

NSAIDs, Antipyretics

Antigout drugs

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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

Mechanism of action

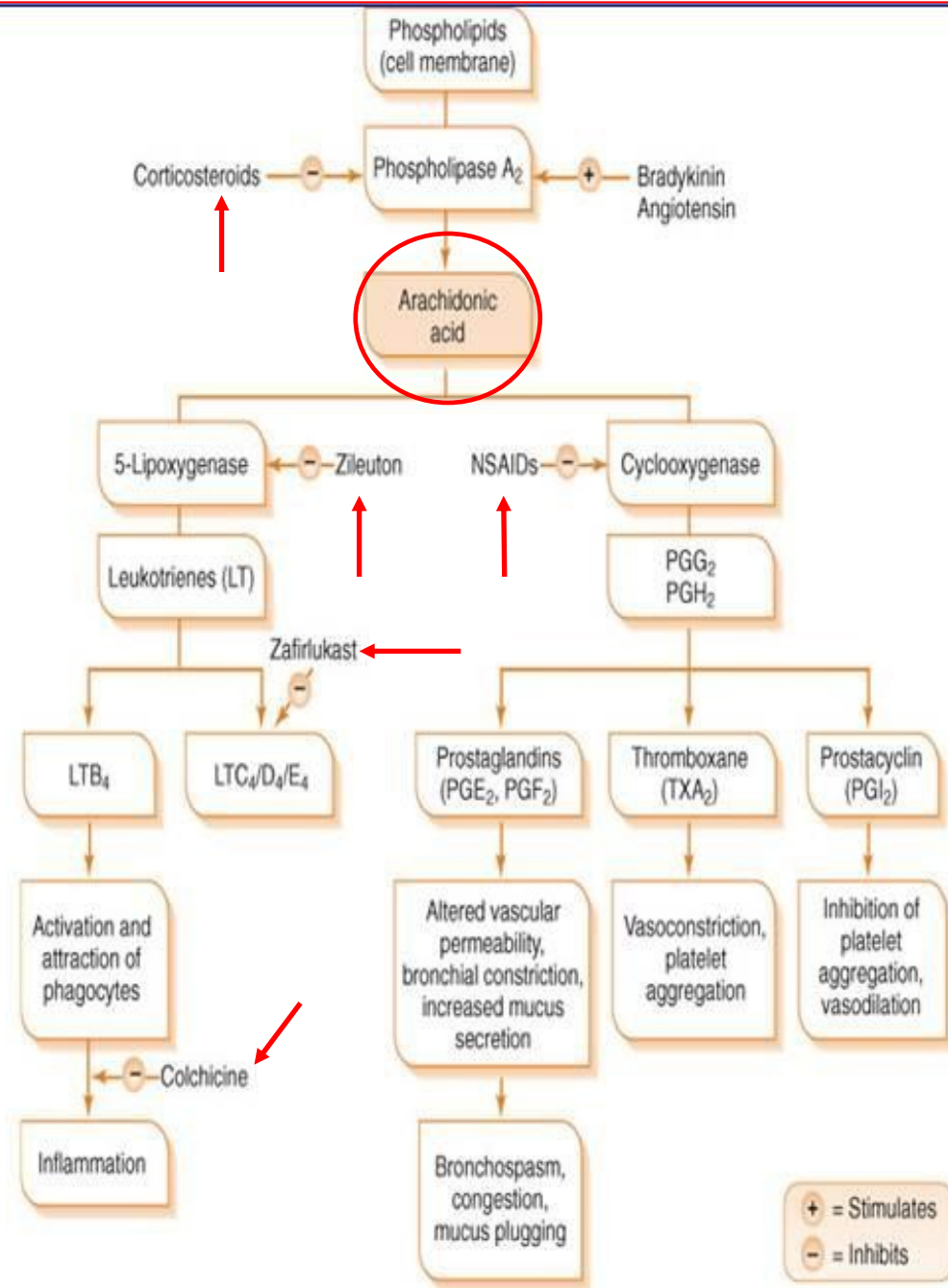
- all of them have similar mechanism of action— inhibition of eicosanoids synthesis (with higher or lower selectivity and strength)
- NSAIDs differ in the strength of COX1/COX2 inhibition and the incidence of typical AE (ulcer disease, bleeding)

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)

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



Classification

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

1. Salicylates

Effects:

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

Salicylic acid derivatives – drugs

NSAIDs:

- ASA (acetylsalicylic acid)
- sodium salicylate
- cholinsalicylate

Therapy of inflammatory bowel disease:

- sulfasalazine
 - sulfapyridine + 5-aminosalicylic acid
- mesalazine

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 metabolism
 - $T_{1/2}$ ASA 15-20 min, $T_{1/2}$ SA 30 hrs depending to dose
 - 80-95% binding to plasma proteins, elimination and excretion via kidneys
 - higher doses – risk of cumulation in a body

Usual dosages

<input type="checkbox"/> antipyretic	500 mg
<input type="checkbox"/> analgesic	500 mg (4 - 6 hrs)
<input type="checkbox"/> anti-phlogistic, -rheumatic, -uratic	3,6 – 4 g/day
<input type="checkbox"/> antiaggregative	30 –100 mg
<input type="checkbox"/> total daily dose	4 g/day

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

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

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, psychiatric disorders, hepatopathy)
- pregnancy (only temporary)
- asthma, allergy, nasal polyps

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-HT₃ spinal receptors
 - elevates PGG₂ to PGH₂ conversion in peripheral tissues
 - influencing the endocannabinoid and vanillin system and Ca²⁺ channels

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**

Pharmacokinetics:

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

AE, CI:

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

3. Pyrazolones

Propyphenazone

- in combinations (with paracetamol and caffeine)
- **AE:** GIT intolerations, rash, bronchospasm, hematopoietic disorders

Metamizole

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

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

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

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

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 patients
 - GIT, cephalgia, depression, confusion, hallucinations, hematoxicity, cartilages destruction

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 occurrence of GIT adverse effect

Piroxicam

- nonselective COX inhibitor, high toxicity

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

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

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)

Adverse effects

- because of COX-1 inhibition:
 - GIT - ↓ cytoprotective PGE₂, PGI₂
⇒ **erosions, ulcerations**
 - thrombocytes - ↓ TXA₂: inhibition of thrombocytes aggregation
⇒ **increased bleeding**
 - PGE₂, PGI₂ 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

Prevention of AE

- dose reduction or DDF change
- combination with protective drugs
 - proton pump inhibitors** (lansoprazole, omeprazole)
 - prostaglandine analogues** (misoprostol)
 - H₂ antihistamines** (ranitidine, famotidine)
- think about preferential or specific COX-2 inhibitors

NSAIDs for local application

- 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

Treatment of gout

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

Treatment of acute gout attack

NSAIDs

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

colchicine

alkaloid 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. application

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.

2. Antiuratics

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



Allopurinol

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

Febuxostat

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

Pegloticase (recombinant uricase)

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