Non-opioid analgesics

non-steroid antiinflammatory drugs

analgesics-antipyretics

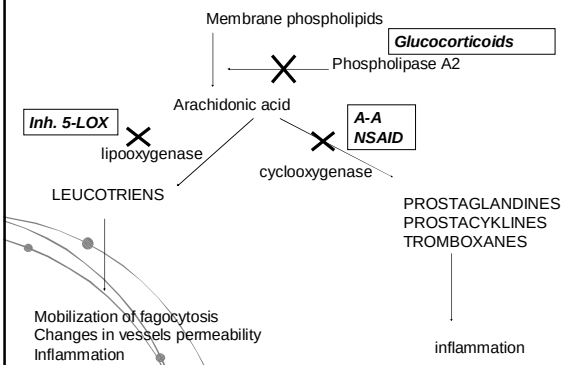
- **analgesics-antipyretics (A-A)** drugs decrease fever and pain
- **non-steroid antiflogistics (NSAID)** - acting against inflammation, pain and fever

A-A and NSAID categories partially overlap

- **antiuratics** – drugs against gout

Cyclooxygenase isoforms

- **COX-1 – constitutive** – prostanoids providing physiological and homeostatic functions (gastroprotective, platelets functions)
- **COX-2 – inducible** – synthesis via pro-inflammatory factors (IL-1, IL-2, TNF-α, oncogens,..)
  - prostanoids ⇒ inflammation, fever, pain
- **COX-3** – central mechanism of analgesic and antipyretic effects (localisation: heart + CNS)



Classes

1. Salicylates
2. Anilin derivates
3. Pyrazolones
4. Derivates of propionic acid
5. Derivates of acetic acid
6. Fenamates
7. Oxikams
8. Preferential inhibitors of COX-2
9. Coxibs

1. Salicylates

Effects

- analgesic
- antiflogistic
- antipyretic
- antirheumatic
- antitrombotic
- prophylaxis of myocardial infarction and brain stroke
- inhibition of platelets functions (antiaggregant)

Drugs

- **ASA** – prodrug metabolised to salicylic acid, the only drug affecting COX irreversibly
  - selective inhibition of platelets functions by irreversible acetylation of COX (for the whole life-time of thrombocyte)
- **Aloxiprin** – is degredated in GIT → ASA and aluminium oxide, slower absorption, safer
- **Natrium salicylate** – inj. In rheumatic fever, paliative care

Derivates of salicylic acid

ASA (acetylsalicylic acid)
cholinsalicylate
lysinsalicylate
diflunisal (↑ analgesic and antiflog. effect, urikosuric, no antipyretic effect)
sulfasalasin (⇒sulfapyridin + 5-aminosalicylic acid)
mesalazin

AE

- **Salicylism (- d.)** – hearing impairment, tinnitus, deafness, vertigo
- **Alergies** - bronchospasms, itching, rash, anaphylactic shock, bronchoconstriction
- **GIT** - nausea, dyspepsia, bleeding, ulcer disease
- **Nephropathy** – reversible decrease of GF
- **Hepatopathy**

CAVE

- Gravidity – according to trimester
- Children - Reye syndrome
- Elderly – more sensitive to AE

Contraindications

- haemophilia and other disorders of haemostasis
- before surgery
- ulcer disease
- gastritis
- **children under 12 years**
  - **Reye syndrome** (hyperpyrexia, acidosis, cramps, vomiting, neuropsychiatric disorders, hepatopathy)
- gravidity (according to trimester)
- asthma, allergies, nasal polyp

Usual dosing

antipyretic effect	**500 mg**
analgesic effect	**500 mg (4 - 6 h)**
antiflogistic,-rheumatic,-uratic	**3,6 – 4 g/day**
antiaggregant	**30 –100 mg**

2. Anilin derivates

Paracetamol (acetaminophen)

- Analgesic, **antipyretic**
- No antiinflammatory effect!!!
- No effect on aggregation and urikemia
- central mechanism on COX-3
- Indirect influence on 5-HT_3 rp in spinal cord
- Fastens peripheral metabolisation of PGG_2 to PGH_2

Pharmacokinetics

- p.o. well absorbed, maximum in 30-60min, low binding to proteins, hepatic metabolisation
- hepatotoxic mtb.- bound to glutathion
- overdose (10-15g)⇒ antidotum: **N-acetylcystein**

AE, CI

- **Allergies**
- **Gravidity**
  - Trimester?
- **Co-morbidity**
  - Alkohol abuse
  - Nephropathy
  - Hepatopathy
  - Phenylketonuria – aspartam is used as korrigens in paracetamol preparations

Usual dosing

- Effects are comparable with ASA but is safer!!
- **1st choice for ¯ fever and pain in children under 12**
- pain in adults
  - 300 to 500 mg each 3-4 h
  - 650 mg each 4 to 6 h
  - 1000 mg each 6 h
- DTD to 4g

