

Analysis of the Use of Gastroprotectors in Patients with Stable and Unstable Angina Who Take Acetylsalytic Acid Preparations

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Annotation: Antithrombotic drugs (antiplatelet agents and anticoagulants) are widely used in cardiology practice for the first and second-degree prevention of thrombotic and thromboembolic complications. However, their use increases the risk of complications associated with bleeding, including gastrointestinal bleeding. The results of capsular videoendoscopy showed that antithrombotic drugs affect not only the upper part of the stomach, but also the lower parts - the small and large intestines.

Therefore, in order to protect the mucous membrane of the gastrointestinal tract and prevent bleeding, it is advisable to use rebamide - a unique drug that combines gastro- and enteroprotective properties. Rebamypid acts on all structural levels of the mucous membrane throughout the gastrointestinal tract. Its effectiveness and safety have been proven in numerous randomized clinical trials.

Keywords: antiplatelets, anticoagulants, gastrointestinal bleeding, epithelial conduction syndrome, gastroenteroprotector, rebamide, proton pump inhibitors.

Introduction

Antithrombotic drugs (antiplatelet agents and anticoagulants) are considered pathogenetically justified in the treatment of many cardiovascular diseases. They improve the prognosis of the

disease and significantly reduce the risk of complications such as myocardial infarction, unstable angina, stent thrombosis, ischemic stroke, and cardiovascular death.

In recent years, as a result of the expansion of the indications for antithrombotic therapy, the proportion of patients receiving double or triple antithrombotic therapy (double antiplatelet agent or antiplatelet agent + anticoagulant) has increased sharply.

However, any antithrombotic drug can cause bleeding complications, including gastrointestinal bleeding. According to the data of the meta-analysis, the risk of gastrointestinal bleeding was twice as high in patients receiving aspirin (ASK) (relative risk was 2.07; 95% confidence interval 1.61-2.66) compared to the placebo group.

Also, in studies involving more than 70 thousand patients with atrial fibrillation, it was found that oral anticoagulants of direct action (OPAC) increased the risk of gastrointestinal bleeding by 25% compared to warfarin.

Gastrointestinal damage associated with antithrombotic drugs

Studies using capsular videoendoscopy have shown that the effect of antithrombotic drugs is not limited to the upper part of the stomach, but also spreads to the lower parts of the intestine, i.e., it affects the small and large intestines.

In one study, patients who applied for gastrointestinal bleeding (n = 181) with detected hidden blood in blood analysis using capsular endoscopy were assessed based on the condition of the intestinal mucosa. Erosive-ulcerative lesions of the small intestine were detected in 45 (25%) patients, 60% of whom received aspirin or NSAIDs.

The frequency of erosions and ulcers in patients receiving aspirin or NSAIDs was 64%, 75%, and 80% respectively. Erosive lesions were mainly observed in patients receiving aspirin, while ulcers were more common in the group receiving NSAIDs. The proportion of ulcers significantly increased in patients receiving aspirin and thienopyridine derivatives simultaneously.

Erosions were detected along the entire length of the intestine, while ulcers were mainly located in the terminal part of the duodenum. These results confirmed the intensification and severity of mucosal damage when aspirin and NSAIDs are used together.

Conduction syndrome and subclinical inflammation of the mucous membrane

According to the universal multi-level protection concept, antiplatelet agents and anticoagulants act on the gastrointestinal tract as external aggressive factors. As a result, not only erosions and ulcers occur, but also the permeability of the mucous membrane to bacteria and toxins increases, and the points of intercellular contact are disrupted.

As a result of this process, slow, low-intensity inflammation develops - that is, the syndrome of increased epithelial permeability. Currently, this syndrome is considered one of the main mechanisms of human pathological processes.

Patients with cardiovascular diseases requiring antithrombotic therapy are often considered comorbid, meaning they simultaneously have gastrointestinal diseases. According to the results of a multicenter study conducted in Russia, gastrointestinal pathologies were detected in 62% of 662 patients receiving POACs.

The most common diseases were the stomach (55%), pharynx (34%), intestines (32%), liver (11%), and pancreas (8%). In addition, 38% of patients have a high risk of bleeding. These data confirm the need to protect the mucous membrane of the gastrointestinal tract in patients receiving POA.

