PRINCIPLES OF EFFECTIVE USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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ABSTRACT

The article provides an overview of references on the rational use of nonsteroidal anti-inflammatory drugs (NSAIDs) in modern medicine. Nonsteroidal anti-inflammatory drugs are a group of drugs with different chemical structures (mostly acid derivatives) that have anti-inflammatory, analgesic, antipyretic, antiplatelet (acetylsalicylic acid, acetylsalicylate, ketoprofen, diclofenac sodium, niflumic acid, indomethacin) effects. NSAIDs are divided according to the selectivity of action relative to cyclooxygenase (COX) isoforms: non-selective COX inhibitors, selective COX-1 inhibitors, approximately equal inhibition of COX-1 and COX-2, selective COX-2 inhibitors. They are characterized by general pharmacological properties: high degree of absorption in the gastrointestinal tract; a high degree of binding to albumins; approximately the same volume of distribution; the ability to accumulate in the focus of inflammation. Indications for NSAIDs use are: acute arthritis and chronic arthritis; acute and chronic pain syndrome of various nature (lower back pain syndrome, joint and soft tissue injuries, migraine, dysmenorrhea, preoperative and postoperative pain, renal colic, fever in various rheumatic and non-rheumatic diseases). Additional indications for prescribing NSAIDs are: pleurisy, pericarditis, erythema nodosum, polycystic lung disease, sciatica. The most frequent and dangerous side effects include gastrointestinal, kidney complications. Special attention is paid to the cardiovascular safety of NSAIDs and, above all, COX-2 inhibitors because of risk of cardiovascular events. The most effective drug with the best tolerability should be selected for a specific patient. Before starting NSAID therapy, the patient's age, comorbidities, previous medical or surgical history, concomitant use of medications (including antiplatelet agents, anticoagulants, corticosteroids, ACE inhibitors, and selective serotonin reuptake inhibitors), H. pylori infection, and blood pressure monitoring should be considered.

Keywords: *inflammation, pain, side effects, gastropathy, selectivity.*

For the first time, the term nonsteroidal anti-inflammatory drugs (NSAIDs) was proposed by Flower J., who emphasized their fundamental differences from glucocorticoids [1]. In terms of frequency of clinical use, NSAIDs are second only to antibacterial drugs. According to World Health Organization, about 20% of the population around the world take NSAIDs. In particular, about 30 million people in the world use these drugs every day [2].

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NSAIDs are a group of drugs with different chemical structures (mostly acid derivatives) that have anti-inflammatory, analgesic, antipyretic, antiplatelet (acetylsalicylic acid, acetylsalicylate, ketoprofen, diclofenac sodium, niflumic acid, indomethacin) effects, as well as desensitizing effects (indomethacin, diclofenac sodium, acetylsalicylic acid) and stimulate the synthesis of interferon (mefenamic acid).

NSAIDs are classified according to their chemical structure as follows:

I. Derivatives of acids.

Arylcarboxylic acids.

Derivatives of salicylic acid or salicylates (acetylsalicylic acid, diflunisal).

Derivatives of anthranilic acid or fenamates (mefenamic acid, niflumic acid).

Arylalkanoic acids.

Derivatives of arylacetic acid (diclofenac sodium).

Derivatives of heteroacetic acid (ketorolac).

Derivatives of indole/indenoacetic acid (indomethacin, sulindac, etodolac).

Derivatives of arylpropionic acid (ibuprofen, naproxen, ketoprofen).

Enolic acids.

Pyrazoline derivatives (phenylbutazone, metamizole).

Oxicams (piroxicam, meloxicam).

II. Some other derivatives: nimesulide, colchicine, celecoxib, nabumetone.

III. Combined drugs:

- arthrotec (diclofenac + misoprostol), ambene (phenylbutazone + dexamethasone);

- aspifat (acetylsalicylic acid + sucralfate), dolaren (diclofenac + paracetamol).

