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Nonsteroidal Anti-Inflammatory Drug-Induced Peptic Ulcer Disease

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for their anti-inflammatory and analgesic effects; however, their prolonged use significantly contributes to peptic ulcer disease (PUD) and its complications, such as bleeding and perforation. The pathogenesis primarily involves cyclooxygenase (COX) enzyme inhibition and direct mucosal injury, leading to impaired gastrointestinal defense mechanisms. Multiple risk factors, including advanced age, a history of ulcers, and the concurrent use of anticoagulants or corticosteroids, significantly increase the risk of ulcers and related complications. Global epidemiological studies demonstrate considerable geographical variation in prevalence rates. Despite higher NSAID usage, high-income countries exhibit relatively lower rates, primarily due to well-established preventive strategies. Prevention should be based on careful risk stratification that accounts for both gastrointestinal and cardiovascular factors. Proton pump inhibitors have demonstrated superior efficacy in both prevention and treatment, while selective COX-2 inhibitors offer an alternative strategy, though they require careful cardiovascular risk assessment. The synergistic interaction between NSAID use and *Helicobacter pylori* infection necessitates testing and eradication, particularly in high-risk patients. NSAID discontinuation remains the primary therapeutic strategy when feasible, with studies showing significantly improved healing rates compared with continued use. Recent advances include the emergence of potassium-competitive acid blockers, which provide rapid and sustained acid suppression, offering promising alternatives for both prevention and treatment. Continued research aimed at optimizing preventive strategies and developing novel therapeutic approaches remains essential for improving clinical outcomes in NSAID-induced PUD.

Keywords Nonsteroidal anti-inflammatory drug; Peptic ulcer; Proton pump inhibitors; Cyclooxygenase 2 Inhibitor; Potassium-competitive acid blockers.

INTRODUCTION

Peptic ulcer disease (PUD) is a significant gastrointestinal disorder characterized by ulcerations in the stomach or duodenum involving breaks that extend through the mucosa and into the underlying layers. The etiology of PUD has undergone a notable transformation in recent decades. While *Helicobacter pylori* infection was historically the predominant cause, the widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and other antiplatelets, has emerged as a leading cause of PUD in current clinical practice.[1,2] In this changing epidemiological landscape, the clinical significance of NSAID-induced PUD has become increasingly prominent with the aging global population. A large retrospective cohort study of 103954 elderly individuals demonstrated that NSAID users experienced a substantially higher ulcer hospitalization rate of 16.7 per 1000 person-years compared to 4.2 per 1000 person-years in nonusers.[3] This increased risk is particularly concerning as these medications are extensively prescribed for chronic conditions such as cardiovascular and musculoskeletal disorders, with prolonged exposure leading to gastrointestinal complications including mucosal injury, ulcer formation, and bleeding.[4,5] Furthermore, the rising prevalence of NSAID use, coupled with the growing older

adult population, has resulted in a considerable healthcare burden worldwide.[6,7]

This review aimed to provide a comprehensive overview of NSAID-induced peptic ulcers, addressing their epidemiology, risk factors, prevention strategies, and current treatments.

EPIDEMIOLOGY AND RISK FACTORS

Global prevalence

NSAID-induced PUD remains a significant public health concern worldwide. Studies report a global prevalence rate of gastric ulcers ranging from 10% to 30% among NSAID users, with a higher burden observed in older populations and those with comorbidities.[2] Complications associated with NSAID-induced PUD include gastrointestinal bleeding, perforation, and obstruction, which contribute substantially to morbidity and mortality.[8] A systemic review highlighted that among NSAID users, the annual incidence of PUD complications ranges from 19.5 to 57.0 cases per 100000 individuals for bleeding and from 3.77 to 14.0 cases per 100000 individuals for perforation.[9] These complications are linked to higher mortality rates, particularly among elderly individuals and people with underlying health conditions. NSAID-induced gastropathy is also a major concern in South Korea, particularly in the elderly population. A study by Lee et al.[10] highlighted the significant prevalence of NSAID-induced ulcers and the heightened risk of complications in older individuals and those with comorbidities. Additionally, a recent study emphasized the substantial global burden of PUD, noting that the incidence of *H. pylori*-related ulcers has declined in many regions due to improved sanitation and eradication programs. However, NSAID-induced ulcers have emerged as a leading contributor to the disease burden, particularly in high-income countries.[11] These findings emphasize the importance of implementing effective preventive measures, particularly in high-risk populations requiring long-term NSAID therapy.

