
1. NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

Classification

- Salicylate derivatives:
  - Acetylsalicylic acid
  - Other salicylates: Diflunisal, Sodium salicylate
- Propionic acid derivatives: Ibuprofen, Ketoprofen, Naproxen, Fenoprofen, Piroprofen, Carprofen, Oxaprozin, Tiaprofen;
- Phenylalkanoic acid derivatives: Flurbiprofen
- Acetic acid derivatives: Etodolac;
- Phenyl acetic acid derivatives: Diclofenac;
- Pirolacetic acid derivatives: Tolmetin;
- Sulfoxides: Sulindac;
- Indol derivatives: Indomethacin;
- Ketones: Nabumetone;
- Pirazolone derivatives: Phenylbutasone, Oxiphenylbutasone, Azapropazone;
- Oxicams: Piroxicam, Ampiroxicam, Meloxicam, Tenoxicam, Droxicam;
- Fenamates: Mefenamic acid, Meclofenamate, Flufenamic acid, Tolfenamic acid, Niflumic acid;
- Other structures: Pirfenidone; Tenidap; Nimesulid; COX-2 inhibitors (Celecoxib, Parecoxib, Valdecoxib, Etoricoxib).

SALICYLATE DERIVATIVES: ACETYLSALICYLIC ACID

Molecular mechanisms of action

- Anti-inflammatory:
- prostaglandin-mediated mechanisms:
  - irreversibly inhibition of COX-1, COX-2 and COX-3;
  - competitive antagonist of receptors for PGE1 and PGF2alfa;
- non-prostaglandin mechanisms:
  - inhibits migration of neutrophils and macrophages into inflammatory site;
  - inhibit the adhesion of PMN to endothelial cells and between them;
  - inhibits the synthesis and release of oxygen free-radicals (in particular, superoxide anion) from the PMN;
  - inhibit the proteolytic enzymes from the monocytes;
  - inhibits the activation of lysosomes and the release of lysosomal enzymes from the monocytes;
  - inhibits the synthesis of collagenases from the monocytes;
  - inhibits the synthesis and the release of osteoclast activating factor;
  - inhibits the rheumatoid factor;
  - inhibits the kinins;
  - inhibits the synthesis of mucopolysaccharides, of proteoglycans and of glycosaminoglycans;
  - inhibits the release of proinflammatory cytokines from synovial cells;
  - stimulates suppressor T lymphocytes.

- **Antipyretic:**
  - central mechanism:
    - inhibit COX in the CNS;
    - inhibits the synthesis and the release of IL-1 from the hypothalamus;
  - peripheral mechanism:
    - vasodilation and sweating which causes heat loss;
    - decreases the sensitivity of peripheral receptor for IL-1.

- **Analgesic:**
  - central mechanism: inhibition of subcortical centers of pain;
  - peripheral mechanism: pain decreases due to the inflammatory effect.

- **Antiplatelet effect:**
  - inhibit thromboxane synthase (this will inhibit the release of thromboxane A2) – this effect occurs only at low doses (80-325 mg/day); when the dose increases, the effect is lost; the effect duration is 5-7 days after the last dose.

**Pharmacokinetics**

- Absorption is good after oral administration (salicylates are absorbed from the gastric and duodeno-jejunal mucosa).
- T1/2 is short (15 minutes) because it is rapidly metabolised by plasma and tissue esterases resulting acetate and salicylate. Salicylate is the active metabolite (it has long t1/2), which is metabolized by conjugation and eliminated unchanged or by renal tubular secretion. Salicylate kinetics is saturable, readily crosses the physiological barriers (including the blood-brain barrier and the placenta), it is concentrated into the synovial liquid.

**Indications:**

- antiplatelet (at doses between 70-80mg/zi and 325mg/zi);
- analgesic;
- antipyretic;
- inflammatory;
- other indication for doses with antiplatelet effect: to slow cataract development, to reduces the frequency of colon cancer.

