



Risk Factors and Prevention of Upper Gastrointestinal Complications Associated with Nonsteroidal Anti-Inflammatory Drugs

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Aim: to present current data about the frequency and risk factors of upper gastrointestinal complications associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and the possibilities of preventing these complications.

Key points. The incidence of gastrointestinal complications associated with NSAIDs is 14.7–30.1 %, with the maximum risk noted in the first two weeks of their administration. The use of selective cyclooxygenase-2 inhibitors is associated with a reduced risk of gastrointestinal complications. All patients who are going to receive NSAIDs should be diagnosed with *H. pylori* and treated with eradication therapy if this infection is detected. Even in patients without risk factors for gastrointestinal complications and with short courses of therapy, coxibs or a combination of NSAIDs and proton pump inhibitors may be considered. Prevention of NSAID-associated lesions of the upper gastrointestinal tract is an indication for the appointment of omeprazole and esomeprazole in accordance with the instructions for medical use. Esomeprazole has a number of pharmacokinetic advantages — a large area under the pharmacokinetic curve, the ability to inhibit CYP450C19, which determines the high efficiency of therapy in fast and ultrafast metabolizers. Previous clinical studies of esomeprazole for the prevention of NSAID-associated lesions of the upper gastrointestinal tract demonstrate high efficacy. In the randomized OBERON study the risk of gastric and duodenal ulcers after 3 months of low-dose acetylsalicylic acid treatment in the esomeprazole group was 7 times lower.

Conclusion. Assessment of risk factors, correction of modifiable risk factors, selection of safer NSAIDs and simultaneous administration of proton pump inhibitors (including esomeprazole) are effective prevention of NSAID-associated upper gastrointestinal lesions.

Keywords: nonsteroidal anti-inflammatory drugs, gastrointestinal tract, gastropathy, erosion, ulceration, bleeding, proton pump inhibitors, esomeprazole

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Факторы риска и профилактика осложнений со стороны верхних отделов желудочно-кишечного тракта, ассоциированных с приемом нестероидных противовоспалительных препаратов

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Цель обзора: представить актуальные данные о частоте и факторах риска осложнений со стороны верхних отделов желудочно-кишечного тракта (ЖКТ), ассоциированных с приемом нестероидных противовоспалительных препаратов (НПВП), и возможностях профилактики данных осложнений.

Основные положения. Частота развития осложнений со стороны ЖКТ на фоне НПВП составляет 14,7–30,1 %, при этом максимальный риск отмечается в первые две недели их назначения. Применение селективных ингибиторов циклооксигеназы-2, включая коксибы, ассоциируется с уменьшением риска желудочно-кишечных осложнений. Всем пациентам, которым планируется назначение НПВП, необходима диагностика *H. pylori* и эрадикационная терапия при выявлении этой инфекции. Даже у пациентов без факторов риска желудочно-кишечных осложнений и при коротких курсах терапии может быть рассмотрен вопрос о назначении коксибов или комбинации НПВП и ингибиторов протонной помпы. Профилактика НПВП-ассоциированных поражений верхних отделов ЖКТ является показанием для назначения омепразола и эзомепразола в соответствии с инструкцией по медицинскому применению. Эзомепразол обладает рядом фармакокинетических преимуществ: большая площадь под фармакокинетической кривой, способность ингибировать CYP450C19, что обуславливает высокую эффективность терапии у быстрых и ультрабыстрых метаболизаторов. Проведенные

клинические исследования эзомеразола для профилактики НПВП-ассоциированных поражений верхних отделов ЖКТ демонстрируют высокую эффективность: например, в рандомизированном исследовании на фоне 3-месячной терапии малыми дозами ацетилсалициловой кислоты риск возникновения язв желудка и двенадцатиперстной кишки в группе эзомеразола был в 7 раз ниже.

Заключение. Оценка факторов риска, коррекция модифицируемых факторов риска, выбор более безопасных НПВП, одновременное назначение ингибиторов протонной помпы, в том числе эзомеразола, позволяют проводить действенную профилактику НПВП-ассоциированных поражений верхних отделов ЖКТ.

Ключевые слова: нестероидные противовоспалительные препараты, желудочно-кишечный тракт, гастропатия, эрозия, язва, кровотечение, ингибиторы протонной помпы, эзомеразол

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for pain relief, inflammation, and fever control. The popularity of NSAIDs in clinical practice is due to the predictable rapid effect, the possibility of using various drugs and dosage regimens (“on demand”, courses or constantly as a basic drug), price availability, and over-the-counter release of some names [1–3].

About 30 million people take NSAIDs every day in the world [1–3]. It should be noted that a significant proportion of patients use NSAIDs independently without a doctor’s prescription, including in doses exceeding the maximum daily dose. According to the analysis of NSAID use in the Russian Federation by rheumatological patients, the most frequently prescribed medications were nimesulide, ketorolac, meloxicam, diclofenac, aceclofenac and lornoxicam in therapeutic doses for an average of 10 months. In addition, 16 % of patients simultaneously with oral NSAIDs independently used intramuscular injections, often exceeding the recommended duration of parenteral administration [4].

