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REBAMIPIDE: EFFECTIVE DRUG IN THE PREVENTION OF NSAID GASTROPATHY

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ABSTRACT

Prevention of the development of complications from the gastrointestinal tract (GIT) is the most important element of the rational use of non-steroidal anti-inflammatory drugs (NSAIDs). For a long time, proton pump inhibitors (PPIs) were the only means of drug prevention of these complications. However, PPIs are effective only for the prevention and treatment of pathology of the upper gastrointestinal tract (NSAID-gastropathy). Today, Uzbek doctors have a new tool for protecting the gastrointestinal mucosa - rebamipide. The action of this drug is different from that of PPIs: it is a typical gastro- and enteroprotector that enhances the synthesis of endogenous prostaglandins and has a significant anti-inflammatory potential. The drug has long been widely used by doctors in Japan, South Korea and China as an effective and safe remedy for the treatment of many diseases of the digestive system. There is a strong evidence base confirming the effectiveness of rebamipide for the prevention and treatment of NSAID gastropathy. According to controlled studies, it is not inferior to the "classic" gastroprotector misoprostol, significantly surpassing the latter in terms of tolerability. This review presents the mechanism of action of rebamipide and presents the main clinical studies that have studied its therapeutic effect in NSAID gastropathy.

KEY WORDS: ***non-steroidal anti-inflammatory drugs; NSAID gastropathy; proton pump inhibitors; misoprostol; rebamipide.***

Until recently, among the pharmacological agents used to protect the gastrointestinal tract ‘Rebagit®, PRO.MED.CS Prague a.o. tract (GIT) from the negative impact of antirheumatic drugs, proton pump inhibitors (PPIs) dominated almost completely. Today, with the advent of a new powerful drug for gastroprotection - rebamipide - the situation can seriously change.

Non-steroidal anti-inflammatory drugs (NSAIDs) have firmly entered clinical practice and everyday life. None of the inhabitants of the Earth wants to put up with pain - the most painful manifestation of diseases and injuries; the world community and the World Health Organization consider the rapid and most complete relief of suffering among the basic principles of respect for human rights. Every patient experiencing pain, regardless of the

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disease that caused it (even if it is incurable), should receive effective analgesic therapy. That is why NSAIDs are so widely used, which are the most convenient and very effective class of analgesics [1-3].

Estimating the scale of NSAID consumption is not easy. Many articles indicate that these drugs are used by 30 million inhabitants of the Earth. However, this estimate seems to be clearly underestimated. So, according to modern statistics, at least 10% of the inhabitants of the Earth suffer from chronic rheumatic diseases, such as osteoarthritis (OA), nonspecific back pain (NPS) and rheumatoid arthritis (RA) [4]. It is obvious that many of these patients periodically, and a significant part constantly, take NSAIDs. According to N. Wilson et al. [5], who analyzed the nature of the treatment of OA in 238,536 residents of Spain for 2006-2011, 14.4% of patients with this disease regularly (i.e., at least half of all days) took oral NSAIDs. In a well-known epidemiological study conducted by H. Breivik et al. [6], covering 15 countries of the European Union and Israel, found that 19% of the inhabitants of developed countries experience chronic pain, the cause of which in the vast majority of cases is the pathology of the musculoskeletal system. Only in five states of the European Union (Great Britain, France, Spain, Germany and Italy) there are about 50 million people suffering from pain, with 11.2 million experiencing severe pain. Most of these patients (approximately 2/3) periodically or regularly take analgesics, mainly NSAIDs: 55% are OTC and 44% are prescription [7].

In the US alone, according to 2010 data, NSAIDs were used regularly (i.e., at least 3 times a week for at least 3 months) by 29 million adults [8]. We do not know how many citizens of Uzbekistan take NSAIDs, but in 2013, with a population of 140 million, almost 14 million packages of these drugs were sold in our country [2].

According to long-term statistics, taking NSAIDs leads to the development of dyspepsia in approximately 20-30% of patients; 10-25% of patients who regularly use these drugs develop endoscopic (detected during esophagogastroduodenoscopy - EGDS) and mostly asymptomatic gastric and duodenal ulcers (duodenal ulcers). The most dangerous complications - bleeding and perforation - annually develop 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 [2, 10, 11].

However, much more often the main symptom of NSAID-gastropathy becomes subclinical blood loss, leading to the development of chronic iron deficiency anemia (IDA). The interest in this pathology is understandable, since even in the absence of life-threatening complications, NSAID gastropathy can have a pronounced negative impact on the patient's health. After all, chronic IDA is accompanied by a significant decrease in the oxygen capacity of the blood, a decrease in resistance to stress, and ultimately increases the risk of developing cardiovascular accidents [2, 11].