The mechanism of action of NSAIDs was discovered by a group of scientists (Vane J., Smith J., Willis A.) in 1992, for which they were awarded the Nobel Prize. It consists in non-selective or selective inhibition of the cyclooxygenase (COX) enzyme, which inhibits the formation of prostaglandins (E1, I2, F2α), thromboxane, as a result of which the intensity of inflammation, pain, and fever decreases. Today, it is known about the existence of 2 isoforms of COX: COX-1 (constitutional), COX-2 (regulated). COX-1 is found in almost all organs and tissues, including the digestive tract, bronchi, kidneys, and platelets. It regulates the synthesis of homeostatic and cytoprotective prostaglandins (PG) in the mucous membrane of the gastrointestinal tract, bronchi, vascular endothelium, platelets, and kidney tubules. COX-2 is predominant in the brain, bone tissue, reproductive organs, juxtaglomerular apparatus of kidneys, monocytes and macrophages. COX-2 is normally found in small amounts, but the expression of this isoenzyme increases sharply in foci of inflammation. Inflammatory mediators (tumor necrosis factor, interleukin-1, etc.) can increase the level of COX-2 tenfold. According to modern ideas, it is believed that COX-2 is involved in the synthesis of "pro-inflammatory" prostaglandins, enhances the activity of inflammatory mediators, such as histamine, serotonin, and bradykinin. Regarding the existence of COX-3 (in animals, it is localized in the central nervous system (CNS), contributes to pain and fever, but does not affect the inflammatory cascade), there has been a debate in scientific circles for many years, and some researchers consider COX-3 to be a variant of COX-1, calling it COX- 1b or SOX 1v [3–5].

NSAIDs are divided according to the selectivity of action relative to COX isoforms:

- non-selective COX inhibitors: (diclofenac, ibuprofen, piroxicam, indomethacin) – the majority belongs to this group NSAIDs;

- selective COX-1 inhibitors: highly selective (low doses of acetylsalicylic acid), and selective (fenoprofen, piroxicam, sulindac);

- approximately equal inhibition of COX-1 and COX-2 (lornoxicam);

- selective COX-2 inhibitors: highly selective – coxibs (celecoxib, rofecoxib, valdecoxib, etoricoxib) and others (meloxicam, nimesulide, etodolac);

- selective COX-3 inhibitors (acetaminophen, metamizole).

COX-1-selectivity increases the likelihood of NSAID-gastropathies, chondrodestructive processes and causes renal toxicity, and COX-2-selective drugs increase the risk of cardiovascular side effects. In addition, COX-2 inhibitors, like other NSAIDs, slightly increase blood pressure. By blocking the formation of PG, NSAIDs reduce the permeability of the vascular wall and the penetration of plasma factors into tissues. At the same time, the activity of guanylate cyclase and the level of cyclic guanosine monophosphate (cGMP) decrease, the division of fibroblasts, the synthesis of collagen, mucopolysaccharides, and the formation of connective tissue are inhibited. The antiproliferative effect of NSAIDs is partly due to the inhibition of the activity of serotonin and bradykinin, which stimulate the division of fibroblasts. Destructive processes in cartilage and bone tissue are unfortunately not inhibited by most NSAIDs. In addition, against the background of the use of classic NSAIDs, the synthesis of proteins necessary for the regeneration of cartilage and bone tissue decreases [4; 6].

The anti-hyaluronidase activity of NSAIDs also helps to reduce the permeability (anti-edematous effect) of blood vessels and cell membranes in the focus of inflammation. NSAIDs reduce the energy supply of the inflammatory reaction, inhibit oxidative phosphorylation, which disrupts the synthesis of glycosaminoglycans and inhibits proliferation processes.

