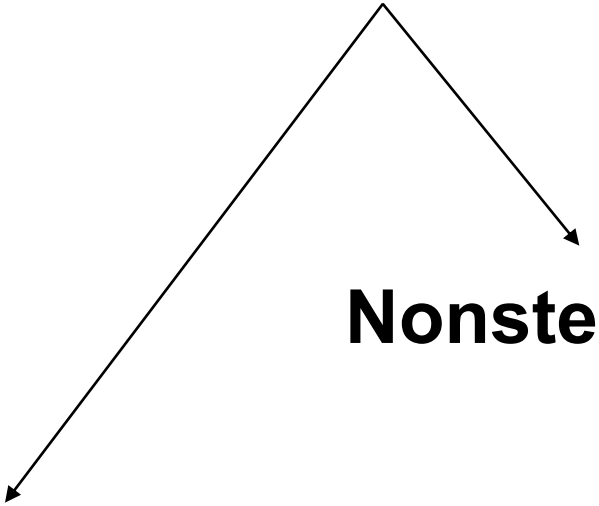
NSAID, antirheumatics, antiuratics, antipyretics

This study material is recommended specifically for practical courses from Pharmacology II for students of general medicine and stomatology. These brief notes could be used to prepare for the lesson and as a base for own notes during courses. Addititonal explanations and information are given in single lessons.

Non-opioid analgesics



Nonsteroidal antiinflammatory drugs

Analgesics-antipyretics

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

- **Nonsteroidal antiphlogistics (NSAID)** - against inflammation, fever and pain

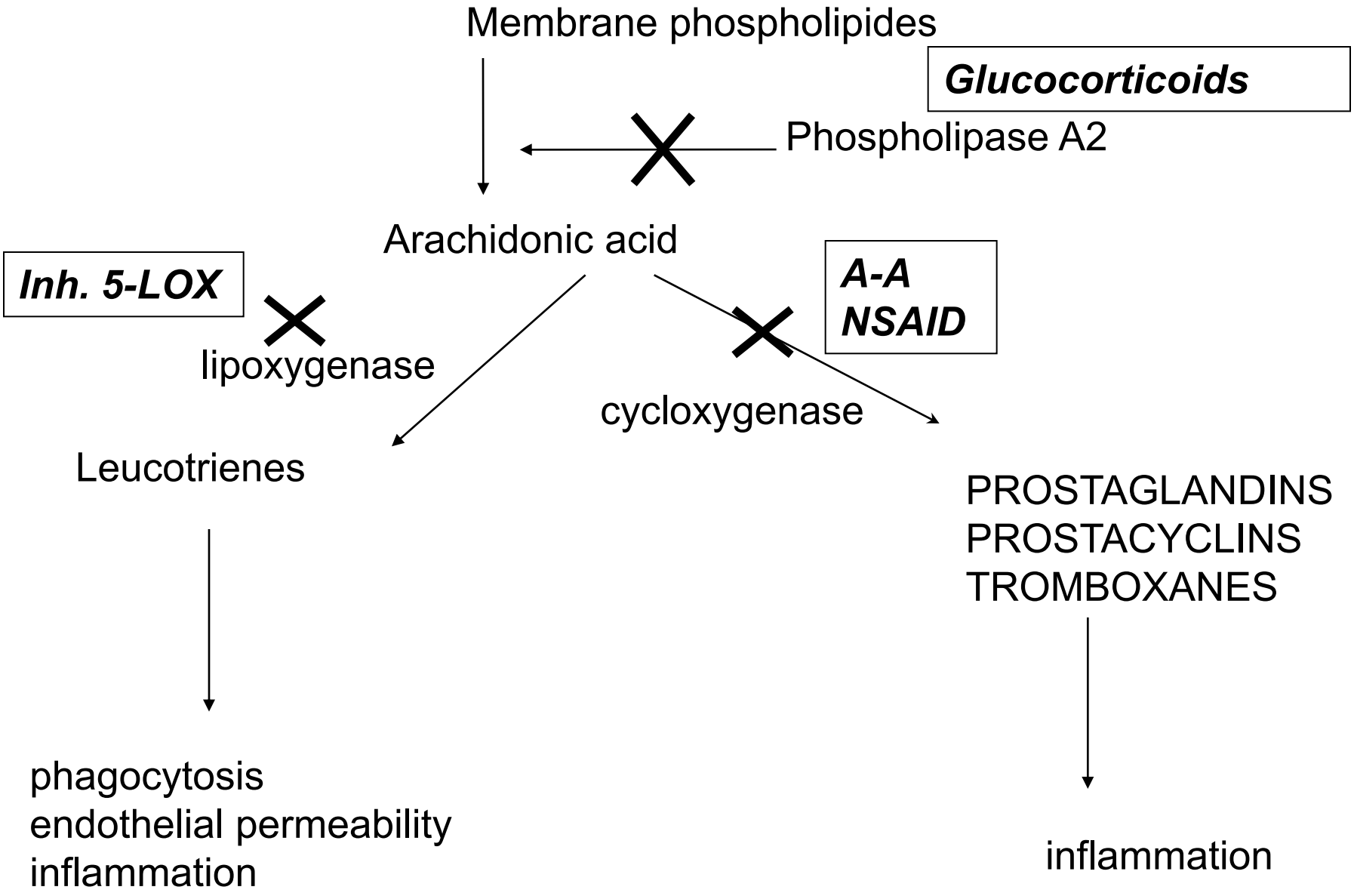
- **Antiuratics** – gout therapy

Mode of action

- all of them have similar mechanism of action– inhibition of eicosanoids synthesis (with higher or lower selectivity and strenght)
- NSAIDs differ in the strenght 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 activitites)
- **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

