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Prospects for the Use of Drugs Affecting the Protective Mechanisms of the Gastrointestinal Mucosa. The Role of Prostaglandin Production Stimulators

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Resume: Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) remain among the most widely prescribed agents worldwide, yet their use is frequently associated with gastrointestinal (GI) complications, including gastroduodenopathies and enteropathies. Traditionally, preventive strategies have focused on upper GI protection through antisecretory therapy. However, damage to the intestinal mucosa remains insufficiently addressed. Rebamipide, a novel gastro- and enteroprotective agent developed in Japan and introduced in Russia in 2016, has demonstrated high efficacy in protecting and repairing both gastric and intestinal mucosa. Its mechanism of action involves stimulation of prostaglandin synthesis, upregulation of endothelial growth factor, activation of the sonic hedgehog and ERK pathways, reduction of oxidative stress, and modulation of intestinal microbiota. Experimental and clinical studies confirm rebamipide's ability to accelerate mucosal healing, reduce NSAID- and ASA-induced injury, inhibit H. pylori adhesion, and exert systemic anti-inflammatory effects through suppression of NF-κB and TNF-α activity. Comparative trials show that rebamipide is as effective as misoprostol but with superior tolerability and fewer gastrointestinal side effects. These findings position rebamipide as a promising pharmacological agent for comprehensive protection of the gastrointestinal tract in patients receiving long-term antiplatelet or NSAID therapy.

Keywords: Rebamipide, gastroprotection, enteropathy, prostaglandins, Helicobacter pylori.

At present, NSAID- and ASA-induced gastroduodenopathies and their complications are quite common in patients receiving this class of drugs. The study of this problem, as well as preventive measures, has mainly focused on the upper gastrointestinal tract (GIT). While gastric secretion plays the leading role in upper GI lesions, the mechanism of intestinal mucosal injury remains insufficiently understood [1]. A promising approach to the prevention and treatment of such pathology, alongside antisecretory therapy, involves the use of agents with gastroprotective effects on the gastric and intestinal mucosa. In 2016, a new drug appeared in the Russian Federation — the effective gastro- and enteroprotector rebamipide (manufactured by *PRO.MED.CS Praha a.s.*) . Currently, it has no analogues in Russia. The first reports on rebamipide appeared in the early 1980s. The drug was developed by Japanese scientists, who also conducted most of the experimental studies [2]. The mechanism of action of rebamipide is based on stimulation of prostaglandin synthesis and expression of the PGE_2 receptor 4, as well as inhibition of 15-hydroxyprostaglandin dehydrogenase, which increases PGE_2 concentration in GI tissues. This leads to a slight reduction in gastric acid secretion and enhanced synthesis of glycoproteins in the gastrointestinal mucus.

In addition, rebamipide increases the expression of endothelial growth factor and its receptor in the gastric mucosa, thereby promoting cell proliferation and re-epithelialization. It restores the activity

of the *sonic hedgehog* signaling pathway, which contributes to the reversibility of gastric cell atrophy [3]. Rebamipide promotes healing and regeneration of the GI mucosa by normalizing tyrosine nitration in the ERK (extracellular signal-regulated kinase) signaling pathway and initiating vascularization through the induction of proangiogenic genes [191]. Moreover, the drug enhances secretion of gastric mucus and antioxidants, reduces lipid peroxidation in the GI tract, and protects against mitochondrial damage and apoptosis of gastric and intestinal epithelial cells during NSAID therapy [4]. Rebamipide inhibits the adhesion of *Helicobacter pylori* to the gastric mucosa, thereby facilitating the antimicrobial effect of antibiotics . It also blocks cellular inflammatory reactions, reduces neutrophil production of proinflammatory cytokines and chemokines induced by *H. pylori*, and improves gastric mucosal blood flow .

It is noteworthy that rebamipide exerts anti-inflammatory effects beyond the gastrointestinal system. The drug has been shown to attenuate TNF-α–mediated inflammatory responses, stabilize macrophage cell lines, and reduce activation of nuclear factor kappa-B (NF-κB), thereby interrupting inflammatory signaling cascades [5]. In summary, the main effects of rebamipide include: induction of prostaglandin (E_2 and I_2) synthesis, improvement of GI mucosal blood flow, reduction of mucosal permeability, scavenging of free radicals, anti-inflammatory activity, and enhancement of gastric mucus secretion. The efficacy of rebamipide has been confirmed by numerous experimental and clinical studies. In rat experiments, rebamipide demonstrated superior healing of ulcerative lesions of various origins while simultaneously preventing their development .

In mouse models, acute small intestinal injury was induced by administering ASA at 200 mg/kg/day for five days, followed by rebamipide at 320 mg/kg/day. Structural changes in the small intestine were assessed by electron microscopy. Mice treated with rebamipide showed less pronounced structural alterations and tighter intercellular junctions. The study concluded that rebamipide improves the barrier structure of the stomach and intestines and promotes intestinal regeneration by regulating cyclooxygenase-2 (COX-2) expression in ASA-induced GI injury [6].