Risk factors

Several risk factors increase the likelihood of NSAID-induced PUD. Advanced age is a significant risk factor due to reduced mucosal repair capacity and higher NSAID usage in older populations.[7] Recent large-scale prospective data quantified this age-related risk, demonstrating that patients aged 65 years or older have significantly increased risk for both overall upper gastrointestinal clinical events (hazard ratio [HR] 2.25, 95% confidence interval [CI], 1.84–2.76) and notably higher risk for complicated events including perforation, obstruction, and severe bleeding (HR 4.09, 95% CI, 2.82–5.92).[12] A prior history of PUD is strongly associated with an increased risk of recurrence, especially in patients who continue NSAID therapy without appropriate gastroprotective measures.[13] The concomitant use of anticoagulants or antiplatelet agents, such as aspirin, further elevates the risk of peptic ulcers and gastrointestinal bleeding.[9] Steroid use, particularly when combined with NSAIDs, has also been shown to heighten the risk of ulceration due to its inhibitory effects on gastric mucosal healing.[2] Additionally, *H. pylori* infection significantly increases the susceptibility to NSAID-induced peptic ulcers, with meta-analyses demonstrating that *H. pylori* infection increases the risk of PUD in NSAID users by 3.53-fold in addition to the risk associated with NSAID use alone.[14,15] Identifying individuals at high risk and implementing preventive measures is crucial to reducing NSAID-associated complications.

Geographical variation

NSAID-induced PUD demonstrates significant geographical variation worldwide. According to the Global Burden of Disease, Injuries and Risk Factors study in 2019, high-income countries showed a relatively low age-standardized prevalence rate of 81.0 per 100000 population (95% uncertainty interval 68.2 to 95.8). This low rate, despite higher NSAID prescriptions, is mainly attributable to systematic preventive strategies, particularly routine gastroprotective agent co-prescription.[6,11] In contrast, low- and middle-income regions face a substantially higher burden, with age-standardized prevalence rates of 140.5–145.3 per 100000 population. South Asia demonstrated the highest burden, with an age-standardized prevalence rate of 156.6 per 100000 population, likely due to limited access to gastroprotective medications and widespread over-the-counter NSAIDs availability.[6] Although the age-standardized prevalence rates showed an overall decreasing trend from 1990 to 2015 across all regions, a mild increase was observed from 2015 to 2019, potentially reflecting the growing use of NSAIDs in the aging population.[6,11]

PATHOPHYSIOLOGY

Cyclooxygenase inhibition mechanism

The main pathogenic mechanism involves the systemic inhibition of cyclooxygenase (COX) enzymes, especially constitutively expressed COX-1. This inhibition leads to reduced prostaglandin synthesis, resulting in decreased mucus and bicarbonate secretion, impaired cell proliferation, and diminished mucosal blood flow—all critical components for maintaining mucosal integrity.[16] The significance of COX inhibition is evidenced by studies demonstrating that exogenous prostaglandin administration can mitigate mucosal damage.[17] Extensive meta-analyses have established varying degrees of gas-