- general mechanism is COX-2 inhibition and their effect in peripheral tissues:
  - PGE_2 and PGI_2 increase nociceptros sensitivity to bradykinin, histamine, serotonine and other pain mediators
  - PG induces vasodilation and ↑endothelial permeability during inflammation
- PGE_2 sets the body temperature onto higher value in hypothalamus

Classification

1. Salicylic acid derivatives
2. Aniline derivatives
3. Pyrazolones
4. Propionic acid derivatives
5. Acetic acid derivatives
6. Fenamates
7. Oxicams
8. COX-2 preferential inhibitors

1. Salicylates

Effects

- Analgesic
- Antiphlogistic
- Antipyretic
- Antirheumatic
- Antitrombotic
- Myocardial infarction and stroke prevention
- Inhibition of platelets functions (antiaggregants)

Salicylic acid derivatives- drugs

ASA (acetylsalicylic acid)

cholinsalicylate

lysinsalicylate

diflunisal (↑ analg. and antiphlog. effect, urikosuric activity, is not antipyretic)

sulfasalazine (⇒sulfapyridine + 5-aminosalicylic acid)

mesalazine

AE

- **Salicylism (↑d.)** – hearing impairment, tinnitus, deafness, vertigo
- **Allergy** - bronchospasm, itching, rash, anaphylaxis, bronchoconstriction (↑LT)
- **GIT** - nausea, dyspepsia, bleeding, ulcer disease
- **Nephropathy** – reversible decrease of glomerular filtration
- **Hepatopathy**

CAVE

- Pregnancy- differs in trimesters
- Children- Rey‘s syndrome
- Elders- more sensitive to AE

ASA interactions

- **Anticoagulants**
- **Antiphlogistics** and other analgeics (except of opioids)
- **Other**
  - valproate – competition on plasma proteins – increase of efficacy
  - peroral antidiabetics – salicylates can increase their efficacy
  - SSRI – potentiate ASA antiaggregative effect (citalopram, fluoxetine)
  - glucocorticoids decrease ASA plasma levels

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 (only temporary)
- asthma, allergy, nasal polyps

Usual dosages

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

2. 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
- nondirect effect on 5-HT_3 spinal receptors
- elevates PGG_2 to PGH_2conversion in peripheral tissues

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

- **Allergz**
- Hepatotoxicity after ↑ doses
- **Comorbidities**
  - Alcohol addiction
  - Nephropathy
  - Hepatopathy
  - Phenylketonuria– aspartam as sweetener in paracetamol preparations

Usual doses

- comparable effect to ASA, but better tolerance!!!
- **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

2. Aniline derivatives

Phenacetin

- Analgesic, **antipyretic**

- Strong nephrotoxicity, in some countries still used in analgesic combinations
- Metabolized to paracetamol

3. Pyrazolones

phenylbutazon

- good antiphlogistic effect, weak analgesic
- Accumulated in joints and effective concentration persists for 3 weeks after last dose
- AUV (for veterinary use)

propyphenazone

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

metamizole

- antiphlogistic and antipyretic effect
- AE – allergy, nausea, vomitus, nephrotoxicity, hematopoesis inhibition
- Usually combined with spasmolytics

4. 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**

5. Acetic acid derivatives

- efficient drugs which differs in the incidence of AE

diclophenac

- antiphlogistic, analgetic, weak antipyretic ef.
- bioavailability 30-70 %
- short biological halftime $\Rightarrow$ retarded DDF
- daily dose 50-150 mg
- more AE than ASA, less than indometacin
  - mild: cephalgia, insomnia, irritation, GIT disorders, photosensitivity

Indications: muscle and postoperative pain, cephalgia, gynecology

Acetic acid derivatives

indometacin

- very strong nonselective COX inhibitor
- toxic $\Rightarrow$ short-time treatment of acute states
- urikosuric effects
- used in gout attacts
- AE in 30 % of pacients
  - GIT, cephalgia, depression, confusedness, hallucinations, hemattoxicity, cartilages destruction

Acetic acid derivatives

sulindac

- prodrug– metabolite is 500x more potent
- adverse skin reactions

6. Fenamates

- N-fenylanthranil acid derivatives
- high efficacy
- high AE incidence – only for the treatment of acute painfull states

