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Medical Therapy for Active Peptic Ulcer Disease

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ABSTRACT

Peptic ulcers occur when the damaging effects of acid and pepsin exceed the body's restorative processes that promote mucosal integrity and repair. Several factors have been identified that can contribute to the development of peptic ulcers, including excessive gastric acid secretion, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), infection with *Helicobacter pylori*, and impaired mucosal bicarbonate secretion. Over time, our understanding of ulcer pathogenesis has increased, leading to the development of various effective therapeutic agents with different mechanisms of action. The aim of this review was to understand the medical therapy for active peptic ulcer disease. The first-line treatment for peptic ulcer disease involves a combination of medications to reduce gastric acid production, protect and repair tissues, and eliminate underlying bacterial infections, particularly *Helicobacter pylori*. Antibiotics such as doxycycline, metronidazole, clarithromycin, and amoxicillin are prescribed to target and eradicate bacterial infections. Cyto-protective agents, including sucralfate, misoprostol, and bismuth subsalicylate, are used to coat and protect the gastrointestinal lining, aiding in healing. Histamine receptor blockers like famotidine, cimetidine, and nizatidine, as well as proton pump inhibitors such as esomeprazole, dexlansoprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole, are employed to reduce stomach acid production and foster mucous lining protection for healing. If patients regularly use nonsteroidal anti-inflammatory drugs (NSAIDs), alternative pain relievers like acetaminophen are recommended to mitigate damage to the mucous lining. Treatment approaches may vary depending on complications, such as bleeding or perforation, with minor medical procedures like endoscopy often utilized to address these issues. Overall, a comprehensive treatment strategy is employed to reduce gastric acid, protect and repair tissues, and eliminate the underlying causes of peptic ulcers, with medications playing a central role in effectively managing the condition.

Introduction

An ulcer in the gastrointestinal (GI) tract can be defined as a break in the mucosal lining that measures 5 mm or larger, exhibiting significant depth during endoscopy or presenting histologic evidence of submucosal extension. On the other hand, an erosion refers to a smaller break in the mucosa, measuring less than 5 mm. It is important to note that the differentiation between an ulcer and an erosion can be somewhat arbitrary. The term "peptic ulcer disease" (PUD) is used to encompass both ulcerations and erosions occurring in the stomach and duodenum, caused by various factors. These lesions are referred to as "peptic" due to the significant role played by the enzyme pepsin, which is proteolytic at an acidic pH and contributes to the development of mucosal breaks, regardless of the underlying cause [1-3].

Decades of research have been dedicated to investigating the role of gastric acid secretion and the impact of factors such as stress, personality type, and genetics on the development of peptic ulcer disease (PUD). The identification of the histamine-2 (H2) receptor and the subsequent development of H2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have significantly revolutionized the treatment of PUD. The discovery of *Helicobacter pylori* (Hp) and its association with PUD has transformed the perception of the disease

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from a chronic and recurring condition to a potentially curable one. Hp infection continues to be a significant cause of PUD worldwide. In developed nations, the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin for cardiovascular purposes, has emerged as a leading cause of PUD, particularly among the elderly population [4, 5].

The annual incidence of peptic ulcer disease (PUD) varies between 0.14% and 0.19% based on physicians' diagnoses in developed countries. However, when considering hospital diagnoses, the incidence is lower, ranging from 0.03% to 0.17%. The prevalence of PUD also varies depending on the diagnostic method used. Physician-diagnosed prevalence ranges from 0.12% to 4.7%, while hospital-diagnosed prevalence ranges from 0.1% to 2.6%. It is important to note that there is significant geographic variation in the prevalence of PUD. For example, in a study conducted in Shanghai, China, involving 1022 volunteers with an average age of 48 years, the prevalence of PUD was found to be 17.2%, with 93% of those affected being infected with *Helicobacter pylori* (Hp) [6-8], the primary risk factors for peptic ulcer disease (PUD) are *Helicobacter pylori* (Hp) infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs). It is worth noting that many patients with PUD have both of these risk factors, as we will discuss further. However, there are cases where PUD patients do not have either of these risk factors, known as Hp-negative and NSAID-negative ulcers. In some of these cases, the ulcers may be caused by conditions such as gastrinoma (Zollinger-Ellison syndrome, or ZES), while others may have idiopathic ulcers with unknown causes.

