NSAIDs, Antipyretics

Antigout drugs

Department of Pharmacology MU

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

- **Nonsteroidal antiinflammatory drugs (NSAIDs)** - against inflammation, fever and pain

A-A and NSAIDs overlap partially

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Mechanism of action

- all of them have similar mechanism of action– inhibition of eicosanoids synthesis (with higher or lower selectivity and strength)

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

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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 → inflammation, fever, pain
- **COX-3** ? – central mechanism of analgesic and antipyretic effect (localization: heart + CNS)

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Classification by COX1/COX2 inhibition

1. Nonspecific inhibitors
   - ASA, ibuprofen, diclofenac, …
2. Preferential inhibitors of COX-2
   - meloxicam, nimesulid
3. Specific inhibitors of COX-2
   - coxibs

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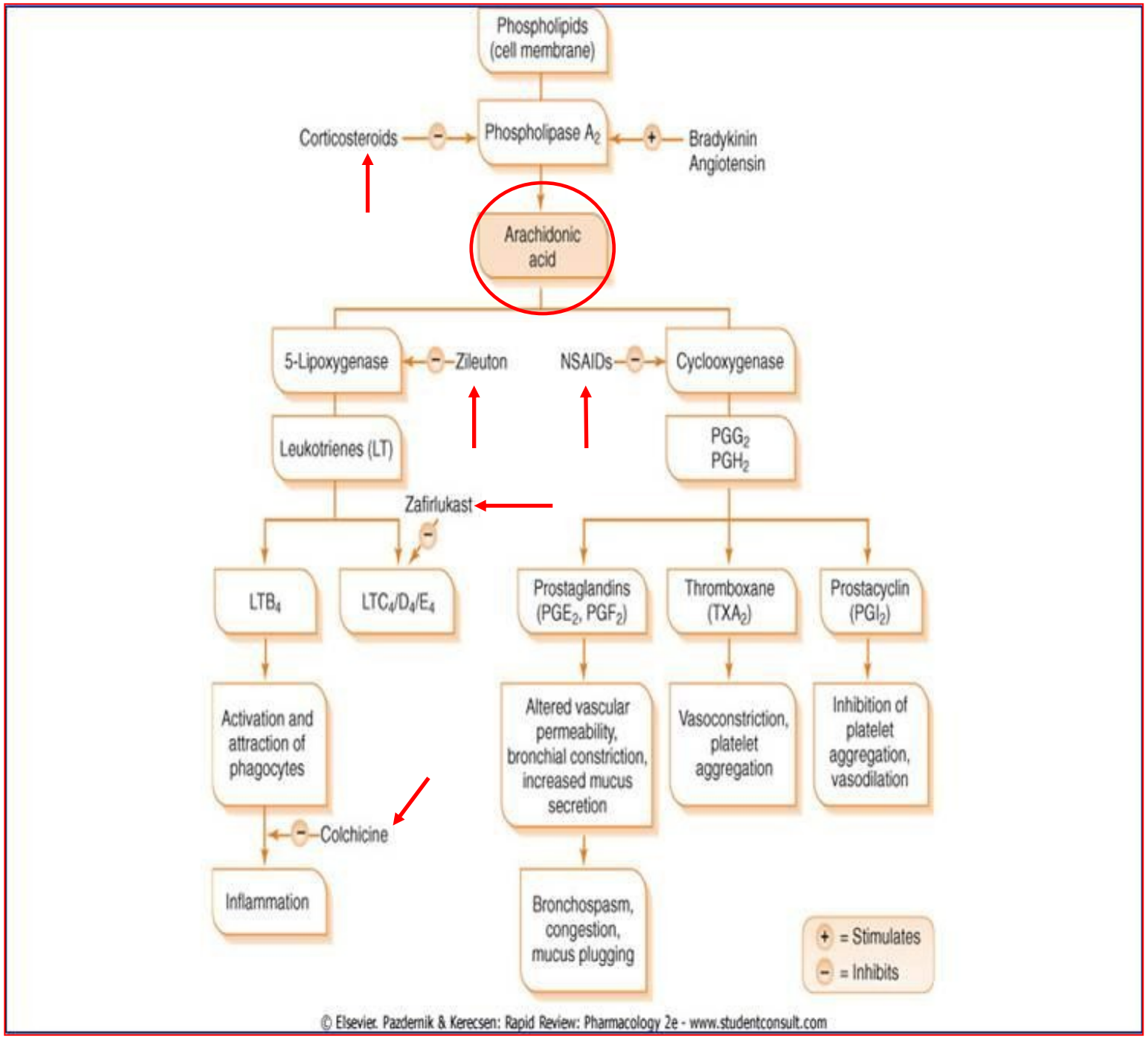
Phospholipids (cell membrane)
Corticosteroids
Phospholipase A_2
Bradykinin
Angiotensin
Arachidonic acid
5-Lipoxygenase
Zileuton
NSAIDs
Cyclooxygenase
Leukotrienes (LT)
PGG_2
PGH_2
Zafirlukast
LTB_4
$LTC_4/D_4/E_4$
Prostaglandins (PGE_2, PGF_2)
Thromboxane (TXA_2)
Prostacyclin (PGI_2)
Activation and attraction of phagocytes
Altered vascular permeability, bronchial constriction, increased mucus secretion
Vasoconstriction, platelet aggregation
Inhibition of platelet aggregation, vasodilation
Colchicine
Inflammation
Bronchospasm, congestion, mucus plugging
+ = Stimulates
− = Inhibits
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Classification

