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Proton Pump Inhibitors. Investigating Their Role in Small Intestinal Bacterial Overgrowth

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Abstract
Proton pump inhibitors (PPIs) are widely used medications known for their effectiveness in reducing gastric acid production and their overall safety profile. Despite being valued for these properties, concerns have been raised regarding potential adverse effects associated with their long-term use. Various studies indicate a higher prevalence of small intestinal bacterial overgrowth (SIBO) in patients on prolonged PPI therapy, with symptoms ranging from bloating and diarrhea to malabsorption and nutrient deficiencies. Diagnosing SIBO primarily involves non-invasive breath tests that measure hydrogen and methane levels produced by bacterial fermentation after ingesting a carbohydrate substrate, such as lactulose or glucose. Direct aspiration and culture of small intestinal fluid offer a more definitive diagnosis but are invasive and less commonly performed. Treatment of SIBO focuses on reducing bacterial overgrowth by using antibiotics.
This review aims to inform clinicians about the possible risks of PPI therapy and the importance of suspecting SIBO in patients with nonspecific gastrointestinal symptoms.

Keywords: "proton pump inhibitors", "PPI", "small intestinal bacterial overgrowth", "SIBO"

Introduction
Gastric acid production is controlled by parietal cells situated in the glands of the fundic mucosa of the stomach [1, 2]. Regulation of parietal cell activity involves various mechanisms, such as the vagus nerve, gastrin, histamine, ghrelin, somatostatin, glucagon-like peptide 1, and other stimulating and inhibiting agents [1].

Stimulation of receptors on the basolateral membrane of the parietal cell triggers the release of secondary messengers inside the cell, activating protein kinases. Finally, activating the parietal cell H^+-K^+-ATPase, commonly called the proton pump, plays a crucial role in the process [3]. The activated proton pump exchanges luminal potassium ions for cytoplasmic hydrogen ions with a one-to-one H^+:K^+:ATP ratio [4]. The hydrogen ions secreted into the gastric lumen combine with luminal chloride ions to create hydrochloric acid, known as HCl. This gastric acid creates a highly acidic environment within the gastric lumen, eliminating food-derived bacteria, aiding food digestion, and enhancing the absorption of minerals such as phosphate, calcium, and iron [1]. Insufficient secretion of hydrochloric acid can present itself in various ways [2].

On a global scale, one of the most commonly used groups of medications is proton pump inhibitors (PPIs) [5]. This class of drugs includes omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole, and dexlansoprazole [6]. Since omeprazole's introduction in 1989, PPIs have become the cornerstone of treating acid-mediated gastrointestinal conditions. PPIs are the first-line treatment for conditions such as esophagitis, non-erosive reflux disease (NERD), peptic ulcer disease (PUD), prevention of nonsteroidal anti-inflammatory drugs (NSAID)-associated ulcers, Zollinger-Ellison syndrome (ZES), and functional dyspepsia. Additionally, PPIs are used alongside antibiotics to eliminate Helicobacter pylori [7]. Moreover, PPIs are commonly used off-label for prophylaxis against gastritis associated with corticosteroids, anticoagulants, chemotherapy, and coronary heart disease [6].

Numerous scientific studies focus on the effects of long-term use of PPIs. This article presents the latest thinking regarding the relationship between PPIs and SIBO and briefly introduces the characteristics of these drugs and the disease.

Proton pump inhibitors

PPIs function by blocking the final step of acid production, inhibiting 70% to 80% of the active potassium pumps situated on the apical membrane of gastric parietal cells. This action halts the secretion of protons into the gastric lumen [8]. The suppression of gastric acid secretion persists until new pumps are synthesized, which can take anywhere from 36 to 96 hours [7,8]. PPIs are primarily prodrugs that necessitate activation within the low pH environment of parietal cells to inhibit the function of the proton pump [9]. Interestingly, PPIs are also vulnerable to degradation by acid [10]. To counteract degradation by gastric acid post-oral administration, these medications are formulated in different delivery systems like enteric-coated tablets, gelatin capsules, or coated granules in powder form for suspension [7]. After oral intake, PPIs are absorbed in the duodenum [9]. Then, they travel through the bloodstream to the secretory canaliculus of a parietal cell. At this location, the weakly basic PPI molecule becomes protonated and concentrated, converting the inactive compound into a reactive form [10]. This drug type effectively forms stable inhibitory complexes solely with active H^+-K^+-ATPase. Activation of the proton pump is triggered by meals [9]. Hence, the timing of PPI administration should coincide with food intake for optimal results. PPIs are best taken 30 to 60 minutes before a meal for maximum efficacy. This timeframe allows for the absorption of the enteric-coated drug and ensures sufficient medication levels in the bloodstream when most proton pumps are susceptible to inhibition [10].

