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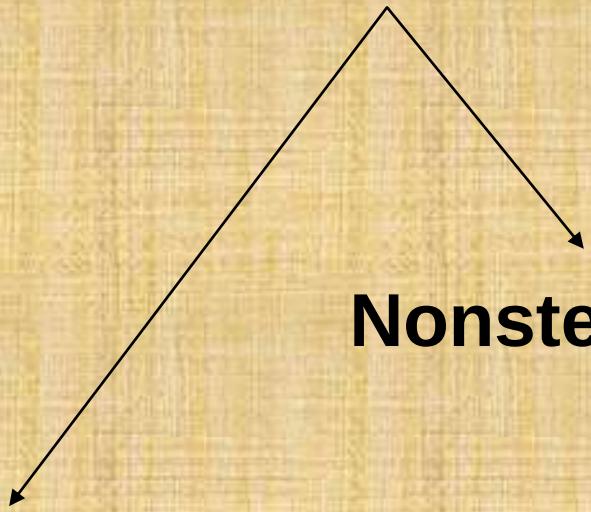
Non-opioid analgesics



Nonsteroidal antiinflammatory drugs

Analgesics-antipyretics

- **Analgesics-antipyretics (A-A)** drugs against fever and pain

- **Nonsteroidal anti-inflammatory (NSAIDs)** - against inflammation, fever and pain

Mechanism of action

- **inhibition of both COX-1 & COX- 2 enzymes Resulting in:**

  inhibition of eicosanoids synthesis:

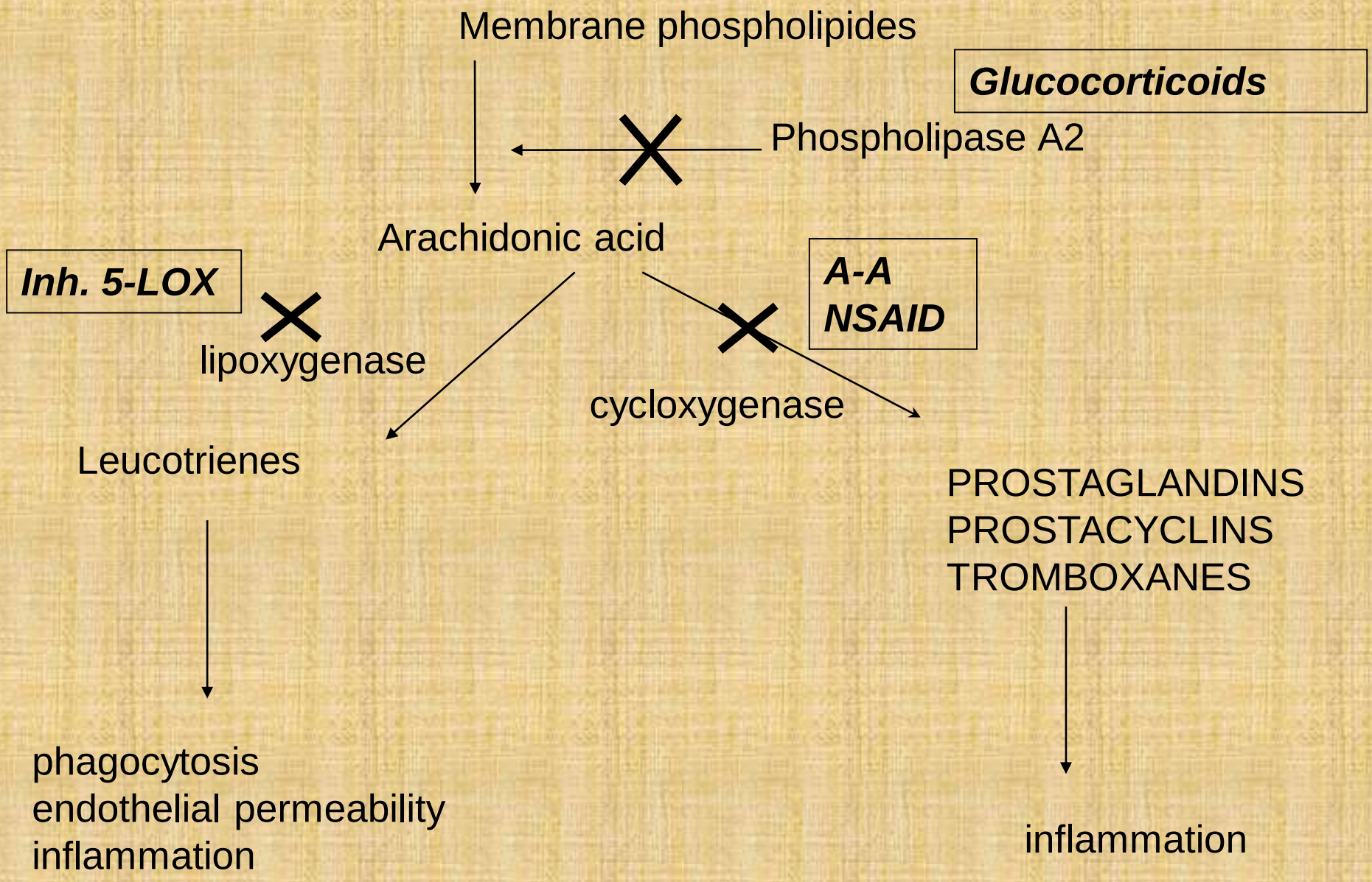
-inhibition of the synthesis of prostaglandins & thromboxane A2.

