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EVALUATION OF THE EFFICACY OF REBAMIPIDE IN PATIENTS WITH NSAID-ASSOCIATED GASTROPATHY

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An increase in the incidence of NSAID-gastropathy is associated with the widespread use of NSAIDs (nonsteroidal anti-inflammatory drugs) in almost all areas of medicine. An important element of the prevention and treatment of NSAID-gastropathy is the use of drugs that have a cytoprotective effect on the gastric mucosa. The cytoprotector rebamipid has great therapeutic potential, confirmed in a variety of experimental and clinical studies. The use of rebamipid is justified both for conditionally healthy individuals if a short course of NSAID therapy is necessary, and for patients who need a long or lifelong intake of them, especially in the presence of risk factors for the development of NSAID-gastropathy.

Key words: NSAID-gastropathy, cytoprotectors, rebamipid.

The relevance of the topic, however, the use of NSAIDs and NDA has a downside. Unfortunately, these medications can cause serious complications, primarily from the gastrointestinal tract. The widespread use of NSAIDs and NDAs has made this problem socially significant and truly global. After all, today these drugs have become the main cause of gastrointestinal bleeding in patients in developed countries of the world. There is a persistence and even an increase in the frequency of this dangerous complication, even against the background of a distinct global decrease in the infection rate of the population with H. Pylori and the frequency of "banal" (associated with infection). pylori) peptic ulcer disease. According to long-term statistics, taking NSAIDs leads to the development of dyspepsia in about 20-30% of patients; 10-25% of patients who regularly use these drugs have endoscopic (detected during esophagogastroduodenoscopy – EGDS) and in most cases asymptomatic ulcers of the stomach and duodenum (duodenum).

The most dangerous complications – bleeding and perforation – develop annually in 5-10 people out of every thousand using NSAIDs. In general, fatal gastrointestinal complications are registered 2 times more often in those taking these drugs than in the general population. A similar situation is observed with the drug: the use of this antithrombotic agent leads to the development of dyspepsia in 30% of patients, single or multiple erosions in more than 50%, stomach ulcers, and duodenal ulcers in about 7%, and large gastrointestinal bleeding in 0.6% annually.

The data of a 6-month randomized controlled trial (RCT) of OBERON, in which the efficacy of esomeprazole PPIs for the prevention of gastrointestinal complications

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when taking NDA (75-25 mg) in 2426 patients was studied, are very indicative. At the end of the follow-up, the incidence of gastric ulcers detected by endoscopic examination was 7.4% in the placebo group; clinically pronounced bleeding was noted in 0.7% of patients. Unfortunately, the negative impact of NSAIDs and NDA is not limited only to the upper gastrointestinal tract. Even relatively short-term use of these drugs can cause damage to the small intestine of NSAIDs-enteropathy. This pathology develops due to increased permeability of the mucous membrane and chronic inflammation associated with penetration into the intestinal wall of bacteria or their components located in the lumen of the intestine. NSAID-enteropathy can be manifested by profuse intestinal bleeding, perforation, and strictures of the small intestine.

Risk factors for NSAID-gastropathy

Risk factors for the development of NSAID-gastropathy are as follows: peptic ulcer in the anamnesis, especially recent and complicated by bleeding;

• age over 65;

• use of high doses of drugs (relative risk (HR) 2.5 in people taking low doses of NSAIDs; HR 8.6 in people taking high doses of NSAIDs; HR 2.8 in the treatment of standard doses of NSAIDs);

• chronic heart failure;

• arterial hypertension;

renal or hepatic insufficiency

• alcohol abuse;

• smoking;

• simultaneous administration of anticoagulants and/ or diuretics, angiotensin-converting enzyme inhibitors;

• simultaneous administration of several NSAIDs (doubling the risk);

• combination of NSAIDs and glucocorticosteroids

• short duration of treatment: the greatest probability of erosions and ulcers of the stomach and duodenum is noted in the 1st month of NSAID use; the development of gastric and duodenal bleeding is observed in 50% of patients using NSAIDs for no more than 7 days; the risk of gastrointestinal tract damage decreases somewhat with prolonged use of drugs (after the 4th month) and remains stable for several years of treatment, which is associated with the process of adaptation due to the rate of mucus production and the appearance of young epithelial cells;

• taking NSAIDs with a long half-life and non-selective concerning cyclooxygenase-2 (COX-2) (according to various data, HR 7.2 in patients treated with NSAIDs for less than 30 days, and HR 3.9 in patients treated for more than 30 days; HR 8.0 in the treatment of less than 1 month, HR 3.3 in the treatment of 1 to 3 months, and an HR of 1.9 when treated for more than 3 months);

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• intramuscular administration of NSAIDs;

• previous violation of the barrier function of the small intestine; violation of bile formation and bile secretion;

• dysbiosis of the small intestine; violation of enterohepatic recirculation of bile acids;

• the presence of rheumatoid arthritis;

• H. pylori infection (independent risk factor).

