Non-opioid analgesics

Prostacyclins:

NSAIDS effect on kidney:

Non-opioid analgesics are drugs that have an analgesic, antipyretic and partly antiphlogistic effect. Their common feature is *influencing the metabolism of prostaglandins*. However, the differences in their effects indicate the presence of other mechanisms that remain unclear[1].

Mechanism of action

Non-opioid analgesics inhibit **cyclooxygenase (COX)**, an enzyme involved in the synthesis of prostaglandins. Cyclooxygenase has two isozymes:

- **COX-1** (constitutive isoenzyme) synthesizes prostaglandins (e.g. PGE_2, PGF_2), which affect a number of physiological functions: protection of the gastric mucosa, increasing blood flow in the kidneys, excretion of Na^+, toning of the uterus, bronchodilation. COX-1 is important for the synthesis of **thromboxane A2 (TXA_2)**, produced by activated platelets. TXA_2 increases their adhesiveness and induces vasoconstriction. COX-1 inhibition therefore has antiplatelet effects and is protective in patients at risk of developing myocardial infarction (MI) or stroke.
- **COX-2** (induced isoenzyme) is activated during inflammation; the resulting prostaglandins sensitize nocisensors, promote inflammation and fever (by resetting the thermoregulatory center in the hypothalamus). COX-2 is important for the production of *prostacyclin (PGI_2)*, which inhibits platelet aggregation and causes vasodilation.

The **antipyretic effect** is given not only by readjusting the hypothalamic thermoregulatory center, but also by influencing vasodilation, or perspiration.

Nonsteroidal anti-inflammatory drugs have **anti-inflammatory effects** only in **higher doses**, when they inhibit the synthesis of prostaglandins, chemotaxis, IL-1 released from macrophages and reduce the production of free radicals.

Analgesic effects occur due to a reduction in the synthesis of prostaglandins, which sensitize nociceptors to inflammatory mediators (bradykinin). We use them mainly for muscle and vascular pain, headache, toothache, dysmenorrhea and in combination with opioids to reduce postoperative pain in surgery. It therefore acts on **somatic pain'**, not visceral.

'*Antiaggregation effect* is shown only by some representatives, mainly ASA. Vzhledem k nežádoucím účinkům způsobených inhibicí COX-1 byla snaha najít selektivní COX-2 inhibitory. Byly objeveny **koxiby** – způsobují méně vředů a krvácivých projevů, některé však zvyšují riziko tromboembolických komplikací.

COX-1 inhibition has an antiplatelet effect. It causes an irreversible COX blockade in platelets, so it is enough to give low doses of *acetylsalicylic acid (ASA)* once a day to achieve the desired effect. Only ASA acts as an irreversible COX block. This is manifested in the absence of a medicinal substance in the body only in thrombocytes, which do not have their own proteosynthetic apparatus and are therefore unable to synthesize new COX, like other cells. The effect of ASA on platelets fully wears off in 7 days (platelet lifespan 7-10 days).

When cyclooxygenase is inhibited, the metabolism of arachidonic acid goes more through the lipooxygenase pathway, and therefore there is a higher production of leukotrienes. Therefore, an asthma attack may occur after administration of these drugs.

Pharmacokinetics

Bioavailability is satisfactory, due to good absorption from the GIT, they undergo enterohepatic circulation.

Regarding distribution, remember that nonsteroidal anti-inflammatory drugs have a high binding to plasma proteins (CAVE: warfarin, sulfonamides, p.o. antidiabetics). They also have good penetration into tissues and body fluids (including synovial fluid). They pass through the blood-encephalic and placental barriers.

There are a number of **medicinal forms'**. For systemic administration, we can choose i.v., i.m., p.o. forms (tablets, capsules, syrups) or suppositories per rectum. Various sprays, gels, emulgels, plasters and creams can be used for local administration, with which, however, it is necessary to think about possible photosensitivity - especially with ketoprofen and ibuprofen.

Side effects

They are often the result of patient non-compliance in the sense of "too often, too much".

