NSAID, antirheumatics, antipyretics

Doc. PharmDr. Jan Juřica, Ph.D.
Mgr. Barbora Ondráčková
MUDr. Jana Nováková, Ph.D.
PharmDr. Jana Rudá-Kučerová, Ph.D.
MVDr. Leoš Landa, Ph.D.

Notes for Pharmacology II practicals

This study material is exclusively for students of general medicine and stomatology in Pharmacology II course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.
Non-opioid analgesics

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

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

A-A and NSAIDs overlap partially

• **Antiuratics** – gout therapy
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 ⇒ inflammation, fever, pain

• **COX-3** – central mechanism of analgesic and antipyretic effect (localization: heart + CNS)
Glucocorticoids

Membrane phospholipides

Phospholipase A2

Arachidonic acid

Inh. 5-LOX

lipoxygenase

Inh. 5-LOX

Leucotrienes

NSAID

cycloxygenase

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 nociceptors sensitivity to bradykinin, histamine, serotonin and other pain mediators
  – PG induces vasodilation and $\uparrow$ 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)
Salicylic acid derivatives - drugs

sulfasalazine (\(\Rightarrow\) 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 antidiabeticss – 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, psychiatric 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
- indirect effect on 5-HT$_3$ spinal receptors
- elevates PGG$_2$ to PGH$_2$ conversion in peripheral tissues
Pharmacokinetics:

- p.o. good absorption, maximum in 30-60min, low protein binding, hepatic metabolism
- production of hepatotoxic mtb.
- binding to gluthathione

• overdose(10-15g)⇒ antidote: **N-acetylcysteine**
AE, CI

• **Allergy**
• **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 caffeine)
metamizole

- antiphlogistic and antipyretic effect
- AE – allergy, nausea, vomitus, nephrotoxicity, hematopoiesis inhibition
- Usually combined with spasmolytics
4. Propionic acid derivatives

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

Indications: muscle and postoperative pain, cephalgia, gynaecology
**Acetic acid derivatives**

**indomethacin**

- very strong nonselective COX inhibitor
- toxic \(\Rightarrow\) short-time treatment of acute states
- urikosuric effects
- used in gout attacks
- AE in 30 % of patients
  - GIT, cephalgia, depression, confusedness, hallucinations, hematoxicity, cartilages destruction
Acetic acid derivatives

sulindac
• prodrug– metabolite is 500x more potent
• adverse skin reactions

aceclofenac
• has significant analgesic and anti-inflammatory effect with good tolerance (low occurrence of GIT adverse effects) - higher adherence to treatment of chronic diseases
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
7. Oxicams

Iornoxicam

• balanced blockade of COX 1 and 2

• good therapeutic efficacy

• profitable safety profile (lower occurrence of GIT adverse effects – compared to other NSAIDs)
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 arthritis
- Does not influence platelet functions
• celecoxib

• parecoxib

• etoricoxib
  – 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 platelet 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)

• $\text{H}_2$ 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 (antiphlogistic) 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, hematopoiesis impair, liver and kidney toxicity
DMARDs

Biologic therapy
• targeted effect on the immune cells involved in rheumatoid arthritis 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 IgG1 fragment
• 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