According to the degree of anti-inflammatory effect, non-steroidal anti-inflammatory drugs are divided into:

NSAIDs with significant anti-inflammatory activity:

- salicylates (acetylsalicylic acid, diflunisal);

- pyrazolidines (phenylbutazone);
- derivatives of indoleacetic acid (indomethacin, sulindac, etodolac);
- derivatives of phenylacetic acid (diclofenac);
- oxicams (piroxicam, meloxicam);
- alkanones (nabumetone);
- derivatives of propionic acid (ibuprofen, naproxen, fenopofen, flurbiprofen, ketoprofen, tiaprofenic acid);
- sulfonanilide derivatives (nimesulide);
- derivatives of other chemical groups (celecoxib).

NSAIDs with weak anti-inflammatory activity:

- derivatives of anthranilic acid (mefenamic acid);
- pyrazolones (metamizole sodium, propifenazone);
- derivatives of paraaminophenol (paracetamol);
- derivatives of heteroarylacetic acid (ketorolac).

By decreasing analgesic activity, NSAIDs can be arranged as follows: lornoxicam → ketorolac → diclofenac (aceclofenac) → indomethacin → ibuprofen → acetylsalicylic acid → ketoprofen; according to the risk of cumulation and unwanted drug interaction: piroxicam → aceclofenac → meloxicam → ketorolac → ibuprofen → diclofenac → lornoxicam. *According to the effect on the metabolism of hyaline cartilage*, NSAIDs can be classified as follows: drugs with chondronegative, chondroneutral and chondroprotective effects. Indomethacin, piroxicam, naproxen and some other traditional NSAIDs have a chondronegative effect on cartilage, chondroneutral – ibuprofen, diclofenac, chondroprotective – aceclofenac, ketoprofen and meloxicam.

The immunosuppressive effect of NSAIDs is moderately pronounced, appears with long-term use and is of a "secondary" nature: by reducing the permeability of capillaries, NSAIDs complicate the contact of immunocompetent cells with antigen and the contact of antibodies with the substrate [1; 4; 7–9].

Most NSAIDs are weak organic acids with a relatively low pH. They are characterized by general pharmacological properties:

- high degree of absorption in the gastrointestinal tract;
- a high degree of binding to albumins (with hypoalbuminemia, the concentration of the "free" drug increases, which can lead to increased toxicity);
- approximately the same volume of distribution;
- the ability to accumulate in the focus of inflammation.

The half-life of NSAIDs (T½) varies widely (from 0.2 h – acetylsalicylic acid to 35–45 h – piroxicam). Conventionally, they are divided into drugs with short T½ (<6 h) and long T½ (>6 h). However, the duration of the anti-inflammatory effect does not always correspond to T½, since the concentration of the drug in the focus of inflammation does not always correlate with the concentration in the blood plasma. Of great importance is the ability of NSAIDs to accumulate in the inflammation zone (for example, the joint cavity) and stay there for a long time in therapeutic concentrations. The therapeutic response also depends on the time required to reach stable (equilibrium) concentrations in the blood plasma (a level corresponding to 3–5 T½ periods). Often, taking drugs with a short T½ twice a day is as effective as multiple intake [4; 7; 10].

Indications for use of the nonsteroidal anti-inflammatory drugs are:

- acute arthritis (gout, exacerbation of chronic joint diseases – rheumatoid arthritis, osteoarthritis, spondyloarthritis, reactive arthropathy in non-rheumatic diseases);
- chronic arthritis (osteoarthritis, rheumatoid arthritis, seronegative spondyloarthritis, arthritis in other rheumatic diseases and non-rheumatic diseases);
- acute and chronic pain syndrome of various nature (lower back pain syndrome, joint and soft tissue injuries, migraine, dysmenorrhea, preoperative and postoperative pain (reduction in the need for narcotic analgesics), renal colic, fever in various rheumatic and non-rheumatic diseases);
- additional indications for prescribing NSAIDs: pleurisy, pericarditis, erythema nodosum, polycystic lung disease, sciatica [4; 11–13].