The most common complication associated with peptic ulcer disease (PUD) is bleeding, with reported annual incidence rates ranging from 19 to 57 per 100,000 individuals (approximately 0.02% to 0.06%). Peptic ulcer perforation (PULP), although less frequent than bleeding, has incidences of 4 to 14 per 100,000 individuals (0.004% to 0.014%). In recent years, there has been a decrease in both uncomplicated PUD cases and the incidence of ulcer complications. A study conducted by Laine and colleagues analyzed a national inpatient database and found that the annual incidence of peptic ulcer bleeding decreased from 48.7 to 32.1 per 100,000 between 2001 and 2009. During the same period, the age- and sex-adjusted case fatality rates from upper gastrointestinal (UGI) bleeding decreased from 3.8% to 2.7%. In 2009, the case fatality rate for UGI bleeding (2.45%) was significantly lower than that for UGI perforation (10.7%). Another study based on a nationwide population-based cohort in Taiwan involving 403,567 patients demonstrated a significant decrease in hospitalizations for complicated peptic ulcers over a 10-year period. The annual incidence of hospitalizations for bleeding duodenal ulcers (DU) or perforated DU decreased from 108 to 40 and from 9.8 to 5.8 per 100,000, respectively. A similar decline was observed for bleeding and perforated gastric ulcers (GU), with rates decreasing from 117 to 61 and from 11 to 6 per 100,000, respectively [9-11].

1. Pharmaceutical compounds

1.1 Antacids

Antacids have the ability to neutralize gastric acid, but they are generally ineffective in healing ulcers. As a result, most physicians do not rely on antacids as the primary treatment for ulcers, but rather recommend their use for alleviating dyspeptic symptoms. One common side effect of antacids that contain magnesium is diarrhea. On the other hand, antacids containing aluminum or calcium may lead to constipation. It is important to exercise caution when using any type of antacid, especially in patients with chronic kidney disease. Magnesium-containing antacids can cause hyper-magnesemia, calcium-containing antacids can cause hypercalcemia, and aluminum-containing antacids can potentially result in neurotoxicity. Therefore, the use of antacids in such patients should be approached with care, if used at all [12].

1.2 H2Ras (H2 Receptor antagonists)

H2 receptor antagonists (H2RAs) function as competitive inhibitors of acid secretion stimulated by histamine, effectively suppressing both basal and meal-induced acid secretion. They are particularly effective when taken in the evening, as they can effectively suppress nocturnal acid output. H2RAs are readily absorbed following oral administration and are not influenced by food intake. Peak blood levels are typically attained within 1 to 3 hours after oral dosing. It is worth noting that H2RAs have the ability to cross both the blood-brain barrier and the placenta [13-16].

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Following oral administration, several H2 receptor antagonists (H2RAs) such as cimetidine, ranitidine, and famotidine undergo first-pass hepatic metabolism, resulting in a reduction of their bioavailability by approximately 35% to 60%. However, nizatidine, another H2RA, does not undergo first-pass metabolism, and its bioavailability approaches 100% when administered orally. The elimination of H2RAs involves a combination of renal excretion and hepatic metabolism. In cases where the creatinine clearance is below 50 mL/min, dose reductions are recommended. For patients undergoing dialysis, substantial removal of H2RAs does not occur, thus dose adjustments are not necessary. Unless accompanied by chronic kidney disease, patients with hepatic failure generally do not require dose reductions. It is important to note that tolerance to the anti-secretory effects of H2RAs can develop quickly and frequently, although the precise mechanism behind this tolerance is not yet fully understood [17].

H2 receptor antagonists (H2RAs) are generally considered safe and well tolerated. According to a meta-analysis of randomized clinical trials, the overall rate of adverse effects associated with H2RAs was not significantly different from that of placebo treatment. However, there have been anecdotal reports and uncontrolled series mentioning a few adverse effects. One notable effect is observed with cimetidine, which exhibits weak anti-androgenic activity. In rare cases, this can lead to conditions such as gynecomastia (breast enlargement in males) and impotence [18, 19].

Both cimetidine and ranitidine have the ability to bind to the hepatic cytochrome P-450 (CYP) mixed-function oxidase system. This binding can result in the inhibition of the elimination of certain drugs that are metabolized through the same system. Examples of such drugs include warfarin, theophylline, phenytoin, lidocaine, and quinidine. On the other hand, famotidine and nizatidine do not exhibit significant affinity for the CYP system [20].

1.3 PPIs (Proton Pump Inhibitors)

Proton pump inhibitors (PPIs) reduce the production of gastric acid by inhibiting the proton pump (H+, K+-ATPase) found in the parietal cells. These medications are designed as prodrugs, meaning they require activation by acid in order to inhibit the H+, K+-ATPase. It is noteworthy that prodrug PPIs are susceptible to degradation by gastric acid after being taken orally, which necessitates the use of enteric coating or antacids to protect them from such degradation [21].