2. Anilin derivates

Phenacetin

- Analgesic, **antipyretic**
- strongly nephrotoxic, negatively inotropic
- in some countries used in combined analgesic preparations
- Metabolised to paracetamol

3. Pyrazolones

phenylbutazon

- good antiinflammatory effect, less analgesic
- concentrates in joints and effective concentration remains for 3 week after last administration
- AUV

propyphenazon

- less toxic
- in combinations (with paracetamol and caffeine)

3. Pyrazolones

metamizol

- antiflogistic and antipyretic effect
- AE – allergies, nausea, vomitus, nephrotoxicity, inhibition of hematopoiesis
- Usually combined with spasmolytics (eg. Algifen = metamizol + pitofenazon + fenpiverin)

4. Propionic acid derivates

ibuprofen
- good analgesic and antiflogistic effect
- Often used in therapy of acute pain
- low AE, probably best tolerated NSAID, indicated also in children

ketoprofen - Ketonal crm, Fastum gel, Ketobene
flurbiprofen - Strepfen
tiaprofenic acid – well penetrates to synovial fluid
- **diseases of joints**

naproxen - Napsyn

5. Acetic acid derivates

- Effective drugs with different AE

diclofenac (Voltaren, Apo-diclo, Inflamac, Fector gel, Olfen)

- antiinflammatory, analgesic, mild antipyretic ef.
- PK: bioavailability 30-70%, short half-life ⇒ retarded forms
- DTD 50-150 mg
- more AE than ASA, but less than indometacin
  - mild: headache, insomnia, irritability, GIT disorders, photosensitivity

Indications: aching muscles, headache, after surgery, painful menstruation…

5. Acetic acid derivates

indometacin (Indometacin supp, Indobene, Vonum cutan)

- Powerful non-selective COX inhibitor with urikosuric effects
  ⇒ used in gout attacks
- toxic ⇒ only short-term administration in acute conditions
- AE in 30% of patients
  - GIT, headache, depression, confusion, hallucinations, damage of haematopoiesis and cartilage

5. Acetic acid derivates

sulindac
- prodrug – metabolite is 500x more effective
- apart from COX inhibition probably can reduce the growth of polyps and precancerous lesions in the colon
- is effective tocolytic
- AE: relatively less irritating to the stomach, skin lesions, toxic to liver and pancreas

6. Fenamates

- Highly potent
- often AE (vomiting, headache, diarrhea, hematemesis, hematuria, skin problems, fever)

→ only for acute conditions (migraine, menstruational or joint pain)

- **tolfenamic, mefenamic, meklofenamic, flufenamic acid**
- **etofenamate**

7. Oxicams

piroxicam
- Well tolerated in most of the patients
- 20 mg once a day
- Pro-roxikam, Flamexin, Reumador

meloxicam
- COX-2 more selective
- less AE
  - Movalis, Recoxa

8. Preferential inhibitors of COX-2

nabumeton

- prodrug
  - Relifex, Rodanol

nimesulid

- scavenger
- Inhibits cartilage-degradating enzymes (elastase, kolagenase)
  - Aulin, Coxtral, Mesulid, Nimesil, Zolan

9. Coxibs

- 100 x more specific to COX-2
  - less AE in GIT, no effects on aggregation or kidney blood flow
- AE – increase in thrombembolic cardiovask. and cerebrovask. attacks (AMI, brain stroke) after chronic treatment
  - rofe- and valdecoxib were withdrawn
- expensive – prescription only by rheumatologist
- for problematic patients with rheumatoid arthritis

9. Coxibs

- **celekoxib** has very safe profile (CVS, GIT)
  - Good for treatment of morbus Bechterev (spondylitis ankylosa)
  - Celebrex, Onsenal
- **parekoxib**
- **etorikoxib**
- **rofekoxib, valdekoxib**
  - increased CVS risk
  - both were withdrawn
- AE:
  - ***thromboembolic cardio- and cerebrovaskular complications***

Safety of NSAIDs

- Generally NSAIDs must be prescribed and recommended with caution, especially to elderly/children
- Risk/benefit of selective NSAIDs is still discussed
- When patient asks for common analgesic, paracetamol is the 1st choice (possibly with co-analgesics)

Often AE of NSAIDs

- **Type A – Augmented** – dose dependent
  - GIT toxicity
  - Nephrotoxicity
  - Bronchospasms –salicylates and others NSAIDs, (not after paracetamol)
  - Inhibition of platelets functions
- **Type B – Bizzare** – unpredictable
  - Allergies
  - Reye syndrome
  - rash …

Adverse effects of NSAIDs

- Results of COX-1 inhibition :
  - GIT - ↓ cytoprotektive PGE_2, PGI_2
    - Þ ***erosions, ulcerations***
  - thrombocytes - ↓ TXA_2: inhibition of aggregation
    - Þ ***bleeding***
  - PGE_2, PGI_2 autoregulate renal functions
    - Þ ***renal insufficiention***
  - ↑ LT production causes bronchoconstriction in predisposed individuals
    - Þ ***asthmatic attack***
  - uterus - ↓ PGE/F: inhibition of contractions
    - Þ ***elongation and complications of labor***

AE solution

- Dose reduction or change of drug form
- Combination with protective drugs
  - proton pump inhibitors (lansoprazol, omeprazol)
  - H_2 antihistaminics – (cimetidin ranitidin, famotidin)
  - antacids
  - prostaglandin analoges (substitution)
- possibly COX-2 selective drugs?

