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The Benefits and Risks of PPI Use in H. Pylori Associated Peptic Ulcer Disease

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Helicobacter pylori (H. pylori) infection is one of the most common causative factors of peptic ulcers, which may affect the stomach and the duodenum. Proton pump inhibitors (PPIs) have become a key ingredient of H. pylori-associated ulcers due to their highly acid-suppressive properties. Numerous clinical trials have proved that PPIs have a beneficial effect on the ulcer healing process in those with H. pylori infection. PPIs are acid pump inhibitors that irreversibly inhibit the H+/K+ ATPase proton pump in gastric parietal cells. Through this mechanism, PPIs reduce the secretion of gastric acid, allowing for a conducive environment that is favorable for ulcer healing. Meta-analyses have repeatedly shown that triple therapy with PPI (proton pump inhibitor) achieves higher ulcer healing rates compared to antibiotics therapy alone, which again stresses the synergistic effect of acid suppression and H. pylori eradication. PPI, in ulcer healing, remains indispensable, however, their effects on the regimen for eradication of H. pylori needs to be considered. PPIs are commonly used as one of the three main components of the standard triple therapy regimen in addition to antibiotics. Nevertheless, the risk of affecting the efficiency of H. pylori eradication using PPIs has been raised. Research may suggest that PPI use can decrease pH in the stomach, thereby compromising the action of antibiotics against H. pylori. Despite their efficacy, PPIs are associated with various risks and adverse effects. Long-term PPI use has been

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linked to an increased risk of enteric infections, including Clostridioides difficile-associated diarrhea, potentially attributable to altered gut microbiota and reduced gastric acidity. This literature review will examine PPI in the context of H. pylori infection, its efficacy in the treatment of ulcers, and related risks.

Keywords: Helicobacter pylori; H. pylori infection; proton-pump inhibitors; PPIs; stomach acidity; gastrointestinal tract issues.

1. INTRODUCTION

Helicobacter pylori (H. pylori) infection is a significant contributor to various gastrointestinal disorders, including gastritis and peptic ulcer disease. Understanding the pathogenesis of H. pylori infection is crucial in elucidating the mechanisms underlying ulcer formation and guiding therapeutic interventions [1].

One of the hallmark features of H. pylori is its urease activity, which enables the bacterium to survive in the acidic environment of the stomach. By hydrolyzing urea into ammonia and carbon dioxide, H. pylori creates a local alkaline environment, facilitating its colonization and persistence within the gastric mucosa [2]. This adaptive mechanism is essential for H. pylori to evade gastric acid-mediated destruction and establish chronic infection, laying the foundation for subsequent pathological changes [3].

The flagella-mediated motility of H. pylori is instrumental in its ability to traverse the mucus layer and reach the gastric epithelium. Once close to host gastric epithelial cells, H. pylori employs an ‘army’ of adhesins to adhere to specific host cell receptors, initiating the process of colonization [4]. This intimate attachment is an important step in the establishment of persistent infection and is facilitated by the interplay between bacterial surface molecules and host cell surface receptors [1].

H. pylori produces an array of effector proteins and toxins that contribute to host tissue damage and inflammation, key features of gastritis and ulceration. Among these virulence factors, cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) are particularly noteworthy. CagA is injected into host cells via a type IV secretion system, where it disrupts intracellular signaling pathways, promotes cell proliferation, and contributes to epithelial damage. VacA, on the other hand, induces vacuolation and apoptosis in host cells, further exacerbating tissue injury and inflammation [3].

2. PROTON PUMP INHIBITORS (PPIS) AND THEIR ROLE IN GASTRIC ULCERS

The human gastrointestinal (GI) tract maintains a finely tuned acidic environment that is suitable for physiological processes such as digestion, nutrient absorption, and microbial balance [5].

Proton pump inhibitors (PPIs) have revolutionized the management of acid-related disorders by selectively inhibiting gastric acid secretion. This section further illuminates the physiological significance of GI acidity and the mechanism of action of PPIs, highlighting their clinical implications [6].