1. Salicylic acid derivatives
2. Aniline derivatives
3. Propionic acid derivatives
4. Pyrazolones
5. Acetic acid derivatives
6. Oxicams
7. Coxibs
8. Other

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1. Salicylates

Effects:

- analgesic
- antiinflammatory
- antipyretic
- antirheumatic
- antiaggregation → inhibition of platelet function

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Salicylic acid derivatives – drugs

<u>NSAIDs:</u>

- ASA (acetylsalicylic acid)
- sodium salicylate
- cholinsalicylate

<u>Therapy of inflammatory bowel desease:</u>

- sulfasalazine
  - → sulfapyridine + 5-aminosalicylic acid
- mesalazine

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Acetylsalicylic acid

- efficiency standard of AA and NSAIDs
- selective inhibitor of COX1 (100-200 : 1)
- irreversible acetylation of COX-1 active centre
- pharmacokinetics:
  - weak acid, complete and rapid absorption in stomach and proximal part of intestine
  - **salicylic acid (SA)** is product of metabolisation
  - $T_{1/2}$ ASA 15-20 min, $T_{1/2}$ SA 30 hrs depending to dose
  - 80-95% binding to plasma proteins, elimination and exkretion via kidneys
  - higher doses – risk of cumulation in a body

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Usual dosages

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

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ASA – adverse effects

- **salicylism (↑d.)** – hearing impairment, tinnitus, deafness, vertigo
- **allergy** - itching, rash, anaphylaxis,…
- **aspirin-induced asthma** - ↑LT
- **GIT** - nausea, dyspepsia, bleeding, ulcer disease
- **„analgetic“ nephropathy** – reversible decrease of glomerular filtration
- **increased bleeding**

CAVE

- pregnancy- differs in trimesters
- children- Rey‘s syndrome
- elders- more sensitive to AE

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ASA interactions

- **anticoagulants**
- **NSAIDs** and other analgesics (except of opioids)
- **other**
  - valproate, sulfonylureas – competition on plasma proteins – increase of efficacy
  - SSRI – potentiate ASA antiaggregative effect (citalopram, fluoxetine)
  - glucocorticoids decrease ASA plasma levels, but increase the risk of GIT bleeding and ulceration

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ASA - 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

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2. Aniline derivatives

Paracetamol (=acetaminophen)

- analgesic, antipyretic, **is not antiinflammatory active**
- does not influence blood coagulation or uric acid levels
- mechanism of action is unclear:
  - central mechanism due to COX-3 inhibition
  - indirect effect on 5-HT_3 spinal receptors
  - elevates PGG_2 to PGH_2conversion in peripheral tissues
  - influencing the endocannabinoid and vanillin system and Ca^{2+} channels

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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 **4 g**

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Pharmacokinetics:

- p.o. good absorbtion, maximum in 30-60 min, low plasma protein binding, hepatic metabolism
- production of hepatotoxic mtb. – binding to gluthathione
- overdose (10 – 15 g) → antidote **N-acetylcysteine**

AE, CI:

- allergy
- hepatotoxicity after ↑ doses
- comorbidities:
  - alcohol addiction
  - nephropathy
  - hepatopathy

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3. Pyrazolones

Propyphenazone

- in combinations (with paracetamole and caffein)
- **AE:** GIT intolerations, rash, bronchospasm, hematopoetic disorders

Metamizole

- analgetic, antipyretic + spasmolytics effect
- combined with spasmolytics (pitofenone, fenpiverine)
- **AE:** rare but serious - the most serious are agranulocytosis and pancytopenia

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4. Propionic acid derivatives

Ibuprofen

- good analgesic and antiinflammatory effect
- used often for acute pain therapy
- low AE incidence, well tolerated NSAID, indicated for children

Ketoprofen

- phototoxicity

Dexketoprofen

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4. Propionic acid derivatives

Naproxen

- longer $T_{1/2}$ (12-15 hrs)
- low gastro- and cardiovascular toxicity compared to other NSAIDs

Tiaprofenic acid

- good penetration to synovial fluid → joints diseases

Flurbiprofen

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5. Acetic acid derivatives

Diclophenac

- antiinflammatory, analgesic, weak antipyretic ef.
- bioavailability 30-70%
- short biological halftime → retarded DDF
- more AE than ASA, less than indomethacin
  - mild: cephalgia, insomnia, GIT disorders, photosensitivity
  - significant risk of cardiovascular AE

