



# The appropriate use of proton pump inhibitors: Single centre experience

Proton pompa inhibitörlerini ne kadar doğru kullanıyoruz? Tek merkez deneyimi

Hasan YARDIMCI<sup>1</sup>, Orhan SEZGİN<sup>2</sup>,

Departments of <sup>1</sup>Internal Medicine and <sup>2</sup>Gastroenterology, Mersin University, School of Medicine, Mersin, İçel, Turkey

**ABSTRACT • Background and Aims:** Proton pump inhibitors are a class of pharmaceuticals that effectively inhibit gastric acid secretion. Their utilisation is increasing on a global scale. However, the use of proton pump inhibitors for off-label and unnecessary indications has also increased significantly. The aim of this study was to evaluate the appropriateness of proton pump inhibitor use. **Materials and Methods:** This study was conducted as a single-centre, cross-sectional observational study. Between 10 March 2022 and 10 April 2022, patients admitted to the Gastroenterology Clinic of Mersin University Faculty of Medicine were examined. The reasons for hospitalisation, demographic data, and pre- and post-hospitalisation drug use of the patients were recorded without the clinical team being aware of the study. **Results:** During the study period, 106 patients were hospitalised in the clinic, with 53% of the patients being male and the mean age being 65.8 years. The most common reasons for hospitalisation were gastrointestinal bleeding, acute pancreatitis and abdominal pain. While 45 (42%) of the hospitalised patients used proton pump inhibitors at home, 24 (53%) of them had appropriate indication. Of the 92 (86.7%) patients who used proton pump inhibitors during hospitalisation, 41 (44.6%) had appropriate indication. **Conclusion:** Proton pump inhibitors represent a class of pharmaceutical agents commonly prescribed for the management of acid-related pathologies, characterised by their favourable safety profile and broad accessibility. However, this widespread utilisation carries inherent risks, including the potential for inappropriate prescriptions. It is imperative to underscore the significance of potential drawbacks, such as adverse effects of a minor severity, financial implications and the necessity for polypharmacy, as highlighted in extant research.

**Key words:** Drug misuse, prophylaxis, proton pump inhibitors, GERD

**ÖZET • Giriş ve Amaç:** Proton pompa inhibitörleri, gastrik asit sekresyonunu etkili bir şekilde bloke eden ilaçlardır. Tüm dünyada kullanımları artmaktadır. Bununla birlikte, gereksiz ve endikasyon dışı proton pompa inhibitörü kullanımının da ciddi şekilde arttığı gözlemlenmektedir. Bu çalışmanın amacı, proton pompa inhibitörleri kullanımının uygunluğunu değerlendirmektir. **Gereç ve Yöntem:** Bu çalışma, tek merkezli ve kesitsel bir gözlem çalışması olarak gerçekleştirilmiştir. 10 Mart 2022- 10 Nisan 2022 tarihleri arasında Mersin Üniversitesi Tıp Fakültesi Gastroenteroloji Kliniğine yatırılan hastalar incelendi. Hastaların yatış nedenleri, demografik verileri, yatış öncesi ve sonrası ilaç kullanımları klinik ekibi çalışmanın farkında olmadan kaydedildi. **Bulgular:** Çalışma döneminde 106 hasta kliniğe yatırıldı. Hastaların %53'ü erkek olup, yaş ortalaması 65.8 yıl idi. Yatış nedenleri arasında en sık görülenler gastrointestinal sistem kanaması, akut pankreatit ve karın ağrısı etiyolojisi araştırılması olarak belirlendi. Yatan hastaların 45'i (%42) evde proton pompa inhibitörleri kullanırken bunların 24'ünde (%53) uygun endikasyon vardı. Hastanede yatış sırasında proton pompa inhibitörleri kullanan 92 (%86.7) hastanın ise 41'inde (%44.6) proton pompa inhibitörleri kullanımı endikasyona uygundu. **Sonuç:** Proton pompa inhibitörleri asit ile ilişkili hastalıkların tedavisinde temel ilaçlar arasında yer almakta ve düşük yan etki profilleri sayesinde yaygın olarak kullanılmaktadır. Ancak, bu durum gereksiz kullanım riskini de beraberinde getirmektedir. Az da olsa ciddi yan etkiler, mali yük ve polifarmasi gibi dezavantajların önemi çalışmalar ile vurgulanmalıdır.

**Anahtar kelimeler:** Uygunsuz ilaç kullanımı, profilaksi, proton pompası inhibitörleri, GERH

## INTRODUCTION

Proton pump inhibitors (PPIs) are pharmaceutical agents that irreversibly bind to the hydrogen-potassium ATPase (H/K ATPase), pump on the lu-

minal surface of the parietal cell membrane in the stomach, effectively inhibiting gastric acid secretion. PPIs are currently the most potent inhibitors

of gastric acid secretion available (1). Gastric acid secretion is a multifactorial and complex process regulated by at least three different stimuli acting on the parietal cell; the paracrine effects of gastrin and histamine and the effects of postganglionic muscarinic acetylcholine. Unlike anticholinergics and histamine 2-receptor antagonists, PPIs inhibit the final common pathway of acid secretion (H/K ATPase), regardless of the stimulus triggering parietal cell activation (1). PPIs are most effective when administered before the first meal of the day, as the concentration of H-K-ATPase in the parietal cells peaks following a period of prolonged fasting. In most individuals, a single daily dose is sufficient to achieve the desired level of acid inhibition. If further inhibition is required, a second dose can be administered before dinner (2). As of 2015, the United States Food and Drug Administration (FDA) had approved six PPIs: omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, and rabeprazole (3).

