Drug Therapy Today
in
Rheumatic Diseases

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A wide range of drugs are currently available for rheumatic diseases

- Analgesic drugs (acetaminophen, opioids)
- NSAIDs (analgesic and anti-inflammatory properties)
- Glucocorticoids (anti-inflammatory properties)
- DMARDs also referred to slow-acting anti-rheumatic drugs (SAARDs)
  - Have a very complex mode of action that often includes an immunomodulating, immunosuppressive or cytostatic component
Nonsteroidal anti-inflammatory drugs

• Act by inhibiting the synthesis of prostaglandins and thromboxanes, a group of lipid mediators formed from arachidonic acid
• Thanks to their analgesic, antipyretic and anti-inflammatory action NSAIDs are the drugs of first choice for the treatment of acute arthritis, chronic arthritis, ankylosing spondylitis and other inflammatory diseases e.g. degenerative diseases of joint and spine, and acute pain syndromes with rheumatic diseases of soft tissues
NSAIDs - mechanism of action

Arachidonic acid

- FAAH
- COX-1
- COX-2
- 5-LOX
- 15-LOX
- 12-LOX

Endocannabinoids
Prostaglandins (PGD$_2$, PGE$_2$, (PGF$_2$, PGI$_2$)
Thromboxanes (TXA$_2$)

Prostaglandins (PGE$_2$, PGI$_2$)

Leukotrienes (LTB$_{4}$, LTC$_{4}$, LTD$_{4}$, LTE$_{4}$)

Lipoxins 12-HETE
Common adverse effect of NSAIDs

- Nephrotoxicity
- Gastrointestinal toxicity
- Tocolysis
- Ophthalmic symptoms
- Can prolong bleeding time due to the inhibition of tromboxane A2 (TXA2)
- Drug interaction
Common used NSAIDs

- Acetylsalicylic acid (>3 g/daily)
- Arylpropionic acid (ibuprofen, naproxen)
- Arylacetic acid (diclofenac, indometacain)
- Thiazinecarboxamides (piroxicam, phenylbutazon)
- Selective COX-2 inhibitors (coxibs)
  - Gastrointestinal tolerance
  - Cardiovascular side effects, nephrotoxicity
Glucocorticoids in the treatment of rheumatic diseases

- First patient with RA to be treated with Cs was a 29-yrs old woman who lay bedridden following 4 yrs (widespread synovitis, severe progressive disease)

- After 3 daily i.m. injections of 100 mg hydrocortisone and she was symptomless and fully ambulant with dramatic response (21-st of September 1949)

- It was a fitting conclusion to 20 years of clinical and laboratory effort by Hench et al. which earned them Nobel Prize in Medicine and Physiology

- The introduction of Cs for RA treatment was greeted with widespread enthusiasm
Glucocorticoids - a variety of actions mechanisms

- The main anti-inflammatory effect is achieved by controlling the rate of synthesis of mRNA and proteins
- Increased of lipocortin synthesis and subsequent inhibition of phospholipase A2
- Reduced production of cytokines their activation, proliferation, differentiation and migration
- Reduced of inflammatory enzymes (collagenases, elastase and plasminogen activator)
- Alteration in T and B cell function (IL-1, IL-2, IL-4, IL-5, IL-6, INF-gamma)
**Glucocorticoids - a variety of actions mechanisms**

- Reduction of Fc and C3 receptor expression
- Changes in white cell traffic (in 4-6 hours and return to normal by 24 hours) due to large intravenous doses, the mechanism of basopenia is not known
  - ▲ neutrophils
  - ▼ lymphocytes, eosinophils and monocytes
- Stabilization of neutrophil lysosomal membranes
- Reduced NO synthesis im macrophages
Glucocorticoids - pharmacokinetics

- Rapidly absorbed from the GI tract and reversibly bound to plasma proteins
- At normal or low plasma concentration binding is largely to globulins
- At higher concentrations there is an increase in albumin-bound and free Cs
- In hypoalbuminemic patients highs dosages leads to high levels of free-Cs and increases side-effects
- Rapidly metabolized in the liver and conjugated and excreted in the urine. It disappears from the blood within 1.5-3 hours, having a half-life of 1 hour
Glucocorticoids - molecular mechanism of action
Glucocorticoids - complications

**MUSCULOSKELETAL**
- myopathy, osteoporosis - vertebral compression, fractures, aseptic necrosis of bone

**GASTROINTESTINAL**
- peptic ulceration (often gastric), gastric haemorrhage, intestinal perforation, pancreatitis

**CENTRAL NERVOUS SYSTEM**
- psychiatric disorders, pseudocerebral tumor

**OPHTALMOLOGICAL**
- Glaucoma, posterior subcapsular cataracts
Glucocorticoids - complications

- CARDIOVASCULAR AND RENAL
  - hypertension, sodium and water retention-oedema, hypokalemic alkalosis
- METABOLIC
  - diabetes mellitus, hyperosmolar non-ketotic coma, hyperlipidemia, induction of obesity
- ENDOCRINE
  - growth failure, secondary amenorrhoea, suppression of hypothalamic-pituitary adrenal system
- INHIBITION OF FIBROPLASIA
  - impaired wound healing, subcutaneous tissue atrophy
Glucocorticoids - complications

- SUPRESSION OF THE IMMUNE RESPONSE
  - superimposition of a variety of bacterial, fungal, viral and parastic infections in steroid-treated patients

*During long treatment every patient should practice osteoporosis prophylaxis: a daily calcium intake of 1500 mg, vitamin D of 1000 IU, physical exercise, in postmenopausal women hormone replacement therapy (HRT), bisphosphonates in high risk fractures patients*
Glucocorticoids — dosages and indications

- RA patients
  - 7.5 – 10 mg/daily of prednisone or methylprednisolone oral (low doses)
  - 20-40 mg of methylprednisolone intra-articular injections
- SLE, PAN (vasculitis) and PM/DM patients (high doses)
  - 1-2 mg/per kg/daily oral or pulses therapy (500-1000 mg of methylprednisolone intravenous for 3-5 consecutive days)
Disease Modifying Antirheumatic Drugs (DMARDs), also known as Slow-Acting Anti-Rheumatic Drugs (SAARDs)

based on today’s understanding, should be used as soon as possible after diagnosis in order to halt joint destruction
Onset of action of various disease-modifying drugs

- **After several days**
  - Biologicals – anticytokine therapy:
    - infliximab, etanercept, adalimumab, anakinra, indicated in the treatment of:
      - **rheumatoid arthritis (RA)**, **psoriatic arthritis (PA)**, **ankylosing spondylitis (AS)**, **juvenile chronic arthritis (JCA)**
  - Monoclonal antibodies anti CD 20 (rituximab) indicated in the treatment of: **rheumatoid arthritis (RA)**
Onset of action of various disease-modifying drugs

• **After 1-3 months**
  - Leflunomide: RA
  - Metothrexate: RA, SLE
  - Cyclosporin: RA, SLE, DM/PM
  - Cyclophosphamide: RA, SLE, DM/PM, PSS, PAN (vasculitis)
  - Sulfasalazin: RA, AS
  - Azathioprine: RA, SLE, DM/PM, PSS
Onset of action of various disease-modifying drugs

- After 4 to > 6 months
  - Chloroquine: **RA, SLE**
  - Hydroxychloroquine: **RA, SLE, SS**
  - Auorothioglucose: **RA**
  - Auranofin: **RA**
  - D-penicillamine: **RA, PSS**