NSAIDs can cause drug-specific side effects: allergic, hepatotoxic, nephrotoxic, and cardiotoxic. However, the most significant in clinical practice are class-specific adverse events from the gastrointestinal tract (GIT). NSAID-associated lesions of the GIT in some cases are asymptomatic or detected by laboratory and instrumental studies. Regardless of the clinical manifestation of the side effect, the use of NSAIDs is associated with the risk of fatal gastrointestinal bleeding [5].

The purpose of the literature review is to present current data on the frequency and risk factors of upper gastrointestinal (GI) complications associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and the possibilities of preventing these complications.

NSAIDs in clinical practice

The mechanism of action of NSAIDs is based on the inhibition of the cyclooxygenase (COX) 2 enzyme, which is involved in the synthesis of prostaglandins (PG) in the inflammatory focus. NSAIDs also inhibit COX-1.

COX-1 (constitutive, obligate form) is present in tissues and is responsible for the constant synthesis of prostanoids (PGE_2 , $\text{PGF}_{2\alpha}$, PGD_2 , 15-d-PGJ_2 , prostacyclin PGI_2 , thromboxane A_2). Prostanoids act as short-lived “tissue hormones” that regulate many physiological functions [6–8]. The resulting effects are determined by the location of PG receptors [6, 7]. For example, the effect of PGE_2 on the EP_3 receptor of gastric epithelial cells causes an increase in the production of mucus and bicarbonates, and activation of this receptor located on the parietal cells of the stomach leads to a decrease in the production of hydrochloric acid, which provides a complex gastroprotective effect [7, 8].

COX-2 is an inducible enzyme appearance of which is determined by mechanical injury to the cell or exposure to pro-inflammatory stimuli (especially tumor necrosis factor alpha, interferon gamma, interleukin 1 and 6). COX-2 activity provides the formation of a large amount of PGE_2 and other prostanoids responsible for the development and maintenance of the inflammatory response [8–10].

Pro-inflammatory and constitutional prostanoids are identical in structure. However, the synthetases that determine the formation of specific biologically active substances in normal and inflammatory conditions differ. Thus, the constitutional synthesis of PGE_2 is carried out by synthetase-1. Under conditions of inflammation, synthetase-2 is activated, which also implements the synthesis of PGE_2 , but in large quantities. In addition, the expression of receptors is noted, the

interaction with which ensures the development of pro-inflammatory biological effects of prostanoids in the focus of inflammation. These receptors also differ from the constitutional ones in their structure. Active PG synthesis under the influence of COX-2 causes pain, fever, and inflammation with the involvement of neutrophils, macrophages, eosinophils, basophils, and T-lymphocytes in the lesion site [8, 9, 11].

Based on the mechanism of action of NSAIDs, it becomes clear that the “target” for the implementation of the anti-inflammatory effects of these drugs is COX-2. The occurrence of side effects from GIT is caused, to a great extent, by COX-1 blockade [8]. Different representatives of this pharmacological group have different affinities for the constitutive (COX-1) and inducible (COX-2) forms of the enzyme.

There are several classifications of NSAIDs based on their chemical structure, but from a practical point of view, it is more interesting to separate these drugs according to the selectivity of exposure to COX-1 and COX-2. A number of authors divide NSAIDs into selective (s-NSAIDs), referring to them only “coxibs” (from the abbreviation “COX-2 inhibitor”) and non-selective (n-NSAIDs). The n-NSAIDs block both isoenzymes (COX-1 and COX-2) in therapeutic doses, thereby increasing the damaging effect of external aggressive factors on the gastrointestinal mucosa [1–3]. Russian experts refer to meloxicam, nimesulide and coxibs as s-NSAIDs. Other representatives of NSAIDs belong to n-NSAIDs [2, 3, 12]. A detailed classification of NSAIDs according to the degree of selectivity is presented in Table 1.

The ratio of COX-1 to COX-2 inhibition determines the potential toxicity of NSAIDs, including more frequent gastrointestinal side effects. For nimesulide, this value is 0.22; for meloxicam — 0.33; diclofenac — 2.2; piroxicam — 33;

indomethacin — 107 [1, 2]. COX-2-selective drugs less damage the upper GIT.

The main indications for the use of NSAIDs are diseases of the musculoskeletal system, including rheumatoid, psoriatic, axial spondyloarthritis, osteoarthritis, gouty arthritis, bursitis, tendovaginitis, accompanied by chronic pain and inflammation. At the same time, NSAIDs are prescribed in a variety of clinical situations and as a means of symptomatic therapy that relieves pain, fever and inflammation, as well as basic pathogenetic therapy to reduce the progression of the disease in the group of spondyloarthritis. NSAIDs can be used as a pathogenetic therapy, that is, helping to slow the progression of the disease, in patients with spondyloarthritis. A number of studies have demonstrated that continuous, long-term (for two years) use of s-NSAIDs reduces the progression of structural changes in the spine in patients with ankylosing spondylitis [13–15].