The development of gastropathy depends on the type of drug used. According to modern ideas, the lower the selectivity of the drug about COX-2,

the higher the probability of developing gastrointestinal pathology when using it. There are several meta-analyses in which the risk of serious gastrointestinal complications was assessed depending on the type of NSAID. Thus, the risk of serious complications increases for several non-selective NSAIDs as follows (if we take the risk for ibuprofen as a unit): ibuprofen (1.0) < fenoprofen, ASA (1.6) <

< diclofenac (1,8) < sulindac (2,1) < di-flunisal, naproxen (2,2) < indomethacin (2,4) < tolmetin (3,0) < piroxicam (3,8) <

< ketoprofen (4,2) < azapropazone (9.2) Data from another meta-analysis indicate the highest risk of gastrointestinal complications while taking indomethacin (HR 2.25), followed by naproxen (HR 1.83), diclofenac (HR 1.73), piroxicam (HR 1.66), ibuprofen (HR 1.43) and meloxicam (OR 1,24). According to H.P. Rang et al., the RR for NSAIDs increases as follows: phenoprofen, ASA < diclofenac < sulindac < diflunisal, naproxen < indomethacin < tolmein < piroxicam < ketoprofen < azapropazone [23].

In a meta-analysis of 22 placebo-controlled studies, which included more than

57 thousand patients, it was found that the incidence of GCC in the placebo group was 0.12% per year, and when using low doses of ASA, this risk doubled (HR 2.07; 95% confidence interval 1.61—2.66)

The effectiveness of PPIs and cytoprotection in the treatment of

In cases where NSAID-gastropathy has developed and manifested either pain and dyspeptic syndrome, or ulcers and/or gastrointestinal bleeding, the NSAID that caused them is canceled and gastroprotection is prescribed. At the same time, there are 2 main pharmacological strategies for managing patients — the appointment of PPIs or cytoprotectors, such as rebamipid, for example.

We conducted our comparative study of the effectiveness of treatment of developed NSAID-gastropathy by using rebamipid (group 1), PPIs (group 2), colloidal bismuth subcitrate (group 3) and a combination of celecoxib with PPIs (group 4). For this purpose, 155 patients with endoscopically confirmed NSAID-gastropathy were examined. An ulcer during endoscopy was defined as a defect with a diameter of 3 mm

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or more, measured using biopsy forceps. Erosions were defined as surface defects with less than 3 mm in diameter, and intra-mucosal hemorrhages were defined as hemorrhagic lesions without superficial mucosal defects. The endoscopic lesion of CO was evaluated using a modified Lanza scale, a number from 0 to 5, during screening and at the end of the study.

All patients with developed NSAID-gastropathy (155 people) for treatment by a simple blind method were randomized into 4 groups: taking rebami-pid (rebait, rebamipide McLeod) 1 tablet 100 mg 3 times/day (1 group, 42 patients), PPIs (control 40 mg) 1 time a day (2 group, 41 patients), colloidal bismuth subcitrate (de-nol) 1 tablet 4 times a day (group 3, 40 patients) or a combination of PPIs (control 40 mg 1 time/day) + celebrex 200 mg 1 time a day (group 4, 33 patients). In patients of groups 1, 2, and 3, the NSAID used was canceled and rebamipid, pantoprazole, or colloidal vis-mut were prescribed, respectively, for 4 weeks. NSAID-gastropathy

Characteristics of the examined patients

Basic characteristics-ki	1 group, n = 42	2 group, n = 41	3 group, n = 40	4 group , n = 33
Gender (Husband/Wife)	18/12	25/16	22/18	17/16
Age (years)	48 ± 11	49 ± 13	42 ± 10	44 ± 11
Stomach ulcers	5 (16,6%)	4 (9,8%)	4 (10%)	4 (12,1%)
Ulcers of the duodenum	5 (16,6%)	8 (19,6%)	7 (17,5%)	5 (15,1%)

The main criterion of effectiveness was the cumulative frequency of healing of erosions and ulcers of the gastroduodenal zone, which was determined after the end of treatment according to VEG data. Secondary efficacy criteria were the relief of dyspeptic symptoms and the frequency of side effects. The severity of symptoms of dyspepsia was assessed on a four-point scale and assessed every week according to the patient's diary. Symptoms of dyspepsia included early satiety, bloating, nausea and vomiting, heartburn and acid belching, and stool disorders.