Several studies have demonstrated that NSAID administration increases reactive oxygen species (ROS) formation, leading to mitochondrial damage and disruption of intestinal mucosal integrity. Rebamipide significantly reduces ROS concentration and the number of damaged intestinal epithelial cells, likely through activation of manganese superoxide dismutase [7]. Another important enteroprotective property of rebamipide is its modulatory effect on intestinal microbiota. It normalizes the concentration of *Enterococcus* and *Enterobacter* species in the ileal mucosa .

The role of *H. pylori* in gastric carcinogenesis is well established; however, its eradication alone does not completely eliminate gastric cancer risk. Experimental studies in rats with chemically induced carcinogenesis have demonstrated a preventive effect of rebamipide: the incidence of gastric cancer in the rebamipide-treated group was significantly lower than in the control group ($p < 0.05$), with a trend toward reduced carcinoma invasion into the muscular layer [8]. Numerous clinical studies have confirmed the therapeutic efficacy of rebamipide . In a large retrospective study involving 530 patients receiving low-dose ASA for one month, those not taking antisecretory or cytoprotective agents had a 9.3% rate of gastric bleeding and a 49.1% rate of acute gastric erosions or ulcers. Among patients on proton pump inhibitors (PPIs), gastric bleeding occurred in 2.1% and ulcers in 18.6% of cases. In the rebamipide group, these rates were 0% and 18.8%, respectively, while patients using other cytoprotectors or antacids had bleeding and ulcer incidences of 3.8% and 38.5%, respectively [9].

A 2013 meta-analysis combining 15 randomized controlled trials (965 patients) demonstrated significantly greater efficacy of rebamipide compared to placebo in preventing NSAID-induced gastroduodenal injury, without any serious adverse effects [10]. In a randomized, double-blind, placebo-controlled, crossover study involving 20 healthy volunteers receiving 81 mg ASA with either placebo or rebamipide (300 mg three times daily for 7 days), the rebamipide group showed significantly less antral mucosal hyperemia compared to placebo ($p = 0.039$) [167]. Another similar study included 32 healthy volunteers divided into four groups: (1) 100 mg ASA + placebo; (2) 100 mg ASA + 100 mg rebamipide three times daily; (3) ASA + clopidogrel 75 mg once daily; and (4)

ASA + clopidogrel + rebamipide. Rebamipide significantly reduced mucosal lesions compared to placebo in both low-dose ASA and ASA + clopidogrel combinations ($p = 0.05$ and $p = 0.01$, respectively) [11]. In a clinical trial of 38 patients receiving ASA 100 mg for more than three months, rebamipide (300 mg/day) was administered for eight weeks to treat enteropathy. Capsule endoscopy showed significantly fewer intestinal erosions and ulcers in the rebamipide group compared to placebo ($p = 0.046$)

Rebamipide has also been compared to misoprostol in terms of efficacy and safety. In a double-blind, randomized, multicenter study of 479 patients receiving continuous NSAID therapy, participants were randomized to rebamipide 100 mg three times daily (n = 242) or misoprostol 200 µg three times daily (n = 237) for 12 weeks. After 12 weeks, the incidence of gastric ulcers was slightly higher in the misoprostol group; however, the overall gastrointestinal symptom score and antacid use were significantly lower in the rebamipide group ($p = 0.0002$ and $p = 0.0258$, respectively) [12]. These findings confirm the high efficacy and safety of rebamipide in the management of NSAID- and ASA-induced gastro- and enteropathies. The beneficial effects of rebamipide extend beyond the GI tract. When used as ophthalmic drops, it reduces IL-6, IL-17, and TNF-α levels in tear fluid, thereby decreasing inflammation . Rebamipide also inhibits inflammatory changes in joints, restores the balance between Th17 and regulatory T cells, and activates the Nrf2/HO-1 oxygenase pathway . Its potential role in inhibiting oxidative stress through suppression of inflammatory cytokine production is currently under investigation [13].

Conclusion: Rebamipide represents a major advancement in the pharmacological prevention and treatment of NSAID- and ASA-induced gastrointestinal complications. Its multifaceted mechanism — combining prostaglandin stimulation, antioxidant and anti-inflammatory actions, mucosal regeneration, and microbiota modulation — ensures broad protective efficacy across the entire GI tract. Clinical evidence demonstrates that rebamipide significantly reduces the incidence of erosions, ulcers, and bleeding while maintaining a favorable safety profile compared with conventional cytoprotectors. Furthermore, its beneficial effects extend beyond gastroprotection, suggesting potential therapeutic value in inflammatory and oxidative stress–related disorders. Continued research may expand its clinical applications and confirm its role as an essential component of modern gastroprotective therapy.

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