According to a series of clinical studies, the regular use of such n-NSAIDs as ibuprofen and naproxen led to damage to the gastric mucosa in 20-50% of healthy volunteers [19-21]. J. Goldstein et al. [19] studied the effect of celecoxib and naproxen on the

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stomach. The study group consisted of 413 healthy volunteers who underwent video capsule endoscopy (VCE). After the initial examination, 356 volunteers were selected for participation in the RCT, who did not have a pathology of the stomach. Of these, 3 groups were formed: the subjects of the 1st group received celecoxib 400 mg, the 2nd group - naproxen 1000 mg + omeprazole 20 mg and the 3rd group - placebo. A repeat study was performed 2 weeks later. As a result, among those taking celecoxib, damage to the gastric mucosa was detected in a significantly smaller number of cases than among those receiving naproxen: 16 and 55% ($p<0.001$). However, even in the celecoxib group, the number of such cases was significantly higher than in the placebo group, in which visible changes were noted in only 7% of those examined ($p<0.05$).

In patients with rheumatic diseases who regularly use NSAIDs, stomach changes are detected more often and are more pronounced. So, in a recent study by Czech scientists I. Tacheci et al. [22] during VCE, changes in the stomach were found in 44.8% of 143 patients with RA and OA treated with NSAIDs, and in 8.4% these were multiple (> 10) erosions and ulcers

The reason for the negative effect of NSAIDs on the gastrointestinal tract is well known. All NSAIDs are inhibitors of the enzyme cyclooxygenase (COX), which forms the precursor of prostaglandins (PG) - the most important mediators of pain and inflammation. The main pharmacological action of NSAIDs is associated with the blockade of the inducible form of COX (COX2), which determines the formation of PG in the area of damage to living tissue. However, in addition to COX2, n-NSAIDs also inhibit the activity of the "constitutional" variety of this enzyme - COX1 - which is involved in the synthesis of PG in the gastrointestinal mucosa. Here, PG play the role of the most important protective factor: they reduce gastric secretion, increase the formation of mucus and bicarbonate, stimulate the reparative potential of epitheliocytes and increase blood flow. N-NSAIDs significantly reduce the formation of PG in the mucosa of the gastrointestinal tract, thereby provoking its damage under the influence of external factors of aggression - hydrochloric acid and pepsin in the stomach and duodenum, bacteria and their metabolic products in the small and large intestine [2, 11, 26].

It is important to note that in order to maintain the stability of the gastrointestinal mucosa, not only the "constitutional" COX1, but also COX2 is of great importance. After all, this enzyme is always expressed in the area of damage, and the PG synthesized due to COX2 take an active part in the repair processes. The integrity of the mucous membrane of the gastrointestinal tract is often violated - it is damaged by rough, irritating food, microorganisms and xenobiotics that penetrate with it, etc.; we should not forget about H. pylori, which infected almost half of the inhabitants of the Earth. Therefore, the blockade of COX2 can slow down the recovery of the mucous membrane and thereby cause its deeper damage [2, 11]. This may explain the negative effect on the gastrointestinal tract of selective COX2 inhibitors (selective NSAIDs - c-NSAIDs), although, of course, it is much less pronounced than that of n-NSAIDs. Quite indicative in this respect is the study by L. Maiden et al. [27], who assessed the frequency

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of gastric changes according to VCE data in 112 patients who received n-NSAIDs and 40 patients who took c-NSAIDs: damage to the gastric mucosa of varying severity was noted in 62 and 50% (differences are not statistically significant).

Based on the pathogenesis of NSAID-induced pathology of the gastrointestinal tract, its drug prevention can be determined by two main directions. The first is an increase in the stability of the mucous membrane, i.e., the elimination of the negative effect of NSAIDs on the synthesis of cytoprotective PGs. This approach was implemented when creating misoprostol, a synthetic analogue of PGE1. This drug has demonstrated efficacy in the prevention and treatment of NSAID gastropathy in patients with RA, which was confirmed by a series of well-designed RCTs [28], including a large 6-month MUCOSA study (n=8843) [29]. Misoprostol was also effective for the prevention of NSAID enteropathy [30, 31]. However, it has an important drawback - frequent adverse reactions (AR), primarily diarrhea [28, 32]. Inconvenient dosing regimen and poor tolerability have limited the use of misoprostol. After the widespread introduction of PPI into clinical practice, it lost its importance as the main gastroprotector.

Another way to protect the gastrointestinal tract from the negative effects of NSAIDs is to eliminate the main factor of aggression that causes damage to the mucous membrane (hydrochloric acid of gastric juice). With effective suppression of gastric secretion, the likelihood of developing erosions and ulcers, even against the background of a significant decrease in mucosal resistance, is significantly reduced [2, 11, 13].