trointestinal risk with different NSAIDs, providing crucial guidance for clinical decision-making. Among non-selective NSAIDs, ibuprofen consistently demonstrates the most favorable gastrointestinal safety profile (risk ratio [RR] 1.84, 95% CI, 1.54–2.20), followed by aceclofenac (RR 1.43, 95% CI, 0.65–3.15), whereas ketorolac (RR 11.50, 95% CI, 5.56–23.78) and piroxicam (RR 7.43, 95% CI, 5.19–10.63) pose substantially higher risks.[18-20] Other commonly used NSAIDs such as naproxen (RR 1.83, 95% CI, 1.25–2.68) and diclofenac (RR 1.73, 95% CI, 1.21–2.46) show intermediate risk profiles.[17] Based on these established risk profiles, NSAIDs can be systematically categorized into low, intermediate, and high-risk groups for gastrointestinal complications (Table 1). This significant variation in risk profiles among traditional NSAIDs has important clinical implications, particularly for patients requiring long-term therapy. These findings led to the development of selective COX-2 inhibitors, which represented a significant advancement in reducing gastrointestinal toxicity while maintaining anti-inflammatory efficacy. By sparing COX-1 activity, these agents preserve the physiological prostaglandin synthesis essential for mucosal defense.[21] However, the relationship between prostaglandin depletion and mucosal injury is not strictly linear, as demonstrated by clinical observations. Some patients with profoundly decreased mucosal prostaglandin levels may not develop gastric lesions, suggesting the involvement of additional protective and damaging factors in the pathogenesis of NSAID-induced ulcerations.[22,23]

Direct mucosal injury mechanism

Beyond COX inhibition, NSAIDs directly compromise mucosal integrity due to their physicochemical properties. These drugs initiate cellular damage by disrupting mucus phospholipids and cell membranes while simultaneously uncoupling mitochondrial oxidative phosphorylation. This initial disruption of mucosal defense is further exacerbated by exposure to luminal aggressive factors, including acid, pepsin, food particles, bile, and potential *H. pylori*.[23-25]

Table 1. Classification of NSAIDs by gastrointestinal risk

GI risk category	NSAID classification
Low risk	Ibuprofen, aceclofenac, celecoxib
Intermediate risk	Rofecoxib, sulindac, diclofenac, meloxicam, nimesulide, ketoprofen, naproxen
High risk	Indomethacin, tenoxicam, piroxicam, ketorolac, azapropazone

NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.

Role of *H. pylori*

H. pylori infection impairs mucosal defense by disrupting the gastric epithelium and reducing bicarbonate and mucus secretion, making the mucosa more vulnerable to the damaging effects of NSAIDs, such as prostaglandin inhibition and direct mucosal irritation.[26] A meta-analysis discussed in the study by Kiltz et al.[27] demonstrates that patients with both *H. pylori* infection and NSAID use have a 3.53-fold higher risk of peptic ulcers and complications, such as ulcer bleeding, with a greater recurrence rate compared to those with either factor alone. While *H. pylori* eradication reduces ulcer risk in NSAID-naive patients, it remains insufficient for chronic NSAID users with recent ulcer complications. This discrepancy arises from the distinct mechanisms through which *H. pylori* infection and NSAIDs contribute to mucosal injury. *H. pylori* induces chronic inflammation, disrupting the gastric environment and weakening mucosal defense, whereas NSAIDs primarily compromise mucosal protection by inhibiting COX-1, leading to reduced prostaglandin synthesis.[27,28] Consequently, even after *H. pylori* eradication, chronic NSAID users remain at a high risk of ulcer recurrence due to persistent prostaglandin depletion and impaired mucosal integrity.

CLINICAL PRESENTATION

Symptoms

Patients with NSAID-induced PUD often experience a wide range of symptoms, varying from mild to severe. According to a systematic review, the most prevalent symptom is abdominal pain, reported in approximately 81% of patients, with epigastric pain specifically accounting for the same percentage. This pain is typically described as burning or gnawing discomfort that may worsen on an empty stomach. Heartburn or acid regurgitation was reported in 46% of cases, while other symptoms include nausea, bloating, early satiety, and occasional vomiting.[29] Additionally, 29% of patients experienced gastrointestinal bleeding, which may present as hematemesis or melena and often serves as the first noticeable sign of an ulcer.[29,30] However, many patients on NSAIDs may remain asymptomatic until complications arise, making early diagnosis challenging.[29]

Complications

Complications from NSAID-induced peptic ulcers can be severe and life-threatening. Bleeding is the most common complication, ranging from chronic blood loss resulting in anemia to acute, massive hemorrhage that may require urgent medical intervention.[30] Another major complication is perforation, which presents as sudden and severe abdominal pain due to the release of gastric contents into the peritoneal cavity, neces-

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sitating immediate surgical repair.[31] Although less frequent, gastric outlet obstruction can occur when inflammation and swelling block gastric emptying, leading to symptoms such as persistent vomiting, early satiety, and significant weight loss.[32] These complications highlight the importance of timely recognition and treatment to reduce the risk of morbidity and mortality associated with NSAID-induced peptic ulcers.