- Digestive system (50% of all adverse effects) - caused by reduced synthesis of PGE2 and PGI (responsible for blood supply to mucous membranes, mucus production and inhibition of HCl secretion), which leads to manifestations of dyspepsia, gastroesophageal reflux, erosions, micro or macro bleeding and an increased risk of developing gastroduodenal ulcers. We have to take into account the increased risk even with low doses of ASA, protection is the administration of proton pump inhibitors.
- **Increased bleeding** (mainly ASA) - blockade of TXA2 synthesis leads to irreversible inhibition of platelet aggregation (*for 7-10 days*).
- Bronchoconstriction and asthma attack (mainly ASA), allergy – a rarer complication caused by increased synthesis of leukotrienes when the cyclooxygenase pathway is blocked.
- **Kidneys –** *retention of fluids and Na+'*, **reduction of the effect of antihypertensives**, changing the hemodynamic conditions (prostaglandins by RAAS balance) in the kidneys, in predisposed individuals, can lead up to to kidney failure. However, more often chronic administration leads to nephropathy.
- CNS – confusion, dizziness, headache, hallucinations (indomethacin).
- **Hematopoiesis** - increased risk of bleeding due to reversible or irreversible inhibition of COX-1 in platelets, aplastic anemia (pyrazolones, indomethacin), neutropenia (indomethacin), [[thrombocytopenia]].
- Liver – elevated transaminases. In ASA CAVE for **Rey's syndrome *(childhood, fatty necrosis of the liver, brain edema -*** *not to be administered in children with febrile illness*)

Non-steroidal anti-inflammatory drugs are contraindicated in the last trimester of pregnancy (risk of premature closure ofductus arteriosus)

'*Coxibs*, despite their numerous benefits, are risky in patients with cardiovascular and GIT disease, due to an increased relative risk of cardiovascular events. Probably due to selective inhibition of endothelial prostacyclin formation with antiaggregatory and vasodilating effects without reduction of proaggregatory thromboxane in platelets.

"Drug interactions with coumarin and other anticoagulants", with III. generation antidepressants and with corticosteroids are significant, when in all cases they *increase the risk of bleeding*. In addition, NSAIDs have a strong binding to proteins, thereby increasing the effectiveness of antidiabetics, anticoagulants and sulfonamides. On the contrary, they can reduce the effect of diuretics, ACE-inhibitors and beta-blockers.

Analgetika – antipyretika

Paracetamol

Paracetamol works in about half of patients. It is the safest analgesic in therapeutic doses. It should be the first choice for geriatric patients, during pregnancy and lactation, or for children. In case of intoxication (10-20 tablets), severe toxic damage to the liver occurs. Even in therapeutic doses, a small amount of toxic product is produced, which is eliminated by binding SH-groups. In case of an overdose, the SH-group donor - **acetylcysteine'** is the antidote. Paracetamol has no anti-inflammatory effects.

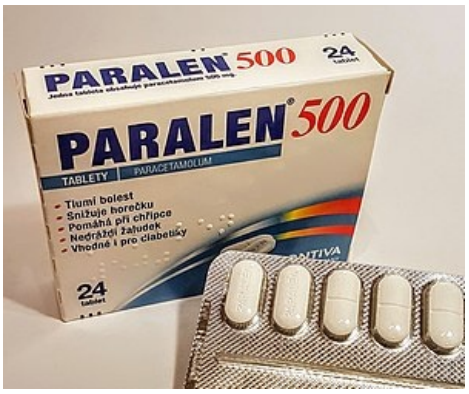
Paracetamol for i.v. administration

Paracetamol inhibits COX-3 in the hypothalamus – antipyretic effect and part of the analgesic effect. The analgesic effect is also caused by an indirect effect on serotonin receptors 5-HT_3 in the spinal cord.

Note: Paracetamol is called ``acetaminophen *in America.*

Metamizole

Metamizole is a cheap and effective analgesic, the main advantage of which is lower irritation of the GIT (it can also be used for peptic ulcer) and spasmolytic effect. It is often used in some countries, but less so in others (e.g. the Czech Republic), due to concerns about agranulocytosis, which occurs very rarely (< 1:10,000). If it appears, the patient has a sore throat and fever. A blood count is needed. After stopping the drug, the condition usually corrects itself. Metamizole is part of ®Algifen. In addition to the classic effects characteristic of NSAIDs, at also acts as a spasmolytic.[2]



Paralen®, paracetamol pro peroral administration

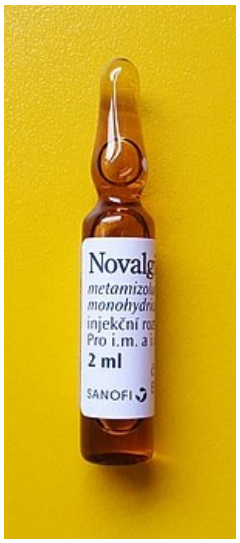
Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAID) have analgesic, antipyretic and anti-inflammatory effects. They are advantageous because they *can suppress pain of various etiology* - inflammatory, visceral, migraine and neuralgia. There is a wide range of pharmaceutical forms available on the market, from tablets to syrups, gels, patches and suppositories. According to their affinity to COX-1/COX-2, they are divided into:

