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Evidence-Based Approaches to the Prevention and Treatment of Nsaid-Induced Gastrointestinal Injury

Raupov Abdurahmon Ortiq o'g'li
Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi
raupov.abdurahmon@bsmi.uz

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Annotation: At present, the management of erosive and ulcerative lesions of the upper gastrointestinal tract (GIT) is a complex clinical challenge, particularly in high-risk patients with cardiovascular and vascular comorbidities receiving antiplatelet and anticoagulant therapy. Despite advances in pharmacological treatment, including H_2-receptor blockers and proton pump inhibitors (PPIs), the incidence of upper gastrointestinal bleeding (UGIB) continues to rise. H_2-receptor blockers provide limited, short-lived acid suppression and carry risks such as tolerance, rebound acid hypersecretion, and potential ischemic complications. PPIs, including omeprazole and pantoprazole, offer superior and sustained acid suppression, with pantoprazole demonstrating the longest duration of effect and lowest potential for drug–drug interactions, making it particularly suitable for critically ill patients. In patients undergoing cardiac or aortic surgery, postoperative UGIB represents a serious complication, often necessitating urgent endoscopic intervention as the preferred method for hemostasis and prevention of rebleeding. Endoscopic techniques include injection therapy, physical methods (electrocoagulation, laser), mechanical methods (clipping), ulcer surface protection, cryotherapy, and adhesive applications. Proper selection of pharmacological and endoscopic therapies, considering drug–drug interactions, patient comorbidities, and

procedural risks, is essential for improving clinical outcomes in this high-risk population.

Keywords: Upper gastrointestinal bleeding, erosive and ulcerative lesions, proton pump inhibitors, H_2-receptor blockers, antiplatelet therapy.

At present, there is a wide range of pharmaceutical agents used for the treatment of erosive and ulcerative lesions of the upper gastrointestinal tract (GIT). These drugs reduce gastric acid production and differ in their mechanisms of action, clinical efficacy, safety profiles, and cost. A particularly important criterion in choosing an antisecretory agent is the potential for safe long-term use, since in NSAID-associated gastropathy and other acid-dependent diseases, patients are often required to take gastric acid secretion inhibitors for many years [1]. Until the 1970s, antacids and cholinolytics were mainly used in the treatment of acid-dependent gastrointestinal diseases. In the 1970s–1980s, two classes of drugs capable of suppressing gastric acid secretion were introduced: **H_2-receptor blockers** for histamine and **proton pump inhibitors (PPIs).**

The efficacy of H_2-blockers has been extensively studied. A meta-analysis by which included 27 randomized, placebo-controlled trials involving 2,500 patients, demonstrated that H_2-blocker use could reduce the incidence of rebleeding, surgical intervention, and mortality by 10%, 20%, and 30%, respectively. However, these data were statistically significant only for surgery and mortality outcomes. In another large analysis**, D. Cook (1992)** concluded that prophylactic use of H_2-blockers in critically ill patients prevented acute erosive and ulcerative lesions of the gastroduodenal zone more effectively than antacids or sucralfate [2]. More recent meta-analyses have shown that intravenous administration of H_2-blockers is ineffective for duodenal ulcer bleeding, while in gastric ulcer bleeding, it only slightly reduces the risk of rebleeding, surgical intervention, and mortality compared with placebo.

This phenomenon is explained by the **"H_2-receptor fatigue"** effect, which can occur as early as the first day of therapy. Moreover, H_2-blockers can aggravate ischemia of the gastric or duodenal wall by blocking vascular H_2-receptors in the submucosal and muscular layers, leading to vasoconstriction and reduced blood flow. Thus, in critically ill patients, H_2-blockers may decrease acid-peptic aggression but simultaneously exacerbate **local ischemia,** a major pathogenic factor in stress-related ulcerogenesis. Their use, especially at high doses, may also negatively affect the liver's detoxification function by inhibiting the cytochrome P450 enzyme system. Additionally, one should consider their potential **negative chronotropic and inotropic effects,** as well as risks of **extrasystole and atrioventricular block.** Currently, **proton pump inhibitors (PPIs)—**such as rabeprazole, omeprazole, esomeprazole, lansoprazole, and pantoprazole—are considered the most effective and safest antisecretory agents. PPIs inhibit the enzyme system responsible for gastric acid secretion, blocking the very core of the parietal cell—the **H^+/K^+-ATPase (proton pump)** [3]. The possibility of using PPIs for **prophylactic purposes** in critically ill patients (e.g., with gastrointestinal bleeding) became feasible after the introduction of **intravenous omeprazole** into clinical practice.

