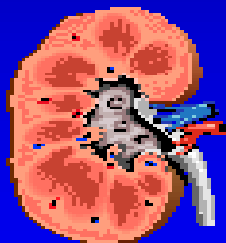
Adverse Effects of common NSAIDs

Upper - GI



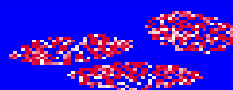
- ➔ Dyspepsia
- ➔ Erosions
- ➔ Anaemia - GI bleeding
- ➔ Ulcers - b leeds/perforations

Renal



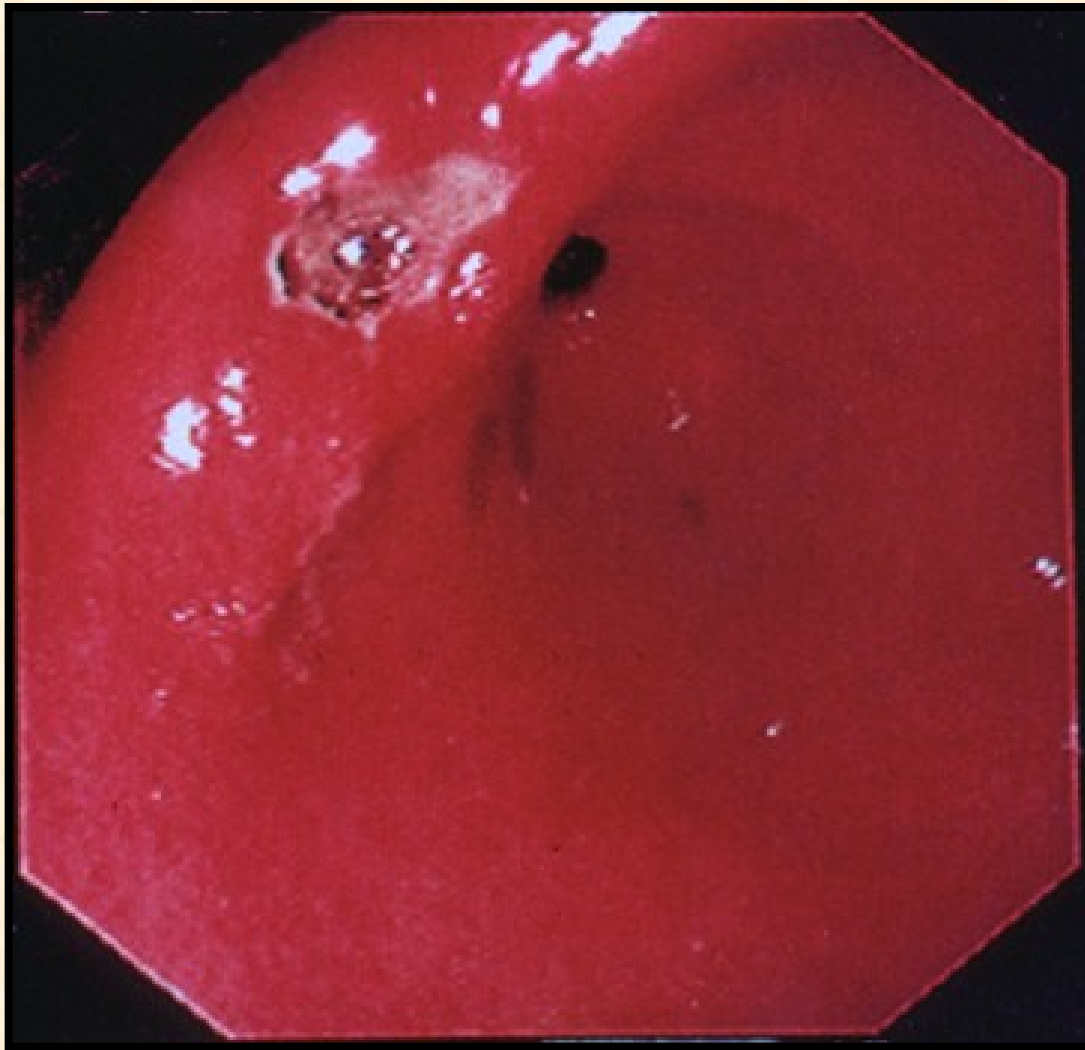
- ➔ Renal dysfunction
- ➔ Renal failure - acute/chronic
- ➔ Blood pressure
- ➔ Heart failure