The absorption of enteric-coated PPIs can be unpredictable, and it takes 2 to 5 hours after oral administration to reach peak serum concentrations. Although the plasma half-life of PPIs is short (approximately 2 hours), their ability to inhibit acid secretion lasts longer due to the covalent binding of the active metabolite of the prodrug to the H+, K+-ATPase. PPIs undergo significant hepatic metabolism, but no dosage adjustments are necessary for patients with significant renal or hepatic impairment. CYP2C19, one of the isoenzymes involved in PPI metabolism, exhibits genetic polymorphism. Approximately 25% of Asians and 3% of white individuals have reduced CYP2C19 activity. This genetic variation results in significantly higher plasma levels of omeprazole, lansoprazole, and pantoprazole, but not rabeprazole [22-24].

Proton pump inhibitors (PPIs) primarily bind to proton pumps that are actively involved in acid secretion, as they require a specific concentration and activation in acidic compartments. During meal stimulation, around 60% to 70% of the proton pumps are actively secreting acid. Therefore, PPIs are most effective when taken immediately before meals. For once-daily dosing, it is recommended to take PPIs right before breakfast. Unlike H2 receptor antagonists (H2RAs), there is no observed tolerance to the anti-secretory effects of PPI therapy [25].

The increase in gastric pH caused by proton pump inhibitors (PPIs) can influence the absorption of several medications. However, this pH alteration typically does not have significant clinical implications, except when PPIs are administered alongside ketoconazole or digoxin [25, 26]. The effective absorption of ketoconazole, an antifungal drug, relies on the presence of gastric acid, which may be hindered by the concurrent use of proton pump inhibitors (PPIs). Therefore, if a patient requires both PPI therapy and antifungal treatment, it is advisable to select an alternative medication instead of ketoconazole. Conversely, an increased gastric pH facilitates the absorption of digoxin, leading to higher levels of the drug in the bloodstream. When PPIs and digoxin are prescribed together, clinicians should consider monitoring plasma digoxin levels to ensure appropriate dosage adjustments.

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The metabolism of proton pump inhibitors (PPIs) involves the CYP system, which means they have the potential to affect the metabolism of other drugs that are eliminated by CYP enzymes. The interaction between PPIs and clopidogrel has received considerable attention. Clopidogrel, a non-aspirin antiplatelet prodrug, undergoes activation by hepatic CYP2C19 and other CYP enzymes to its active metabolite. PPIs competitively inhibit CYP2C19, thereby reducing the antiplatelet effect of clopidogrel. A meta-analysis of observational studies revealed a significant increase in major adverse cardiovascular events, including cardiovascular deaths, among patients who received concomitant treatment with PPIs and clopidogrel [27, 28]. However, prospective studies and large-scale randomized controlled trials (RCTs) have not yet confirmed a definitive association between the use of proton pump inhibitors (PPIs) and clopidogrel. Despite the varying and inconclusive findings, regulatory authorities in the USA and Europe have issued warnings regarding the use of certain PPIs in patients who are concurrently taking clopidogrel [29, 30].

There are additional concerns regarding the safety of prolonged proton pump inhibitor (PPI) usage. Thus far, the use of PPIs has been associated with various conditions, including osteoporosis, hypomagnesemia, gastric cancer, enteric infections, interstitial nephritis, pneumonia, dementia, and NSAID-enteropathy. However, there is currently insufficient evidence to establish a definitive link between these conditions and PPI use. It is possible that future evidence may emerge to demonstrate a causal relationship. In the meantime, the prolonged use of PPIs without a strong indication should be discouraged [31].

1.4 P-CAB (Potassium-Competitive Acid Blocker)

Potassium-competitive acid blocker (P-CAB) therapy works by competing with potassium to inhibit the H+, K+-ATPase in parietal cells, which is the final step in the acid secretory pathway. Unlike proton pump inhibitors (PPIs), P-CABs are stable in acidic environments and do not require activation as prodrugs. Currently, vonoprazan is the only commercially available P-CAB in Japan and some other countries. Vonoprazan provides near-maximum inhibition from the first dose and its effect lasts for 24 hours [32]. Two phase 3 randomized controlled trials (RCTs) demonstrated that vonoprazan (20 mg once daily) was comparable to lansoprazole (30 mg once daily) in terms of effectiveness for the healing of gastric ulcers (GUs) and duodenal ulcers (DUs) [33, 34]. Two additional randomized trials demonstrated that both 10 mg and 20 mg doses of vonoprazan were equally effective to a 15 mg dose of lansoprazole in preventing the recurrence of ulcers associated with long-term use of NSAIDs and low-dose aspirin [35].