- **tolfenamic acid**
- **mefenamic acid, meclofenamic ac., flufenamic ac.**
- **etofenamic acid**

7. Oxicams

piroxicam

- well tolerated even after chronic administration
- 20 mg daily

meloxicam

- COX-2 more selective
- lower AE incidence

8. COX-2 preferential inhibition

nabumetone

- prodrug, hepatic activation

nimesulide

- scavenger
- inhibits enzymes (elastases, collagenases) destroys cartilage

Coxibs

- 100 x more selective to COX-2
  - lower AE in GIT, do not influence thrombocyte aggregation or renal perfusion
- increase of thrombembolisms (myocardial infarction, strokes) after chronic use
  - rofe-and valdecoxib already withdrawn

- expensive– prescription restrictions (revmatologists)
- For problematic patients with rheumatic artritis
- Does not influence platelet functions

- 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 platet 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 or DDF change
- 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

Rheumatic diseases– therapeutic strategies

1. **NSAID**
2. **DMARDs + Biolog. therapy**
3. **Other antirheumatics**
   - steroid antiphlogistics (glucocorticoids)
   - cytostatics and antimetabolites
   - imunosuppressants
   - proteolytické enzymy

Chronic therapy!

DMARDs

- chloroquine
- hydroxychloroquine

} antimalarics

  - antiphlogistic and immunomodulant
  - leukocyte chemotaxis inhibition
  - in milder forms of disease
  - AE: skin symptoms, retinal impairment

DMARDs

sulfasalazine

- **E. coli cleaves sulfasalazine in colon into aminosalicylate (antiphlogstic) and sulfonamide (antibiotic)**
- **gradual dose increase – effect onset in 1 – 2 months**

Golden salts

- **natrium aurothiomalate (i.m.), auranofin (p.o.)**
  - **inhibits phagocytosis**
  - **30-40 % AE: skin and mucosal changes, hematopoesis impair, liver and kidney toxicity**

DMARDs

Biologic therapy

- targeted effect on the immune cells involved in rheumatoid artritis pathophysiology
- anti-TNF drugs:
  - fast onset of effect, inhibition of progression, relaps after withdrawal
  - risk of infectious disease, CI live vaccines immunization

AE: GIT problems, weakness, BP changes, increased risk of infections, allergy

infliximab

- recombinant monoclonal antibody
- create complexes with TNF-α
- suitable for combination with methotrexate

etanercept

- recombinant protein from TNF receptor *z* subunit and IgG1fragment
- binds to TNF-α

Other antirheumatics

1. **Antiphlogistic steroids**
   - **glucocorticoids**
2. **Cytostatics and antimetabolites**
   - methotrexate
   - azathioprine
   - cyclophosphamide
3. **Immunosuppressants**
   - cyclosporin A
4. **Proteolytic enzymes**
   - bromelain
   - papain
   - trypsin

Gout

Gout pathophysiology

Primary

- genetically conditioned metabolic impairment of uric acid pathwa

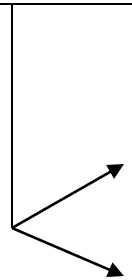
$\Rightarrow$ urate crystals deposition in joints and cartilages

Secondary

- excessive nucleotide destruction (cancer disease)
- insufficient uric acid renal excretion
- increased intake of uric acid from diet (sea fruit, alcohol, …)

- Problematic drugs
  - ASA low doses inhibits uric acid secretion
  - thiazid diuretics (hydrochlorothiazid)
  - immunosuppressants

Gout pharmacotherapy



- Acute gout attack
- Hyperuricaemia therapy/ gout prevention

Acute attack therapy

inflammation inhibition, pain

leukocyte migration inhibition

Hyperuricaemia therapy/ gout prevention

uric acid excretion

uric acid synthesis inhibition

diet

Acute gout attack- therapy

- First aid– fast relief from pain and inflammation suppression
- NSAID
  - **diclophenac**, **indometacin**, **kebuzone**
- **Colchicine** (Colchicum autumnale)
  - mitotic poison
- inhibits also phagocytosis and leukocyte migration
- AE– serious diarrhoea – rehydration is necessary

Chronic therapy of gout

Uricosurics

probenecid

- can be combined with renal excreted antibiotic (antivirotics) to prolong their effect
- interactions:
  - salicylates
  - heparine - probenecid stimulates its effect
- probenecid can interfer with these drugs plasma levels:
  - Indometacin, ketoprofen
  - methotrexate
  - nitrofurantoin – antibiotic
  - zidovudine – antiretrovirotic

Chronic gout therapy

Uricosurics

Benzbromaron

uric acid proximal tubule reabsorption inhibition

Hepatotoxic, withdrawn from market

Antiuratics

- Hypoxanthine $\xrightarrow{\text{XO}}$ xanthine $\xrightarrow{\text{XO}}$ uric acid
- **Allopurinol**
- hypoxanthine isomer, xanthinoxidase (XO) competitive inhibition
  - do not combine with purine analogues (cytostatics) because of increased toxicity
- **Febuxostat**