-inhibition of interleukin-1.

- NSAIDs differ in the strength of COX1/COX2 inhibition and the incidence of typical AE (ulcer disease, bleeding).

Cyclooxygenases

- **COX-1 – constitutive** – prostanoids involved in physiological processes (gastroprotective effects, platelet activities)
- **COX-2 – inducible**– activity enhanced by proinflammatory factors(IL-1, IL-2, TNF-α, oncogenes,..)
  - prostanoids $\Rightarrow$ inflammation, fever, pain
- **COX-3** – central mechanism of analgesic and antipyretic effect (localization: heart + CNS)


Membrane phospholipides
Glucocorticoids
Phospholipase A2
Arachidonic acid
Inh. 5-LOX
A-A
NSAID
lipoxygenase
cycloxygenase
Leucotrienes
PROSTAGLANDINS
PROSTACYCLINS
TROMBOXANES
phagocytosis
endothelial permeability
inflammation
inflammation

Effects of NSAIDs

Group of drugs that sharing the capacity to induce the following pharmacological actions :

- **Analgesic**
- **Antipyretic**
- **Anti-inflammatory**
- **Anti-platelet**
- **Effect on the kidney function**

Classification

1. Salicylic acid derivatives
2. Indole derivatives:indomethacin.
3. Propionic acid derivatives:ketoprofen
4. Oxicams
5. COX-2 preferential inhibitors
6. Aniline derivatives:paractamol

Classification of NSAIDs

- **Non-Selective COXs Inhibitor**

- **Selective COX2 Inhibitor**

Common therapeutic uses

- 1-Analgesic and antipyretic due to inhibition of PGE1 &2.
- 2-Antiinflamamtory due to inhibition of formation of inflammatory prostaglandins PGE1 &2 .
- 3-Antiplatelet due inhibition of thromboxane A2 in the platelet more that PGI2 in the vessel wall.
- 4-Treatment of dysmenorrheal: due inhibition of formation of PGF2α.
- 5-Treatment of precipitate labor due inhibition of formation of PGF2α in the uterine smooth muscles.
- 6-Treatment of patent ductus arteriosus
- 7-Treatment of gout
- In acute gout :indomethacin are used for its analgesic and anti-inflammatory effect.
- In chronic gout they are used for its uricosuric effect.

