

# NSAIDs, Antipyretics

## Antigout drugs

### Copyright notice

The presentation is copyrighted work created by employees of Masaryk university.

Students are allowed to make copies for learning purposes only.

Any unauthorised reproduction or distribution of the presentation or individual slides is against the law.

□ **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- $\alpha$ , 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

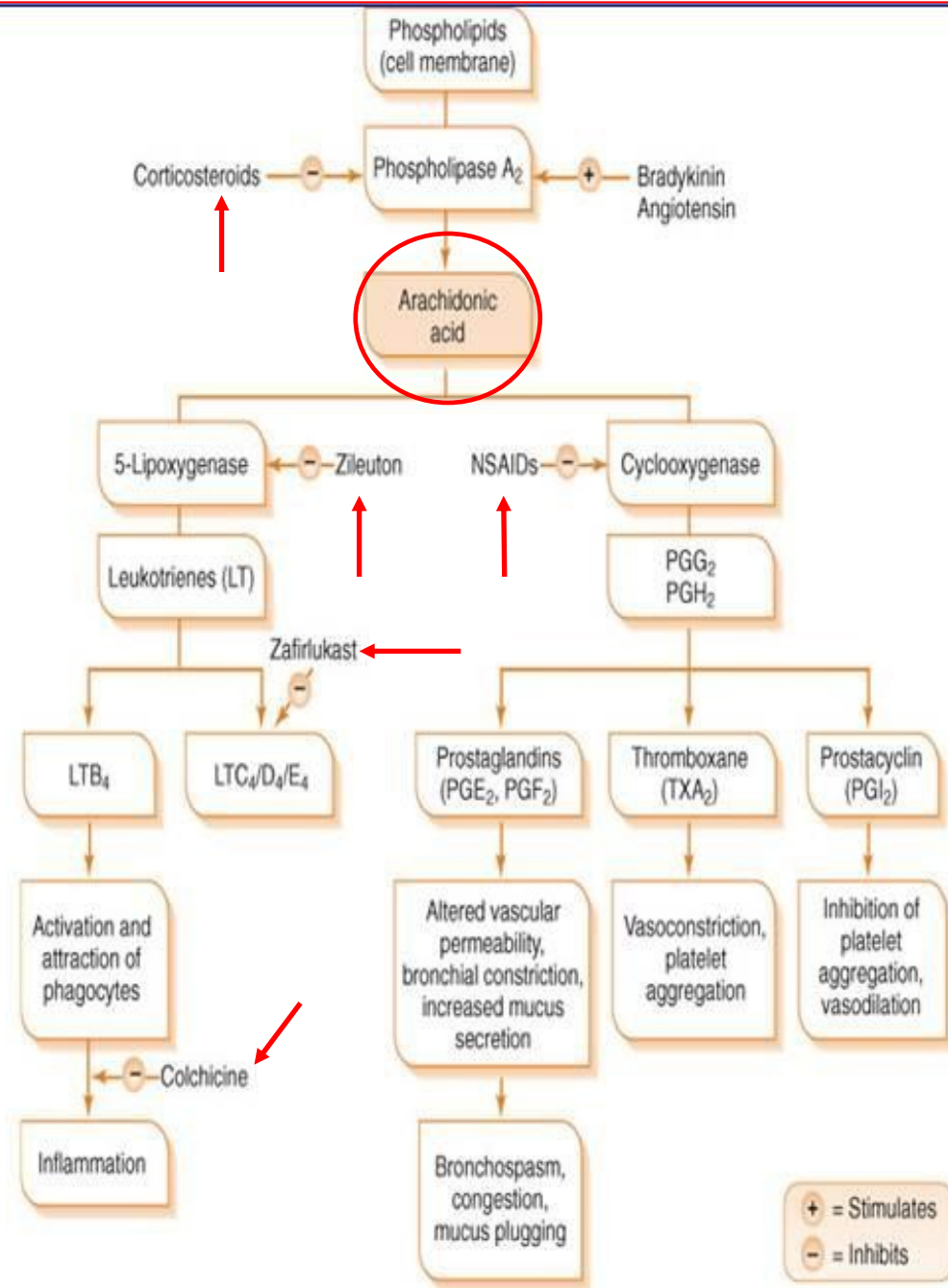
- ASA, ibuprofen, diclofenac, ...

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

# 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-HT<sub>3</sub> spinal receptors
  - elevates PGG<sub>2</sub> to PGH<sub>2</sub> conversion in peripheral tissues
  - influencing the endocannabinoid and vanillin system and Ca<sup>2+</sup> 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 + spasmolytic 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 PGE<sub>2</sub>, PGI<sub>2</sub>  
⇒ **erosions, ulcerations**
  - thrombocytes - ↓ TXA<sub>2</sub>: inhibition of thrombocytes aggregation  
⇒ **increased bleeding**
  - PGE<sub>2</sub>, PGI<sub>2</sub> 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)
  - H<sub>2</sub> 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)