PREVENTION STRATEGIES

The prevention of NSAID-induced PUD and its complications requires an integrated approach that considers both gastrointestinal and cardiovascular risks (Table 2). According to the 2020 revised edition of the Korean guidelines for drug-induced peptic ulcers, patients with low gastrointestinal and cardiovascular risks can use non-selective COX inhibitors without additional prophylactic measures. For individuals with a high cardiovascular risk, particularly those on aspirin, antiplatelets, or anticoagulants, co-administration of proton pump inhibitors (PPIs) is recommended to mitigate the increased risk of ulcer bleeding. In patients with high gastrointestinal risk but low cardiovascular risk, selective COX-2 inhibitors or non-selective COX inhibitors combined with PPIs are effective preventive strategies. When both gastrointestinal and cardiovascular risks are elevated, NSAIDs should ideally be avoided. However, if necessary, a combination of non-selective COX inhibitors and PPIs is preferred, with misoprostol or H2-receptor antagonists (H2RAs) as alternative options where PPI use is not feasible.[33]

Proton pump inhibitors

PPIs are considered the most effective strategy for preventing NSAID-induced peptic ulcers. By suppressing gastric acid secretion through irreversible inhibition of H+/K+ ATPase in gastric parietal cells, PPIs provide robust gastro-protection and promote mucosal healing.[34] Numerous studies have highlighted the effectiveness of PPIs in minimizing the risk of ulcer development among chronic NSAID users, especially in high-risk individuals. A randomized clinical trial of 343 Japanese patients with a history of peptic ulcers requiring long-term NSAID therapy demonstrated that esomeprazole 20 mg once daily was significantly more effective than placebo in preventing ulcer recurrence. The Kaplan–Meier estimated ulcer-free rate of over 24 weeks was markedly higher in the esomeprazole group (96.0%; 95% CI, 92.8%–99.1%) than in the placebo group (64.4%; 95% CI, 56.8%–71.9%; $p<0.001$). Importantly, esomeprazole maintained its preventive efficacy regardless of *H. pylori* status, with similar ulcer-free rates in patients who are *H. pylori*-positive (96.3%) and *H. pylori*-negative (95.5%). Additionally, the type of NSAID used (whether a selective COX-2 inhibitor or a traditional NSAID) did not substantially impact esomeprazole's protective effect in this study.[35] Another pivotal study further supports the use of PPIs for NSAID-induced ulcer prevention. The efficacy of PPI prophylaxis was convincingly demonstrated in a large-scale multicenter study that combined the VENUS and PLUTO trials. This randomized, double-blind study of 1429 high-risk patients showed that esomeprazole significantly reduced NSAID-associated ulcer development compared to placebo. The life-table estimate of ulcer occurrence at six months was markedly lower with esomeprazole (5.2% with 20 mg and 4.6% with 40 mg) compared to placebo (17.0%, $p<0.001$). This protective effect was observed in both traditional NSAID and selective COX-2 inhibitor users, with consistent risk reduction across both groups.[36] Furthermore, this study demonstrated that PPI co-therapy improved NSAID-associated upper gastrointestinal symptoms and was well tolerated across both doses. These findings suggest that esomeprazole 20 mg provides optimal gastroprotection in at-risk patients requiring chronic NSAID therapy, regardless of the type of NSAID used. These results, along with previous evidence, establish PPI prophylaxis as a cornerstone strategy for preventing NSAID-induced ulcers in high-risk patients, leading to its incorporation into current clinical practice guidelines as a standard of care for ulcer prevention in chronic NSAID users.[33,37]

H2-receptor antagonists

H2RAs provide an alternative preventive strategy for NSAID-induced PUD through the competitive inhibition of histamine H2 receptors in gastric parietal cells. A large-scale randomized controlled trial demonstrated that high-dose famotidine

Table 2. A comprehensive strategy for preventing NSAID-induced PUD based on gastrointestinal and cardiovascular risks