The pronounced analgesic effect of NSAIDs contributes to their use not only in diseases of the musculoskeletal system, but also in pain syndrome of various localization — headache (including migraines), toothache, lumbago, sciatica, neuralgia, radiculopathy, pain syndrome in oncological diseases, post-traumatic and postoperative pain syndrome. According to international standards, NSAIDs are first-line drugs for the treatment of primary dysmenorrhea, surpassing the group of antispasmodics in effectiveness [16, 17]. Data from systematic reviews demonstrates the high efficacy of ibuprofen and naproxen compared to other NSAIDs in the treatment of primary dysmenorrhea [18–20].

In infectious and inflammatory diseases of the oropharynx and upper respiratory tract (pharyngitis, tonsillitis, otitis media, acute respiratory viral diseases), NSAIDs in combination therapy reduce the severity of inflammation [1–3].

Table 1. Classification of NSAIDs by selectivity for COX

Таблица 1. Классификация НПВП по селективности в отношении ЦОГ

Selectivity for COX-1 or COX-2 Селективность в отношении ЦОГ-1 или ЦОГ-2	Drug preparations Лекарственные препараты
Pronounced selectivity for COX-1 <i>Выраженная селективность в отношении ЦОГ-1</i>	Acetylsalicylic acid, indomethacin, ketoprofen, piroxicam <i>Ацетилсалициловая кислота, индометацин, кетопрофен, пироксикам</i>
Moderate selectivity for COX-1 <i>Умеренная селективность в отношении ЦОГ-1</i>	Diclofenac, ibuprofen, naproxen <i>Диклофенак, ибупрофен, напроксен</i>
Approximately equivalent inhibition of COX-1 and COX-2 <i>Примерно равноценное ингибирование ЦОГ-1 и ЦОГ-2</i>	Lornoxicam <i>Лорноксикам</i>
Moderate selectivity for COX-2 <i>Умеренная селективность в отношении ЦОГ-2</i>	Etodolac, meloxicam, nimesulide <i>Этодолак, мелоксикам, нимесулид</i>
Выраженная селективность в отношении ЦОГ-2 <i>Pronounced selectivity for COX-2</i>	Celecoxib, etoricoxib <i>Целекоксиб, эторикоксиб</i>

According to randomized clinical trials (RCTs), the analgesic efficacy of various NSAIDs (s-NSAIDs and n-NSAIDs) in medium and high therapeutic doses for injuries, surgeries, and diseases of the musculoskeletal system is almost the same [17, 18]. However, a number of studies have shown that in patients with severe pain syndrome in the units of anesthesiology and neurology, lornoxicam surpassed indomethacin, diclofenac, ketorolac, ketoprofen, naproxen, and tramadol in the strength of anti-inflammatory and analgesic effects, approaching the severity of pain relief to opioid analgesics [21–23].

In some rheumatological diseases, differences in the effectiveness of the use of s-NSAIDs and n-NSAIDs were revealed. Thus, according to van der D. Heijde et al., etoricoxib at a dose of 90 mg/day was more effective than naproxen at a dose of 1000 mg/day in patients with axial spondyloarthritis, which resulted in a significant reduction in back pain and an improvement in the functional activity of the spine [24].

The analgesic and anti-inflammatory effects of NSAIDs are dose dependent. This is confirmed, in particular, by the data of a meta-analysis of 10 RCTs ($n = 1785$), which evaluated the effect of celecoxib in dosages of 200 and 400 mg with a single dose for the relief of acute pain. The authors demonstrated that increasing the dose of the drug showed a faster achievement of analgesic and anti-inflammatory effects (the NNT index (number needed to treat — the number of patients who should be treated to achieve the effect in one patient) decreased more than twofold from the initial level) [25]. A meta-analysis of 76 RCTs ($n = 58,451$) showed that higher doses of diclofenac, naproxen, and etoricoxib increased the degree of pain relief in osteoarthritis [26].

In clinical practice, the choice of NSAIDs is determined not only by the severity of the main therapeutic effects, but also by the risk of adverse effects on the GIT, cardiovascular system, and kidneys, which is especially important in comorbid patients.

Side effects of NSAIDs

Adverse events associated with NSAID use may include dyspepsia, heartburn, and abdominal discomfort (40–60 % of patients), as well as more serious, threatening complications such as gastrointestinal ulcers, bleeding, perforation, strictures, and intestinal obstruction [2, 3, 27]. The incidence of gastrointestinal complications according to various authors is 14.7–30.1 % [1, 3, 28]. According to endoscopic studies, 5.3–30 % of patients who regularly take NSAIDs develop asymptomatic ulcers, more often in the antrum of the stomach.