Common side effects

- 1-Gastritis & peptic ulcer due to inhibition of protective prostaglandins PGE1&2.
- 2-Nephritis: as a result of inhibition of formation of vasodilator prostaglandins PGE1&2 and PGI2 .
- 3-Bleeding due to excessive inhibition of thromboxane A2 .
- 4-Bronchospasm due to decrease formation of bronchodilator prostaglandins in bronchial smooth muscles (PGE1&2).

1. Salicylates

Effects

- A- ***Local actions:***
- 1- Salicylic acid:
- a- Keratolytic to removes corns, warts.
- b- Anti fungal and antiseptic.
- 2- Methyl salicylate: irritant, used as conter irritant for painful muscles or joints.

- ***B-Systemic actions***
- They inhibit CNS and peripheral clo-oxygenase enzyme
- 1- CNS :
- - *Analgesic* :
- *centrally by elevating pain threshold in subcortical area (thalamus)
- *peripherally due to their anti inflammatory effect.
- - *Antipyretic* (probably mediated through inhibition of PGE 2 synthesis) Salicylates lower high body temperature in fevers but have no effect on normal body temp. It acts on HRC in hypothalamus leading to heat loss through:
- 1-Mobiilzation of fluids from tissue to blood ---> increase sweating
- 2- Dilatation of cutaneous blood vessels
- 3- Excessive sweating (diaphoretics) .
- ***N.B.*** : Toxic dose ---> hyperpyrexia due to uncoupled oxidative phosphorylation (Large dose> 5 g/day) .

2- Anti-inflammatorv action: (Large dose> 5 g/day) :
- Inhibit protease and hydrolase enzymes (damaging tissue enzymes)
- Inhibit hyaluronidase and fibrinolysin ----> decrease capillary permeability .
- Inhibit antigen antibody reaction through increased ACTH ---> increase cortisone release

3- CVS and blood:

-Small therapeutic dose of salicylates decreases blood pressure due to vasodilatation by prostaglandin independent mechanism through inhibition of tyrosine kinase.
- Salicylates with large dose ---> dcrease Bl.pr. due to inhibition of VMC and direct action on the walls.

4-Blood

Inhibit platelet aggregation with small dose of acetyl salicylic acid (75 /150mg) due to inhibition of thromboxane A2 (reduce thrombotic tendency).

- Hypoprothrombinemia : (Large dose 5 g/day) silycylates, it competes with vit K. leading to decrease synthesis of prothrombin and factor VII IX and X ---> increase bleeding tendency.

- In patients with glucose 6 phosphatedehydrogenase enzyme deficiency ---> haemolysis of R.B.Cs. (idiosyncracy).

4- Respiration and acid base balance:

Small dose up to 1 gm ---> no effcet . Large dose ---> stimulation of respiratory center directly and through Co2 production from uncoupling of oxidative phosphorylation leading to hyperventilation ---> loss of *Co2* ---> respiratory alkalosis.

- Toxic dose causes metaboilc acidosis in children.

Salicylates may precipitate acute bronchial asthma in susciptable patients by inhibition of cycloxygenase enzyme, therefore arachidonic acid will be acted upon by lipoxygena e enzyme ---> excess leukotrienes .

5- GIT:

a- Nausea and vomiting by central effects due to stimulation of CTZ also peripheral due to local irritation.

b- Gastric irritation and hyperacidity induced by local release of acetylsalicylic acid and systemically by decrease synthesis of PG E_1 and PGI ---> ulceration ---> bleeding. Also inhibition of PGr ---> decrease mucus secretion (No protection) .

7- Kidney (blood uric acid)

a- Small dose (less than5 g/day) : decrease uric acid excretion by distal convoluted tubules ---> hyperuricaemia ---> worsen gout.

b- Large dose (> 5 g/day) : decrease uric acid reabsorption from proximal convoluted tubules ---> uricosuric effect ---> treat gout . 8- Endocrine actions:

a- Stimulate adrenaline release from adrenal medulla.

b- Stimulate hypothalamus ---> anterior pituitary ---> increase ACTH secretion ---> adrenal cortex ---> increase adrenal cortical hormone levels.