Inhibitors and their limitations: necessity of using rebamide

In patients who traditionally take antiplatelet agents (especially aspirin) or nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PNI) are used to protect the

gastrointestinal mucosa. Ideally, the duration of NSAID treatment should be the same as the duration of taking aspirin or NSAIDs, i.e., in most cases, they are prescribed for a long time.

However, with prolonged use of PPI, various adverse effects are observed. According to studies, the risk of the following diseases increased in patients receiving long-term PPIs:

- ✓ dementia - 4-80%;
- ✓ bone fractures - 30-400%;
- ✓ infections - up to 600%;
- ✓ micronutrient deficiency - 60-70%;
- ✓ intestinal dysbiosis - 200-800%;
- ✓ chronic kidney diseases - 10-20%.

Also, some studies show that prolonged use of PPI can be associated with the risk of death and cardiovascular complications (heart attack, stroke).

Main shortcomings of the SRI

The main limitation of PPIs is that they only prevent erosive-ulcerative lesions in the upper parts of the stomach, and do not affect pathological processes in the **lower parts (intestine) **.

On the contrary, studies have shown that when PPI is taken in combination with NSAIDs, it intensifies damage to the mucous membrane of the intestine and can even provoke bleeding from the lower part. Therefore, it is not advisable to routinely recommend PPI to all patients receiving antithrombotic therapy.

PPIs are useful only in cases of ulcers or bleeding in the upper part of the stomach, and in other cases, they do not provide safety.

Geriatric review of PPIs

Cardiological diseases are more common in elderly patients. Therefore, antithrombotic therapy is mainly used in the elderly - they have a high risk of both thrombosis and bleeding. At the same time, the long-term adverse effects of PPI are more pronounced in them.

According to specialists of the Russian Association of Gerontologists, long-term prescription of PPI in the elderly is not always beneficial; in some cases, it is advisable to reduce or stop it ("depress scrubbing").

In 2019, the Russian Center for Gerontology developed an algorithm for reducing PPI in the elderly, in which it was noted that PPI can be safely abolished for some patients.

Justification for the use of rebamid

Taking into account the limitations of PPI and the need for protection of both the stomach and intestines, the use of a drug combining gastro- and enteroprotective properties - rebamid - is logically justified.

Rebamypid was created in Japan more than 30 years ago and now exists in Russia under the name "Rebagit." Its impact is manifested as follows:

- ✓ in the stomach, prostaglandin enhances the synthesis of E2 and I2, which increases the protective function;
- ✓ reduces high intestinal conductivity;
- ✓ restores the stability of the smooth layer;
- ✓ reduces inflammation.

The peculiarity of rebamide is that it affects all structural levels of the gastrointestinal tract:

In the mucous layer - mucus is restored;

In epithelial cells - they regenerate cells and "restore" junction points;

At the level of blood circulation - improves microcirculation and normalizes the inflammatory response.

Clinical effectiveness and research results of rebamide

The effectiveness of rebamide in treating erosive and ulcerative lesions of the gastric and duodenal mucosa, including those associated with antiplatelet agents and anticoagulants, has been proven in a number of studies.

In some studies, rebamide was used in patients receiving dual antithrombotic therapy. For example, in one randomized clinical study, the effectiveness of rebamide in preventing stomach ulcers in patients receiving dual antithrombotic therapy for a long time (≥ 1 year) was confirmed. Another experimental study showed that the effect of rebamide on the prevention of gastric bleeding induced by aspirin and clopidogrel is comparable to that of other antisecretory drugs.

Meta-analysis results

In 2021, a network meta-analysis was published based on the results of 10 randomized clinical trials ($n = 503$). This study evaluated the effectiveness of 11 different drugs in preventing aspirin-induced gastropathy.

According to the results, the combination of omeprazole + rebamide has a higher effectiveness compared to other gastroprotectors. Ranitidine + bismuth citrate was in second place, and omeprazole monotherapy was in third. The lowest effectiveness was observed in geranyl geranylacetone and placebo.