Aceclofenac

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5. Acetic acid derivatives

Indomethacin

- very strong nonselective COX inhibitor
- toxic → short-time treatment of acute states
- urikosuric effects→ used in gout attacks
- AE in 30 % of pacients
  - GIT, cephalgia, depression, confusion, hallucinations, hematoxicity, cartilages destruction

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6. Oxicams

- high plasma protein binding (interactions!)
- long biological halftime (once daily dosing)
- different COX affinity

Meloxicam

- COX-2 more selective
- lower AE incidence

Lornoxicam

- nonselective COX inhibitor
- low occurence of GIT adverse effect

Piroxicam

- nonselective COX inhibitor, high toxicity

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7. Coxibs

- 100 x more selective to COX-2 (**specific** COX-2 inhibitors)
  - lower AE in GIT
  - do not influence thrombocyte aggregation or renal perfusion
- good analgesic effect, not suitable for treatment of acute or transient pain → effect is progressing slowly
- prescription and indication restrictions
- **I:** osteoarthritis, rheumatoid arthritis, ankylosing spondylitis
- **AE:** increase of thrombembolisms (myocardial infarction, strokes) after chronic use

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7. Coxibs

Celecoxib

Parecoxib – only inj.

Etoricoxib

Pharmacokinetics:

- after p.o. administration good absorption from GIT, but not too fast, max levels reach in 2-4 hours
- fat diet slows down absorption

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8. Other

Nimesulide

- preferential inhibitor of COX-2
- inhibits enzymes destroys cartilage (elastases, collagenases), due to occurrence of AE, indication of treatment of painful osteoarthritis has been taken
- is not the first choice medicine in any of indications
- **PK:** lipophilic, short elimination half-life (1,5-5 hrs), analgesia up to 12 hrs
- **AE:** hepatotoxicity (max duration of therapy 15 days)

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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***

- coxibs:
  - thromboembolic cardiovascular and cerebrovascular complications

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Prevention of AE

- dose reduction or DDF change
- combination with protective drugs
  - **proton pump inhibitors** (lansoprazole, omeprazole)
  - **prostaglandine analogues** (misoprostol)
  - **H_2 antihistamines** (ranitidine, famotidine)

- think about preferential or specific COX-2 inhibitors

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NSAIDs for local aplication

- ketoprofen, ibuprofen, naproxen, indomethacin, diclophenac, nimesulide, piroxicam
- flurbiprofen (lozenges), choline salicylate (oral gel)
- **DDF:** creams, gels, solutions (sprays), patches, lozenges
- **AE:** hypersensitivity reaction, phototoxic reaction

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Treatment of gout

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Drugs

1. **Acute gout attack**
   - strong anti-inflammatory action
   - pain-killers
   - inhibition of leucocyte migration to the joint
2. **Hyperuricemia therapy / prevention of gout attack**
   - increase of uric acid excretion
   - block of synthesis

+ diet

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Treatment of acute gout attack

NSAIDs
higher doses (i.m., p.o., p.r.)
some have preferably uricosuric effect
indometacine, diclofenac, piroxicam

colchicine
alcaloid obtained from *Colchicum autumnale*
p.o. every 2-4 hrs
mitotic poison, inhibits phagocytosis and leukocyte migration
AE: severe diarrhea – rehydratation!

glucocorticoids
local adm. (i.a.) – **triamcinolone**
systemic (p.o., i.m., i.v.) – **prednison**, **methylprednisolon**

canakinumab
IL-1 inhibitor, human monoclonal antibody
patients who do not tolerate NSAIDs and GC
s.c. aplication

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Chronic treatment of gout

1. Uricosurics

- inhibit reabsorption of uric acid in primary tubulus

Lesinurad

- only in combination with xantin oxidase inhibitors

Probenecide

- sometimes used with antibiotics or antivirotics to make them stay longer in the body
- Not registered in Czech Rep.

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2. Antiuratics

- inhibit syntesis of urine acid by inhibition **xantin oxidase (XO)**

Allopurinol

- isomer of hypoxanthin, competitive inhibition of xanthin oxidase
- inhibits *de novo* syntesis of purines
- not combine with cytostatics of purine structure (azathioprin, 6-mercaptopurin) – allopurinol ↑ their toxicity!
- **AE:** usually well tolerated, most common:
- rash, GIT intoleration, hypersensitive reaction

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Febuxostat

- **MA:** non-purine inhibitor of xantinoxidase
- clinical trials proved higher efficacy than allopurinol
- **AE:** gout attacts, liver function abnormalities, diarrhoea, nausea, headache

Pegloticase (recombinant uricase)

- **MA:** transforms uric acid to alantoin with better solubility
- **AE:** anaphylactic shock, reaction to infusion, gout attacts at the beginning of therapy
- i.v. aplication (only to inpatient)

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