The highest antisecretory potential is observed in PPIs. It is this class of antiulcer drugs, as noted above, that is today the main means of preventing and treating NSAID-induced gastrointestinal complications. Indeed, PPIs effectively prevent the development of dyspepsia, erosions and ulcers, as well as gastrointestinal bleeding [2, 11, 13]. However, PPIs have an effect only at the level of the upper gastrointestinal tract. However, PPIs can increase the risk of developing this pathology [33, 34]. This is primarily due to an increase in the contamination of the intestine with opportunistic and pathogenic flora, caused by a significant decrease in the acidity of gastric juice. A series of population-based studies have shown that taking PPIs increases the risk of developing an infection caused by Salmonella, Campylobacter, Clostridium, and other microorganisms by a factor of 2–5 [35, 36]. In addition, there is an association between PPI use and the development of microscopic colitis. Thus, in a case-control study (comparison of 1211 patients with microscopic colitis and 6041 individuals without this disease), the odds ratio (OR) for PPI was 3.37 [37].

It is obvious that a completely different approach is required to prevent intestinal damage associated with the use of NSAIDs or NDA. And such an approach is the use of rebamipide, a drug that is still little known to Uzbek rheumatologists and therapists. Rebamipide, a derivative of quinolinone, was developed by the Japanese company Otsuka Pharmaceutical Company and has been used in clinical practice since 1990. For a number of reasons (related to the marketing policy of manufacturers), the drug is

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used mainly in Asian countries - Japan, South Korea and China, where it gained a reputation as an effective and safe remedy for the treatment of diseases of the digestive system [38-40].

Unlike PPIs, this drug does not suppress the secretion of hydrochloric acid, but has a different, very multifaceted pharmacological effect that determines its effectiveness as a gastro- and enteroprotector. Probably, the most valuable property of rebamipide is a dose-dependent increase in the synthesis of PGE2 and PGb in the gastrointestinal mucosa [38-41]. Rebamipide also increases the formation of a macromolecular glycoprotein complex (which determines the protective properties of surface mucus) [41], binds reactive oxygen species and inhibits lipid peroxidation [42], stimulates the expression of growth factors, in particular epidermal growth factor and fibroblast growth factor [43], blocks voltage-dependent Ca2+ channels, preventing an increase in the concentration of this ion inside cells [44]. In addition, it has anti-inflammatory properties, inhibiting the formation of a number of cytokines, including H. pylori-induced hyperproduction of interleukin 8 [45] and adhesion molecules (ICAM-1) [46]. An important element of the enteroprotective potential of rebamipide is its ability to enhance the synthesis of alpha-defensins, natural peptide "antibiotics" that are produced by Paneth cells of the small intestine and play an important role in the natural antibacterial defense system [47].

The efficacy and safety of rebamipide for the prevention of NSAID-induced gastrointestinal injury has been extensively tested. Thus, in 2013 S. Zhang et al. [48] presented a meta-analysis of 15 RCTs (n=965) that investigated the therapeutic effect of the drug. It was significantly more effective than placebo and was not inferior to other gastroprotective agents: misoprostol, PPIs, and N-blockers. In addition, rebamipide significantly reduced the risk of developing erosive and ulcerative changes in the intestine: OR compared with placebo was 2.7 (95% confidence interval - CI 1.02-7.16).

An example of a comparison of rebamipide and placebo for the prevention of NSAID gastropathy is the recent RCT GLORIA, in which 75 patients with RA, OA and NBS took NSAIDs in combination with rebamipide 100 mg 3 times a day or placebo for 3 months. It is curious that c-NSAID celecoxib was chosen as the NSAID, which is considered the safest representative of this drug group for the gastrointestinal tract. However, in the placebo group, "safe" celecoxib caused ulcers in 5 patients and intolerable dyspepsia in 1 (17.6% of complications in total). In the rebamipide group, no serious gastrointestinal complications were noted while taking celecoxib (p = 0.0252) [49].

The most interesting are the works in which rebamipide was compared with misoprostol, which has a similar mechanism of action. Thus, the data of RCT STORM, which compared the preventive effect of rebamipide 300 mg/day and misoprostol 600 mcg/day (both drugs were prescribed 3 times a day) in 332 patients who regularly took various NSAIDs (aceclofenac, diclofenac , fenoprofen, ibuprofen, naproxen and sulindac). Interestingly, almost half of the patients in both groups (48.5 and 41.7%) had H. pylori. The results of prevention were evaluated according

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to the data of endoscopy, which was performed before and after 12 weeks of treatment. As a result, rebamipide was in no way inferior to misoprostol: the incidence of gastric and duodenal ulcers was 4.0 and 3.9% [50].

