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Optimising the Complex Treatment of Patients with Ischaemic Heart Disease and Acid Dependent Gastrointestinal Tract Disorders: A Focus on Rebamipide as a Novel Gastro and Enteroprotective Strategy

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Abstract Aspirin-induced gastropathies continue to pose a substantial clinical challenge due to their high prevalence and risk of serious gastrointestinal complications. Emerging evidence identifies rebamipide as a potent gastro- and enteroprotective agent with multifactorial mechanisms, including stimulation of prostaglandin synthesis, enhancement of mucosal regeneration, and attenuation of oxidative stress. Preclinical studies demonstrate that rebamipide preserves mucosal integrity and reduces epithelial apoptosis in both gastric and small intestinal tissues exposed to aspirin. Clinical trials indicate that its efficacy in preventing aspirin-induced gastrointestinal lesions is comparable to proton pump inhibitors and misoprostol, while exhibiting superior tolerability and fewer adverse effects. Beyond the stomach, rebamipide exerts protective effects on the small intestine, mitigating inflammation and maintaining barrier function. Moreover, it positively modulates gut microbiota and enhances mucosal blood flow, contributing to comprehensive gastrointestinal protection. Collectively, these findings support the use of rebamipide as a safe and effective therapeutic strategy for the prevention and management of aspirin-associated gastroduodenopathies.

Keywords Rebamipide, Aspirin, Gastroprotection, Enteropathy, Proton pump inhibitors, Mucosal regeneration

1. Introduction

Over the past several decades, considerable attention has been devoted to identifying strategies to minimize the risk of gastrointestinal (GI) complications in patients receiving acetylsalicylic acid (ASA). A central approach to enhance the safety of ASA therapy involves administering the lowest effective dose within the therapeutic range. Accumulating evidence has consistently demonstrated a dose-dependent ulcerogenic potential associated with ASA [1]. In a case–control study involving 3,236 patients, the likelihood of hospitalization due to ulcer-related bleeding decreased progressively with lower ASA doses (75 mg: OR 2.3; 95% CI 1.2–4.4; 150 mg: OR 3.2; 95% CI 1.7–6.5; 300 mg: OR 3.9; 95% CI 2.5–6.3). Similarly, data from the CURE trial indicated that the incidence of major bleeding in patients with acute coronary syndrome (ACS) was directly influenced by ASA dosage: patients receiving less than 100 mg per day exhibited a bleeding rate of 1.9%, those on 101–199 mg per day had a rate of 2.8%, and patients administered 200–325 mg per day experienced a rate of 3.7% ($p = 0.0001$) [2].

In a larger cohort comprising 12,526 individuals, analysis of varying ASA doses revealed that only daily doses of 75–81 mg were associated with a comparatively low risk of GI injury, whereas higher doses significantly elevated the likelihood of adverse events. Moreover, the most substantial reduction in cardiovascular outcomes was observed with doses ranging from 75 to 150 mg per day, a finding consistently reflected in both national and international clinical guidelines. Notably, a meta-analysis conducted by McQuaid and Laine did not detect a statistically significant difference in bleeding frequency between the 75–162.5 mg group (OR 2.22; 95% CI 1.61–3.06) and the 162.5–325 mg group (OR 2.35; 95% CI 0.98–5.66), underscoring the complex relationship between ASA dose and gastrointestinal safety [3].

These findings emphasize the critical importance of optimizing ASA therapy by balancing its cardioprotective benefits against the potential risk of GI complications, particularly in populations with heightened vulnerability to bleeding events. In recent years, enteric-coated and buffered formulations of acetylsalicylic acid (ASA) have become increasingly prevalent in clinical practice. Nevertheless, robust, large-scale randomized trials directly comparing plain, enteric-coated, and buffered ASA remain limited. It is

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widely postulated that enteric-coated ASA exhibits reduced gastrotoxicity, as the coating allows the tablet to bypass the acidic environment of the stomach, facilitating absorption in the alkaline milieu of the small intestine and thereby minimizing direct contact with the gastric mucosa. The improved safety and tolerability of enteric-coated ASA were corroborated in a multicenter German study, which evaluated adverse events in 1,156 patients receiving enteric-coated ASA compared with 1,570 patients on conventional ASA. The enteric-coated formulation demonstrated superior tolerability, with lower incidences of dyspepsia, heartburn, bloating, and epigastric pain. Endoscopic assessment of asymptomatic patients on long-term ASA therapy revealed gastric mucosal erosions in 90% of individuals receiving standard ASA, in contrast to 60% in those administered enteric-coated preparations [4].