The annual rate of serious complications (perforation, bleeding, and obstruction) ranges from 1 to 1.5 %. The maximum risk of developing NSAID gastropathy is noted in the first two weeks of taking the drug [1–4, 7, 29].

Some studies show that NSAID use is associated with the risk of developing not only gastrointestinal, but also cardiovascular and renal complications. When prescribing NSAIDs, cardiovascular risks should be considered, especially in comorbid age patients. For example, in a large CNT meta-analysis (754 RCTs, more than 230,000 patients), the risk of serious vascular complications (non-fatal myocardial infarction, non-fatal stroke, or vascular death) increased with diclofenac, ibuprofen, and s-NSAIDs (coxibs) intake. In contrast, naproxen use was not associated with an increased risk of serious vascular complications. It should be noted that in all RCTs standard doses of NSAIDs were used [30]. In general, various large-scale RCTs demonstrate a high risk of cardiovascular complications when taking any NSAIDs, which is directly correlated with the dose of NSAIDs [1, 3, 7, 26].

The mechanism of the negative effect of NSAIDs on the GIT is associated with the blockade of the COX-1 enzyme. A decrease in the protective factors of the mucous membrane leads to its damage by external factors of aggression: hydrochloric acid in the upper GIT, intestinal contents in the small and large intestine. Bacterial flora, including *Helicobacter pylori* (*H. pylori*), also plays a significant role in this process [31–33]. The mechanism of esophageal damage associated with NSAID use is mainly associated with an indirect decrease in the effectiveness of protective antireflux mechanisms and the resistance of esophageal mucosa to the damaging effect of gastric reflux [34].

Many studies have been conducted evaluating the negative impact of NSAIDs on various parts of GIT.

In 2012, a systematic review and meta-analysis of observational studies (SOS project) demonstrated the variability of the risk of upper gastrointestinal complications when using various NSAIDs in clinical practice. Aceclofenac, celecoxib, and ibuprofen had minimal relative risk; diclofenac, meloxicam, nimesulide, and ketoprofen had moderate relative risk; tenoxicam, naproxen, and indomethacin had high relative risk; and piroxicam and ketorolac had very high relative risk [35]. In another study, indomethacin, diclofenac, and naproxen showed a statistically significantly higher risk of bleeding than ibuprofen [36].

Based on the understanding of the mechanisms of development of gastrointestinal complications

associated with COX-1 blockade, a logical conclusion was made about the possibility of wider use of s-NSAIDs, which are safer than n-NSAIDs. Indeed, there are a number of studies demonstrating greater efficacy and safety of nimesulide compared to naproxen [37] and other n-NSAIDs [4, 12, 38] in rheumatological patients. Other authors show that meloxicam is safer for GIT in comparison with n-NSAIDs [39].

A low risk of serious gastrointestinal complications is observed with the use of coxibs (highly selective COX-2 inhibitors), which is confirmed by two large-scale RCTs – CLASS and SUCCESS-1 [40, 41]. In the CLASS study, the use of high doses of celecoxib (800 mg/day) for 6 months was associated with a reduced risk of gastrointestinal complications compared to diclofenac and ibuprofen at standard therapeutic doses (150 and 2400 mg/day, respectively), but the differences were not significant. The authors attributed this to the fact that in 20 % of cases patients received additional acetylsalicylic acid, which increased the risk of gastrointestinal complications in the celecoxib group [40]. The SUCCESS-1 study evaluated already standard daily doses of celecoxib (200 mg and 400 mg), diclofenac (100 mg), and naproxen (1000 mg) for 3 months. Celecoxib is associated with a significantly lower risk of gastroenterological complications compared to diclofenac and naproxen [41].

The positive data obtained for celecoxib does not apply to etoricoxib. So, in the MEDAL study, where the main goal was to assess the effect of this drug on the risk of developing cardiovascular disasters, it was found that the frequency of gastrointestinal bleeding while taking etoricoxib was comparable to diclofenac. An unpleasant discovery was also the almost identical frequency of side effects of diclofenac and etoricoxib from the distal GIT, mainly due to intestinal bleeding [42].

NSAID-associated intestinal complications are also associated with COX-1 blockade, which leads to increased epithelial permeability, translocation of bacteria through the intestinal mucosa, chronic inflammation, and the action of aggressive intestinal contents. NSAIDs can also have a direct damaging effect on the intestinal mucosa [42]. Damage to the mucous membrane of the jejunum and ileum can be accompanied by extremely poor complaints in the form of flatulence, sometimes diarrhea and abdominal pain; erosions, ulcers and their complications may develop [42]. When analyzing the effect of s-NSAIDs and n-NSAIDs on the mucosa of the small intestine, the high safety of selective drugs is shown. J. Goldstein et al. demonstrated a significantly lower incidence of

damage to the small intestinal mucosa when taking celecoxib compared to naproxen [43].