**Contraindications:**

- peptic ulcer;
- young children with viral febrile illness (viral respiratory infections, measles, chickenpox);
- asthma and other allergies;
- pregnancy, lactation;
- severe renal impairment, hepatic impairment;
- haemophilia A;
- endogenous psychoses.

**Adverse and toxic effects**

- Gastrointestinal (also for doses with antiplatelet effect) from superficial ulceration and microbleeds, to perforation of the digestive mucosa.
- Liver: acute liver failure (Reye syndrome) in young children with febrile viral infections, hepatitis in patients with asymptomatic chronic autoimmune disease (lupus, rheumatoid arthritis).
- Renal: retention of water and NaCl, interstitial tubulopathy.
- Bronchitis: bronchoconstriction (only in people with asthma).

- Hematologic:
  - toxic dose: anticoagulant effect (toxic doses inhibit coagulation factors in the liver);
  - those with collagen: autoimmune hemolytic anemia.
- Cardiovascular: toxic dose determine vasodilation (hypotension) and myocardial depression.
- CNS
  - low doses: discrete euphoric effect;
  - high doses: stimulate the respiratory center (hypercapnie), salicylism (deafness, tinnitus, vertigo);
  - Toxic dose: inhibition of the respiratory center (causes metabolic acidosis), hyperthermia, hallucinations, delirium, coma.
- immunosuppression on the cellular components (suppressor T lymphocytes are stimulated).
- immunological reactions type I and type III.
- worsening of articular cartilage lesions.
- Other effects:
  - inhibition of respiratory enzymes tissue, inhibition of ATP-dependent reaction (producing uncoupling of oxidative phosphorylation);
  - at doses ≤ 2 g / day increase uricemia;
  - at ≥ 4 g / day decrease uricemia.

Interactions
- Do not associate acetylsalicylic acid:
  - in antiplatelet doses with nitrite/nitrate because increase the risk of bleeding (can be done under the supervision of cardiologist);
  - with other NSAIDs, uricosuric drugs (probenecid, sulfinpyrazone), phenytoin, methotrexate, oral antidiabetic because they increase plasma concentrations of acetylsalicylic acid due to displacement from plasma proteins;
  - Glucocorticosteroids lowers plasma levels of salicylates;
  - Acetylsalicylic acid decrease the diuretic diuretics and natriuretic effects of loop diuretics (decrease also furosemide antihypertensive effect), reduces the pharmacological activity of spironolactone;
  - Acetazolamide increase the elimination of salicylates;
  - Acetylsalicylic acid competes with Penicillin G for renal tubular secretion mechanism;
  - Ammonium chloride decreases the clearance of salicylates;
  - Alcohol aggravates gastrointestinal bleeding caused by salicylates.

OTHER SALICYLATE DERIVATIVES: COLINSALICILAT SODIUM, SODIUM SALICYLATE, MAGNESIUM SALICYLATE, SODIUM TIOSALICILAT, SALICILSALICILIC ACID (SALSALATE), DIFLUNISAL


Pharmacodynamic effects: weak anti-inflammatory, analgesic and antipyretic effects of moderate, compared with aspirin.

Advantages: less focus in the synovium, articular cartilage harm less can be administered to individuals with haematological, renal, bronchial.

Indications: chronic rheumatic inflammatory diseases (rheumatoid arthritis, osteoarthritis, etc.), analgesic (biliary colic, dysmenorrhea etc).

Adverse effects and contraindications: similar to acetylsalicylic acid.

DIFLUNISAL:
- antipyretic effect is weak than aspirin;
- action is longer; it is less gastric irritative than acetylsalicylic acid; it forms salicylate and acetate by metabolism.