Despite these advantages, enteric-coated ASA has not fully mitigated the risk of gastrointestinal injury. Endoscopic studies have reported increased occurrences of erosive and ulcerative lesions in the small intestine among users of enteric-coated ASA. In a cohort of 1,402 patients, the incidence of upper GI bleeding was comparable across different ASA formulations, although the risk of anemia was slightly elevated in the enteric-coated group. It is also important to acknowledge that the enteric coating can significantly delay ASA absorption and reduce its bioavailability, potentially contributing to apparent drug pseudo-resistance. A systematic review encompassing 17 epidemiological studies (2,150 patients with serious GI complications, including bleeding and perforation, and 11,500 controls) demonstrated that the relative risk of GI complications was essentially equivalent between enteric-coated and conventional ASA, with relative risks of 2.4 (95% CI 1.9–2.9) and 2.6 (95% CI 2.3–2.9), respectively [5].

Collectively, these findings highlight that while enteric-coated ASA offers improved gastrointestinal tolerability, careful monitoring and individualized risk assessment remain essential to optimize therapeutic outcomes and minimize adverse events. In Russia, a buffered formulation of acetylsalicylic acid (ASA) has been developed, combining ASA with a non-absorbable antacid, magnesium hydroxide. Magnesium hydroxide exerts a protective effect on the gastric mucosa by adsorbing hydrochloric acid and forming a buffer complex. Additionally, antacids decrease pepsin activity, provide a mucosal coating, and bind cytotoxic compounds such as lysolecithin and bile acids, which can damage the gastric lining. Buffered ASA formulations are often better tolerated, owing to faster absorption and reduced contact time with the gastric mucosa. However, in a study involving healthy volunteers comparing standard and buffered ASA, endoscopic evaluations revealed no significant differences in mucosal changes [6]. The mild superficial mucosal alterations and minimal clinical symptoms observed with both enteric-coated and buffered ASA are of limited clinical significance and should not be interpreted as a guarantee of enhanced protection against severe, life-threatening gastrointestinal complications.

In patients at high risk of GI complications, some experts propose substituting ASA with clopidogrel. Nevertheless, the clinical justification for such substitution remains controversial. Clopidogrel may also exhibit ulcerogenic potential, potentially due to inhibition of platelet function and decreased release of platelet-derived growth factors, which play a critical role in mucosal repair. This hypothesis is supported by a large hospital-based cohort study including 2,777 patients with prior upper GI bleeding and 5,532 matched controls, in which ASA use increased the risk of bleeding by 2.7-fold (95% CI 2.0–3.6). Clopidogrel and other thienopyridine derivatives were not associated with a lower bleeding risk than ASA, with an odds ratio of 2.8 (95% CI 1.9–4.2) [7]. Similarly, in a randomized study by Chan et al., 320 patients with prior ASA-induced ulcer bleeding were assigned to receive either clopidogrel 75 mg daily or ASA 80 mg daily combined with esomeprazole 20 mg daily. The rate of recurrent ulcer bleeding over 12 months was twelve times higher among patients receiving clopidogrel compared with those on ASA plus esomeprazole, underscoring the need for further research in this area.

Acid-suppressive therapy remains the primary approach for preventing aspirin-induced gastroduodenopathies. Historically, H2-histamine receptor antagonists were widely employed for this purpose, reducing gastric hydrochloric acid secretion by parietal cells and lowering acid production by 38–67% within 24 hours at standard doses. These agents demonstrated a preventive effect against ASA-induced upper GI mucosal injury [8]. While effective in managing ulcerative esophagitis and duodenal ulcers, H2-blockers have not shown efficacy in treating ASA-induced gastric ulcers. Furthermore, although they may alleviate ulcer-related symptoms, H2-blockers can potentially contribute to progressive mucosal damage and increase the risk of bleeding. Consequently, H2-receptor antagonists are no longer recommended for the treatment of NSAID- or ASA-induced gastropathies.