Therapeutic uses:

- - Local uses :
- - Salicylic acid:
- - Keratolytic (removes and warts)
- - Antifungal and antiseptic
- - Remove scales (hair lotion)
- - Methyl salicylates counter irrtant for arthritis and myositis.
- Systemic uses :
- 1-Analgesic: headache arthralgia, toothache.
- 2- Antipyretic (non specific, non causal)
- 3- Symptomatic treatment of common cold
- 4-Propylaxis of thromboembolic diseases (SD=75 150mg/day)
- 6- Rheumatoid arthritis 5-6 g/day .
- 7- Acute rheumatic fever

- **Drug interactions:**
- 1- Can displace other drugs from plasma proteins as dicoumarol and oral hypoglycemic
- 3- Barbiturates poteniates analgesic effect of salicylates .

Salicylic acid derivatives- drugs

-ASA (acetylsalicylic acid)

-cholinsalicylate

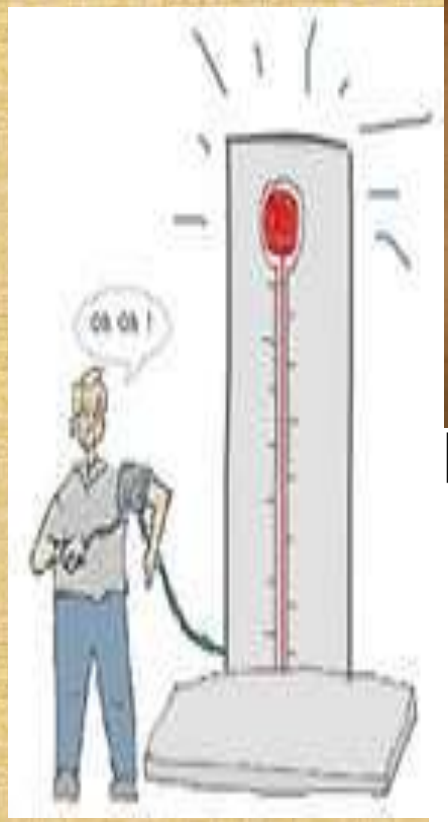
-diflunisal (↑ analg. and anti-inflam. effect, urikosuric activity, is not antipyretic)

-sulfasalazine (⇒sulfapyridine + 5-aminosalicylic acid)

AE

- **Salicylism (↑d.)** – hearing impairment, tinnitus, deafness, vertigo
- **Allergy -** itching, rash, anaphylaxis, bronchoconstriction (↑LT)
- **GIT** - nausea, dyspepsia, bleeding, ulcer disease
- **Nephropathy** – reversible decrease of glomerular filtration
- **Hepatopathy**
- Children- Rey‘s syndrome
- Elders- more sensitive to AE

ADVERSE effects Related to High doses



Contraindications

- hemophilia and other diseases influencing blood coagulation
- administration prior to surgery
- gastroduodenal ulcers
- gastritis
- **children to 12 years**
  - **Rey‘s syndrome** (hyperpyrexia, acidosis, seizures, vomiting, psichiatric disorders, hepatopathy)
- Pregnancy.
- asthma, allergy

Usual dosages

- antipyretic **500 mg**
- analgesic **500 mg (4 - 6 hrs)**
- anti-inflamm-rheumatic, - uratic **3,6 – 4 g/day**
- antithrombotic **30 –100 mg**

2. Pyrazolones

phenylbutazon

- good antiinflammatory effect, weak analgesic

propyphenazone

- less toxic
- in combinations (with paracetamole and caffein)

3. Propionic acid derivatives

ibuprofen

- Good analgesic and antiphlogistic effec
- Used often for acute pain therapy
- Low AE incidence, well tolerated NSAID, indicated for children

ketoprofen

flurbiprofen

naproxen

tiaprofenic acid – good penetration to synovial fluid

⇒ **joints diseases**

4. Acetic acid derivatives

- efficient drugs which differs in the incidence of AE

a-diclophenac

- Antiinflamm., analgesic, weak antipyretic effect.
  - SE:mild: cephalgia, insomnia, irritation, GIT disorders, photosensitivity