Results of treatment of NSAID-gastropathy

Pathology	1 group, n = 42 (%)	2 group, n = 41 (%)	3 group, n = 40 (%)	group, n = 33 (%)
Stomach ulcers	1 (3,3%)	1 (2,4%)	1 (2,5%)	1 (3,4%)
Duodenal ulcers	1 (3,3%)	-	1 (2,5%)	1 (3,4%)

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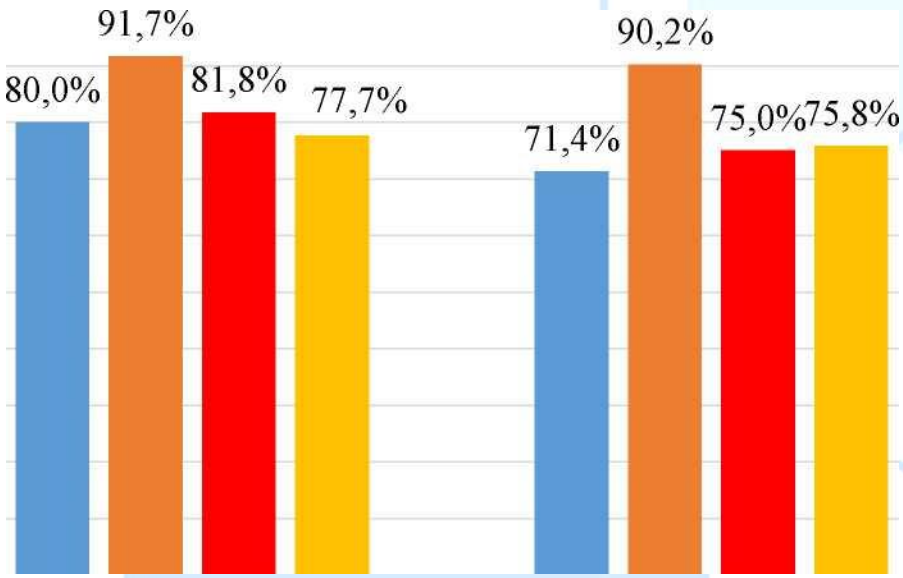
Total ulcers	2 (6,6%)	1 (2,4%)	2 (6,6%)	2 (6,8%)
COOLANT changes by	12 (28,6%)*	4 (9,8%)	10 (25%)*	8 (24,2%)*

All patients completed the prescribed course of treatment completely, and in most cases the treatment was effective. Gastric ulcers and/or duodenal ulcers in groups 1, 2, 3, and 4 were completely healed, respectively, in 8 out of 10 (80%), 11 out of 12 (91.7%), 9 out of 11 (81.8%) and 7 out of 9 (77.7%) patients (fig. 43). As can be seen from the presented data, during 1 month of treatment, scarring of NSAID-induced ulcers was accompanied by a marked improvement in the condition of the gastroduodenal zone (according to the Lanza scale). The best results were demonstrated by pantoprazole monotherapy, in which significantly better results were recorded from the stomach and duodenum (cumulative frequency

healed ulcers and erosions) compared with 3 other groups (90.2% vs. 71.4%, 75%, and 75.8% in the groups of rebamipide, bismuth, and pantoprazole in combination with celecoxib, respectively, $p < 0.05$). The results of the use of rebamipide and colloidal bismuth were approximately comparable with the use of the combination of celecoxib + pantoprazole, in which 7 out of 9 gastroduodenal ulcers completely healed, despite the continued use of a selective COX-2 inhibitor.



Normalization of the endoscopic picture

■ Rebamipid ■ Pantoprazole ■Bismuth ■ Pantoprazole+Celecoxib ■

Conclusion

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The experimental data and the results of clinical studies carried out from the standpoint of evidence-based medicine allow us to conclude that rebamipide is a highly effective and safe means of preventing and treating NSAID-gastropathy, which can be used as monotherapy. It is necessary to note the expediency of its use even with short—term NSAID intake, since the risk of developing gastropathy, including its complicated course, is highest in the first 7 to 30 days of NSAID use, especially in people with risk factors. The prescription of the drug is justified for conditionally healthy individuals if a short course of NSAID therapy is necessary. Also, the use of rebamipid is indicated for patients who need long-term or lifelong NSAID intake. As demonstrated above, the drug, when taken prophylactically, significantly reduces the risk of developing gastropathy. Therefore, rebamipide can be prescribed not only as a therapeutic agent for already-developed gastropathy but also for the prevention of the disease in the presence of risk factors in the patient.

It should be noted that the drug is most effective when taking 100 mg 3 times a day. The course of treatment is 2-4 weeks, however, as the research results show, the greatest effectiveness is achieved when the course is extended to 8-12 weeks. Currently, rebamipid has appeared on the Russian pharmaceutical market under the trade name Rebagit, 100 mg tablets No. 30.

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