The timing of medication administration plays a crucial role in achieving maximum acid suppression and, consequently, the desired therapeutic outcomes [3]. When taking PPIs once daily, it is recommended to take them before breakfast [10]. If a patient needs to take the medication twice daily, the second dose should be taken before the evening meal rather than at bedtime [8]. PPIs have a short plasma half-life and, as a result, a short duration of effect [3]. These drugs bind strongly to proteins and are metabolized by the hepatic cytochrome P450 (CYP) system [7, 10]. Variability in acid secretion control may be observed among patients due to polymorphisms in the cytochrome P450 system. It is important to note that resistance to PPIs is rare or non-existent [8].

The analysis conducted by Shanika et al., as part of a systematic review of global trends in PPI usage, demonstrated that individuals aged 65 and above had the highest prevalence of PPI usage, followed by those aged 49 years or younger, accounting for 37.1% and 34.7% of total users, respectively. Moreover, a significant portion of PPI consumers, about a quarter, reported using these medications for over a year [6]. While many PPIs are generally viewed as safe, studies have shown a concern for their overprescription in both primary and secondary healthcare settings [11]. Although most PPI drugs have a favorable safety profile, a small percentage of patients may experience side effects like headaches, nausea, abdominal pain, or diarrhea [8]. Long-term use of PPIs has been associated with potential risks such as malabsorption of essential vitamins and minerals, leading to conditions like hypomagnesemia and deficiencies in vitamins B12, iron, and calcium [12]. Some concerns that prolonged PPI use could contribute to issues like accelerated bone mineral loss, osteoporosis, fractures, kidney disease, acute kidney injury, dementia, gastric hyperplasia, and metaplasia [13]. Furthermore, the use of PPIs has been linked to an elevated risk of enteric and extraintestinal infections, notably Clostridioides difficile (CDI) and pneumonia [12]. This heightened susceptibility to infections is attributed to the hypochlorhydria induced by PPIs, which compromises the natural defense mechanisms against ingested bacteria, leading to alterations in intestinal flora, bacterial colonization, and increased vulnerability to enteric infections [13].

Small intestine bacterial overgrowth

SIBO presents as an imbalance in the small intestine marked by increased bacterial presence, potentially including bacteria more commonly found in the colon [14, 15]. The actual prevalence of SIBO in the general population is uncertain due to the requirement of diagnostic testing [14, 16]. Research estimates suggest a prevalence range of 2.5% to 22%, with a noted increase with age and among individuals with underlying health conditions [14]. The small intestine has several natural defense mechanisms, such as gastric acid, bile, and pancreatic secretions, which help to prevent excessive bacterial growth. Additionally, the ileocecal valve blocks the retrograde movement of anaerobic bacteria from the colon [15]. Various health conditions are associated with an increased risk of SIBO, including disorders affecting intestinal structure or motility, pancreatic insufficiency, and chronic liver disease [17]. Factors like reduced stomach acid (hypochlorhydria) and specific anatomical abnormalities like fistulas, strictures, and small bowel diverticulosis can also contribute to the development of SIBO [15]. Patients with SIBO may exhibit no symptoms or present with various clinical manifestations. The most common symptoms include abdominal distension, excessive gas, flatulence, abdominal fullness, diffuse abdominal cramps, and altered bowel habits [14].

Reported signs are nonspecific, and no definitive symptom is specific to SIBO [15]. Some patients may experience weight loss and are at risk of undernutrition and malabsorption, mainly when diarrhea is present. Physical examinations typically do not show significant abnormalities [14]. Due to the wide range of reported signs, symptoms alone are insufficient for a SIBO diagnosis [16]. The gold standard diagnostic method involves culturing aspirates obtained endoscopically from the small intestine, usually from the distal duodenum [14]. Microbiological analysis of the small bowel can identify and quantify the responsible organisms. In healthy adults without gastrointestinal symptoms, bacterial counts in the small intestine rarely exceed 10^3 colony-forming units (CFU) per milliliter [15]. A SIBO diagnosis is usually made with a positive test result showing a threshold of $\geq 10^3$ CFU/mL [14, 16]. However, this diagnostic method has limitations such as invasiveness, cost, potential inability to detect certain bacterial strains, and the risk of sample contamination [16]. In clinical practice, breath testing is commonly used as a safe and non-invasive alternative [14]. Patients ingest a carbohydrate substrate before the test, which is metabolized by gut microbes, producing gases like hydrogen and methane. Glucose and lactulose are the most frequently used carbohydrates in breath tests [16]. Since human cells cannot produce hydrogen and methane, measuring these gases allows for insights into the intestinal microbiome [15]. These gases are absorbed into the bloodstream from the gut and exhaled through the lungs [16]. Elevated levels of these gases indicate increased fermentation of undigested sugars by small bowel microorganisms [14]. Notably, microbial culture and breath testing results may not always align, emphasizing the importance of considering the complete clinical context for accurate diagnosis [15, 16].