Risk factors for NSAID-associated upper gastrointestinal tract lesions

Based on numerous retrospective and prospective studies, the main risk factors for erosive and ulcerative lesions of the upper gastrointestinal mucosa when taking NSAIDs were identified [44–46]:

- age over 65 years;
- smoking;
- *H. pylori* infection;
- the presence of peptic ulcer disease;
- the presence of concomitant diseases (coronary heart disease, arterial hypertension, liver failure, advanced stages of chronic kidney disease);
- concomitant use of NSAIDs with glucocorticosteroids (corticosteroids), anticoagulants, antiplatelet agents, cyclosporine A and methotrexate, selective serotonin reuptake inhibitors;
- use of high-dose NSAIDs;
- a combination of several NSAIDs;
- long-term treatment with NSAIDs.

One of the most important modifiable risk factors for NSAID-associated gastric lesions is *H. pylori* infection. The use of NSAIDs against the background of *H. pylori* infection increases the risk of erosive and ulcerative lesions and bleeding from the upper GIT. According to the recommendations for the management of patients with peptic ulcer disease of the Japanese Society of Gastroenterology, eradication therapy is indicated for patients with *Helicobacter pylori* infection who are scheduled to receive NSAIDs [47]. In a 2012 meta-analysis, the effectiveness of eradication therapy to prevent erosive and ulcerative lesions of GIT was most pronounced in patients who had not yet received NSAIDs, as well as in representatives of the Asian race [48].

It should be noted that the use of proton pump inhibitors (PPIs) against NSAIDs has great protective potential compared with eradication therapy [49].

Prevention of NSAID-associated upper GIT lesions

Various groups of pharmacological agents can potentially be effective for the prevention and treatment of upper gastrointestinal mucosal lesions that occur during the use of COX inhibitors: antacids, gastroprotectors, H₂-histamine blockers, PPIs, and potassium-competitive acid blockers. In accordance with current clinical guidelines, PPIs are the basic drugs for preventing and treating most acid-dependent diseases [50, 51]. The results of clinical studies demonstrate the advantage of

PPIs in terms of efficacy and safety over other groups of drugs and in patients with acid-related diseases [52, 53]. In foreign recommendations, a new class of drugs — potassium-competitive acid blockers is an alternative to PPIs [47]. A number of studies have demonstrated the high efficacy of vonoprazane, but this drug is not yet available in the Russian Federation [54, 55].

Approaches to the prevention and treatment of NSAIDs gastropathies are presented in domestic and foreign publications. There is an algorithm of prevention and treatment of NSAIDs gastropathies in Russian clinical guideline from the 2015 “Rational use of NSAIDs in clinical practice”. According to this algorithm, patients who are scheduled to be prescribed NSAIDs are divided into risk groups for NSAID-associated gastrointestinal complications, which determines the need for gastroprotective therapy (Table 2) [3].

At the same time, the document of the Japanese Society of Gastroenterologists “Evidence-based clinical practice guidelines for peptic ulcer disease” (2020), which addresses the issues of prevention and treatment of NSAID-related gastropathies, suggests a different algorithm that involves the therapy of antisecretory drugs in all cases with the exception of coxibs therapy in the absence of risk factors for complications [47] (Fig. 1).

According to the current Japanese guidelines, even in patients who do not receive small doses of acetylsalicylic acid and do not have a history of

ulcers, coxibs or NSAIDs can be combined with PPIs. Concomitant therapy of PPIs is recommended for age-related patients; patients with serious concomitant diseases; patients taking large doses of NSAIDs, receiving small doses of acetylsalicylic acid, any antithrombotic drugs, biphosphonates, corticosteroids with NSAIDs.

A series of studies have described the feasibility of prescribing PPIs to patients who have been treated with NSAIDs for more than 3 months [56, 57]. In patients receiving small doses of acetylsalicylic acid, who have a history of gastric and duodenal ulceration, complicated by bleeding, the option of choice is the combined use of coxibs and PPIs. If gastric and duodenal ulcers have not been accompanied by bleeding in the past, a combination of NSAIDs or coxibs with PPIs may be used in clinical practice [58].

Treatment of NSAID-induced ulcerative lesions of the upper GIT involves the withdrawal of COX inhibitors and the appointment of pharmacological treatment; if the withdrawal of NSAIDs is not possible, the parallel use of PPIs. In a number of studies, the duration of acid-suppressive therapy in patients with NSAID-induced erosive and ulcerative lesions of the upper GIT was 8 weeks [59, 60].

Thus, according to domestic and foreign publications, the basic drugs for the prevention and treatment of NSAID-associated lesions of the upper GIT are proton pump inhibitors.