1.5 Mucosal Protective Agents

Sucralfate is a compound consisting of an aluminum salt of sulfated sucrose. When exposed to gastric acid, the sulfate anions in sucralfate can bind to positively charged proteins in damaged tissue through electrostatic interactions. Sucralfate, prescribed at a dosage of 1g four times daily, is equally effective as H2 receptor antagonists (H2RAs) in healing duodenal ulcers (DUs) and has received FDA approval for this indication in the USA. Due to its poor solubility, sucralfate is minimally absorbed (<5%) and is excreted through the gastrointestinal route. Its lack of systemic absorption suggests no systemic toxicity associated with sucralfate. However, the impact on aluminum accumulation in the body has not been sufficiently studied in chronic kidney disease patients receiving sucralfate, so it is advisable to avoid sucralfate in this population. Significant drug interactions with sucralfate are rare and can be prevented by administering it separately from other medications [36].

Colloidal bismuth preparations, such as colloidal bismuth sub-citrate and bismuth subsalicylate (e.g., Pepto-Bismol), have shown modest effectiveness in healing peptic ulcers, although the exact mechanism is not fully understood. These bismuth salts form complexes with mucus, which seems to provide a coating effect on ulcer craters. It has been suggested that bismuth induces increased synthesis of mucosal prostaglandins and secretion of bicarbonate, contributing to its therapeutic effects. Bismuth salts also possess antimicrobial activity against H. pylori (Hp) and have been FDA-approved in the USA for use in combination with other agents. Bismuth is minimally absorbed and primarily excreted in the feces. In the colon, bacterial action converts bismuth salts to bismuth sulfide, giving the stools a black color. Only trace amounts of bismuth are absorbed in the upper gastrointestinal tract, and it is slowly excreted in the urine for a period of three months

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or longer. Short-term, standard-dose therapy with bismuth carries minimal risk of toxicity. However, prolonged and high-dose administration, especially in patients with chronic kidney disease, may pose a potential risk of bismuth encephalopathy, which can manifest as neuropsychiatric symptoms [37].

Misoprostol is an FDA-approved prostaglandin E1 analog used for the prevention of NSAID-induced peptic ulcer disease (PUD). This medication not only enhances mucosal defense mechanisms but also inhibits gastric acid secretion by blocking histamine-stimulated cyclic 3',5'-cyclic adenosine monophosphate (AMP) production. After oral administration, misoprostol is well-absorbed and reaches peak plasma concentration in approximately 30 minutes, with a serum half-life of around 1.5 hours. It does not affect hepatic CYP450 enzymes. Misoprostol metabolites are excreted in the urine, and dose adjustments are not necessary for patients with chronic kidney disease. The most common adverse effect of misoprostol is dose-dependent diarrhea, which occurs in up to 30% of patients and can limit its usefulness. Diarrhea is believed to be caused by prostaglandin-induced increases in electrolyte and water secretion in the intestines and/or accelerated intestinal transit time. Taking misoprostol with food may help reduce the occurrence of diarrhea. It is important to note that misoprostol also stimulates uterine smooth muscle and is contraindicated in women who may be pregnant [38].

2. *H pylori* associated Ulcers

There is a strong consensus in the medical community that eradicating *H. pylori* infection not only promotes the healing of peptic ulcers but also significantly reduces the risk of ulcer recurrence and related complications [39-42]. Testing for *H. pylori* (Hp) infection is mandatory in patients with duodenal ulcers (DU) since the infection accounts for 80% to 90% of DU cases. If a diagnosis of DU is made through endoscopy, gastric biopsy specimens should be taken to detect Hp infection. There is solid evidence that a 10- to 14-day course of Hp eradication therapy is typically sufficient to heal DUs, without the need for additional anti-secretory therapy. Routine follow-up endoscopic examinations to confirm healing and test for Hp eradication after antibiotic therapy are not generally recommended for patients with uncomplicated DUs. However, noninvasive tests like the urea breath test can be used to confirm Hp eradication. The necessity of continuing anti-secretory therapy after a 7- to 14-day course of Hp eradication therapy in patients with gastric ulcers (GU) is somewhat controversial. However, one week of antibacterial therapy without acid suppression has been shown to effectively heal Hp-related Gus [39]. According to a meta-analysis of trials focused on gastric ulcer (GU) healing, Hp eradication therapy demonstrated comparable outcomes to ulcer-healing medications. However, for patients with large or complicated GUs, additional antisecretory therapy may be beneficial in promoting ulcer healing. It is recommended to conduct follow-up endoscopy in patients with large or complicated GUs to document healing, rule out malignancy, and confirm successful eradication of H. pylori (Hp) [40].

3. NSAID Ulcers

In the treatment of NSAID-related duodenal ulcers (DUs) and gastric ulcers (GUs), conventional doses of H2 receptor antagonists (H2RAs) have shown greater effectiveness in healing DUs compared to GUs. However, there is limited evidence regarding the efficacy of H2RAs in healing peptic ulcers when patients continue to take NSAIDs. As a result, H2RAs are not the preferred choice for patients with ulcers who require uninterrupted NSAID therapy [43].