- **non-selective'** (mixed - inhibition of both isoforms) - there are many of them, they are risky in terms of damage to the GIT, e.g. **ibuprofen**, **diclofenac**, oxicams
- **preferential** (they mainly inhibit COX-2) - e.g. **nimesulide** (hepatotoxic, contraindicated in other liver diseases[3]), **meloxicam**,
- **selective** (coxibs) - eg **celecoxib**, **parecoxib}}**

Main Substances

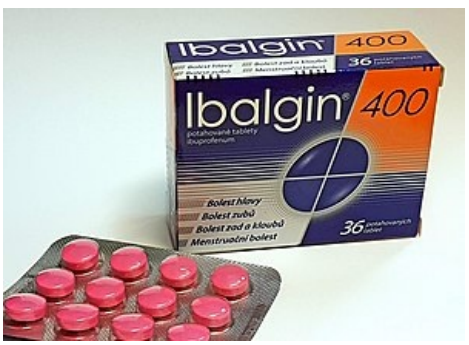
Acetylsalicylic acid, ASA) has antiplatelet effects, it is administered in small doses as a preventive measure for MI, cerebrovascular accidents; it is no longer used as an analgesic and antipyretic. It is absorbed in the stomach, so the onset of action is very fast. It is contraindicated in children with a viral illness (influenza, varicella) due to the risk of developing **Rey's syndrome** - vomiting, CNS depression, severe liver damage (hepatocerebral syndrome). It is better to give paracetamol or ibuprofen. Another contraindication is the third trimester of pregnancy, when it can cause closure of the ductus arteriosus Botalli of the fetus. When it comes to drug interactions, ASA significantly blocks the effects of uricosuric, which results in accumulation of uric acid, therefore ASA should not be given to patients with this therapy.



500mg/ml metamizole vial

Ibuprofen is among the most frequently prescribed antirheumatic drugs. Due to intestinal absorption, it has a slower onset than ASA. It is an alternative to paracetamol for febrile conditions in children.

Piroxicam belongs to the *oxicams*. All drugs of this group have a slower onset, therefore they are not suitable for the therapy of acute pain. On the contrary, thanks to the long half-life, they are excellent for "chronic pain", when it is possible to administer them only in one daily dose.



Ibalgin® 400 mg tbl., ibuprofen for peroral administration

Diclofenac in a dose of 50 mg has a comparable effect to 200 mg of ibuprofen. It is absorbed in the intestine and its disadvantage is a significant first pass effect. Forms with rapid onset and retarded variants - with gradual release - are available.

'*Celecoxib* is classified as a *coxib*. Coxibs selectively inhibit COX-2, so they have fewer GIT side effects and are indicated especially for individuals with already developed gastro- or enteropathy when using NSAIDs. Patients with ulcer disease can also benefit from them. In the body, their metabolism takes place via "cytochrome P450 C29".

Links

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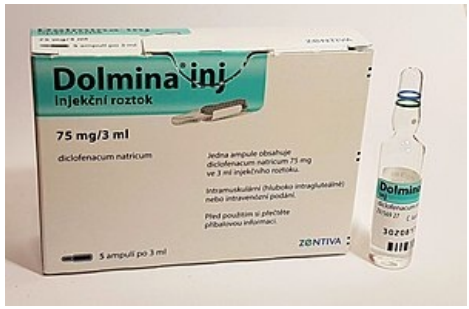
- Analgesics
- Prostaglandins
- Opioid analgesics



Dolmina®, diclofenac for i.m. or i.v. use

Sources

- LINCOVÁ, D a H FARGHALI, et al. *Základní a aplikovaná farmakologie.* 1. vydání. Praha : Galén, 2007. 0 s. ISBN 80-246-0538-4
- JAN, Švihovec a Kolektiv KOLEKTIV. *Farmakologie.* 1. vydání. Grada Publishing a.s., 2018. 1008 s. s. 304-308. ISBN 9788024755588

References

1. LÜLLMANN, Heinz. *Pharmacology and Toxicology.* 2nd Czech edition. Grada, 2004. 725 pp. Chapter 11.4. ISBN 80-247-0836-1.
2. KÖTTER, Thomas – DA COSTA, Bruno R. – FÄSSLER, Margaret. Metamizole-Associated Adverse Events: A Systematic Review and Meta-Analysis. *PLOS ONE.* 2015, vol. 10, p. e0122918, ISSN 1932-6203. DOI: 10.1371/journal.pone.0122918 (http://dx.doi.org/10.1371%2Fjournal.pone.0122918).
3. SPC O LIEKU AULIN,. *SPC - AULIN* [online]. [cit. 2017-01-12]. <https://www.sukl.cz/modules/medication/detail.php?code=0012895&tab=texts