Table 2. Risk factors for gastrointestinal complications during NSAID therapy and treatment options

Таблица 2. Факторы риска осложнений со стороны ЖКТ на фоне терапии НПВП и варианты выбора терапии

	Low risk <i>Низкий риск</i>	Moderate risk <i>Умеренный риск</i>	High risk <i>Высокий риск</i>
Risk factors <i>Факторы риска</i>	—	Age over 65 <i>Возраст старше 65 лет</i> Dyspepsia <i>Диспепсия</i> Smoking <i>Курение</i> Taking glucocorticosteroids <i>Прием глюкокортикостероидов</i> <i>H. pylori</i> infection <i>Инфицирование H. pylori</i>	History of ulcers (including ulcers complicated by bleeding or perforation) <i>Язвенный анамнез (включая язвы, осложненные кровотечением или перфорацией)</i> History of gastrointestinal bleeding or perforation <i>Желудочно-кишечное кровотечение или перфорация в анамнезе</i> Taking low doses of acetylsalicylic acid <i>Прием низких доз ацетилсалициловой кислоты</i>
Therapy <i>Терапия</i>	Any NSAIDs <i>Любые НПВП</i>	н-НПВП + ИПП, с-НПВП non-selective NSAIDs + PPIs, selective NSAIDs	Coxibs + PPIs <i>Коксибы + ИПП</i>

Note: NSAIDs — non-steroidal anti-inflammatory drugs, PPIs — proton pump inhibitors.

Примечание: НПВП — нестероидные противовоспалительные препараты, н-НПВП — неселективные НПВП, с-НПВП — селективные НПВП, ИПП — ингибиторы протонной помпы.

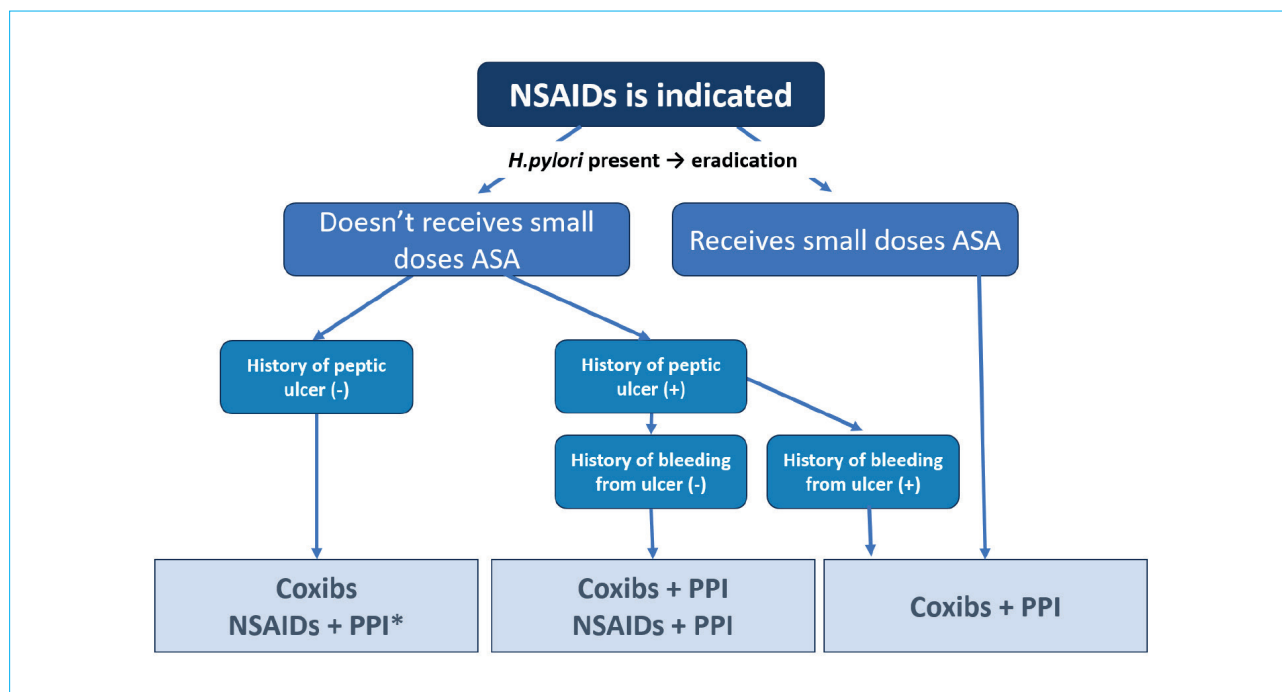


Figure 1. Algorithms for selecting drugs in patients who are planned to be prescribed NSAIDs (according to [47]): NSAIDs — non-steroidal anti-inflammatory drugs, ASA — acetylsalicylic acid, PPI — proton pump inhibitors, * — preferably in patients over 65 years of age; with serious concomitant diseases; on high doses of NSAIDs, receiving low doses of acetylsalicylic acid, any antithrombotic drugs, bisphosphonates, glucocorticosteroids in parallel with NSAIDs