PROPIONIC ACID DERIVATIVES: IBUPROFEN, KETOPROFEN, NAPROXEN, FENOPROFEN, PIRPROFEN, CARPROFEN, OXAPROZIN, TIAPROFEN
Ketoprofen inhibits also lipoxygenase and leukotriene B4 synthesis.
Pharmacodynamic effects:
- antiinflammatory effect (medium intensity);
- analgesic (Pirprofen has the strongest analgesic effect from these derivatives);
- antipyretic effect (medium intensity compared with acetylsalicylic acid);
- antiplatelet effect (independent of dose).
Pharmacokinetics: rapid absorption, t1/2 short (except: Ketoprofen, Naproxen, Oxaprozin, Carprofen). Ketoprofen is bound on plasma proteins (99%), but does not interfere with the plasma transport of coumarin oral anticoagulant or cardiac glycosides.
Indications:
- inflammatory diseases: chronic rheumatic diseases (rheumatoid arthritis, osteoarthritis, etc.), ENT diseases, dentistry, gynecology, etc.;
- analgesic in dysmenorrhea, postoperative, biliary colic, etc.
- other indications:
  - Ibuprofen: migraine, antipyretic and analgesic in children;
  - Ketoprofen, Naproxen: acute gout; Oxaprozin: chronic therapy of gout;
  - Pirprofen: analgesic in cancer (advantage: does not cause addiction, does not cause constipation).
Contraindications: peptic ulcer, hemophilia, severe renal failure, hepatic failure, heart failure, severe hypertension, acute myocardial infarction, asthma (except ketoprofen), pregnancy, lactation, children (except Ibuprofen).
Adverse effects:
- CNS: tinnitus, hearing loss, vertigo, headache; asymptomatic meningitis in patients with lupus;
- lower gastrointestinal events compared with aspirin: irritation of the mucosa, ulceration, bleeding;
- retention of water and NaCl;
- other: medulotoxicity ( aplastic anemia, granulocytopenia, agranulocytosis), nephrotoxicity (interstitial nephritis, nephrotic syndrome, acute renal failure), hepatotoxicity, immunological reactions type I, II, III.
Interaction: Ketoprofen is the only NSAID that can be administered to patients receiving coumarin oral anticoagulants or digitalis.

FENILALCANOIC ACID DERIVATIVES: FLURBIPROFEN
Mechanism of action: inhibition of COX-1 = COX-2;
Pharmacodynamic effects: moderate anti-inflammatory and analgesic effects, mild antipyretic effect compared to aspirin.
Pharmacokinetics: enterohepatic circulation, concentrates well in the synovial liquid.
Indications:
- chronic rheumatic inflammatory diseases (rheumatoid arthritis, osteoarthritis, ankylosing anilopoeitica, juvenile arthritis, etc.);
• analgesic in biliary colic, dysmenorrhea, migraine, surgery etc.
• intraoperatively topic in ophthalmology (to prevent myositis).
Adverse effects: reduced frequency of gastrointestinal symptoms (15-20% of patients treated po), granulocytopenia, autoimmune haemolytic anemia.

ACETIC ACID DERIVATIVES: ETODOLAC
Mechanism of action: inhibition of COX-1 < COX-2;
Pharmacodynamic effects: anti-inflammatory effect (medium intensity as compared with aspirin). Advantage: it can greatly reduce acute gastric lesions.
Indications: inflammatory joint diseases (rheumatoid arthritis, osteoarthritis, ankylosing ankiopoetic etc).
Adverse effects: similar to other NSAIDs; headache, sleepiness / insomnia, confusion, paraesthesia, tremor, rash.

PHENYLACETIC ACID DERIVATIVES: DICLOFENAC
Mechanism of action: inhibition of COX-1 = COX-2;
Pharmacodynamic effects: strong anti-inflammatory, analgesic.
Advantages: high concentrations in the synovial liquid, cartilage injuries do not worsen.
Pharmacokinetics: absorption is very good; metabolism is hepatic, present first-pass effect and enterohepatic circulation; elimination is through kidney (2/3) and bile (1/3).
Indications:
• inflammatory joint diseases (rheumatoid arthritis, osteoarthritis, etc.) and extraarticular;
• acute gout crisis;
• analgesic in biliary colicative pain, renal surgery, phlebitis, thrombophlebitis, osteoarticular trauma, dysmenorrhea etc;
• prophylaxis of myositis in ophthalmology.
Adverse effects:
• gastrointestinal irritation (it is very strong);
• retention of salt and water (it is very strong);
• increase serum transaminases;
• medulotoxic (granulocytopenia) and nephrotoxic – these effects are weak.