2.1 Gastrointestinal pH Variability

The GI tract exhibits a dynamic pH gradient, with the stomach harboring the lowest pH levels, around 1.0, essential for food breakdown and nutrient processing [7].

Gradual pH elevation occurs from the small bowel (pH 6.5) to the colon (pH 6.5-7.0), influencing the absorption of vital nutrients such as biotin, folate, vitamin B12, and electrolytes [8].

Gastrointestinal acidity not only aids digestion but also plays another important role in maintaining the microbiome and regulating electrolyte balance, underscoring its physiological importance.

2.2 Mechanism of PPIs

PPIs, exemplified by omeprazole and lansoprazole, exert their pharmacological effects by irreversibly inhibiting the H+/K+-ATPase proton pump in gastric parietal cells. Initially synthesized through modified compound screening, PPIs have undergone extensive development to enhance safety and efficacy [9].

Despite initial safety concerns, subsequent studies have refuted associations with increased malignancy risk. The availability of multiple PPI formulations, both prescription and over-the-counter, underscores their widespread clinical use [10].

2.3 Pharmacokinetics and Pharmacodynamics

PPIs are pro-drugs concentrated in acidic parietal cell canaliculi, where they bind irreversibly to cysteine residues of H+/K+-ATPase pumps. Administration before meals optimizes their efficacy, as stimulated parietal cells translocate H+/K+-ATPases into canaliculi, maximizing PPI binding [11].

This irreversible inhibition persists for approximately 24 hours, rendering PPIs highly effective in suppressing gastric acid production. Notably, PPIs induce profound hypochlorhydria, elevating gastric pH from 2.0 to over 6.0 within hours of administration, a 10,000-fold change with lasting effects [12].

2.4 Clinical Applications

PPIs demonstrate clinical efficacy across various acid-related disorders, including peptic ulcer disease, gastroesophageal reflux, eosinophilic esophagitis, and hypersecretory conditions like Zollinger-Ellison syndrome [13].

Their widespread use stems from established efficacy and perceived safety. However, concerns regarding long-term use and potential adverse effects necessitate judicious prescribing and regular monitoring [14].

3. EFFECTS OF PROTON PUMP INHIBITORS ON THE GUT MICROBIOME

3.1 Esophagus

The esophageal disorders, mainly GERD (Gastroesophageal Reflux Disease), represent a great challenge in healthcare, as a significant rise in their incidence has been detected in recent decades. [15].

Nowadays, PPIs are the first-line treatment for these diseases, which explains their effectiveness in relieving symptoms and preventing complications like erosive esophagitis and esophageal adenocarcinoma (EAC) [16].

While diagnostic testing for underlying conditions like H. pylori infection or confirmation of the presence of BE is widespread, there is an underutilization of this testing in clinical practice, indicating that evaluating comprehensive evaluation should be emphasized [17].

Recent studies suggest that disruption of the esophageal microbiome is a common event in esophagitis and BE compared to healthy controls. Unique microbial fingerprints, including alternations in the established dominance of different bacteria, are linked to various disease states [18].

Importantly, a higher prevalence of Gram-negative anaerobes and microaerophilic bacteria are frequently observed in patients with esophagitis and BE. Their presence may increase inflammation via TLR4 activation and NF-kB pathway induction. Secondly, the microbiome composition may also be the reason for increased acid exposure proximal to the esophagus which in turn aggravates the esophageal injury [19].

PPIs demonstrate this antagonistic property through the two mechanisms of acid exposure reduction and esophageal microbiome modulation. Through the permanent substitution of gastric acid production, PPIs relieve the acid reflux in the distal esophagus, in which case, the disease (BE to EAC) progression might be halted. Similarly, PPIs have direct effects on the microbiome of the esophagus and thus might interfere with the pro-inflammatory and carcinogenic pathways [12].