Currently, proton pump inhibitors (PPIs) are recognized as the cornerstone in the management of erosive and ulcerative gastrointestinal (GI) lesions, including those induced by NSAIDs and aspirin. PPIs exert their therapeutic effect by selectively inhibiting the H^+/K^+-ATPase (proton pump) in gastric parietal cells, thereby suppressing the final step of acid secretion. The efficacy of PPIs has been consistently demonstrated in numerous large-scale clinical trials [9]. For instance, the ASRONAUT randomized trial, which included 535 patients with upper GI ulcers or erosions on continuous NSAID therapy, revealed that after eight weeks, mucosal healing occurred in 87% of patients receiving PPIs compared with 67% in the H2-blocker group. Specifically, duodenal ulcer healing rates were 92% with PPIs versus 81% with H2-blockers.

A large cohort study in Japan indicated that increased PPI utilization among patients taking NSAIDs and low-dose ASA substantially reduced GI bleeding rates, from 160 to 23.2 per 100,000 person-years. Similarly, an Italian multicenter study in geriatric centers demonstrated that pre-endoscopy

administration of PPIs for at least one week effectively prevented ulcer formation during both acute and chronic NSAID exposure. Conversely, H2-blockers failed to provide gastroprotection, with ulcer risk paradoxically increasing (OR = 6.3–10.9), highlighting their inadequacy for NSAID-gastropathy prevention. The OBERON multicenter randomized trial (n=2,426) assessed the efficacy of esomeprazole at 20 mg and 40 mg in H. pylori–negative patients at high risk of ulcer formation receiving ASA 75–325 mg at least five times per week. After 26 weeks of endoscopic follow-up, ulcer incidence was 1.5% (95% CI 0.6–2.4) in the 40 mg group, 1.1% (95% CI 0.3–1.9) in the 20 mg group, and 7.4% (95% CI 5.5–9.3) in the placebo group ($p<0.0001$ for both esomeprazole groups versus placebo) [10]. While PPIs remain the most effective and widely used agents for treating ASA-associated GI lesions, their role in managing NSAID-induced enterocolopathies is less clear. Clinical evidence does not consistently support their efficacy in this context, and combined NSAID-PPI therapy may exacerbate intestinal injury by altering gut microbiota, notably reducing Actinobacteria and Bifidobacteria populations in the jejunum by up to 80% [11]. Furthermore, opportunistic bacterial overgrowth may result from diminished gastric acidity.

Population-based studies have also associated PPI use with a 2–5 fold increased risk of infections caused by pathogens such as Salmonella, Campylobacter, and Clostridium species. Dual et al. conducted a meta-analysis showing that PPI therapy was linked to a 2.9-fold increase in the risk of Clostridium difficile infection (95% CI 2.4–3.4), with the incidence of C. difficile diarrhea rising from 1 to 22 per 100,000 population between 1994 and 2004 [12]. Beyond the stomach, proton pumps are expressed in multiple tissues, including the intestinal epithelium, gallbladder, renal tubules, corneal epithelium, skeletal muscle, immune cells (neutrophils, macrophages, lymphocytes), and osteoclasts, implicating systemic effects from prolonged PPI use. Long-term blockade of proton pumps outside the gastric mucosa may precipitate serious complications, including community-acquired pneumonia, with a pooled odds ratio of 1.5 (95% CI 1.09–1.76). Additionally, concerns have been raised regarding the impact of chronic PPI therapy on postmenopausal osteoporosis and fracture risk, with meta-analyses indicating a 25% increase in hip fractures (OR 1.25; 95% CI 1.14–1.37) and a 50% increase in vertebral fractures (OR 1.5; 95% CI 1.32–1.72) [16]. Helicobacter pylori infection may further exacerbate mucosal atrophy under long-term PPI therapy, as demonstrated in a prospective study of 231 patients with gastroesophageal reflux disease, where omeprazole administration without prior eradication led to increased corpus gastritis activity [13]. Moreover, PPIs interact pharmacologically with numerous commonly used drugs, which may further complicate therapy.