PIROLACETIC ACID DERIVATIVES: TOLMETIN
Mechanism of action: inhibition of COX-1 < COX-2;
Pharmacodynamic effects: anti-inflammatory, analgesic, antipyretic (medium intensity).
Pharmacokinetics: it present enterohepatic circulation, t1/2 is short.
Advantage: it can greatly reduce acute gastric lesions.
Indications: rheumatoid arthritis, osteoarthritis, ankylosing ankiopoetică, juvenile arthritis.
Adverse effects: like other NSAIDs; allergic reactions.

SULFOXIDES: SULINDAC
It is a prodrug.
Pharmacokinetics: in the liver it is biotransformed into active metabolite (sulfide), present enterohepatic circulation.
Indications:
• inflammatory joint diseases (rheumatoid arthritis, osteoarthritis, etc.);
• analgesic.
Adverse effects:
- gastrointestinal irritation (ulcers, gastrointestinal bleeding);
- medulotoxicity (aplastic anemia, agranulocytosis);
- nephrotoxicity;
- increase serum transaminases;
- immunological reactions type I and III.

**INDOLE DERIVATIVES: INDOMETHACIN**

_MEchanism of action:_ inhibition of COX-1 >> COX-2.

_Pharmacodynamic effects:_ strong anti-inflammatory effect, very weak analgesic effect, medium intensity antipyretic effect.

_Pharmacokinetics:_ very good absorption; elimination through kidneys.

_Indications:_
- inflammatory joint diseases (rheumatoid arthritis, osteoarthritis, etc.);
- extraarticular inflammatory disorders (pericarditis, pleuritis, pleurisy, uveitis, etc);
- acute gout;
- analgesic in biliary colic, renal surgery, dysmenorrhea etc.
- patent ductus arteriosus in the newborn;
- fever (from Hodgkin’s disease, fever refractory to other therapies).

Adverse effects:
- gastrointestinal irritation (it is very strong): abdominal pain, ulcers, bleeding, diarrhea, hemorrhagic pancreatitis, cholestatic jaundice, acute toxic hepatitis;
- retention of salt and water (it is very strong);
- CNS: headache, dizziness, mental depression, hallucinations, psychosis, nightmares, delirium;
- articular cartilage injuries;
- medulotoxicity (aplastic anemia, neutropenia, thrombocytopenia);
- nephrotoxic (it is very strong);
- hyperkalaemia;
- retinal lesions (after chronic administration of high doses);
- immunological reactions type I and III.

**KETONES: NABUMETONE**

It is a prodrug.

_MEchanism of action:_ inhibition of COX-1 = COX-2.

_Pharmacokinetics:_ the compounds of metabolism are more active than the parent compound.

_Indications:_ rheumatoid arthritis, osteoarthritis.

_Adverse effects:_ diarrhea, nausea, abdominal pain, headache; rash; increased serum transaminases.

**PYRAZOLONE DERIVATIVES: PHENYLBUTAZZONE, OXIFENILBUTAZZONE, AZAPROPAZON**

_MEchanism of action:_ inhibition of COX-1> COX-2;

_Pharmacodynamic effects:_ strong anti-inflammatory, analgesic, antipyretic effects.

_Pharmacokinetics:_ absorption is very good; it is bound to plasma proteins (>90%); hepatic metabolism to active compounds; elimination through kidney, t1/2 long.
Indications:
- chronic rheumatic inflammatory diseases (rheumatoid arthritis, osteoarthritis, ankylosing anklipoetică etc.);
- thrombophlebitis, thrombosis, muscle pain, frostbite;
- acute gout.

Adverse effects: gastrointestinal irritation (superficial ulcers, gastrointestinal bleeding) water and salt retention, hepatotoxicity, nephrotoxicity, medulotoxicity (aplastic anemia, agranulocytosis, granulocytopenia), optic neuritis, immunological reactions type I and II.