Based on current evidence, proton pump inhibitors (PPIs) have demonstrated superiority over standard-dose H2 receptor antagonists (H2RAs) in healing NSAID-induced peptic ulcers. In a randomized comparison study, involving patients who continued taking NSAIDs, the healing rate at 8 weeks was 85% and 86% for patients treated with esomeprazole (20 or 40 mg/day), while it was 76% for those receiving ranitidine (150 mg twice daily). Another study focused on patients with NSAID-associated gastric ulcers who continued NSAID use. The healing rate at 8 weeks was found to be 69% and 73% for patients treated with lansoprazole (15 or 30 mg/day), whereas it was only 53% for those receiving ranitidine (150 mg twice daily). These findings suggest that PPIs are more effective than H2RAs in healing NSAID-induced peptic ulcers [44-46].

When administered to ulcer patients who continued taking NSAIDs, misoprostol was found to heal ulcers in 67% of patients within 8 weeks. In comparison, only

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26% of patients treated with a placebo showed ulcer healing [47]. Nevertheless, it should be noted that misoprostol is not as effective as PPI therapy in healing NSAID-associated ulcers. In a randomized trial, the efficacy of full-dose misoprostol (200 μg four times daily) was compared to omeprazole (20 or 40 mg daily) in patients with duodenal ulcers (DU) or gastric ulcers (GU) who continued NSAID treatment [48]. At the end of an 8-week period, duodenal ulcers (DU) had healed in 89% of patients who received either dose of omeprazole, and in 77% of those who received misoprostol. Similarly, gastric ulcers (GU) had healed in 87% of patients who received 20 mg of omeprazole, 80% of those who received 40 mg of omeprazole, and 73% of those who received misoprostol. Although the use of misoprostol for the treatment or prevention of peptic ulcers is rare nowadays, two randomized trials have demonstrated its effectiveness in healing small bowel ulcers and erosions in patients with obscure bleeding who were taking NSAIDs and low-dose aspirin [49, 50].

4. Additional causes of ulcers

In cases where the cause of a peptic ulcer can be attributed to factors other than H. pylori (Hp) infection or NSAID use (such as gastrinoma), it is crucial to treat the underlying disorder. The management of idiopathic, non-Hp, non-NSAID ulcers primarily involves acid anti-secretory therapy, typically with a proton pump inhibitor (PPI), which is often prescribed for long-term use as maintenance therapy. This approach is similar to the long-term use of anti-secretory therapy in preventing NSAID-induced ulcers in patients at moderate to high risk [51].

5. REFRACTORY ULCERS

The majority of peptic ulcers typically heal within 8 weeks of initiating anti-secretory therapy. However, in a small yet significant proportion of patients, the ulcers persist despite conventional treatment, leading to a condition known as refractory peptic ulcer. Due to the lack of a standardized definition for refractory peptic ulcer, comparing studies becomes challenging. Some patients with refractory ulcers continue to experience symptoms of ulcer disease, which can be severe. In other cases, the refractory ulcer may be asymptomatic and only identified during endoscopy, such as during the 8-week follow-up examination to assess the healing of a gastric ulcer (GU) [52].

When dealing with a patient whose ulcer fails to heal despite undergoing conventional therapy, the clinician should consider asking the following questions:

- Has the patient been adherent to the prescribed treatment?

- Is the ulcer penetrating nearby organs such as the pancreas or liver?

- Has *Helicobacter pylori* (Hp) infection been ruled out or successfully treated? False-negative test results for Hp should be considered.

- Is the patient still using NSAIDs? A thorough history should be obtained to identify any over-the-counter NSAID use, including low-dose aspirin, and if possible, NSAIDs should be discontinued.

- Does the patient smoke? Strong counseling should be provided to encourage smoking cessation.

- Has the duration of ulcer treatment been sufficient? Larger ulcers may require a longer duration of therapy for healing, typically beyond 12 weeks of anti-secretory therapy.

- Is there evidence of a hyper-secretory condition? A family history of gastrinoma, multiple endocrine neoplasia type I (MEN I), chronic diarrhea, hypercalcemia due to hyperparathyroidism, or ulcers in the post-bulbar duodenum or proximal jejunum may indicate a diagnosis of Zollinger-Ellison syndrome (ZES).

- Is the ulcer truly peptic? Other conditions such as neoplasms, infections (e.g., cytomegalovirus), cocaine use, eosinophilic gastroenteritis, or Crohn's disease can cause ulcerations in the stomach and duodenum that mimic peptic ulcers and should be considered and appropriately excluded.

For truly refractory peptic ulcers, treatment options may include a more prolonged course of anti-secretory therapy, often at a higher dose of the previous proton pump inhibitor (PPI). In rare cases, elective ulcer surgery may be necessary to attempt healing of a symptomatic refractory or penetrating ulcer [52].