	Low CV risk	High CV risk†
Low GI risk	Non-selective COX inhibitors	Non-selective COX inhibitors with PPIs
High GI risk*	Selective COX-2 inhibitors, or non-selective COX inhibitors with PPIs	Avoid NSAIDs if possible If necessary use non-selective COX inhibitors with PPIs

*Old age, peptic ulcer history, use of a high dose of NSAID, concomitant use of aspirin, anti-platelet agent, anticoagulant, or steroid; †Aspirin, anti-platelet agent, or anticoagulant users for prevention of serious cardiovascular events.
NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease; GI, gastrointestinal; CV, cardiovascular; COX, cyclooxygenase; PPIs, proton pump inhibitors.

(40 mg twice daily) significantly reduced the cumulative incidence of gastric ulcers compared to placebo (8% vs. 20%, p=0.03) over 24 weeks in chronic NSAID users. The protective effect was even more pronounced for duodenal ulcers, with cumulative incidence rates of 2% vs. 13% (p=0.01) for high-dose famotidine versus placebo.[38] However, direct comparisons with PPIs have consistently demonstrated the superiority of PPIs in preventing NSAID-related gastrointestinal complications. A comprehensive meta-analysis revealed that patients receiving H2RAs had a significantly higher risk of NSAID-induced upper gastrointestinal complications than those receiving PPIs (odds ratio 2.1, 95% CI, 1.6–2.8, p<0.001). In this analysis, complications occurred in 4.8% of patients receiving H2RAs compared to 2.3% of those on PPIs.[39] Additionally, a comparative study evaluating famotidine versus pantoprazole for the prevention of aspirin-related peptic ulcer recurrence found a significantly higher cumulative ulcer recurrence rate at 48 weeks in the famotidine group compared to the pantoprazole group (17.6% vs. 3.8%, p=0.0052).[40] These findings have led current clinical guidelines to recommend H2RAs as an alternative option when PPIs are contraindicated or poorly tolerated rather than as first-line therapy for the prevention of NSAID-induced PUD.

Misoprostol

Misoprostol, a synthetic prostaglandin E1 analog, has been shown to effectively reduce the incidence of NSAID-induced peptic ulcers by enhancing mucosal defense mechanisms and reducing gastric acid secretion. A randomized clinical trial demonstrated that misoprostol significantly reduced NSAID-induced ulcer formation compared to placebo. After 12 weeks, duodenal ulcers developed in 2 of 320 patients (0.6%, 95% CI, 0.2%–3.9%) receiving misoprostol versus 15 of 323 patients (4.6%, 95% CI, 2.8%–8%) in the placebo group (p=0.002). Similarly, gastric ulcers occurred in 6 of 320 patients (1.9%, 95% CI, 0.8%–4.4%) with misoprostol versus 25 of 323 patients (7.7%, 95% CI, 5.1%–11.4%, p=0.001).[41] These findings demonstrate the efficacy of misoprostol in preventing NSAID-induced ulcers. However, its clinical application is limited by gastrointestinal side effects, especially diarrhea and abdominal discomfort, which frequently lead to treatment discontinuation.[17]

Selective COX-2 inhibitors

Selective COX-2 inhibitors represent a significant advancement in reducing gastrointestinal toxicity while maintaining anti-inflammatory efficacy. By selectively inhibiting COX-2 while sparing COX-1 activity, these agents preserve the protective prostaglandins in the gastric mucosa.[16] Clinical trials have demonstrated the efficacy of celecoxib, a COX-2 inhibitor, in reducing ulcer incidence compared to non-selective NSAIDs such as naproxen.[42] The CLASS study demonstrated this benefit, showing a significantly lower rate of symptomatic ulcers and complications with celecoxib (2.08%) compared with traditional NSAIDs (3.54%, p=0.02) in patients with osteoarthritis and rheumatoid arthritis.[43] This gastroprotective effect can be further enhanced when combined with PPIs, as demonstrated by Chan et al.[44] who found that the combination significantly reduced recurrent ulcer bleeding in high-risk patients than with COX-2 inhibitor alone (0% vs. 8.9%, p=0.0004). Despite their improved gastrointestinal safety profiles, COX-2 inhibitors present important clinical considerations. These agents generally cause fewer gastrointestinal side effects and lead to reduced treatment discontinuations compared to non-selective NSAIDs.[45] However, their use requires careful evaluation of cardiovascular risk. Meta-analyses have demonstrated significant cardiovascular risks, with data showing a 53% increased risk of myocardial infarction with COX-2 inhibitors compared with non-selective NSAIDs. Though not reaching statistical significance for overall vascular events (RR 1.16, 95% CI, 0.97–1.36), these findings have prompted increased caution in prescribing practices.[46] Current guidelines recommend careful risk stratification before initiating COX-2 inhibitors, especially in patients at high risk of cardiovascular events.