OXICAMS: PIROXICAM, AMPYROXICAM, MELOXICAM, TENOXICAM, DROXICAM
Mechanism of action: inhibition of COX-1 and COX-2; Piroxicam inhibits COX-1 >> COX-2; Meloxicam is relatively selective COX-2.
Pharmacodynamic effects: anti-inflammatory and analgesic effects are stronger.
Pharmacokinetics: absorption is not influenced by food; they are highly bound to plasma proteins (99%); renal elimination, very long t1/2 (Tenoxicam has the longest t1/2).
Advantages: high concentrations in the synovial liquid, less articular cartilage injuries.

Indications:
- inflammatory rheumatic joint diseases (rheumatoid arthritis, osteoarthritis, ankylosing anklipoetică etc.) and extraarticular (periarthritis, tendinitis);
- acute gout.

Adverse effects: CNS (headache, vertigo, tinnitus); the gastrointestinal irritation is uncommon; retention of water and salt; immunological reactions type I and III.

FENAMATES: MEFENAMIC ACID, MECLOFENAMATE, FLUFENAMIC ACID, TOLFENAMIC ACID, NIFLUMIC ACID
Mechanism of action: inhibition of COX-1 and COX-2;
Pharmacodynamic effects: strong analgesic effect, weak anti-inflammatory effect.
Determine severe injuries of:
- articular cartilages (the administration in adults should be for less than 1 week);
- cartilage growth (absolute contraindication for children with less than 18 years).

Indications: analgesic in rheumatic diseases, dysmenorrhea, thrombophlebitis, traumatic pain in ENT, gynecology, etc..

Adverse effects:
- meclofenamate, flufenamic acid determine diarrhea;
- mefenamic acid determine diarrhea, rash;
- niflumic acid determine gastrointestinal irritation, prolonged administration causes impairment in renal and hepatic function, hematologic disorders.

NIMESULIDE
Mechanism of action: selectively inhibits COX-2, inhibits neutrophil activation, inactivate oxygen free radicals.
Pharmacokinetics: an active compound is formed by metabolism.
Indications:
- articular and extraarticular inflammatory diseases;
- antipyretic;
- analgesic.

Adverse effects: rash, headache, nausea, vomiting, abdominal pain.
SELECTIVE COX-2 INHIBITORS: CELECOXIB, PARECOXIB, VALDECOXIB, ETORICOXIB

Pharmacodynamic effects: inhibits natriuresis, causes retention of water and NaCl.
Pharmacokinetics: well absorbed (lipophilic food delays the absorption of Celecoxib); metabolised in the liver (Parecoxib is transformed into an active compound: Valdecoxib); renal elimination.
Indications:
- inflammatory joint disease (osteoarthritis, rheumatoid arthritis);
- analgesic.
Adverse effects: gastrointestinal effects of low intensity (nausea, diarrhea, bleeding), edema of lower limbs, hypertension.
Contraindications: renal failure.

2. ANALGESIC – ANTIPYRETIC DRUGS WITHOUT ANTI-INFLAMMATORY EFFECT

Classification:
- Pirazolone derivatives: Aminofenasone; Metamizole;
- Phenacetine and its active metabolite, Acetaminophen;
- Zomepirac.
- Ketorolac.
Mechanism of action: inhibition of COX.
Pharmacodynamic effects: analgesic and antipyretic.

METAMIZOLE (OR DIPYRONE)
Aminofenazone (aminopyrine) is no longer used in therapy. Its derivative, Metamizole (or Dipyrone) it is used in some countries.
Pharmacodynamic effects of Metamizole: analgesic (very efficient for renal or biliary collicative pain, dysmenorrhea) and antipyretic.
Adverse effects: allergic reactions, medulotoxicity (aplastic anemia, granulocytopenia) hepatotoxicity.