Рисунок 1. Алгоритмы выбора препаратов у пациентов, которым планируется назначение НПВП (по [47]): NSAIDs — нестероидные противовоспалительные препараты, ASA — ацетилсалициловая кислота, PPI — ингибиторы протонной помпы, * — предпочтительно у пациентов старше 65 лет; имеющих серьезные сопутствующие заболевания; находящихся на больших дозах НПВП, получающих параллельно с НПВП малые дозы ацетилсалициловой кислоты, любые анти тромботические препараты, бифосфонаты, глюкокортикостероиды

Proton pump inhibitors for the prevention and treatment of NSAID-associated upper GIT lesions

The appearance of a class of PPI drugs became possible after the discovery by A. Gansser and J. Forte in 1973 H^+/K^+ -ATPase (proton pump), an enzyme that consumes the energy of ATP molecules and is responsible for acidification of stomach contents. Reducing the pH in the stomach to a level of 1–2 is achieved by creating a millionfold proton gradient on the parietal cell membrane — the largest gradient of ion concentrations in mammalian tissues. Since its discovery, the structure and function of H^+/K^+ -ATPase has been in the center of interest of researchers, since the proton pump has become the main target for drugs aimed at treating acid-related diseases [61].

In 1975, thymoprazole became the first experimental proton pump-blocking molecule. In 1979, the first PPI, a derivative of thymoprazole — omeprazole, was registered. The omeprazole molecule, being a prodrug and weak base, selectively accumulates and is activated by protonation

under low pH conditions in the secretory tubules of gastric parietal cells. After protonation and structural changes, the active forms of omeprazole (sulfenamide, sulfenic acid) lose the ability to pass through biomembranes (cation trap). Sulfenamide and sulfenic acid irreversibly bind to the cysteine residues of active H^+/K^+ -ATPases, blocking the proton pump, resulting in a decrease in stimulated and basal secretion of hydrochloric acid [62].

In the following decades, other representatives of the PPI class (lansoprazole, pantoprazole and rabeprazole) were registered on the pharmacological market. These molecules have a number of pharmacokinetic and pharmacodynamic differences, as well as variable clinical efficacy. The next most important step after the discovery of the PPI class was the registration of the levorotatory stereoisomer of omeprazole (esomeprazole) in 2001 [62].

The study of stereoisomers is a separate discipline — stereochemistry, which researches the influence of the spatial structure of molecules on chemical properties (static stereochemistry) and

the characteristics of chemical reactions (dynamic stereochemistry) [63]. Omeprazole is a racemic mixture of dextro- and levorotatory isomers in equal proportions. Preclinical studies have shown that omeprazole molecules are metabolized by cytochrome P450 (CYP) 2C19 to form hydroxy- and 5-O-desmethyl metabolites and the CYP3A4 isoenzyme to form sulfone. At the same time, the activity of these isoenzymes in relation to the levo- and dextrorotatory isomers is different (stereoselective metabolism). Under laboratory conditions, it was demonstrated that the clearance (the volume of blood plasma cleared of a substance per unit of time) of esomeprazole metabolites is three times less than the clearance of metabolites of the dextrorotatory stereoisomer of omeprazole [64].

Further in vivo studies confirmed a lower clearance of the levorotatory isomer of omeprazole, which leads to a larger area under the pharmacokinetic curve (AUC) compared to racemate or the dextrorotatory isomer [64].

The pharmacokinetic advantages of the levorotatory isomer over the racemic mixture of omeprazole are most pronounced in fast metabolizers of CYP2C19, as well as with long-term use. Significant pharmacokinetic advantages in fast metabolizers are explained by the fact that esomeprazole molecules have the ability to inhibit CYP2C19. When CYP2C19 is slowed the intensity of the enzyme's functioning in fast metabolizer is like in the slow metabolizer. The severity of CYP2C19 inhibition increases with each subsequent administration of the levorotatory isomer of omeprazole. The enzymatic activity of CYP2C19 is gradually restored approximately 3–4 days after esomeprazole is discontinued [65].

The revealed feature of the effect of esomeprazole on the enzymatic activity of CYP2C19 seems extremely important, given that a significant number of Russian patients are normal, ultrafast and fast metabolizers, which leads to a decrease in the effectiveness of standard acid-suppressive therapy regimens. A domestic study demonstrated that 10 % of patients who were scheduled for eradication therapy had genotype 17*17* (ultrafast metabolizers) and 29 % had 1*17* genotype (fast metabolizers) [66].

According to the clinical guidelines on the pharmacogenetics of PPIs, the effectiveness of esomeprazole does not depend on the CYP2C19 genotype and is equally predictable in fast and slow metabolizers, which does not require dose adjustment [67].