PPIs are indicated for the treatment of conditions such as peptic ulcer disease, upper gastrointestinal tract (GI) bleeding, *Helicobacter pylori* eradication, the prevention of gastro-duodenal ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs), Zollinger-Ellison Syndrome, gastroesophageal reflux disease (GERD), and functional dyspepsia. In patients at high risk of gastrointestinal bleeding, gastroprotection is recommended when using NSAIDs or aspirin. According to the American Gastroenterological Association (AGA) guidelines, individuals over the age of 60, those with severe medical comorbidities, those taking multiple NSAIDs or aspirin, or those on antithrombotics or oral corticosteroids are considered to be at high risk (4,5).

A significant rise in the utilization of proton pump inhibitors (PPIs) has been observed in many countries in recent years. This increase is largely attributed to the widespread use of PPIs in the

treatment of dyspepsia and the prevention of gastrointestinal bleeding in patients on anti-platelet therapy or non-steroidal anti-inflammatory drugs (NSAIDs). Additionally, the perception that PPIs have minimal side effects has contributed to their growing use (6). However, despite the expanding indications for PPI use, numerous studies have highlighted a high prevalence of inappropriate PPI prescriptions. This study aimed to evaluate the extent to which PPIs are prescribed appropriately according to their indications, both in outpatient settings and among hospitalized patients.

## MATERIALS and METHODS

Following approval from the ethics committee (Approval by Mersin University Faculty of Medicine Ethics Committee dated 20.03.2024 and numbered 2024/301 is available), the study population included all patients hospitalized in the Gastroenterology Clinic of Mersin University Faculty of Medicine between March 10, 2022, and April 10, 2022. Data on reasons for hospitalization, comorbidities, demographic information, medications used prior to hospitalization, and treatments administered during hospitalization were recorded by a physician external to the Gastroenterology clinic without the knowledge of the clinical team.

Indications for the use of PPIs included peptic ulcer disease, gastrointestinal bleeding, *Helicobacter pylori* eradication, Zollinger-Ellison syndrome, gastroesophageal reflux disease (both erosive esophagitis and non-erosive reflux disease), functional dyspepsia, and gastroprotection for NSAID use in patients at high risk of gastrointestinal bleeding, as well as for patients using aspirin or antiplatelet therapy.

## RESULTS

During the study period, 106 patients were admitted to the clinic. Of these, 56 (53%) were male

and 50 (47%) were female, with a mean age of 65.8 years. The three most common reasons for hospitalisation were search for gastrointestinal bleeding, acute pancreatitis and abdominal pain etiology, respectively. The indications and frequencies of hospitalisation, as well as the rates of PPI use in hospital and at home in patients hospitalised with these indications, are demonstrated in Table 1.

When evaluating the appropriateness of PPI use, it was found that among the 45 patients (42.2%) who used PPIs at home, 24 (53.3%) had an appropriate indication for their use, while 21 (46.6%) were found to have used them inappropriately. In the hospital, 41 patients (44.6%) had an indication for PPI use, but of the 92 patients (86.7%) using PPIs, a total of 51 (55.4%) received treatment in the absence of a valid indication. The mean age of patients who used PPI inappropriately was 64.25 years.

In this study, 27 patients hospitalised with gastrointestinal bleeding, 17 (62,9%) were found not to be receiving PPI at home. Of these 17 patients, 6 (35.3%) had an indication for PPI use at home.

Of the 51 patients who were hospitalised and received PPIs for inappropriate indications, 30 (58.8%) experienced abdominal pain irrespective of the underlying cause.

## DISCUSSION

Proton pump inhibitors (PPIs) are currently the most effective pharmaceutical agents for inhibiting the secretion of hydrochloric acid. They have supplanted mainly histamine 2 receptor antagonists for many clinical indications, including functional dyspepsia, gastroesophageal reflux disease (GERD), and drug-induced upper gastrointestinal injury. The high prevalence of acid-related upper gastrointestinal diseases, combined with the efficacy, tolerability, and cost-effectiveness of PPIs, has significantly increased their utilization in both hospital and outpatient settings. Today, PPIs are among the ten most widely used medications globally (5).