Synthetic prostaglandin E1 (PGE1) analogs, such as misoprostol, have emerged as effective alternatives for preventing and treating NSAID-induced gastropathies, particularly under hypoacidic conditions where H2 blockers and PPIs are less effective [18,19]. Meta-analyses of 33 randomized controlled trials, including the large-scale MUCOSA study, have demonstrated that misoprostol significantly reduces the risk of serious GI lesions, ulcer perforation, and recurrence compared with placebo [20]. The OMNIUM study reported gastric ulcer healing rates of 62% at six weeks and 72% at eight weeks, and duodenal ulcer healing rates of 61% and 77%, respectively. Despite its efficacy, clinical use of misoprostol is limited by cost, inconvenient dosing, and adverse effects such as diarrhea, dyspepsia, hypotension, and facial flushing [14]. NSAID- and ASA-induced gastroduodenopathies remain highly prevalent. While upper GI lesions are primarily driven by gastric acid secretion, mechanisms underlying intestinal mucosal injury are incompletely understood. Promising strategies for prevention and treatment include gastroprotective agents targeting both gastric and intestinal mucosa. In this context, rebamipide, a novel gastro- and enteroprotector available in Russia, has demonstrated efficacy through stimulation of prostaglandin synthesis, upregulation of the PGE2 receptor 4, and inhibition of 15-hydroxyprostaglandin dehydrogenase, leading to increased PGE2 levels in GI tissues. These mechanisms result in modest reduction of gastric acid secretion and enhanced mucosal glycoprotein synthesis [15].

Rebamipide has emerged as a potent gastro- and enteroprotective agent with multifaceted mechanisms of action. It enhances the expression of endothelial growth factor (EGF) and its receptor within the gastric mucosa, promoting cellular proliferation and re-epithelialization. Additionally, rebamipide restores activity in the sonic hedgehog signaling pathway, facilitating reversibility of gastric cell atrophy. The drug further supports mucosal healing by normalizing tyrosine nitration within the ERK (extracellular signal-regulated kinase) pathway and stimulating angiogenesis through the induction of proangiogenic gene expression [16]. Rebamipide also augments gastric mucus secretion and antioxidant defenses, mitigates lipid peroxidation in the gastrointestinal tract, and protects against mitochondrial damage and apoptosis of gastric and intestinal epithelial cells during NSAID therapy. Moreover, rebamipide inhibits adhesion of Helicobacter pylori to the gastric mucosa, thereby enhancing the bactericidal efficacy of antibiotics, while also attenuating H. pylori–induced inflammatory responses and improving mucosal blood flow.

Beyond its gastrointestinal effects, rebamipide exhibits systemic anti-inflammatory properties. It has been shown to attenuate TNF-α–mediated inflammatory pathways, stabilize macrophage function, and suppress activation of nuclear factor kappa-B (NF-κB), thereby modulating downstream inflammatory signaling [17]. Collectively, the pharmacological effects of rebamipide include stimulation of prostaglandin synthesis (E_2 and I_2), enhancement of mucosal blood flow, reduction of mucosal permeability, scavenging of reactive oxygen species, anti-inflammatory activity, and promotion of gastric mucus secretion. These effects have been consistently validated in both experimental and clinical settings. In animal models, rebamipide accelerated healing of

ulcerative lesions of diverse etiology while simultaneously preventing lesion development.

In murine models of acute small intestinal injury induced by ASA (200 mg/kg/day for five days), subsequent administration of rebamipide (320 mg/kg/day) preserved intestinal structure and maintained tighter intercellular junctions, as demonstrated by electron microscopy. The study indicated that rebamipide enhances mucosal barrier integrity and promotes intestinal regeneration via modulation of COX-2 expression in ASA-induced injury [18]. NSAID therapy is known to increase reactive oxygen species (ROS), contributing to mitochondrial dysfunction and disruption of intestinal mucosal integrity; rebamipide effectively reduces ROS levels and protects epithelial cells, likely through activation of manganese superoxide dismutase. Furthermore, rebamipide exerts beneficial effects on gut microbiota, normalizing concentrations of Enterococcus and Enterobacter species in the ileal mucosa.