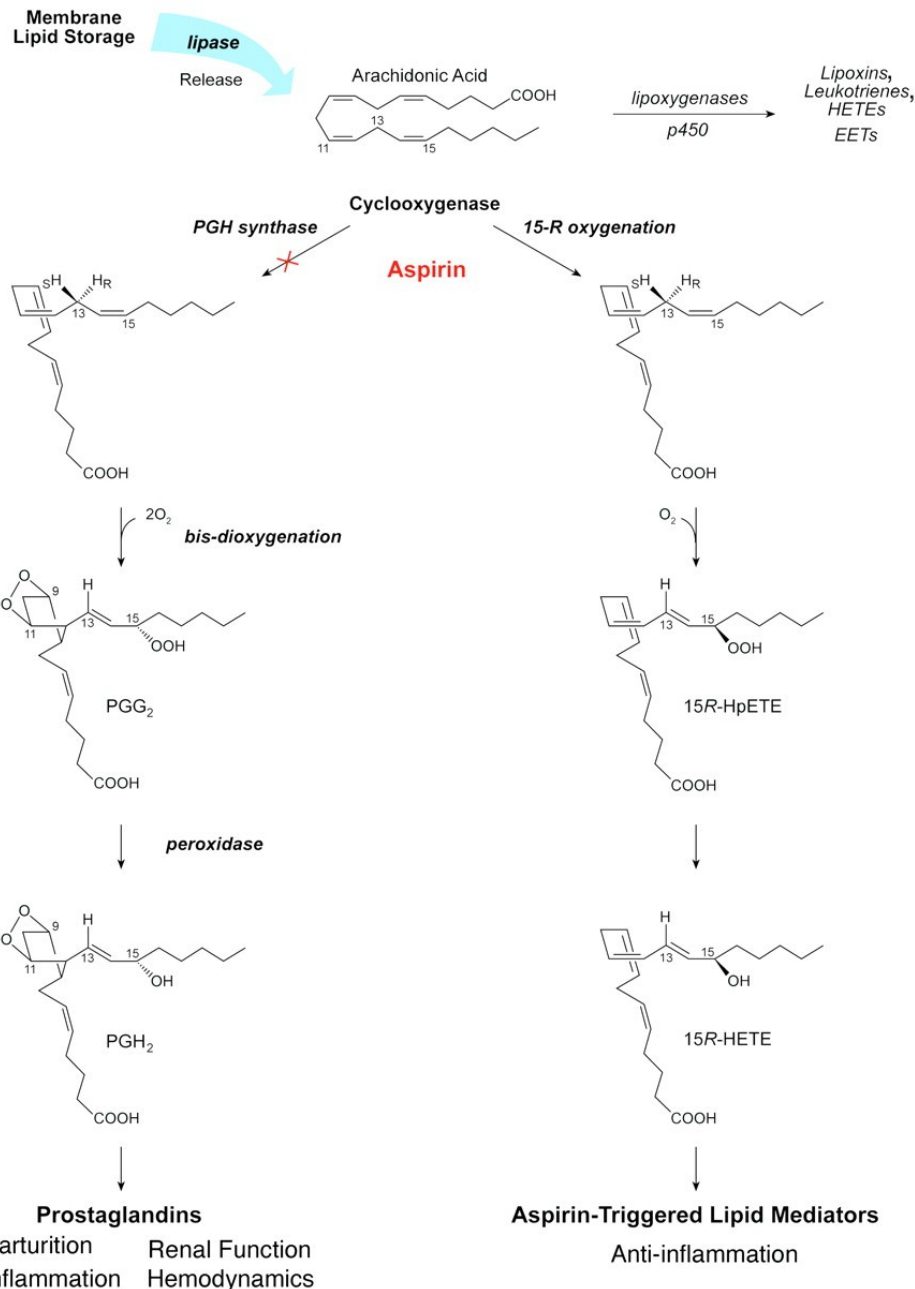
Anti-platelet effects



- ➔ Contributes to b lood loss

Endoscopic Picture of Gastric Ulcer





Biochemical Pathway Inhibited by Aspirin

Aspirin (Acetyl salicylic acid)

Pharmacological Actions

Analgesic

- Central and peripheral action

Antipyretic
the set

- Act in hypothalamus to lower

point of temperature control

elevated

by fever

- Also causes sweating

Anti-inflammatory
prostaglandin

- Inhibition of peripheral

synthesis

Respiratory stimulation

- Direct action on respiratory

Aspirin (Acetyl salicylic acid)

Metabolic effects

- $\uparrow$ peripheral O_2 consumption (uncoupled oxidative phosphorylation)
- Hence $\uparrow$ CO_2 production with $\uparrow$ respiration, and
- Direct analeptic action – respiratory alkalosis
- Renal loss of bicarbonate with sodium, potassium and

water dehydration

Aspirin (Acetyl salicylic acid)

Metabolic acidosis

- Effects on kreb's cycle
 - ↑ ketone body, salicylic acid in blood
 - Renal insufficiency due to vascular collapse, dehydration

Uricosuric effects

- Hypoglycaemia or even hyperglycaemia can occur
- Reduces renal tubular reabsorption of urate
- < 2g/d may cause retention of urate
- But treatment of gout requires 5-8g/d
- Antagonises the uricosuric action of other drugs

Aspirin (Acetyl salicylic acid)

Reduced platelet adhesion

- Irreversible inhibition of COX by acetylation
- Prolongs bleeding time
- Useful in arterial disease

Hypothrombinaemia

- Occurs with large doses i.e $> 5\text{g/day}$

Aspirin (Acetyl salicylic acid)

Overdosage

- Ingestion of > 10 g can
- Cause moderate/severe poisoning in an adult

Clinical features : **Salicylism**

Symptoms

- Tremor
- Tinnitus,
- Hyperventilation
- Nausea
- Vomiting and sweating
- Management- mainly supportive