H. pylori eradication

Testing and eradication of *H. pylori* infection represent a crucial preventive strategy in patients requiring long-term NSAID therapy. The clinical significance of *H. pylori* eradication is supported by substantial evidence demonstrating the synergistic effect between *H. pylori* infection and NSAID use in increasing peptic ulcer risk.[28] Meta-analyses have shown that among NSAID users, *H. pylori* infection significantly increases the risk of peptic ulcer development by 3.53-fold in addition to the inherent risk associated with NSAID use.[15] This increased risk is particularly notable for ulcer complications, with *H. pylori*-positive NSAID users having significantly higher rates of bleeding complications compared to *H. pylori*-negative users.[15] Furthermore, a randomized controlled trial demonstrated that preemptive *H. pylori* eradication significantly reduces the incidence of peptic ulcers in patients who are NSAIDs-naive starting NSAID therapy. In the study, peptic ulcers developed in only 7% of patients who received eradication therapy compared to 26% in the control group (p=0.005).[47] Based on these findings, The Maastricht IV Consensus recommends routine testing and eradication of *H. pylori* in patients at risk of ulcers, particularly before initiating NSAID therapy, to mitigate long-term complications.[48] Such strategies are further supported by economic analyses that highlight their cost-effectiveness in

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reducing NSAID-associated ulcer morbidity.[49]

TREATMENT

NSAID discontinuation

Studies have consistently demonstrated that the discontinuation of NSAIDs plays a crucial role in healing NSAID-induced peptic ulcers. The therapeutic value of NSAID discontinuation has been well established through comprehensive clinical research, with randomized controlled trials showing significantly improved healing outcomes compared to continued NSAID use, even with acid suppression therapy.[50] In particular, a randomized controlled trial investigating ulcer healing rates found that gastric and duodenal ulcers healed at significantly higher rates when NSAIDs were discontinued. Specifically, duodenal ulcer healing rates reached 81% in patients who discontinued NSAIDs compared with 61% in those who continued NSAIDs while receiving acid suppression therapy (p=0.02). For gastric ulcers, healing rates were 68% with NSAIDs discontinuation versus 67% with continued NSAIDs use under acid suppression, though this difference did not reach statistical significance.[51] These clinical findings demonstrate the significant therapeutic benefit of NSAID discontinuation, although implementing this approach requires careful clinical assessment. The decision to discontinue NSAIDs requires careful consideration of both the risks of continued NSAID exposure and the patient's underlying condition requiring anti-inflammatory therapy. When discontinuation is feasible, it should be implemented promptly to optimize healing outcomes. For patients who cannot discontinue NSAIDs owing to their underlying conditions, alternative therapeutic strategies should be considered in consultation with the treating physician.