3.2 Stomach

PPIs are a vital part of the H. pylori eradication therapy, they exert direct bacteriostatic action against H. pylori and indirectly suppress the bacterial activity by elevating gastric pH. The PPIs-made environment is basically anti-H. pylori which means the PPI-made environment prevents and accelerates ulcer healing, thus an efficacy of the ulcer management. Though they are considered effective in non-ulcer dyspepsia and functional gastric conditions, their efficacy in these conditions is not well-defined, and further research is required [20].

The acidity of the stomach, however, is one of the main characteristics that make it unique in the gastrointestinal tract and also shapes the gastric microbiome composition. H. pylori is the most dominant microbe in the stomach ecology, occupying the majority of the bacterial community [21]. Acid suppression by PPIs is the key mechanism behind the effect of H. pylori on the gastric environment that changes the H. pylori abundance and distribution. With its predominant antrum infection, H. pylori may move to the corpus under PPI therapy, while in corpus-predominant cases, gastritis and achlorhydria develop, which emphasizes the bidirectional relationship between H. pylori and gastric acidity [16].

Proton pump inhibitors (PPIs) are viewed as a cause of gastric bacterial overgrowth, especially in the condition of H. pylori infection. There is a greater pH change in people with H. pylori infection who are using PPIs, thereby risking bacterial overgrowth. The omission of H. pylori results in oral flora dominance such as Streptococcus and common commensals like Lactobacillus and Clostridium spp., which shows the changes in the microbial ecology that govern PPI therapy [22].

3.3 Small Intestine

Even though PPIs remarkably lower gastric pH they mainly do not affect the pH of the small bowel. The pH of the majority of the small bowel remains unchanged. However, the pH of the stomach and proximal duodenum could be significantly altered. Nevertheless, gastric acid neutralization by PPIs is implicated in small intestinal bacterial ecosystem indirectly, which in turn, creates a condition for bacterial overcrowding and dysbiosis [23].

Studies have always shown a causal link between PPI use, which is marked by an increased number of bacteria and their diversity in the proximal small bowel. Glucose hydrogen breath tests and duodenal aspirates have determined higher SIBO rates among PPI users in comparison to non-users and meta-analyses, there was a rise of three times in the risk of SIBO. Bacteria such as Escherichia coli, Enterococcus spp., and Klebsiella pneumoniae are the most commonly seen organisms in SIBO related to the use of PPI therapy. These bacteria are the main causes of microbial dysbiosis [24].

Patients with SIBO may be asymptomatic but gas and bloating sensation may be the first clinical manifestation due to increased intracellular carbohydrate fermentation. Moreover, iron and vitamin B12 deficiency may appear because of microbial competitive uptake and fat malabsorption due to bacterial deconjugation of bile acids [25].

These clinical complications make it obvious that SIBO screening should be part of the routine check-up of people who have been on PPI therapy for a long time. Therefore, patients on PPI must be monitored carefully and appropriate interventions should be made in case of SIBO [15].

4. CONCLUSION

The PPIs are the proton pump inhibitors that are very important in management of the H. pylori ulcers and they are used as both treatment and preventive agents. PPIs, by reducing gastric acid secretion, make an environment in which ulcers can heal easily and therefore the risk of peptic ulcer disease is significantly reduced. Moreover, PPIs are vital components for the successful eradication of H.pylori using antibiotics. They improve the effectiveness of antibiotic therapy and promote successful H.pylori eradication.

In addition, the administration of PPIs is not without hazards. The prolonged use of PPI has been confirmed to have various adverse effects, like increased risk of enteric infections, micronutrient deficiencies, and potential changes in the gastrointestinal microbiome. Additionally, recent studies point to a possible association between PPI use and SIBO conditions which stress the aspect of accurate monitoring and proportionate prescribing.

Although there are such drawbacks as the possibility of developing antibiotic resistance, the advantages of PPI therapy in H. pylori-associated ulcer therapy outweigh the risks in the majority of clinical cases. Nevertheless, healthcare providers must carefully balance the possible risks and benefits of long-term PPI use, tailoring treatment plans to the individual health needs of each patient with regular follow-up visits to assess whether PPI therapy is still needed.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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