ACETAMINOPHEN
Phenacetin is no longer used in therapy. It has powerful analgesic and antipyretic effect, but no anti-inflammatory effect. It is strongly nephrotoxic.
Pharmacodynamic effects of Acetaminophen: strong analgesic (postpartum in migraine, dysmenorrhea) and antipyretic.
Pharmacokinetics: Acetaminophen is the active metabolite of phenacetin. It is metabolized to N-acetyl-p-benzakinone (strong hepato- and nephrotoxic compound).
Indications: analgesic and antipyretic (it is drug of choice in children with viral infections).
Adverse effects: hepatotoxicity, haematological (leukopenia, thrombocytopenia, aplastic anemia, hemolytic anemia in G6PD deficiency), methemoglobinemia.
Acute acetaminophen poisoning: the antidote is N-acetylcysteine.

ZOMEPIRAC
Zomepirac was withdrawn from market in some countries due to its medulotoxicity.

Pharmacodynamic effects: strong analgesic, moderately antipyretic effect.

KETOROLAC
It is derived from acetic acid.

Pharmacodynamic effects: strong analgesic (preferably postoperative opioids instead).

Adverse effects: gastrointestinal irritation, nephrotoxicity, abrupt discontinuation (after 2 weeks of dosing) cause withdrawal effects.

3. DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Classification:
1. Antimalarial drugs: Chloroquine, Hydroxichloroquine;
2. Gold compounds: Sodium aurothiomalate, Aurothioglucone, Auranofin;
3. Penicillamine;
4. Sulfasalazine.
5. Immunosuppressants:
   - Cyclosporine;
   - alkilating agents: Ciclophosphamide, Chlorambucil;
   - purine agonists: Azathioprine, Mercaptopurine;
   - antimetabolites: Methotrexate;
   - other immunosuppressants: Leflunomide.
   - nonselective immunomodulating drugs: Levamisol; Lobenzaride.

Effects occurs after:
- 1-3 months of treatment for antimalarial drugs;
- 4 months of treatment for organic compounds with gold;
- 3-4 months for D-penicillamine treatment.

CHLOROQUINE, HYDROXYCHLOROQUINE

Mechanisms of action:
- stabilize lysosomal membranes by inhibiting lysosomal enzymes;
- block migration of neutrophils and macrophages;
- inhibit the nucleic acid synthesis by inhibiting DNA and RNA polymerase;
- inhibit phospholipase A2;
- decrease cytokine production by phagocytes.

Indications:
- chronic autoimmune diseases (rheumatoid arthritis, SLE, etc.);
- antimalarial and antiprotozoar (against Entamoeba histolytica).

Adverse effects:
- gastrointestinal symptoms, headache, pruritus, anorexia, clouding vision, urticaria;
- medulotoxicity (haemolytic anemia in G6PD deficiency);
- CNS symptoms (headache, vertigo, tinnitus, psychosis, convulsions);
- other: skin reactions, alopecia / thinning of hair, hypotension, ECG changes (changes in T wave, QRS widening).

**Contraindications:** psoriasis, porphyria, abnormal retinal and other eye disorders, chronic hepatitis, hepatic dysfunction, alcoholism, haematological, neurological diseases.

**ORGANIC COMPOUNDS WITH GOLD: AUROTHIOMALAT SODIUM AUROTHIOGLUCÖZĂ, AURANOFIN**

**Mechanisms of action:**
- stabilize lysosomal membranes by inhibiting lysosomal enzymes;
- inhibit the formation and release of inflammatory mediators;
- inhibit the release of oxidizing radicals;
- inactivation of complement;
- Auranofin inhibits PGE2 release from synovial cells.

They are concentrated into the synovial liquid.

**Indications:** rheumatoid arthritis, polyarticular juvenile.

**Adverse effects:** skin pigmentation, pancytopenia, nephrotic syndrome, hepatotoxicity, peripheral neuritis.

**Contraindications:** association with D-penicillamine, pregnancy, lactation, hepatic / renal failure.

**D-PENICILLAMINE**

It is a metabolite of penicillin.