Although their chemical structures differ, all PPIs share the same **mechanism of action.** In the acidic environment, they form active metabolites that **covalently bind to the SH-groups** of the α-subunit of H^+/K^+-ATPase via disulfide bonds (S–S). The inhibitory process involves the following stages: absorption from the gastrointestinal tract; accumulation in the secretory canaliculi of parietal cells; structural transformation in the acidic milieu; and covalent binding to the proton pump's sulfhydryl groups. Inhibition of the proton pump stops hydrochloric acid synthesis **independently of the stimulus type or intensity** acting on the parietal cell. To resume acid secretion, the parietal cell must synthesize new enzyme protein, a process that takes about

18 hours. Differences in the metabolism of PPIs—and consequently, their influence on gastric acidity—play an important role in the treatment of acid-dependent disorders. Since all PPIs are metabolized in the liver via the cytochrome P450 enzyme system, potential drug–drug interactions cannot be excluded, particularly in elderly patients who frequently have both acid-related diseases and polypharmacy [4].

Clinically significant interactions may occur when PPIs are co-administered with other drugs that have a **narrow therapeutic index** (e.g., warfarin). Even minor changes in pharmacokinetics in such cases can lead to substantial alterations in therapeutic efficacy and increased risk of adverse effects [5].

Such interactions are especially relevant in elderly populations, where the number of concurrently administered drugs, genetic variability in metabolism, and comorbidities significantly increase the likelihood of altered pharmacokinetics and side effects. Drug–drug interactions remain a frequent cause of **therapeutic failure** and **adverse drug reactions,** underscoring the importance of individualized selection and monitoring of PPI therapy. Warfarin is a drug of choice due to its stable anticoagulant effect, high bioavailability, rapid gastrointestinal absorption, and attainment of peak plasma concentration approximately 90 minutes after oral administration [6]. The drug accumulates in the liver, where both of its isomers are metabolized primarily by the cytochrome P450 (CYP450) enzyme system. The CYP450 enzymes are capable of metabolizing almost all known chemical compounds and are membrane-bound in humans. To date, over 55 CYP450 isoenzymes have been identified. These isoenzymes, together with flavoproteins, form enzyme complexes known as NADPH-cytochrome P450 reductase, grouped into three families: P450I, P450II, and P450III. Each cytochrome can metabolize multiple drugs. On each CYP450 molecule, there is a site capable of binding drugs. When two active drugs compete for the same binding site on the enzyme, the metabolism of the less active drug slows, prolonging its action. The activity of CYP450 is influenced by the very drugs it metabolizes: some compounds induce CYP450, accelerating the metabolism of other drugs, which reduces their bioavailability [7].

Another type of drug–drug interaction occurs within the CYP450 system. Different drugs may compete for metabolism by a single enzyme. Protease inhibitors are examples of drugs that compete with others for CYP450-mediated metabolism. These drugs are metabolized first, forcing other drugs to wait until the enzymes complete processing the inhibitors. During this delay, the plasma concentration of the waiting drug increases. This phenomenon is known as “CYP450 suppression.” Many xenobiotics, including drugs, can act as inducers or inhibitors of the CYP450 system [8].

Omeprazole, introduced to the pharmaceutical market in 1989 (around the same time the term “NSAID-induced gastropathy” emerged), is the first widely used proton pump inhibitor (PPI) . It has been extensively studied, including its interactions with other drugs. Omeprazole is completely metabolized and is almost not excreted unchanged. Most omeprazole is metabolized via the CYP2C19 isoenzyme, with a smaller fraction (≈10%) via CYP3A4 [9]. Another well-studied and widely used PPI in Europe and America is pantoprazole (brand names: Panum, Nolpaza, Sanpraz, Controloc, etc.). In Russia, pantoprazole was introduced relatively recently . Pantoprazole is effective for the therapy and prophylaxis of stress-induced gastric erosions. It is rapidly absorbed and eliminated primarily via CYP2C19, has lower affinity for hepatic CYP isoforms compared with omeprazole, and does not significantly interact with drugs metabolized by most CYP isoforms. Pantoprazole is metabolized into inactive metabolites, predominantly by the CYP2C19 isoform, which exhibits genetic polymorphism.