Contraindications for use of the nonsteroidal anti-inflammatory drugs are:

- erosive and ulcerative lesions of the gastrointestinal tract, especially in the acute stage;
- pregnancy and breastfeeding;
- significant liver and kidney function disorders;
- cytopenia;
- increased sensitivity to the drug;
- the patient's profession that requires constant concentration of attention and precise coordination of movements [7].

Side effects of the nonsteroidal anti-inflammatory drugs are listed in *Table 1.*

NSAIDs are a group of drugs that are relatively dangerous in terms of side effects. The toxic effects of NSAIDs are caused by inhibition of COX-1 activity and disruption of prostaglandin synthesis in the gastrointestinal mucosa, kidneys, endothelium, and platelets.

The most frequent and dangerous side effects include gastrointestinal complications. Most often, NSAIDs cause symptoms of dyspepsia – heartburn, epigastric pain, nausea, vomiting, diarrhea, constipation, which occur with long-term use in 30–40% of patients and in 5–15% of cases are the reason for stopping treatment. The second most frequent manifestation of the toxic effect of NSAIDs on the digestive tract is gastropathy. The term "NSAID-gastropathy", which was introduced in 1986 by Roth S.H. means erosive-ulcerative gastrointestinal lesions on the background of taking NSAIDs. NSAID-gastropathies are characterized by some features: the appearance of ulcers associated with taking NSAIDs, acute multiple erosions or ulcers, localization of ulcers in the antral part of the stomach, little or asymptomatic course, frequent manifestations, disappearance after withdrawal of the drug. There are several factors that increase the risk of NSAID gastropathy. They include:

- age (over 60 years old);
- history of gastrointestinal pathology (especially peptic ulcers and gastric bleeding);
- taking high doses of NSAIDs (low doses taking of NSAIDs is linked to relative risk of NSAID gastropathy, high doses – the risk is tripled);
- simultaneous intake of several NSAIDs (risk doubles);
- simultaneous use with glucocorticoids (the risk increases 10 times);
- long-term use of NSAIDs (more than 3 months);
- taking NSAIDs with a long half-life and non-selective COX-2 (the most toxic – piroxicam, naproxen, indomethacin, the safest – meloxicam, nimesulide, celecoxib);
- therapy with anticoagulants and/or antiplatelet agents.

Other risk factors are the presence of rheumatoid arthritis, female gender, smoking, alcohol intake, helicobacter infection. They should be taken

Table 1. Frequency of occurrence and types of side effects of nonsteroidal anti-inflammatory drugs

Side effects	Frequency, %
Gastrointestinal	
Dyspepsia (poorly correlated with complications from the gastrointestinal tract)	>10
Erosions and ulcers (more often in the stomach)	1–5
Intestinal damage (possible cause of anemia)	1–5
Liver damage (usually a moderate increase in liver enzymes)	1–5
Esophageal damage	<1
Renal (more often caused by indomethacin)	
Glomerular filtration disorders	1–5
Increase in blood pressure	1–5
Papillary necrosis	<1
Interstitial nephritis	<1
Neurological	
Headaches (more often indomethacin)	1–5
Aseptic meningitis (ibuprofen, ketoprofen, flurbiprofen, naproxen)	<1
Dermal	
Itching, skin rash	<1
Hematological (most often – phenylbutazone, very rarely – indomethacin), including agranulocytosis	<1
Hypersensitivity (most often acetylsalicylic acid): asthma, urticaria, pneumonitis	<1
Others	
Ototoxicity (most often acetylsalicylic acid)	<1
Infertility in women	<1
Stomatitis, sialoadenitis, carditis, vasculitis, pancreatitis (more often phenylbutazone)	<1
Bronchospasm (COX-2 inhibitors cause less often than "standard" NSAIDs)	<1

into consideration before initiating NSAID therapy. Complications of NSAID-gastropathy include gastrointestinal bleeding and perforation.