Rheumatic diseases – strategies of treatment

1. **NSAID**
2. **DMARDs + Biolog. treatment**
3. **Others antirheumatics**
   - steroid antiflogistics (= glucocorticoids)
   - cytostatics and antimetabolites
   - imunosupressants
   - proteolytic enzymes

Chronic treatment !

DMARDs

- **According to current czech guidelines:**
  - **Most often used DMARDs – antimalarics, sulfasalazin, metotrexate, leflunomid**
  - **Less often used – gold salts, azathioprin, cyklosporin A, cyklofosfamid**

DMARDs

- **chlorochin**
- **hydroxychlorochin**

} **antimalarics**

- **antiinflammatory and imunomodulant effects**
- **inhibition of leukocytar chemotaxis**
- **In less severe form of disease**
- **AE: skin problems, damage of retina**

DMARDs

sulfasalazin

- **Slow incerase in dosing → onset of effects in 1-2-months**

soli Au

- **Natrium aurothiomalate (i.m.), auranofin (p.o.)**
- **inhibit fagocytosis and thus also immune response**
- **30-40% AE: skin and mucosal problems, damage of haematopoiesis, hepatotoxicity, nephrotoxicity**

DMARDs

Leflunomid

imunomodulans (inhibition of pyrimidin synthesis)

USA – approved as a drug preventing rejection of organs in allotransplantation

DMARDs

Biological treatment

- targeted on immune cells and mediators taking part in development of RA
- anti-TNF drugs:
  - fast onset of effect, stop progression of disease but relapse happens after stopping the medication
  - risk of infections, CI vaccination with attenuated agents

AE: GIT, weakness, changes of blood pressure, infections, allergies

Infliximab, adalimumab

- rekombinant monoclonal Ab
- create a complex with TNF-α
- suitable combination with methotrexate

etanercept

- rekombinant protein of TNF receptor subunit + fragment of IgG = solubile TNF receptor

Others – rituximab, abatacerp

Other antirheumatics

1. Steroid antiinflammatory drugs
- glucocorticoids

2. Cytostatics and antimetabolites
- metotrexate
- azathioprin
- cyklofosfamid

3. Immunosupressants
- cyklosporin A

4. Proteolytic enzymes
- bromelain
- papain
- trypsin

Gout

Ethiology of gout

primary
- Genetically conditioned impairment in uric acid metabolism

⇒ Deposit of urates in cartilage and joints

secondary
- Excessive degradation of purines (eg. in cancer)
- Insufficient excretion of uric acid (kidney problem)
- Increased intake of uric acid in food (sea fruit, alcohol…)

- Problematic drugs
  - Low doses of ASA inhibit excretion
  - thiazid diuretics (hydrochlorothiazid)
  - immunosupressants

drugs **used in** gout

- Acute attack
- Therapy of hyperurikemia / prevention of attack

Therapy of acute attack

supression of inflammation, pain
inhibition of leucocytes migration into joint

Therapy of hyperurikemia / prevention of attack

excretion of uric acid
decrease in synthesis
diet

Acute attack

- 1st aid – fast relief form pain and supression of inflammatory processes
- NSAID
  - **diclofenac**, **indometacin**, **kebuzon**
- **kolchicin** (Colchicum autumnale) (autumn crocus, meadow saffron)
  - Mitotic toxin
- Inhibits fagocytosis and migration of leucytes
- AE – severe diarrhea –rehydratation!!

Chronic therapy

Urikosurics

probenecide

- Sometimes is used with ATB (antivirotics) to decrease their renal excretion and elongate half-life
- interactions:
  - salicylates
  - heparin - probenecid increase bleeding
- probenecide can influence levels of these drugs:
  - Indometacin, ketoprofen
  - methotrexate
  - nitrofurantoin – chemoterapeutic
  - zidovudin – antiretrovirotic

Chronic therapy

Urikosurics

Benzbromaron

inhibition of uric acid reabsorption in proximal tubulus

Hepatotoxic, withdrawn

Chronic therapy

Antiuratics

xo **xo**

- Hypoxantin ⇒ xantin ⇒ uric acid
- **Allopurinol**
- isomer of hypoxantin, competitive inhibition of xanthinoxidase (XO)
  - Should not be co-administered with drugs with purin-derived molecule (e.g. azathioprin, 6-merkaptopurin)