Experimental studies in rats with chemically induced gastric carcinogenesis have demonstrated a protective effect of rebamipide, with a significantly lower incidence of gastric cancer and reduced invasion into the muscularis layer compared to controls ($p < 0.05$) [19]. Clinical studies corroborate these findings. In a retrospective study of 530 patients receiving low-dose ASA for one month, those without cytoprotective therapy exhibited 9.3% gastric bleeding and 49.1% acute gastric erosions or ulcers. Patients on PPIs experienced bleeding and ulcer rates of 2.1% and 18.6%, respectively, while rebamipide recipients showed rates of 0% and 18.8%, respectively. Those on other cytoprotective agents or antacids had bleeding and ulcer incidences of 3.8% and 38.5%.

A meta-analysis encompassing 15 randomized controlled trials ($n = 965$) confirmed that rebamipide is significantly more effective than placebo in preventing NSAID-induced gastroduodenal injury, without notable adverse events. In a crossover study involving 20 healthy volunteers administered 81 mg ASA with either placebo or rebamipide (300 mg thrice daily for seven days), rebamipide markedly reduced antral mucosal hyperemia compared to placebo ($p = 0.039$) [20]. Similarly, in a study of 32 volunteers, rebamipide significantly attenuated mucosal lesions in both low-dose ASA and ASA + clopidogrel regimens ($p = 0.05$ and $p = 0.01$, respectively). In a cohort of 38 patients on long-term ASA (100 mg/day), eight-week rebamipide therapy resulted in fewer intestinal erosions and ulcers as assessed by capsule endoscopy ($p = 0.046$).

Rebamipide has also been compared to misoprostol in double-blind, randomized, multicenter trials. Among 479 patients on continuous NSAID therapy, those receiving rebamipide (100 mg three times daily, $n = 242$) demonstrated lower gastrointestinal symptom scores and reduced antacid use compared to patients on misoprostol (200 μg three times daily, $n = 237$) over 12 weeks ($p = 0.0002$ and $p = 0.0258$, respectively) [21]. These findings highlight the efficacy and tolerability of rebamipide in NSAID- and ASA-induced gastro- and enteropathies. Additionally, rebamipide exerts extra-gastrointestinal benefits. When administered as ophthalmic drops, it reduces IL-6, IL-17, and TNF-α levels in tear fluid, mitigating ocular inflammation. It also modulates immune responses in joint tissues, restores Th17/regulatory T cell balance, and activates the Nrf2/HO-1 pathway, suggesting potential roles in controlling oxidative stress and systemic inflammatory cascades.

2. Conclusions

Aspirin- and NSAID-induced gastrointestinal disorders remain a prevalent clinical concern due to the balance required between cardioprotective benefits and GI safety. Traditional strategies, including dose optimization, enteric-coated or buffered ASA formulations, and acid-suppressive therapy, partially mitigate gastric injury but do not fully prevent erosive or ulcerative lesions, particularly in the small intestine. Proton pump inhibitors and misoprostol demonstrate substantial gastroprotective efficacy; however, their use may be limited by systemic adverse effects, altered microbiota, or tolerability issues. Emerging evidence positions rebamipide as a multifaceted gastro- and enteroprotective agent, capable of enhancing mucosal regeneration, stimulating prostaglandin synthesis, reducing oxidative stress, and modulating inflammatory pathways. Both preclinical and clinical studies consistently demonstrate its effectiveness in preventing and treating ASA- and NSAID-induced gastroduodenal and intestinal lesions, with a favorable safety profile and improved tolerability compared to conventional therapies. Furthermore, rebamipide exhibits systemic anti-inflammatory and immunomodulatory effects, suggesting potential benefits beyond the gastrointestinal tract. Collectively, these findings support the integration of rebamipide into therapeutic strategies aimed at optimizing gastrointestinal protection in patients requiring long-term ASA or NSAID therapy, highlighting its role as a safe, efficacious, and comprehensive cytoprotective agent.

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