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Pharmacological Approaches to the Management of Aspirin-Induced Gastroduodenopathies in Patients with Ischemic Heart Disease – Traditional Strategies

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Abstract: Aspirin-induced gastroduodenopathies represent a major clinical problem in patients with ischemic heart disease who require long-term acetylsalicylic acid (ASA) therapy. Despite the proven cardiovascular benefits of ASA, its ulcerogenic potential significantly limits tolerability and adherence. Traditional pharmacological strategies to mitigate gastrointestinal (GI) injury include dose reduction, enteric-coated or buffered formulations, and the use of gastroprotective agents such as H_2-receptor blockers, proton pump inhibitors (PPIs), and prostaglandin analogs. While low-dose ASA (75–150 mg/day) effectively balances antiplatelet efficacy with a reduced risk of GI bleeding, enteric-coated and buffered forms have not fully prevented mucosal injury. PPIs remain the most effective agents for preventing and healing erosive and ulcerative lesions associated with ASA use, although long-term therapy carries risks such as Clostridium difficile infection, osteoporosis, and drug interactions. Misoprostol, a prostaglandin E_1 analog, offers comparable efficacy to PPIs in preventing NSAID- and ASA-induced gastropathies but is limited by adverse effects and poor tolerability. The optimization of therapy should consider patient risk profiles, drug interactions, and the balance between cardioprotective efficacy and gastrointestinal safety.

Keywords: Aspirin-induced gastropathy, ischemic heart disease, acetylsalicylic acid, proton pump inhibitors, gastrointestinal bleeding.

For many years, active efforts have been made to find ways to reduce the risk of gastrointestinal (GI) damage in patients treated with acetylsalicylic acid (ASA). One of the key strategies to improve the safety of ASA therapy is **dose reduction within the therapeutic range**. Several studies have confirmed the **dose-dependent ulcerogenic effect** of ASA [1]. In a case–control study (n=3236), the risk of hospitalization due to ulcer bleeding decreased as the ASA dose was reduced (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). The CURE study also demonstrated that the incidence of major bleeding in patients with acute coronary syndrome (ACS) depended on the ASA dose: for <100 mg, the bleeding rate was 1.9%; for 101–199 mg, 2.8%; and for 200–325 mg, 3.7% (p=0.0001) [2]. In another study involving 12,526 patients, analysis of different ASA doses showed that **only 75–81 mg per day** was associated with a low risk of GI injury, unlike higher doses . The greatest reduction in cardiovascular events was observed at doses of **75–150 mg per day**, which is reflected in both national and international guidelines. However, a meta-analysis by K.R. McQuaid and L. Laine found no significant difference in the frequency of bleeding between doses of 75–162.5 mg (OR 2.22, 95% CI 1.61–3.06) and 162.5–325 mg (OR 2.35, 95% CI 0.98–5.66) .

In recent years, **enteric-coated and buffered forms of ASA** have been widely used. However, large randomized comparative trials between plain, enteric-coated, and buffered forms have not yet been conducted. It is generally believed that enteric-coated ASA is **less gastrotoxic**, as it bypasses

the stomach and is absorbed in the alkaline environment of the small intestine, avoiding direct contact with the gastric mucosa. The **safety and tolerability** of enteric-coated ASA were confirmed in a multicenter German study comparing side effects in 1156 patients taking enteric-coated ASA versus 1570 patients taking conventional ASA. Enteric-coated ASA showed better tolerability, with fewer complaints of dyspepsia, heartburn, bloating, and stomach pain [139]. Endoscopic examination of asymptomatic patients receiving long-term ASA therapy revealed gastric mucosal erosions in 90% of those taking regular ASA, compared with 60% of those taking enteric-coated forms [3].