Currently, the esomeprazole molecule has a significant evidence base for the prevention and treatment of NSAID-associated lesions of the upper GIT.

In J.M. Scheiman et al. study 400 patients were randomized to groups taking s-NSAIDs + placebo and s-NSAIDs + esomeprazole 20 mg. During 6 months therapy gastric ulceration developed in 16.5 % of patients in the placebo group and only in 0.9 % in the esomeprazole group [68]. The OBERON randomized clinical trial included 2,426 patients treated with acetylsalicylic acid at a dosage of 75–325 mg. Patients were also randomly assigned to groups taking acetylsalicylic acid + placebo and acetylsalicylic acid + esomeprazole 20 mg. The risk of gastric and duodenal ulcers in the esomeprazole group was 7 times lower after 3 months of therapy [69]. A single-center, prospective, randomized, double-blind study included 441 patients admitted to the hospital for upper gastrointestinal bleeding during n-NSAID therapy for arthritis. Patients were included in the study after the ulcer defect had healed and tested negative for *H. pylori*. All patients were prescribed celecoxib 400 mg daily, 137 received concomitant therapy with esomeprazole 20 mg twice daily, and 136 patients received placebo for 12 months. Recurrent ulcerative bleeding occurred in 8.9 % of patients in the placebo group and none in the esomeprazole group [70].

Currently, according to the instructions for PPIs registered in the Russian Federation (omeprazole, lansoprazole, rabeprazole, pantoprazole, dexlansoprazole), only omeprazole and esomeprazole have an official indication “prevention of gastric and duodenal ulcers associated with NSAID use in patients at risk”. The official instructions for esomeprazole indicate the possibility of using the drug in a dosage of 20 or 40 mg once a day for this indication [71].

The safety of PPIs is a very important issue due to the need for long-term therapy in combination with NSAIDs. In the American Gastroenterological Association document on deprescribing it is indicated that long-term acid-suppressive therapy is necessary for patients with severe erosive esophagitis, esophageal ulcer or peptic stricture, Barrett's esophagus, eosinophilic esophagitis, idiopathic pulmonary fibrosis, and a real risk of gastrointestinal bleeding [72].

Considering that patients with GERD often require long-term PPI therapy, the latest American College of Gastroenterologists clinical guidelines for the diagnosis and treatment of GERD include a chapter on safety issues. In accordance with the principles of evidence-based medicine, experts formulate the following consolidated position. Studies that have identified increased risks of adverse drug reactions with long-term use of PPIs (pneumonia, stomach cancer, bone fractures,

nephropathy, deficiency of certain vitamins and minerals, heart attacks, strokes, dementia) have significant methodological disadvantages, which does not allow establish a causal relationship between the use of PPIs and an adverse reaction. Better methodological studies have shown that PPIs do not significantly increase the risk of each of the listed conditions, except for acute intestinal infections and *C. difficile* infection. At the same time, the benefits of PPIs significantly outweigh the potential risks of adverse drug reactions associated with their use [73].

The safety of long-term use of esomeprazole was demonstrated in the multicenter randomized open-label LOTUS study, which included patients with GERD and hiatal hernia: 288 patients underwent laparoscopic fundoplication, 266 received esomeprazole for 5 years. The two treatment methods were equally effective, and no significant adverse events occurred during five years of esomeprazole administration, including changes in laboratory parameters such as hemoglobin, alkaline phosphatase, calcium, homocysteine, gastrin, vitamin B₁₂, and chromogranin A [74].

Conclusion

Active use of NSAIDs, associated with an increased risk of various complications, the most common of which are gastroenterological problems, dictates the need to manage the risks of NSAID-associated lesions of the upper GIT. This

approach implies identification of risk factors for complications, correction of modifiable risk factors (*H. pylori* eradication), differentiated selection of NSAIDs and the need to prescribe PPI.

The studies conducted show that the risks of cardiovascular complications associated with coxibs correlate with the risks associated with the use of other NSAIDs. Recent international recommendations indicate the possibility of starting combination of NSAIDs and PPIs or monotherapy by coxibs in patients without risk factors for gastrointestinal complications. This trend may be explained by the fact that the risks of gastrointestinal complications associated with the use of NSAIDs exceed the potential risks associated with the use of PPIs. From a clinical point of view, it is most appropriate to use a PPI cover in patients of older age groups; with serious concomitant diseases; receiving large doses of NSAIDs; receiving small doses of acetylsalicylic acid, any antithrombotic drugs, biphosphonates, corticosteroids simultaneously with NSAIDs. It is important to remember that gastroenterological side effects most often occur in the first two weeks of therapy. Therefore, it is necessary to prescribe PPIs against the background of short courses of NSAIDs.

In accordance with the available evidence base and instructions for registered medicinal products, the official indication for the prevention of gastric and duodenal ulcers associated with NSAID use is relevant only for omeprazole and esomeprazole.

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