The management of SIBO should encompass three key aspects: identifying and addressing underlying causes, treating the overgrowth, and evaluating potential nutritional deficiencies [18]. Antibiotics play a central role in overgrowth therapy, with rifaximin commonly selected as a primary treatment option [19, 20]. This antibiotic offers the advantage of effectively targeting both aerobic and anaerobic bacteria and Gram-positive and Gram-negative bacteria [18]. Rifaximin positively affects the intestinal immune system and microbial virulence [20]. A systematic review with meta-analysis conducted by Gatta and Scarpignato concluded that rifaximin therapy is safe and clinically effective in eliminating SIBO [18]. Other antibiotics recommended for SIBO treatment include metronidazole, amoxicillin-clavulanic acid, ciprofloxacin, neomycin, norfloxacin, doxycycline, tetracycline, and trimethoprim-sulfamethoxazole [21]. Studies have shown a higher success rate with rifaximin than metronidazole [22]. The use of probiotics in SIBO treatment is also discussed. A meta-analysis and systematic review by Zhong et al. indicated that probiotics supplementation benefited individuals with SIBO, providing effective decontamination and relief from abdominal pain [23]. It is essential to consider that the efficacy of probiotic therapy in SIBO management varies depending on the specific strains used, as not all probiotics yield equal results [14]. However, the literature has reported that probiotics may also induce SIBO [21]. Further research is necessary to fully understand the role of probiotics in SIBO management [14].

PPIs and SIBO

PPI administration is known to reduce gastric acid secretion, potentially impacting the gut microbiome [24]. The connection between PPI therapy and SIBO was first explored in 2008, although findings in the literature remain contradictory [25, 26].

Weitsman et al. divided participants into two groups: 59 patients taking PPIs and 118 individuals not on PPIs. Samples were collected and analyzed for SIBO through endoscopy and duodenal fluid aspiration. The study showed a SIBO prevalence of 24.1% among PPI users and 28.8% among non-users ($p=0.591$), indicating no significant association between PPI use and SIBO prevalence [24]. In a separate study, Ratuapli et al. retrospectively assessed SIBO prevalence in 1191 patients, including 48% taking PPIs. Analysis of glucose hydrogen breath testing (GHBT) results showed no notable difference in SIBO rates between PPI users and non-users [27].

On the contrary, Jacobs and colleagues' study demonstrated that using PPIs independently raises the risk of SIBO. They found that patients on PPIs had 2.72 times higher odds of developing the disease compared to those not using PPIs [28]. In a separate study by Compare et al. on NERD patients, all participants initially tested negative for GHBT. However, after six months of esomeprazole treatment (20 milligrams twice daily) for 42 individuals, 11 participants showed a positive GHBT result ($p<0.05$). Additionally, those with a positive GHBT had significantly higher scores for bloating, flatulence, abdominal pain, and diarrhea compared to those with a negative GHBT. These findings suggest that prolonged PPI use may lead to the development of bowel symptoms and contribute to SIBO [29].

Furthermore, Lombardo et al. investigated SIBO prevalence among patients undergoing long-term PPI therapy. They studied 200 GERD patients on PPIs for a median of 36 months, 200 IBS patients not using PPIs for at least three years, and 50 healthy individuals abstaining from PPIs for a minimum of 10 years. GHBT results showed positivity in 50% of PPI users, 24.5% of IBS patients, and 6% of healthy controls. The difference in SIBO prevalence between PPI users and non-users was statistically significant ($p<0.001$) [30]. Meta-analyses, including studies by Su et al. and Lo et al., further support the association between PPI use and an increased risk of SIBO [26, 31].

The literature documents strategies for lowering the risk of SIBO in patients undergoing PPI treatment. Revaiah et al. found that incorporating prokinetics alongside PPIs may decrease the likelihood of SIBO occurrence [32].

Conclusions

On a global level, one of the most commonly prescribed drugs is PPIs. These medications are often overused, and some patients take them without clear medical necessity. While generally considered safe, PPIs, like all drugs, can have side effects. Research has primarily focused on the potential long-term adverse effects of these medications. Studies indicate that PPIs can disrupt the body's natural defense against bacteria by impacting gastric acid secretion. Research on the relationship between PPI use and SIBO has led to differing conclusions, but meta-analyses support a connection between PPI therapy and SIBO development. Patients with bacterial overgrowth may experience nonspecific symptoms, primarily affecting the gastrointestinal system. If SIBO is suspected based on clinical symptoms, appropriate tests like small intestine aspirate culture or a breath test should be conducted.

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