Recently, new evidence has emerged of the benefits of rebamipide as an agent for the prevention of NSAID gastropathy. T.N. Kim et al. [51] conducted a large-scale RCT in which 479 patients who took NSAIDs (mainly aceclofenac, meloxicam and nabumeton) for 12 weeks received rebamipide 300 mg/day or misoprostol 600 μg/day as prophylaxis. According to endoscopic examination, the number of gastric and duodenal ulcers in patients of both groups was almost the same. But at the same time, cancellations due to NR in the misoprostol group were noted almost 2 times more often (Fig. 1). Dyspepsia in the rebamipide group occurred much less frequently and was less pronounced. So, its severity (on a scale of 0-3 points) at the end of the study in the rebamipide and misoprostol groups averaged 0.44+1.05 and 0.67+1.24 points ($p<0.05$), and the number of antacid tablets used to relieve dyspepsia was 7.19+15.49 and 11.18+22.79 ($p<0.05$), respectively.

Of course, the experience of using rebamipide in volunteers is extremely important. However, of much greater interest are clinical studies in which the therapeutic and prophylactic effect of the drug was studied in real patients with NSAID gastropathy. Recently, two works by Japanese scientists have been published on this issue. Thus, in a 4-week study by S. Kurokawa et al. [56] compared the therapeutic effect of rebamipide 300 mg/day and placebo in 61 patients who had taken NSAIDs and/or NDA for more than 3 months. All patients underwent VCE before and after the course of therapy. It turned out that the number of gastric erosions in the main group significantly decreased, while in the control group it increased in comparison with the initial level ($p<0.001$; Fig. 2). Similar dynamics was noted in relation to the number of ulcers: -0.5±1.6 and 0.1±0.7 ($p=0.024$), as well as the level of blood protein. The latter indicator significantly decreased in the control group, which reflects plasma exudation in the small intestine associated with NSAID gastropathy.

As can be seen, today there are a large number of clinical studies performed in compliance with all the rules of evidence-based medicine, demonstrating the advantage of rebamipide in comparison with placebo for the prevention and treatment of NSAID-induced gastrointestinal pathology. Moreover, we are talking about complications from the upper gastrointestinal tract.

The ability of rebamipide to have a cytoprotective and anti-inflammatory effect made it possible to successfully use it not only in drug pathology of the gastrointestinal tract, but also in other diseases of the digestive system. Thus, a series of large-scale studies performed in Japan, South Korea and China convincingly shows a higher frequency of healing of H. pylori-associated gastric and duodenal ulcers, as well as the resolution of chronic antral gastritis when using rebamipide against or after standard anti-Helicobacter pylori therapy. [58-60].

T. Kamada et al. [61] evaluated the dynamics of the histological picture of H. py/ori-associated chronic gastritis in 103

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patients who underwent a course of anti-Helicobacter pylori therapy. According to the study plan, half of the patients received rebamipide 300 mg/day for 12 months and half received placebo. By the end of the observation, the severity of inflammatory changes in the lesser curvature of the stomach (assessed by the modified Sydney system) was significantly less in the active therapy group compared to the placebo group: 1.12±0.08 and 1.35±0.08 points, respectively (p=0.043).

Thus, for Uzbek doctors, rebamipide is a new and promising tool for combating complications caused by NSAIDs and LDA. Rebamipide can be an effective tool for the prevention and treatment of NSAID gastropathy. The therapeutic and prophylactic potential of rebamipide in NSAID gastropathy has been shown in many RCTs, it is well tolerated and practically does not cause serious complications. One might think that the drug will find wide application in rheumatic diseases as an important means of improving the safety of pharmacotherapy.

CONCLUSION

Rebamipide is a gastroprotector, the main pharmacological action of which is associated with an increase in the synthesis of endogenous PGs and growth factors in the gastrointestinal mucosa, an antioxidant effect, suppression of the expression of pro-inflammatory cytokines and adhesion molecules, stimulation of the formation and release of alphadefensins by Paneth cells, etc.

Clinical studies conducted in Japan, South Korea and China confirm the effectiveness of rebamipide for the prevention and treatment of NSAID gastropathy.

According to RCTs, rebamipide is not inferior in effectiveness to the "classic" gastroprotector misoprostol and significantly outperforms it in tolerability.

The standard dose of rebamipide is 100 mg 3 times a day for up to 8 weeks. At the same time, as evidenced by the data of a number of clinical studies, rebamipide is well tolerated and at a much higher dose (300 mg 3 times a day) and can be safely used in courses up to 6-12 months.

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