However, the introduction of enteric-coated ASA has **not completely solved the problem** of GI injury. Endoscopic evaluations revealed an **increased frequency of erosive and ulcerative lesions** in the small intestine with enteric-coated ASA. In a study of 1402 patients, the rates of upper GI bleeding were similar between ASA formulations, though the risk of anemia was slightly higher among those using enteric-coated ASA [4]. It is also worth noting that the enteric coating can **significantly delay ASA absorption** and reduce its bioavailability, which may contribute to **pseudo-resistance** to the drug. A systematic review of 17 epidemiological studies (2150 patients with serious GI complications—bleeding, perforation—and 11,500 controls) found that the relative risk of complications with enteric-coated and conventional ASA was nearly identical: 2.4 (95% CI 1.9–2.9) and 2.6 (95% CI 2.3–2.9), respectively [5].

In Russia, a **buffered form of ASA** has been developed, consisting of ASA combined with a non-absorbable antacid, **magnesium hydroxide.** Magnesium hydroxide protects the gastric mucosa by adsorbing hydrochloric acid and forming a buffer complex. In addition, antacids reduce pepsin activity, have a coating effect, and bind lysolecithin and bile acids, which are harmful to the gastric mucosa [6]. Buffered formulations are often better tolerated due to faster absorption of ASA and shorter mucosal contact time. However, in a study involving healthy volunteers taking regular and buffered ASA, **no significant endoscopic differences** were found [7]. The milder superficial mucosal changes and minimal clinical symptoms observed with enteric-coated and buffered ASA **lack major clinical significance** and should not be considered indicators of greater safety in preventing life-threatening GI complications.

There is also an opinion that in patients at **high risk of GI complications**, ASA may be substituted with **clopidogrel**. However, the justification for such substitution remains debated. Clopidogrel may also exert **ulcerogenic effects**, potentially related to inhibition of platelet function and decreased release of platelet-derived growth factors, which are crucial for mucosal repair . This hypothesis is supported by a large hospital-based study involving 2777 patients with previous upper GI bleeding and 5532 matched controls. ASA use significantly increased bleeding risk 2.7-fold (95% CI 2.0–3.6). Clopidogrel and other thienopyridine derivatives were **not safer than ASA**, with an odds ratio of 2.8 (95% CI 1.9–4.2) for bleeding associated with their use [8]. In a randomized study conducted by **F. Chan et al.,** the possibility of prescribing **clopidogrel** as an antiplatelet agent in patients who had experienced ulcer bleeding due to long-term ASA therapy was evaluated. The study included **320 patients** who, after an episode of ulcer bleeding, were assigned to receive either **clopidogrel 75 mg daily** or **ASA 80 mg daily combined with esomeprazole 20 mg daily.** The likelihood of **recurrent ulcer bleeding within 12 months** was found to be **12 times higher** in patients taking clopidogrel compared with those receiving ASA plus esomeprazole . Considering these findings, this issue requires further investigation.

Most often, **acid-suppressive agents** are used to prevent aspirin-induced gastroduodenopathies. Previously, **H2-histamine receptor blockers** were commonly used for this purpose. Their mechanism of action is based on **reducing hydrochloric acid secretion** by gastric parietal cells. In standard doses, they decrease acid production by **38–67%** within 24 hours after administration. These drugs demonstrated a **preventive effect** against ASA-induced mucosal injury in the upper GI tract [9]. Their efficacy has been confirmed for **ulcerative esophagitis** and **duodenal ulcer disease;** however, they have **not proven effective** for the treatment of **aspirin-induced gastric ulcers** . It has also been observed that, while alleviating ulcer symptoms, **H2-blockers may contribute to the**

progression of mucosal injury and increase the risk of bleeding. Therefore, these agents are **no longer recommended** for the treatment of NSAID- or ASA-induced gastropathies.