Pantoprazole is a highly effective H^+/K^+-ATPase inhibitor, reducing both basal and stimulated gastric acid secretion regardless of the type of stimulus. The duration of PPI action depends on the rate of synthesis of new proton pumps rather than the plasma half-life. Following a single 40 mg intravenous dose, the plasma half-life of pantoprazole is approximately one hour. However,

acid suppression persists for about three days, reflecting the balance between newly synthesized proton pumps and inhibited molecules. A single IV dose provides rapid (within 1 hour), dose-dependent inhibition of acid production: 40 mg reduces acid production by 86%, 60 mg by 98%, and 80 mg by 99%, also decreasing gastric volume[10].

In humans, the half-life of acid suppression after administration is approximately: lansoprazole – 13 hours, omeprazole – 28 hours, pantoprazole – 46 hours. Pantoprazole thus produces the longest duration of acid suppression among these PPIs, due to its specific binding to cysteine at position 822 in the gastric proton pump, which determines its prolonged effect. This feature is critical because acid production recovery depends on proton pump protein turnover. Pantoprazole also has the lowest potential for drug–drug interactions, owing to its low affinity for CYP450 metabolizing isoenzymes and phase II conjugation pathways. This makes it particularly suitable for intensive care patients receiving multiple concurrent medications, ensuring a favorable safety profile [11].

PPIs may cause adverse effects by impairing cellular functions. For example, rabeprazole, acting in lysosomes of nonspecific immune cells (first line of defense against bacterial and viral infections), increases the frequency of infections and inflammatory events (rhinitis, pharyngitis, upper respiratory infections) in 2–5% of patients [12]. In contrast, pantoprazole demonstrates the best tolerability among PPIs, with only 1.1% of patients reporting minor adverse effects. Headache and diarrhea occur most frequently with esomeprazole (6.2% and 3.9%, respectively) and least with pantoprazole (1.3% and 1.5%) .

Extensive studies in the USA, Europe, and Australia have investigated the co-administration of clopidogrel, aspirin, or both, aiming to identify safer alternatives with lower gastrointestinal toxicity. Evidence supports the use of PPIs in patients on aspirin and NSAIDs, particularly when dual therapy with aspirin and clopidogrel is indicated. Safety and drug–drug interactions are critical considerations, as clopidogrel and PPIs share CYP450 isoenzymes, potentially reducing clopidogrel's antiplatelet activity. However, clinical evidence remains inconclusive [13]

An Australian study of 300 patients receiving clopidogrel evaluated concomitant use of esomeprazole (n=74), pantoprazole (n=152), and a control group (n=74, no PPI). No significant reduction in clopidogrel's antiplatelet effect was observed with esomeprazole versus control. The study also showed no substantial differences between pantoprazole and esomeprazole regarding clopidogrel's activity. However, most US studies indicate that pantoprazole co-therapy is more effective and safer than omeprazole with antiplatelet therapy. A study in Ontario on patients >60 years hospitalized for acute myocardial infarction (2002–2007) analyzed 13,636 patients receiving clopidogrel for one year. Among them, 2,682 received PPIs for 30 days post-discharge and 4,224 for 90 days. Omeprazole, rabeprazole, or lansoprazole use with clopidogrel for 90 days was associated with a 40% increase in recurrent myocardial infarction, which was not observed with pantoprazole [14].

In Russia, numerous studies have evaluated anti-Helicobacter therapy using omeprazole and pantoprazole [15]. Data indicate that triple therapy with pantoprazole is more effective than with omeprazole, largely due to CYP2C19 genetic polymorphism, which affects PPI metabolism. Currently, it is known that about 60% of drugs, including PPIs, are metabolized via CYP3A4 and CYP2C19, emphasizing the importance of selecting a PPI with predictable outcomes for treatment success. CYP2C19 polymorphism reduces omeprazole's efficacy, whereas pantoprazole is minimally affected.

Regarding gastrointestinal complications from different NSAIDs in Russia, large-scale comparative studies are lacking. Retrospective analysis at the Institute of Rheumatology of the Russian Academy of Medical Sciences assessed selective NSAIDs (celecoxib, meloxicam, nimesulide) in 810 patients with rheumatoid disease. The incidence of ulcers and erosions on esophagogastroduodenoscopy did not differ significantly among these drugs. In summary, the data highlight contradictory findings regarding PPI choice for prophylaxis and treatment of

erosive and ulcerative lesions in patients receiving antiplatelet therapy, especially in elderly patients on multiple drugs or medications with narrow therapeutic indices[16].