**Mechanisms of action:**
- chelating agent for gold, copper, mercury, arsenic;
- stabilize lysosomal membranes by inhibiting lysosomal enzymes;
- inhibit the synthesis of collagen and mucopolysaccharides;
- inhibit the rheumatoid factor;
- complement inactivation.

**Indications:**
- rheumatoid arthritis unresponsive to treatment with gold compounds;
- heavy metal poisoning;
- Wilson disease.

**Adverse effects:**
- hematologic: leukopenia, thrombocytopenia, aplastic anemia;
- autoimmune diseases: myasthenia gravis, lupus, hemolytic anemia, thyroiditis, Goodpasture's syndrome;
- proteinuria, nephritis;
- metallic taste, anorexia, nausea, vomiting;
- alopecia.

**Contraindications:** pregnancy, lactation, chronic renal failure, allergy to penicillin.

**SULFASALAZINE**

It contains a molecule 5-aminosalicylic acid bound to sulfapyridine by a diazo bond.

**Mechanism of action:** dose of 2 g/day in the colon it is split the azo bond and it is released the active 5- salicylate.

**Indications:**
- rheumatoid arthritis, juvenile arthritis, ankylosing ankllopoeiță;
- Crohn's disease.

**Adverse effects:** nausea, vomiting, abdominal discomfort, headache, inhibit the absorption of folic acid, allergic reactions, severe spinal marrow depression, neurological or psychiatric disorders.
LEFLUNOMIDE
It is a prodrug.

Mechanisms of action:
- relatively selective inhibition of COX-2;
- inhibits the release of inflammatory mediators (histamine, 5-HETE);
- inhibits T and B lymphocyte proliferation and antibody response of B cells by blocking dihydro-orotic dehydrogenase (block pyrimidine synthesis);
- inhibits IL-2 and TGF-alpha;
- inhibit gene expression (granzyme B and perforin) involved in the rejection of transplanted tissue;
- stimulation of macrophage functions and inhibition of postreceptor signal transmission biological of IL-4.

Pharmacodynamic effects: immunosuppression, antiinflammatory.

Indications:
- rheumatoid arthritis, myasthenia gravis, lupus, autoimmune nephritis, allergic encephalomyelitis
- prevent acute rejection of allogeneic tissue transplants;
- prevention infestation with Leishmania major, with Listeria monocytogenes.

Adverse effects:
- increases blood pressure, rash, ulcers, abdominal pain, diarrhea, increase serum transaminases.

Therapeutic efficiency is equal to or better than cyclophosphamide, adverse effects are less severe.

LEVAMISOLE

Mechanisms of action:
- promotes differentiation and maturation of T lymphocytes;
- normalizes regulatory functions of T cells;
- stimulates the formation of suppressor T lymphocytes;
- increases phagocytic activity of macrophages and granulocytes;
- increases circulating immune complexes;
- oxygen free-radical scavenger.

Adverse effects: blood dyscrasias (leukopenia, agranulocytosis, thrombocytopenia), rash, mucosal ulcers, influenza-like disease, abnormal taste, nausea, vomiting, reversible immune glomerulonephritis type headache, dizziness, drowsiness / excitation, hypotension, fever.

Indications:
- rheumatoid arthritis;
- chronic hepatitis (type B, toxic, autoimmune), biliary cirrhosis, chronic pancreatitis;
- as adjuvant in recent gynecological inflammation, pulmonary tuberculosis, glomerulonephritis and nephrotic syndrome resistant to corticosteroids, warts, erosive or ulcerative injuries of the gastrointestinal tract, oligospermia, Hodgkin's disease, colorectal cancer, gastrointestinal choriocarcinoma, breast cancer, lung cancer, malignant melanoma, kidney cancer;
- schizophrenia.

Contraindications: hepatic or renal impairment.
LOBENZARIDE

Mechanisms of action:

- enhances the proliferation and differentiation of helper T cells;
- stimulates NK cell activation;
- stimulates the production of IFN-alpha;
- decreases production of IL-1 in human mast cells;
- increases expression of receptors for the Fc fragment of Ig on human lymphocytes;
- inhibits T cell proliferation by inhibiting cytokine production by macrophages.