Currently, **proton pump inhibitors (PPIs)** occupy a leading position in the treatment of **erosive and ulcerative GI lesions,** including NSAID- and aspirin-induced gastropathies. Their mechanism involves **inhibiting the H^+/K^+-ATPase (proton pump)** in gastric parietal cells, thereby **blocking the final stage of gastric acid secretion.** Their effectiveness has been confirmed in numerous large-scale studies [10]. The **ASRONAUT randomized trial** demonstrated the superiority of PPIs over H2-blockers. The study included **535 patients** with ulcers or erosions of the upper GI tract who were on continuous NSAID therapy. After **8 weeks of treatment,** mucosal healing occurred in **87% of patients** receiving PPIs, compared to **67%** in the H2-blocker group. For **duodenal ulcers,** the healing rate was **92% with PPIs** versus **81% with H2-blockers** .

In a large **Japanese cohort study,** an increased use of PPIs among patients receiving NSAIDs and low-dose ASA was associated with a **reduction in GI bleeding rates**—from **160 to 23.2 per 100,000 people per year** [11]. A major **Italian study** conducted in geriatric centers showed that **PPI use for at least one week before endoscopy (EGD)** eliminated the risk of ulcer formation during both acute and chronic NSAID use. Surprisingly, **H2-blockers provided no gastroprotective effect;** in fact, the **risk of ulceration increased** (OR=6.3–10.9), confirming the **inappropriateness of using H2-blockers** for NSAID-gastropathy prevention and treatment .

The efficacy of **esomeprazole** at different doses (20 mg and 40 mg) was evaluated in the **OBERON multicenter randomized trial (**n=2426), involving **H. pylori–negative patients** at high risk of ulcer formation who received **ASA 75–325 mg at least five times per week.** Endoscopic follow-up after **26 weeks** showed that both doses of esomeprazole effectively prevented ulcer formation compared with placebo. The ulcer incidence was **1.5% (95% CI 0.6–2.4)** for the 40 mg group, **1.1% (95% CI 0.3–1.9)** for the 20 mg group, and **7.4% (95% CI 5.5–9.3)** for placebo ($p<0.0001$ for both esomeprazole groups vs. placebo) [12]. Undoubtedly, PPIs are considered the most effective and widely used agents for the treatment of ASA-associated GI lesions. However, their beneficial effects in NSAID-induced enterocolopathies remain controversial. Clinical trials have not confirmed their efficacy in this condition . Moreover, combined use of PPIs and NSAIDs has been shown to increase the severity of enteropathy by negatively affecting the intestinal microbiota. Some studies indicate that this combination reduces Actinobacteria and Bifidobacteria spp. populations in the jejunum by up to 80% [13]. Additionally, overgrowth of opportunistic bacteria has been observed due to a significant reduction in gastric acidity.

A series of population-based studies demonstrated that PPIs increase the risk (2–5 fold) of infections caused by Salmonella, Campylobacter, Clostridium, and other microorganisms . S. Dual et al. conducted a meta-analysis summarizing the risk of Clostridium difficile infection in PPI users, reporting an odds ratio of 2.9 (95% CI 2.4–3.4). Since the widespread adoption of PPIs over the last decade, the incidence of C. difficile diarrhea has increased dramatically—from 1 per 100,000 population in 1994 to 22 per 100,000 in 2004 [14].PPIs have systemic effects, as proton pumps are present not only in gastric parietal cells but also in the intestinal epithelium, gallbladder, renal tubules, corneal epithelium, muscle tissue, immune cells (neutrophils, macrophages, lymphocytes), and osteoclasts . Long-term PPI-induced blockade of proton pumps outside gastric mucosa can lead to serious complications . A link has also been established between PPI use and community-acquired pneumonia. A 2012 meta-analysis of nine population-based studies confirmed this association, with an odds ratio of 1.5 (95% CI 1.09–1.76) [15].