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Table. Risk Factors for NSAID Ulcers*

Risk factor	Risk ratio
History of complicated ulcer	13.5
Use of multiple NSAIDs (including aspirin, COX-2 inhibitors)	9
Use of high doses of NSAIDs	7
Use of an anticoagulant	6.4
History of an uncomplicated ulcer	6.1
Age >70 years	5.6
Hp infection	3.5
Use of a glucocorticoid	2.2

*Not all NSAIDs pose the same risk.

6. PREVENTION OF ULCER DISEASE

Most studies investigating ulcer prophylaxis have primarily utilized endoscopy as the endpoint to assess the effectiveness of different treatment regimens, rather than relying on clinical endpoints. The definition of an "endoscopic ulcer" has been arbitrarily set as a circumscribed mucosal defect with a diameter of 5 mm or more and a perceivable depth. However, some studies have relaxed this criterion to include flat mucosal breaks with a diameter of 3 mm or more as ulcers. The differentiation between small ulcers and erosions is subjective and prone to inter-observer variability. The clinical significance of these minor endoscopic findings remains uncertain. It is assumed that endoscopic findings roughly correlate with clinical outcomes in individuals at low-to-average risk of developing ulcer complications. However, it is unclear whether the results of endoscopic studies can be extrapolated to high-risk patients. Due to the limited number of prospective trials evaluating the true clinical efficacy of ulcer prophylactic agents, clinical judgment heavily relies on data that predominantly employ endoscopic endpoints [53].

Ulcer prophylaxis is typically not required for H. pylori (Hp) ulcers if the infection can be successfully eradicated from the stomach. Therefore, the utilization of ulcer prophylaxis regimens primarily focuses on preventing NSAID-induced ulcers in patients at moderate to high risk. The risk factors for developing NSAID-induced ulcers are outlined in the provided table. Later, we will discuss pharmaceutical agents that can help reduce the occurrence of NSAID-induced ulcers. Ulcer prophylaxis is also commonly employed in patients with idiopathic ulcers. Among the listed agents, anti-secretory agents are the most frequently used for preventing idiopathic ulcers [53].

6.1 Antacids

A common practice among clinicians is to prescribe antacids alongside NSAIDs for patients, aiming to alleviate dyspeptic symptoms and potentially prevent ulcers. However, there is no proven efficacy of antacids in preventing NSAID-induced ulcers. In fact, antacids can mask dyspeptic symptoms, leading to a false perception of ulcer protection and an increased risk of silent ulcer complications with prolonged NSAID use. Therefore, it is advisable to discourage the co-prescription of antacids to individuals at risk for ulcers who are taking NSAIDs [52].

6.2 H2RAs

The use of standard doses of H2 receptor antagonists (H2RAs) is not effective in preventing NSAID-induced gastric ulcers (GUs), and it may even be detrimental, as mentioned earlier. A systematic review of randomized trials involving NSAID users found that doubling the standard daily dose of H2RAs significantly reduces the risk of endoscopic NSAID-induced duodenal ulcers (DUs) and GUs. However, it remains unclear whether high-dose H2RAs effectively prevent complications associated with NSAID-induced ulcers. In contrast, H2RAs appear to be more effective in preventing ulcers associated with low-dose aspirin than with NSAIDs. In a multicenter randomized trial conducted over 12 months among low-dose aspirin users at risk of recurrent ulcer bleeding, there was no statistically significant difference in the incidence rates of recurrent bleeding between patients receiving a proton pump inhibitor (PPI) and those receiving an H2RA [54-56].

6.3 Misoprostol

Randomized controlled trials (RCTs) have evaluated the effectiveness of misoprostol in preventing ulcers induced by NSAIDs [56, 57]. A comprehensive review of these trials found that various doses of misoprostol (ranging from 400 to 800 μg/day) were all associated with a decreased risk of endoscopic ulcers caused by NSAID usage [55]. Nevertheless, it should be noted that only the

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administration of the full dose of misoprostol (800 μg/day) has been shown to effectively reduce complications associated with ulcers [56]. In a double-blind randomized trial involving patients with rheumatoid arthritis who were prescribed NSAIDs, the use of misoprostol (200 μg four times daily) resulted in a 40% reduction in gastrointestinal (GI) complications compared to the placebo group (reducing the rate from 0.95% to 0.57% in the misoprostol group). However, it is important to note that up to 30% of patients receiving misoprostol in this trial experienced GI upset, which limited its clinical utility. Although endoscopic studies suggested that lower doses of misoprostol, such as 200 μg two or three times daily, could prevent NSAID-induced ulcers with fewer adverse effects than the full dose, these lower doses were not effective in preventing ulcer complications [56, 58].

