COMMENTARY article

Long-term use of proton pump inhibitors: Possible unwanted effects and mitigation strategies

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Abstract: Proton pump inhibitors are among the most widely prescribed and frequently used medications worldwide, primarily indicated for the management of acid-related gastrointestinal disorders such as gastroesophageal reflux disease, peptic ulcer disease, Zollinger–Ellison syndrome, and for Helicobacter pylori eradication regimens. Their widespread and frequently protracted usage, including over-the-counter intake, has been facilitated by their potent acid-suppressive action and short-term safety profile. However, during the past 20 years, concerns regarding potential adverse effects of long-term proton pump inhibitor therapy have emerged. These problems span multiple organ systems and include nutrient deficiencies, bone fractures, renal disease, infections, cardiovascular and neurological effects, and possible associations with malignancy. The mechanism of proton pump inhibitors is carefully examined in this study, along with the evidence supporting their long-term adverse effects, and possible ways to reduce risks without reducing therapeutic benefit.

Introduction

Proton pump inhibitors (PPIs) have revolutionized the management of gastric acid-related disorders since their introduction in the late 1980s. The gastric H^+/K^+-ATPase enzyme (the proton pump) in parietal cells is irreversibly inhibited by medications like omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole, which results in a significant and long-lasting suppression of gastric acid secretion [1]. Compared with earlier therapies such as histamine-2 receptor antagonists and antacids, PPIs provide superior acid control, improved mucosal healing, and better symptom relief [2-5]. PPIs are frequently prescribed for nonspecific gastrointestinal symptoms, dyspepsia, and stress ulcer prophylaxis in addition to approved indications [6, 7]. The availability of PPIs without a prescription in many nations has increased their use [8, 9]. Crucially, even though short-term PPI therapy (4-8 weeks) is usually safe and effective, a sizable percentage of patients continue treatment for months or years without obvious long-term benefits [10, 11]. According to epidemiological research, 40.0-60.0% of long-term PPI users might not have a good reason to keep taking their medication. Since acid suppression can disrupt regular physiological functions, such as nutrient absorption, gut microbiota balance, and host defense against infections, this trend has sparked worries about possible long-term negative effects [12, 13].

Mechanism of PPIs: PPIs are weak bases that enter the bloodstream through the small intestine and travel to the gastric parietal cells. They are protonated and transformed into active sulfonamide intermediates in the acidic environment of the secretory canaliculi [1]. Acid secretion is irreversibly inhibited as a result of these intermediates' covalent binding to cysteine residues on the H+/K+-ATPase [14]. Despite having relatively

short plasma half-lives, PPIs have a prolonged duration of action because they permanently block the proton pump, which suppresses acid secretion until new proton pumps are synthesized. It usually takes several days of continuous therapy to achieve maximum acid suppression [15, 16]. Even though this mechanism has therapeutic benefits, long-term suppression of gastric acid can interfere with normal protective and digestive processes, which is the biological basis for many of the long-term negative effects that have been suggested.

Pattern of long-term PPI use: A common definition of long-term PPI use is ongoing treatment for more than eight to twelve weeks. Chronic gastroesophageal reflux disease, Barrett's esophagus, preventing NSAID-induced ulcers in high-risk patients, and hypersecretory conditions are common causes of prolonged use. On the other hand, improper long-term use usually results from: Failure to reassess the ongoing need for therapy, continuation after hospital discharge for stress ulcer prophylaxis, empirical use for nonspecific dyspeptic symptoms, or patient-driven continuation due to fear of symptom recurrence.

Unwanted effect of PPI use: Gastric acid helps release vitamin B12 from the proteins in food. When acid production is suppressed for a long time, this process can be affected, which may lead to less absorption of protein-bound vitamin B12. Many observational studies have found a link between long-term use of PPIs for two years or more and vitamin B12 deficiency, especially in older adults [17]. Vitamin B12 deficiency can result in anemia, peripheral neuropathy, problems with thinking, and mental health issues. While the overall risk might seem low, it becomes an important concern for patients with other risk factors like malnutrition or advanced age [18]. Hypomagnesemia is a known but uncommon side effect of long-term PPI use. The suggested mechanism is that it disrupts magnesium absorption in the intestines through transient receptor potential melastatin channels. Severe hypomagnesemia can cause muscle cramps, seizures, irregular heartbeats, and low calcium levels [19]. Calcium absorption may be hampered by decreased stomach acidity, particularly for calcium carbonate, which requires an acidic environment. Since acid aids in the conversion of ferric iron to ferrous iron, it may also affect iron absorption. Especially in high-risk groups, these difficulties may indirectly result in anemia and problems with bone health [20]. It appears that gastric fundic polyps are caused by the stomach mucosa's cystic response to prolonged, substantial physiological alterations brought on by acid inhibition [21, 22]. A study including 599 individuals undergoing gastroscopy found that long-term PPI usage was associated with a fourfold increase in the incidence of fundic gastric polyps, although the risk of dysplasia was negligible [23]. PPI-induced acute interstitial pneumonia is uncommon, while more instances are being reported [24].

PPI use reduction strategy: On-demand treatment or a progressive dosage reduction may lessen rebound acid hypersecretion in individuals. In certain circumstances, switching to antacids or a histamine-2 receptor inhibitor can be explored. To avoid needless long-term usage, it is essential to inform patients about the recommended length, possible hazards, and a safe way to stop using PPIs. Prescribe PPIs at the lowest effective dose, use the shortest duration necessary, reassess indication periodically, especially after symptom resolution, monitor serum magnesium in long-term users, assess vitamin B12 levels in high-risk populations, ensure adequate calcium and vitamin D intake, particularly in elderly patients, consider weight reduction, elevation of the head of the bed, and avoidance of late meals.

Conclusion: Proton pump inhibitors are effective and generally safe medications when used appropriately. Long-term usage, however, has been linked to a number of possible adverse consequences that might impact several organ systems in humans. Although the exact cause of many consequences is yet unknown, these issues are clinically significant due to the extensive and sometimes needless long-term use of proton pump inhibitors. Therapeutic benefits can be maximized while damage is minimized with a balanced strategy that prioritizes acceptable indications, frequent evaluation, risk stratification, and patient education. Clinicians should strive for prudent, evidence-based use of proton pump inhibitors that is customized to each patient's requirements rather than completely avoiding them.

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