At the same time, monotherapy with rebamide was not evaluated separately in these studies, which indicates the need for further study of its potential.

Rebamipide and enteropathy

The effectiveness of rebamipide in the prevention and treatment of aspirin-induced enteropathy has also been proven in several randomized studies ($n=4$). In these studies, rebamide was compared with placebo and showed higher effectiveness each time.

In one study (Watanabe et al., 2015), a high dose of rebamide (300 mg, 3 times a day, 8 weeks) was used. As a result, the number and severity of injuries to the intestinal mucosa have significantly decreased, and the safety of the drug has been fully confirmed.

According to the results of meta-analysis, which included 15 clinical studies, it was found that rebamide is 2.7 times more effective in treating erosions and wounds than placebo (OR 2.70; 95% CI 1.02-7.16; $p = 0.045$).

Rebamide in Russian research

In a study conducted in Russia, the effect of rebamide on the protection of the intestinal mucosa was assessed in 60 patients with irritable bowel syndrome (diarrheal form). The patients were divided into three groups:

1. Trimebutin monotherapy,
2. Rebamipide monotherapy,
3. Trimebutin + rebamipide combination.

The results of the two-month treatment were as follows: rebamide strengthened the intestinal barrier, reducing enterocyte damage and inflammation. The level of zonulin (a marker of

intestinal conductivity) decreased only in the group receiving rebamide. These results once again confirmed the enteroprotective potential of rebamide.

Replacement of rebamide against the background of anticoagulant therapy

It is undoubtedly necessary to prescribe gastroprotectors to patients taking aspirin or NSAIDs. However, in patients taking anticoagulants, this strategy is not always clear, since oral anticoagulants of direct action do not have an ulcerogenic effect and the risk of bleeding with them is lower than with aspirin.

A study conducted in Russia showed that the frequency of prescribing gastroprotectors in patients receiving PAA is low, which does not completely prevent gastrointestinal bleeding.

662 patients (average age - 70 years, 47% men) were included in the study. Of these, 65% previously received POA, and 35% of patients were prescribed the drug for the first time. Among the patients:

- ✓ 50% - rivaroxaban,
- ✓ 35% - apiksaban,
- ✓ 15% - didbigatran ethexylate.

Gastroprotectors were prescribed to only 57% of patients: 94% of them received proton pump inhibitors (PNI), 23% - rebamide. Among the three recipients of antithrombotic therapy, this indicator reached 90%, i.e., those at high risk frequently took rebamide.

HIV Bleeding Risk Assessment and Expert Recommendations

Due to the long duration of anticoagulant therapy, the problem of ensuring the safety of patients is of great importance. Therefore, in December 2021, the "Expert Consensus on Reducing the Risk of Gastrointestinal Bleeding in Patients Taking Oral Anticoagulants" was published in Russia.

In this document:

High risk criteria for gastrointestinal bleeding are presented;

the necessity of protecting the gastrointestinal mucosa when taking anticoagulants is substantiated;

an algorithm for risk assessment and selection of gastroenteroprotective therapy has been proposed.

Also, its abbreviated version for surgery - "Algorithms for diagnosis and treatment to reduce the risk of gastrointestinal bleeding in patients taking anticoagulants" - was published in 2022.

Recommendations for a combination of rebamipide and PNI

Experts recommend the combined use of PPI and rebamide to reduce the risk of gastrointestinal bleeding.

According to the recommendations:

- ✓ A combination of PNI and rebamide should be taken for at least 3 months;
- ✓ subsequently, the dose of PNI can be reduced or continued as needed;
- ✓ Rebamide should be taken during the anticoagulant therapy period, i.e., for a long time.

Also, from the point of view of minimizing the risk of bleeding from the gastrointestinal tract, the anticoagulant Apiksaban is considered a priority and is recommended as the first option.

Hulosa

Rebamipide, as a gastro- and entero-protector, protects the gastrointestinal mucosa throughout the entire tract. It is effective and safe in preventing damage associated with antiplatelet agents and anticoagulants.

Clinical studies have shown that the combined use of rebamipide with PNI significantly reduces the risk of gastrointestinal bleeding and increases the patient's safety during long-term anticoagulant therapy.

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