The question of the effect of proton pump inhibitors (PPIs) on the progression of postmenopausal osteoporosis and the increased risk of osteoporotic fractures remains open. Authors of recent studies addressing this issue have concluded that there is a significant association between long-term PPI use and the occurrence of osteoporotic fractures [16]. S. Ngamruengphong et al. conducted a meta-analysis that included 10 epidemiological studies. According to their findings, PPI therapy was associated with a 25% increase in the risk of hip fractures (OR 1.25; 95% CI 1.14–1.37) and a 50% increase in the risk of vertebral fractures (OR 1.5; 95% CI 1.32–1.72) . Several studies have also

demonstrated that during long-term PPI therapy, in the presence of Helicobacter pylori infection, the bacteria may migrate from the antral region to the gastric body, resulting in rapid development of inflammation and mucosal atrophy . According to a prospective study by E. Kuipers et al., which included 231 patients with gastroesophageal reflux disease infected with H. pylori, participants received omeprazole at a daily dose of 20 mg for 12 months. Initially, 111 patients underwent eradication therapy, while 120 did not. In the first subgroup, both antral and corpus gastritis showed a reduction in severity. However, in the second subgroup, the activity of corpus gastritis increased [17]. Another adverse aspect of PPI use is their pharmacological interaction with several widely used drugs in clinical practice . Thus, although PPIs are considered highly effective agents for the prevention and treatment of erosive and ulcerative lesions of the upper gastrointestinal (GI) tract, their efficacy in treating intestinal lesions has not been clearly demonstrated. Moreover, long-term PPI therapy carries the risk of significant side effects .Currently, synthetic analogs of prostaglandin E1 (misoprostol) have shown promising results. These agents were specifically developed for the prevention and treatment of NSAID-induced gastropathies. They are particularly effective under hypoacidic conditions, where the use of H2 blockers and PPIs is less meaningful [18].

Synthetic PGE1 analogs significantly reduce the risk of destructive mucosal changes in the gastrointestinal tract during NSAID therapy. Studies have shown that these agents are almost as effective as PPIs in preventing and treating NSAID-induced gastropathies [19]. The potential role of PGE1 analogs in preventing NSAID-induced gastropathies was confirmed in a meta-analysis of 33 randomized controlled trials, published in the Cochrane Library (2000) . The large-scale MUCOSA study provided strong evidence supporting the prophylactic efficacy of misoprostol in preventing NSAID-related gastropathies. The incidence of serious GI lesions among NSAID users receiving misoprostol was 0.76%, compared with 1.5% in the placebo group. Ulcer perforation occurred 10 times less frequently among patients taking misoprostol than in the control group [20]. In the OMNIUM study, after 6 weeks of misoprostol therapy, gastric ulcer healing occurred in 62% of patients, and duodenal ulcer healing in 61%. After 8 weeks, these rates increased to 72% and 77%, respectively . However, according to other authors, adding 600 mg of misoprostol to standard PPI therapy did not reduce the recurrence rate of bleeding or mortality in patients with GI bleeding associated with NSAID or aspirin use . Most studies, nevertheless, demonstrate a high efficacy of misoprostol in the prevention and treatment of NSAID gastropathies, comparable to PPIs [21]. Despite this, its clinical use is limited due to high cost, inconvenient dosing, and frequent side effects such as diarrhea, dyspepsia, systemic vasoplegia (hypotension, facial flushing, headaches) .

Conclusion. Aspirin remains a cornerstone in the secondary prevention of cardiovascular events; however, its chronic use poses a significant risk of gastrointestinal mucosal damage. Reducing the ASA dose within therapeutic limits effectively minimizes the risk of ulceration, though it does not eliminate it. Enteric-coated and buffered formulations improve tolerance but fail to fully prevent GI injury. Proton pump inhibitors have become the standard for gastroprotection, providing superior efficacy in ulcer prevention and healing compared to H_2-receptor antagonists. Nonetheless, long-term PPI use is associated with potential adverse effects, including infections, micronutrient deficiencies, and bone metabolism disorders. Misoprostol offers an effective alternative, particularly in hypoacidic states, but its clinical use is constrained by cost and side effects. Therefore, the choice of gastroprotective strategy in ASA-treated patients with ischemic heart disease should be individualized, aiming for optimal cardiovascular benefit while minimizing gastrointestinal complications.

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