It should be noted that the risk of ulcers directly depends on the dose and duration of NSAID treatment. To reduce the likelihood of ulceration, it is necessary to use the minimum effective dose of the drug for a short period of time. These recommendations are usually ignored. A clear relationship between symptomatic side effects, endoscopic ulcers, and severe complications is often lacking. In addition, in patients without symptomatic side effects, gastric ulceration during endoscopy is detected with the same frequency or even more often than in patients with these effects. Therefore, when choosing NSAIDs, the doctor should first of all pay attention to the risk factors of severe complications, and secondly to the subjective complaints of patients [1–15].

When symptoms of dyspepsia appear in patients with a low risk of developing damage to the digestive tract, first of all, it is necessary to cancel the NSAID, or reduce its dose (if possible), or replace the drug with another one with a better safety profile. It is a false statement that injectable and rectal forms of NSAIDs have a less damaging effect on the gastric mucosa. With rectal or parenteral use, the direct toxic effect of NSAIDs is excluded, while the synthesis of protective prostaglandins is disturbed by any method of administration of NSAIDs.

Proton pump inhibitors (PPIs) are the drugs of first choice in the treatment of NSAID gastropathies. The dose is selected individually. In patients with a high risk of cardiovascular complications and simultaneous NSAID gastropathy, the strategy of combining a non-selective NSAID (for example, diclofenac) and a PPI is more appropriate than replacing an NSAID with a highly selective one, which can increase the risk of thrombotic complications.

Although misoprostol (a synthetic analog of prostaglandin E1) is inferior in effectiveness to proton pump inhibitors, it can be considered the drug of choice for the prevention of the development of ulcers in patients receiving NSAIDs.

With long-term use of NSAIDs, 60–70% of patients may also develop asymptomatic enteropathy, which is accompanied by minor blood loss (1–10 ml daily) and protein loss, which leads to iron deficiency anemia and hypoalbuminemia. The mechanisms of enteropathy are the same as those of gastropathy. Much less often, NSAIDs cause damage to the large intestine – colonopathy. The spectrum of damage varies from colitis to perforations, bleeding, and complicated diverticulitis.

All NSAIDs can cause kidney complications. The starting point for renal dysfunction when using NSAIDs is inhibition of PG synthesis. PGs are modulators of renal vascular tone, excretion of electrolytes (sodium, potassium) and water. NSAIDs are characterized by the ability to cause rapid retention of sodium and water, a decrease in glomerular filtration and renal blood flow, hypertension, hyperkalemia, edema, and acute renal failure. In addition, interstitial nephritis, renal papillary necrosis, membranous nephropathy, glomerulonephritis with minimal changes may develop.

NSAIDs can also increase liver enzyme levels, but severe hepatotoxicity is rare. Hepatotoxic action of NSAIDs can, first of all, be manifested in chronic liver diseases. Also, the hepatotoxic effect of NSAIDs can be manifested by hepatogenic encephalopathy – Reye's syndrome, which is based on generalized mitochondrial damage in children with congenital defects of mitochondrial enzymes due to inhibition of oxidative phosphorylation and impaired β-oxidation of fatty acids. A rare, very dangerous emergency condition that occurs in children and male adolescents (more often at the age of 4–15 years) during the treatment of fever in viral diseases – more often influenza and other respiratory viral infections, less often measles, chicken pox, etc., with drugs that contain acetylsalicylic acid, which is characterized by rapidly progressive toxic encephalopathy and the development of fatty infiltration of the liver. Reye's syndrome is accompanied by hyperammonemia, increased activity of aminotransferases in blood serum (more than 3 times) with a normal level of bilirubin.

Side effects of NSAIDs from the hematopoietic system are manifested by thrombocytopenia, anemia, leukopenia.