Indications: muscle and postoperative pain, cephalgia, gynaecology

b-indomethacin

- very strong nonselective COX inhibitor
- toxic $\Rightarrow$ short-time treatment of acute states
- urikosuric effects
- used in gout attacks

6. Oxicams

-piroxicam

-meloxicam

-lornoxicam

7. Selective COX-2 inhibitors

Coxibs

- 100 x more selective to COX-2
  - lower AE in GIT.
  - not influence renal perfusion.
  - Does not influence platelet functions, (**have no inhibitory effect on (COX-1 enzyme) so can be given in hemophilic patients.**
- increase of thrombembolisms (myocardial infarction, strokes) after chronic use
  - rofe-and valdecoxib already withdrawn
- Expensive.
- For problematic patients with rheumatic artritis

- celecoxib
- parecoxib
- etoricoxib
- rofecoxib
  - increases CVS risk
  - withdrawn from market

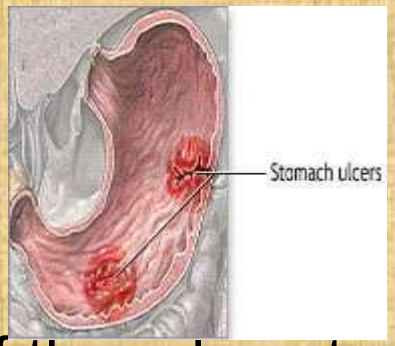
AE:

thrombembolic cardio and cerebrovascular complications

Frequent NSAIDs AE

- **Type A – Augmented** – dose dependent
  - GIT toxicity
  - Nephrotoxicity
  - Bronchospasm – after salicylates and other NSAIDs, (NOT after paracetamol)
  - inhibition of platelet functions
- **Type B – Bizzare** – non-predictable
  - Allergy
  - Rey‘s syndrome
  - rash …

Adverse effects



- because of COX-1 inhibition:
  - GIT - ↓ cytoprotective PGE_2, PGI_2
    ⇒ ***erosions, ulcerations***
  - thrombocytes - ↓ TXA_2: inhibition of thrombocytes aggregation
    ⇒ ***increased bleeding***
  - PGE_2, PGI_2 regulation of renal functions
    ⇒ ***renal failure***
  - ↑ LT production induces in predisposed people bronchoconstriction
    ⇒ ***asthma attack***
  - uterus - ↓ PGE/F: inhibition of constriction
    ⇒ ***prolongation and complications during delivery***

Prevention of AE

- Dose reduction
- Combination with protective drugs
- Antiulcerotics– proton pump inhibitors (lansoprazole, omeprazole)
- prostaglandine analogues (substitution)
- H_2 antihistamines – (cimetidine, ranitidine, famotidine)
- antacids
- think about selective COX-2 inhibitors

Aniline derivatives

-Paracetamol (acetaminophen)

indications:

- Analgesic, **antipyretic**

- IS NOT ANTIINFLAMMATORY active!
- does not influence blood coagulation or uric acid levels
- central mechanism due to COX-3 inhibition

Pharmacokinetics:

- p.o. good absorbtion, maximum in 30-60min, low protein binding, hepatic metabolism
- production of hepatotoxic mtb.- binding to gluthathione

- overdose(10-15g)$\Rightarrow$ antidote: **N-acetylcysteine**

AE, CI

- **Allergy**
- Hepatotoxicity after ↑ doses
- **Comorbidities**
  - Alcohol addiction
  - Nephropathy
  - Hepatopathy

Usual doses

- **drug of choice to ↓ fever and pain in children younger than 12 years**
- Pain in adults
  - 300 to 500 mg every 3-4 hrs
  - 650 mg every 4 to 6 hrs
  - 1000 mg every 6 hrs
- Total daily dose up to 4g

-Phenacetin

- Analgesic, **antipyretic**

- Strong nephrotoxicity.
- Metabolized to paracetamol

Conditions in which *paracetamol is a suitable drug* **In patients with :**

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