6.4 PPIs

Proton pump inhibitors (PPIs) have been shown to significantly decrease the risk of both duodenal and gastric ulcers as observed through endoscopic examination [55]. Studies have compared the effectiveness of proton pump inhibitors (PPIs) with H2 receptor antagonists (H2RAs) and misoprostol in patients receiving NSAIDs. Two six-month studies compared omeprazole 20 mg once daily with standard-dose ranitidine (150 mg twice daily) and half-dose misoprostol (200 μg twice daily) [44, 48]. Omeprazole demonstrated higher efficacy compared to standard-dose ranitidine and showed similar effectiveness to half-dose misoprostol in preventing endoscopic ulcers. The superiority of omeprazole over ranitidine in preventing NSAID-related ulcers was primarily attributed to a greater reduction in endoscopic duodenal ulcers (DUs). A posthoc analysis revealed that the additional protection provided by omeprazole compared to ranitidine was primarily seen in individuals with H. pylori (Hp) infection. Another endoscopic study compared high-dose misoprostol (200 μg four times daily) with two doses of lansoprazole (15 and 30 mg daily) for the prevention of ulcers in long-term NSAID users without Hp infection but with a history of gastric ulcers (GU) [58]. Misoprostol demonstrated greater effectiveness in preventing gastric ulcers (GU) compared to both doses of lansoprazole. However, the practical advantage of misoprostol over lansoprazole was limited due to a high withdrawal rate observed in the misoprostol group. In a direct comparison study focusing on endoscopic ulcer prevention, involving patients with rheumatoid arthritis receiving NSAIDs, two doses of pantoprazole were compared with omeprazole at a dosage of 20 mg per day. The six-month probabilities of remaining ulcer-free were 91%, 95%, and 93% for pantoprazole 20 mg, pantoprazole 40 mg, and omeprazole 20 mg, respectively [59].

Two multicenter randomized clinical trials, conducted simultaneously, compared the efficacy of esomeprazole (20 or 40 mg) with placebo in preventing ulcers among patients taking NSAIDs or COX-2 inhibitors for a duration of six months. The patients included in both studies were negative for H. pylori (Hp), aged over 60, and had a history of gastric ulcers (GU) or duodenal ulcers (DU). Overall, the incidence rates of ulcers were 17.0%, 5.2%, and 4.6% in the placebo group, esomeprazole 20 mg group, and esomeprazole 40 mg group, respectively [60].

The evidence regarding the ability of PPIs to reduce the risk of NSAID-associated peptic ulcer bleeding primarily relies on observational studies and one randomized trial conducted in high-risk patients. A comprehensive case-control study revealed a significant reduction in the risk of upper gastrointestinal (UGI) bleeding among chronic NSAID users who received PPI therapy (relative risk, 0.13; 95% CI, 0.09 to 0.19). In the randomized trial, long-term omeprazole therapy for six months was compared to one week of Hp eradication therapy in Hp-infected patients with a recent history of NSAID-related ulcer bleeding who continued to use naproxen. The occurrence of recurrent ulcer bleeding was observed in 18.8% of patients undergoing eradication therapy, while only 4.4% of patients receiving omeprazole experienced recurrence [61, 62].

6.5 COX-2 Inhibitors (In Place of NSAIDs)

The utilization of COX-2 inhibitors presents a potential solution for reducing gastrointestinal (GI) toxicity associated with NSAIDs while maintaining their therapeutic benefits [63, 64]. A systematic review of randomized trials demonstrated that COX-2 inhibitors, when compared to nonselective NSAIDs, resulted in a significantly lower incidence of gastroduodenal ulcers (relative risk, 0.26; 95% CI, 0.23 to 0.30), reduced occurrences of ulcer complications (relative risk, 0.39; 95% CI, 0.31 to 0.5), and fewer instances of withdrawals

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due to gastrointestinal (GI) symptoms [65]; Nevertheless, it should be noted that the protective effect of COX-2 inhibitors against ulcer development is nullified when used concurrently with low-dose aspirin [28].

Based on current evidence, COX-2 inhibitors have shown comparable effectiveness to a combination of nonselective NSAIDs with a PPI in patients at risk for ulcers. In a randomized comparison study, where patients were either H. pylori (Hp) negative or had undergone Hp eradication, the incidence of recurrent bleeding within 6 months was similar between the group receiving diclofenac plus omeprazole and the group receiving celecoxib for secondary prevention of ulcer bleeding (6.4% vs. 4.9% respectively). However, a subsequent follow-up endoscopic study revealed that approximately 20% to 25% of patients in either treatment group developed recurrent endoscopic ulcers at 6 months, indicating that neither treatment completely eliminates the risk of recurrent bleeding in high-risk patients. In a 13-month double-blind randomized trial involving patients with a history of NSAID-associated ulcer bleeding, a comparison between celecoxib alone and celecoxib combined with esomeprazole showed that 8.9% of those in the celecoxib-alone group experienced recurrent ulcer bleeding, while none of the patients in the combined therapy group had recurrence (P = 0.0004) [66, 67].