Proton pump inhibitors

PPIs play a crucial role in NSAID-induced peptic ulcer treatment by promoting healing and preventing recurrence. The therapeutic efficacy of PPIs in treating NSAID-induced peptic ulcers has been consistently demonstrated through multiple controlled trials.[34] A double-blind, multicenter study of NSAIDs-associated gastric ulcers showed that lansoprazole achieved significantly higher healing rates than ranitidine (69% with 15 mg and 73% with 30 mg lansoprazole versus 53% with ranitidine; p<0.05).[52] The superiority of PPIs over other gastroprotective agents was further established in the OMNIUM study, which demonstrated that omeprazole was more effective than misoprostol for both gastric and duodenal ulcer healing. After eight weeks of treatment, gastric ulcer healing rates were 87% with omeprazole 20 mg compared to 73% with misoprostol (p=0.004), whereas duodenal ulcer healing rates were significantly higher with omeprazole (93% for 20 mg, 89% for 40 mg) than with misoprostol (77%, p<0.001). Additionally, omeprazole demonstrated better tolerability, with fewer adverse events (48% for 20 mg and 46% for 40 mg) compared to misoprostol (59%). Although PPIs demonstrate considerable therapeutic efficacy as a group of acid suppressants for the treatment of NSAID-induced ulcers, comparative pharmacokinetic studies have revealed subtle variations in the acid suppression profiles among individual agents. However, current evidence does not conclusively support significant variations in therapeutic outcomes among the different PPIs.[34] Therefore, the selection of a specific PPI is typically influenced by considerations such as cost, availability, and patient-specific factors rather than differences in efficacy.

RECENT ADVANCES

Potassium-competitive acid blockers

Potassium-competitive acid blockers (P-CABs) have emerged as a significant advancement in the management of acid-related diseases, including the treatment and prevention of NSAID-induced peptic ulcers. Unlike PPIs, P-CABs directly and reversibly inhibit the H+/K+ ATPase enzyme, offering rapid and sustained gastric acid suppression.[53] Recent clinical evidence supports the efficacy of several P-CABs. Vonoprazan has demonstrated non-inferiority to traditional PPIs, such as lansoprazole, in both efficacy and safety for treating gastric or duodenal ulcers.[54] Similarly, tegoprazan has shown potential effectiveness for treating and preventing NSAID-induced ulcers in a randomized clinical trial where it achieved a healing rate of 96.2% for gastric ulcers compared to 94.1% with lansoprazole (p=0.015), confirming its non-inferiority.[55] Moreover, tegoprazan provided rapid and sustained acid suppression, significantly reducing nocturnal acid breakthrough episodes compared to dexlansoprazole, underscoring its potential advantages for managing NSAID-induced gastrointestinal complications.[56] Fexuprazan has also demonstrated potent acid suppression and protective effects. In a randomized controlled trial on erosive esophagitis, it showed comparable efficacy and safety to esomeprazole, highlighting its potential for future studies and therapeutic applications in NSAID-induced ulcers.[57] Collectively, these findings establish P-CABs as a novel and effective option for addressing the challenges posed by NSAID-induced PUD.

CONCLUSION

NSAID-induced PUD remains a significant healthcare challenge worldwide, with its prevalence continuing to rise as the

global population ages and NSAID use increases. Multiple risk factors, including advanced age, history of peptic ulcers, and concurrent use of anticoagulants or corticosteroids, substantially increase the likelihood of ulcer development and complications. The synergistic interaction between NSAID use and *H. pylori* infection emphasizes the importance of infection testing and eradication in high-risk patients. Prevention strategies must be carefully tailored to individual risk profiles, with different approaches required for patients with varying levels of gastrointestinal and cardiovascular risks. PPIs have consistently demonstrated efficacy in both the prevention and treatment of NSAID-induced ulcers, particularly in high-risk patients requiring long-term NSAID therapy. Selective COX-2 inhibitors offer an alternative strategy for reducing gastrointestinal toxicity, though careful cardiovascular risk assessment is essential. The emergence of P-CABs represents a promising advancement in acid suppression therapy and offers new options for prevention and treatment. Continued research aimed at optimizing preventive strategies and developing novel therapeutic approaches remains essential for improving clinical outcomes in patients with NSAID-induced PUD.

Authors' Contribution

Conceptualization: Dong-Kyu Lee. Data curation: Kyoung A Ko. Formal analysis: Dong-Kyu Lee. Investigation: Dong-Kyu Lee. Methodology: Kyoung A Ko. Project administration: Dong-Kyu Lee. Resources: Kyoung A Ko. Software: Kyoung A Ko. Supervision: Dong-Kyu Lee. Validation: Kyoung A Ko. Visualization: Dong-Kyu Lee. Writing—original draft: Kyoung A Ko. Writing—review & editing: Dong-Kyu Lee. Approval of final manuscript: all authors.

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