A particular patient group includes those with complicated courses of erosive and ulcerative lesions of the upper gastrointestinal tract (GIT), manifesting as gastrointestinal bleeding (GIB). This situation is especially critical for patients with vascular and cardiovascular diseases, who are required to take antiplatelet and anticoagulant therapy. Despite significant advances in ulcer disease treatment, the incidence of ulcer bleeding continues to rise, currently reaching 90–103 cases per 100,000 adults per year [17].,.Additionally, in modern clinical practice, cardiac and aortic surgeries, often performed under cardiopulmonary bypass, are increasingly common. Acute gastro-duodenal bleeding occurring postoperatively in certain cardiac surgery patients represents one of the most serious complications. The severity and extent of the surgery, presence of intra- and postoperative complications, and the use of anticoagulants and antiplatelet agents for thromboembolic prophylaxis make performing laparotomy for GIB highly undesirable.

In this patient category, the source of bleeding is identified primarily through urgent endoscopic intervention, which determines the level and location of bleeding, evaluates its nature and stage, and can serve as a primary method for hemostasis and prevention of rebleeding. Experience from the Russian Scientific Center for Surgery of the Russian Academy of Medical Sciences and our own data (RKNPK) indicates that all patients scheduled for cardiac surgery, particularly under cardiopulmonary bypass, should undergo planned upper GIT endoscopy, regardless of anamnesis findings. Emergency endoscopic interventions for gastro-duodenal bleeding occurring after cardiac or aortic surgery are the methods of choice both for achieving primary hemostasis and managing recurrences, allowing most patients to avoid laparotomy. Urgent gastro-duodenoscopy (EGDS) is performed for patients in critical condition (e.g., acute myocardial infarction, stroke, early postoperative period), using various therapeutic techniques. EGDS also allows the prediction of rebleeding risk, guiding further patient management. Patients on anticoagulant therapy are recommended to undergo correction of coagulopathy [18].

Injection therapy involves local infiltration of the bleeding source with agents that achieve hemostasis through: mechanical compression, vasoconstriction, and enhanced local thrombosis. Current injection solutions include epinephrine, distilled water, cyanoacrylate, epinephrine combined with ethanolamine or polidocanol, thrombin, tetradecyl sulfate, ethanol, and hypertonic epinephrine (1:10,000). Sustained hemostasis is observed in 85–95% of cases. Among the most common physical methods is electrocoagulation (mono- and bipolar techniques). Argon plasma coagulation (APC) is widely used, relying on thermal high-frequency current delivered via a stream of ionized argon plasma. Laser photocoagulation is another physical method, with the advantage of non-contact application. However, meta-analyses and clinical studies forming the basis of international guidelines on non-variceal upper GIT bleeding indicate that no thermocoagulation method offers significant superiority over others [19]. A meta-analysis by Bardou et al. (McGill University), including twenty studies, demonstrated no statistically significant differences in efficacy between thermocoagulation, multipolar electrocoagulation, laser coagulation, and injection therapy. Laser therapy is increasingly limited in emergencies due to high cost and bulky equipment.

The primary mechanical method is endoscopic clipping, which involves applying metallic clips to the visible vessel or bleeding site using an applicator passed through the endoscope channel. Another approach to hemostasis is the application of adhesive compositions, including cyanoacrylate-based medical glues (MK-6, MK-7, MK-8), film-forming polymethacrylate aerosols (Lifuzol, Gastrozol, Statisol), and fibrin-based glues (Tachocomb). However, as monotherapy, these are often less effective in practice due to low adhesiveness, technical complexity, requirement for thorough drying of the surface, prolonged contact time with mucosa, and the need for repeated application [20].

Conclusion: The management of erosive and ulcerative lesions of the upper GIT in high-risk patients requires a multifaceted approach combining effective pharmacological therapy and timely endoscopic intervention. Proton pump inhibitors, particularly pantoprazole, provide robust, long-lasting acid suppression with a favorable safety profile and minimal drug–drug interactions, making them the preferred choice in patients on multiple medications or at risk of stress-related mucosal injury. Urgent endoscopic hemostasis remains the cornerstone in the treatment of acute gastrointestinal bleeding, reducing the need for surgical intervention and allowing risk stratification for rebleeding. Individualized therapy, careful monitoring of anticoagulant and antiplatelet regimens, and consideration of comorbid conditions are crucial for optimizing outcomes and minimizing complications in this vulnerable patient population.

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