Indications: rheumatoid arthritis.

4. DRUGS USED IN GOUT

ACUTE ATTACK OF GOUT:
- Colchicine
- NSAIDs: Indomethacin, Ibuprofen, Ketoprofen, Naproxen, Phenylbutasone, Piroxicam, Tenoxicam, Diclofenac

COLCHICINE

Mechanisms of action:

- inhibits tubulin polymerization in macrophages;
- inhibits the movement of macrophages to uric acid crystals (prevents the phagocytosis of crystals);
- inhibits leukocyte migration into the inflammatory site;
- inhibits release of lysosomal enzymes and proinflammatory mediators;
- inhibits the formation of leukotrienes B4.

Pharmacokinetics: rapid gastrointestinal absorption, wide tissue distribution (gastro-intestinal mucosa, liver, kidney, intraleucocitar) slow elimination in the feces (70%) and urine.

Indications:
- gout: treatment and prophylaxis of acute crisis (in combination with uricosurics);
- other indications: amyloidosis, family mediterranean fever.

Adverse effects:
- gastrointestinal (diarrhea, nausea, vomiting, abdominal pain);
- rare: blood dyscrasias (leukopenia, neutropenia, agranulocytosis, aplastic anemia), rash, alopecia, azoospermia, anovulatory cycles.

Contraindications: severe renal or hepatic impairment, pregnancy, lactation.

LONG-TERM CONTROL OF GOUT

Drugs used for long-term control of gout:
- xanthine-oxidase inhibitors: Allopurinol.
- uricosuric drugs: Probenecid, Oxaprozin, Sulfinpyrazone.
ALLOPURINOL

**Mechanism of action:** inhibits xanthine oxidase (decrease xanthine and hypoxanthine oxidation).

**Pharmacodynamic effects:** decreases uricemia (blood concentrations of uric acid) and increases elimination of uric acid through urine.

**Pharmacokinetics**
- rapid gastrointestinal absorption, it is metabolised to an active compound (aloxantine) with weak action of xanthine oxidase inhibition;
- wide tissue distribution (gastrointestinal mucosa, liver, kidney, intraleucocitar);
- slow elimination in the feces (70%) and urine.

**Indications:** treatment of gout.

**Adverse effects:** gastrointestinal symptoms (epigastric pain, nausea, diarrhea), itchy rash, vasculitis, inhibition of hematopoiesis (leukopenia), liver and kidney damage.

**Contraindications:** acute gout attacks, pregnancy, lactation, renal or hepatic impairment.

PROBENECID

**Mechanism of action:** inhibition of tubular reabsorption of uric acid.

**Indications:** treatment of gout.

**Adverse effects:** gastrointestinal irritation, allergic skin reactions, uric kidney stones.

**Contraindications:**
- acute gout attacks;
- hyperuricaemia secondary to hematologic malignancies;
- peptic ulcer;
- renal failure;
- deficiency in G6PD.

**Interaction:**
- delay elimination of Penicillin G, indomethacin, sulphonylurea antidiabetic drugs, methotrexate, iodinated derivatives;
- uricosuric action of is reduced by salicylates or thiazide diuretics.

SULFINPYRAZONE

**Mechanism of action:** inhibition of tubular reabsorption of uric acid.

**Pharmacodynamic effects:**
- uricosuric effect stronger than Probenecid, but is more toxic.
- antiplatelet effect.

**Indications:** treatment of gout.

**Adverse effects:** gastrointestinal irritation (ulcer or gastrointestinal bleeding), allergic skin reactions, bone marrow depression.

**Contraindications:** peptic ulcer, renal or hepatic impairment, pregnancy.

**Interaction:**
- decreases the clearance of oral antidiabetic drugs, oral anticoagulants;
- acetylsalicylic acid inhibits its uricosuric effect.