Since NSAIDs are often prescribed to elderly and senile people with comorbidities (hypertension, coronary heart disease, and diabetes), special attention is paid to the cardiovascular safety of NSAIDs and, above all, COX-2 inhibitors (risk of cardiovascular events). If there is no increased likelihood of developing cardiovascular events, the introduction of NSAIDs with a favorable GI profile is recommended: etoricoxib, celecoxib, diclofenac, ibuprofen, and nimesulide. Ketorolac and ketoprofen are less acceptable in this situation. If the patient has a significant cardiovascular risk, selective COX-2 inhibitors, as well as diclo-

fenac and ibuprofen in high doses, are contraindicated. If the patient is already taking low-dose acetylsalicylic acid for secondary prevention of cardiovascular complications, naproxen is considered the best choice for concomitant use for a short period of time. Other side effects occur much less often and are determined by individual intolerance of one or another drug [7; 15; 16].

Quite often, NSAIDs are used with other drugs. At the same time, it is necessary to take into account the possibility of their interaction (*Table 2*).

When planning pharmacotherapy, it is advisable to consider the following:

1. The anti-inflammatory effect of NSAIDs directly depends on their affinity for COX, as well as on the level of acidity of the solution of the selected drug (information is provided in the instructions for use), which ensures concentration in the area of inflammation. The analgesic and antipyretic effect develops faster, the more neutral the pH of the NSAIDs solution. Such drugs penetrate the central nervous system faster and suppress the centers of pain sensitivity and thermoregulation.

2. The shorter the half-life, the weaker the enterohepatic circulation, the less risk of cumulation and unwanted drug interaction, and the safer the NSAIDs are [6].

It is necessary constantly remember that:

- patients with arterial hypertension or heart failure should be prescribed NSAIDs, which have the least effect on renal blood flow;
- it is necessary to strive for the appointment of minimum doses and short courses of NSAIDs for the elderly;
- when pregnant women take NSAIDs, there is often a delay in pregnancy and a slowdown in labor;
- in order to prevent the development of esophagitis, it is advisable not to lie down for 15 minutes after using NSAIDs;
- NSAIDs should be prescribed with particular caution to patients with bronchial asthma, erosive-ulcerative lesions of the gastrointestinal tract, tendency to bleeding, liver diseases, and impaired kidney function.

Conclusions

When using NSAIDs, certain rules of appointment and dosage must be followed. The most effective drug with the best tolerability should be selected for a specific patient. Before starting NSAID therapy, the patient's age, comorbidities, previous medical or surgical history, concomitant use of medications (including antiplatelet agents, anticoagulants, corticosteroids, ACE inhibitors, and selective serotonin reuptake inhibitors), H. pylori infection, and blood pressure monitoring should be considered. A drug new to the patient should be prescribed starting with the lowest dose followed by a further increase after 2–3 days. With long-term course prescription, NSAIDs are taken after meals. Also, taking NSAIDs can be synchronized with the maximum increase in symptoms of the disease. The simultaneous use of two or more NSAIDs is inadvisable due to the increased risk of side effects, a decrease in the concentration of drugs in the blood, and a decrease in the expected effect.

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Disclosure Statement

The authors have no potential conflicts of interest to disclosure, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Table 2. Interaction of nonsteroidal anti-inflammatory drugs with other drugs

Drug	The result of the interaction	Recommendations
Indirect anticoagulants	Increased risk of gastrointestinal bleeding	Dynamic side effect monitoring
β-blockers	Decreased antihypertensive effect	Blood pressure control
Potassium-sparing diuretics (triamterene)	Decreased kidney function	Monitoring kidney function
Thiazide and loop diuretics	Reduction of natriuretic and antihypertensive effects of diuretics	The dose of diuretics can be adjusted
Other NSAIDs	Increased risk of NSAID-gastropathy	Dynamic side effect monitoring
ACE inhibitors	Decreased antihypertensive effect, increased risk of nephrotoxicity and hyperkalemia	Blood pressure control, monitoring kidney function, potassium level
Fluoroquinolones	Increased risk of seizures	Dynamic side effect monitoring

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