Despite the improved gastric safety profile associated with COX-2 inhibitors, there have been significant concerns regarding the cardiovascular risks of this new class of NSAIDs. The VIGOR study revealed that the incidence of acute myocardial events, although low, was four times higher among patients receiving rofecoxib compared to those receiving naproxen. The debate regarding whether this disparity in myocardial infarction rates was due to naproxen's antiplatelet property or rofecoxib's pro-thrombotic effect ensued. Additional data concerning the cardiovascular hazards of COX-2 inhibitors were obtained from two long-term studies focused on colon polyp prevention, utilizing either rofecoxib (the Adenomatous Polyp Prevention on Vioxx [APPROVE] study) or celecoxib (the Adenoma Prevention with Celecoxib [APC] study) [68, 69]. In the APPROVE study, interim data at 18 months indicated that patients receiving a daily dose of 25 mg rofecoxib had twice the risk of experiencing serious cardiovascular events compared to those who received a placebo. As a result of this unexpected finding, rofecoxib was voluntarily withdrawn from global markets in 2004. In the APC study, interim data at 33 months revealed that serious cardiovascular events were significantly more frequent among patients taking high-dose celecoxib (400 mg twice a day) compared to the placebo group (hazard ratio, 1.9; 95% CI, 1 to 3.3). The MEDAL program involved a pre-planned pooled analysis of cardiothrombotic events from three trials, where patients with osteoarthritis or rheumatoid arthritis were randomly assigned to receive either etoricoxib (60 mg or 90 mg daily) or diclofenac (150 mg daily). After an average treatment duration of 18 months, the rates of cardiothrombotic events were similar between the two treatment groups [70].

Based on current evidence, it appears that both COX-2 inhibitors and nonselective NSAIDs, except for full-dose naproxen (1000 mg/day), carry an increased risk of cardiothrombotic events. A meta-analysis of randomized trials focusing on COX-2 inhibitors (primarily rofecoxib and celecoxib) demonstrated that all COX-2 inhibitors were associated with a higher cardiothrombotic risk compared to placebo (risk ratio, 1.42; 95% CI, 1.13 to 1.78). This heightened risk was primarily attributed to an increased likelihood of experiencing myocardial infarction, with limited variation in other vascular outcomes. Celecoxib showed a dose-dependent increase in cardiothrombotic events. Notably, there was no significant disparity in cardiothrombotic risk between COX-2 inhibitors and nonselective NSAIDs, except for naproxen (500 mg twice daily), which exhibited a different outcome. In a meta-analysis of observational studies, high-dose rofecoxib (≥25 mg per day), diclofenac, and indomethacin were linked to an elevated risk of cardiothrombotic events, while celecoxib did not show a significant increase in cardiothrombotic risk, although the possibility of an increased risk with doses exceeding 200 mg/day could not be completely excluded [71]. A large-scale, randomized, noninferiority trial was conducted to compare celecoxib with naproxen and ibuprofen in patients with arthritis, primarily osteoarthritis, and increased cardiovascular risk. The study enrolled over 24,000 patients with an average treatment duration of 20 months and a mean follow-up period of 34 months. Celecoxib, with an average daily dose of approximately 200 mg, was found to be non-

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inferior to ibuprofen (approximately 2000 mg/day) or naproxen (approximately 850 mg/day) in terms of cardiovascular safety. Patients treated with celecoxib experienced a significantly lower risk of adverse gastrointestinal (GI) events compared to those receiving naproxen or ibuprofen. Additionally, the risk of adverse renal events was significantly lower with celecoxib compared to ibuprofen. However, it should be noted that the proportion of patients who continued concomitant low-dose aspirin during the study period was unclear, and the number of patients with a history of GI bleeding was very limited. As a result, it remains uncertain whether the advantage of celecoxib over naproxen or ibuprofen can be extended to patients taking concomitant aspirin with a high risk of GI bleeding. In another randomized trial spanning 18 months, which involved patients at high risk of both cardiovascular and GI adverse events requiring concomitant low-dose aspirin and an NSAID, the combination of celecoxib and a proton pump inhibitor (PPI) was found to be superior to naproxen plus a PPI in reducing the risk of recurrent ulcer bleeding [72-74].

Conclusion

In summary, the treatment strategy for peptic ulcer disease involves a comprehensive approach to reduce gastric acid, protect and repair tissues, and eliminate the underlying causes of ulcers. Medications play a central role in effectively managing the condition by targeting bacterial infections, reducing acid secretion, and promoting mucous lining protection and healing.

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