Pyrazolone Derivatives

Phenylbutazone & Oxyphenbutazone

- Oxyphenbutazone is the metabolite of Phenylbutazone
- Common characteristics
 - Administered parenterally or orally
 - Well absorbed orally
 - High protein binding about 90%
- Long half-life Phenylbutazone
 - $T_{1/2} = 50\sim60$ hrs
- Oxyphenbutazone $T_{1/2} =$ several days

Phenylbutazone & Oxyphenbutazone

- Anti-inflammatory and anti-rheumatic effect are strong, but antipyretic effect is weak
 - Reduces capillary permeability
 - Inhibits biosynthesis of prostaglandin

Adverse Effects

- Epigastric discomfort
- Nausea and vomiting
- Peptic ulceration, aplastic anaemia
- Hepatitis and nephritis

Indomethacin (Indole acetic acid)

- Absorption rapid and complete
- High protein binding about 90%
- Metabolism mainly in the liver
- Excreted out in urine, bile and excreta
- 10%-20% of it is excreted in urine in the original nature
- Its half-life is 2-3 hours

Indomethacin

Actions and uses

- Strong inhibitory effect on both COX-1 and COX-2
- Decrease granulocytes migration and lymphocytes proliferation
- Prominent anti-inflammatory and antipyretic effect and apparent analgesic effect on pains caused by inflammation

Uses of Indomethacin

- Acute rheumatic and rheumatoid arthritis
- Ankylosing spondylitis and osteoarthritis
- Often effective in fever associated with cancer and other fevers that cannot be easily controlled
- **Adverse reactions are relatively more**
- So used only in patients
 - Who can not tolerate other drugs or
 - Whose therapeutic effect is not prominent

Adverse Reactions of Indomethacin

Gastrointestinal reactions

- Anorexia, vomiting, peptic ulcer
- Abdominal pain,
- Occasionally perforation, bleeding, diarrhoea
- Sometimes acute pancreatitis

CNS reactions

- Headache
- Dizziness occasionally
- Mental confusion

Sulindac

- Prodrug
- Active form: Sulfometabolites
- Its potency is weaker than Indomethacin but stronger than Aspirin
- Sulindac are transformed into active metabolites by gastric mucosa
- Its indications are similar to that of Indomethacin

Mefenamic Acid

- NSAID used to treat pain, including menstrual pain
- Also prescribed as an antipyretic drug for oral administration
- Decreases inflammation (swelling) and uterine contractions
- Related to the inhibition of prostaglandin synthesis

Mefenamic Acid

Side effects

- Upset stomach(together with food or milk)
- Drowsiness may also occur

Mild side effects

- Headaches, nervousness and vomiting

Serious side effects

- Include diarrhoea, blood vomiting, blurred vision
- Skin rash, itching and swelling, sore throat and fever

Contra indications

- Avoid in patients with kidney & liver insufficiency

Arylpropionic Acids

Ibuprofen, Naproxen, ketoprofen

- Analgesic, antipyretics and anti inflammatory
- Used to treat rheumatic arthritis and osteoarthritis
- Strong nonselective inhibitors of COX
- Absorption is rapid after administrated orally

Arylpropionic Acids

- Gastrointestinal adverse reactions are slight and easily tolerated
- Alternative to aspirin
- Protein binding is almost 99%
- Metabolized in the liver and excreted by the kidney

Piroxicam

- Absorption: complete
- Non selective COX inhibitor
- Similar therapeutic effect and fewer adverse reactions than Aspirin, Indomethacin and Naproxen
- Main advantages: long plasma $t_{1/2}$ (about 36~45 hrs) once a day
- Used in rheumatoid arthritis, Post operative pain

Selective COX-2 Inhibitors

Meloxicam

- Is of the same sort with piroxicam
- Strong anti-inflammatory effect and few adverse reactions
- Its indications are similar to piroxicam
- Also cause hemorrhage of digestive tract and Ulcer

Nimesulide

- A new type of NSAIDS
- Selective inhibitor of COX-2 having strong anti-inflammatory effect and few adverse reactions
- Absorption is complete
- Its protein binding is 99% and its bioavailability is high
- Often used in the therapy of rheumatoid arthritis, osteoarthritis, toothache, dysmenorrha
- **Adverse effect** Hepatotoxic

Diclofenac

- Inhibit cyclooxygenase
- Most potent NSAID
- Decreased prostaglandin in epithelium of stomach makes more sensitive to gastric acid
- Minimum side effects

Diclofenac

- Used for
 - Musculoskeletal complaints especially arthritis (Rheumatoid arthritis, osteoarthritis, spondylarthritis)
 - Gout attacks, and
 - Pain management in case of
 - Kidney stones and gall stones
 - In treatment of acute migraines
 - To treat mild to moderate pain (Post-operative or post-traumatic pain)
 - Particularly when inflammation is also present
 - Effective against menstrual pain

Compound Preparations

- Are not better than single drug in therapeutic effect
- Maybe more adverse reactions
- Preferable to use single drug