A growing body of research is examining both the appropriate and inappropriate use of PPIs, which are among the most commonly prescribed medications worldwide (7). Notably, a substantial proportion of PPI users in Western populations need more valid indications for their use. For instance, a study conducted in Greece analyzed discharge prescriptions for 1693 adult patients admitted to a hospital in Thessaloniki between July 2005 and December 2006. The results showed that 430 patients (25.4%) were prescribed PPIs, but only 81 patients

**Table 1** Indications for hospitalization and PPI use rates at home and in hospital among patients included in the study

Diagnosics	Number of Patients n (%)	Use of PPI at Home n (%)	Use of PPI in Hospital n (%)
Gastrointestinal bleeding	27 (25.5%)	10 (37%)	27 (100%)
Acute pancreatitis	15 (14.2%)	8 (53.3%)	14 (93.3%)
Etiology of abdominal pain	12 (11.3%)	3 (25%)	12 (100%)
IBD	11 (10.4%)	5 (45.4%)	7 (63.6%)
Cholelithiasis	8 (7.5%)	4 (50%)	7 (87.5%)
Cholangitis	5 (4.7%)	3 (60%)	5 (100%)
Others	28 (26.4%)	12 (42.8%)	20 (71.4%)
Total	106	45	92

IBD: Inflammatory bowel diseases; PPI: Proton pump inhibitor.

(18.8%) had appropriate indications (8). Similarly, a study by Walker and McDonald in 2001 found that 67% of outpatients in a district general hospital in the United Kingdom were prescribed PPIs for reasons not supported by consensus guidelines, while 51% of inpatients received PPIs without any valid indication (9). In our study, it was observed that 55.4% of hospitalised patients received PPIs with inappropriate indications. In Ireland, a study by Sebastian et al. evaluated the treatment of all patients in a tertiary care hospital on a randomly selected day, revealing that 87 patients (32%) were on PPIs, with no valid indication identified in 63% of cases. The only factor associated with inappropriate prescribing was increasing age [10]. In our study, the mean age of patients who were inappropriately administered PPIs was almost equivalent to the mean age of all inpatients. Moreover, a separate study by Parente et al. analyzed patients hospitalized for one month in a university hospital in Northern Italy, finding that 46.8% of the 799 hospitalized patients received acid-suppressant treatment. Ranitidine was the most commonly used medication, accounting for 44.4% of cases, followed by pantoprazole (31.8%) and omeprazole (23.0%). Indications for use included 60.4% for stress ulcer prophylaxis and prevention of NSAID-induced ulcers. Alarming, 68% of treatments did not follow appropriate indications determined by consensus guidelines. Furthermore, of the patients who received unnecessary prophylactic therapy during hospitalization, 56.4% were discharged on this treatment, and 46% continued to receive inappropriate treatment three months later (11). In the present study, the most common reasons for the use of PPI among hospitalised patients were examined. The results indicated that 30 patients (32.6%) were given PPI with an inappropriate indication due to abdominal pain, while 27 patients (29.3%) were given PPI with an appropriate indication due to gastrointestinal bleeding. The study revealed that 47% of inpatients used inappropriate

PPI at home, while 53% used inappropriate PPI during hospitalisation.

Long-term and frequent use of proton pump inhibitors (PPIs) is associated with an increased risk of adverse effects (12). In addition to well-documented side effects, prolonged PPI use has been linked to neuroendocrine cell hyperplasia and tumors in the stomach, osteoporosis, pneumonia, hypochlorhydria-atrophic gastritis in patients with *Helicobacter pylori*, and potentially gastric cancer. However, the strength of the evidence supporting these associations remains unclear (13). Therefore, treatment indications should be clearly defined. Concurrently, there is a necessity to engage in more frequent discourse surrounding the proven serious side effects of PPIs (e.g. enteric infections, community-acquired pneumonia, hip fracture, hypomagnesaemia, chronic renal failure) (14) to dispel the pervasive misconception that PPIs are relatively 'innocent' drugs in the eyes of physicians.

In outpatient settings, it is essential to establish specific indications for treatment, inform patients about potential side effects and appropriate dosages, determine a treatment duration, encourage follow-up, and ensure that the drug is gradually discontinued through dose reduction. In the context of antithrombotics, NSAIDs, and corticosteroids, careful patient selection for prophylaxis is crucial. Factors leading to unnecessary PPI prescriptions include; the use of these medications for gastrointestinal symptoms that lack definitive diagnoses, their relatively benign side effect profiles, and patients' frequent requests for repeat prescriptions (15). In the present study, 30 patients were hospitalised with an aetiology of abdominal pain and treated without a definitive indication for PPI. This finding indicates that the utilisation of PPIs for gastrointestinal symptoms without a definitive diagnosis, in conjunction with their relatively innocuous side effect profile, exerts a significant influence on the physicians at our clinic.

The risk of acid hypersecretion and rebound effects following discontinuation may further contribute to patients' reluctance to stop treatment (16). Therefore, it is imperative to taper off the medication gradually. As proposed by Nardino et al., it is essential to initiate treatment based on specific indications for hospitalized patients, prioritize prophylaxis in selected individuals for stress ulcer prevention, and either discontinue prophylaxis at discharge or arrange a follow-up visit, even if the indication persists (17). The initiation of PPIs in elderly patients, particularly those who are frail, may serve to protect physicians from potential complications; however, failure to discontinue treatment started during hospitalization can lead to inappropriate ongoing use [18,19]. The mean age of inappropriately prescribed PPIs was 64.25 years in our study, which suggests that physicians in our clinic are more protective in elderly and frail patients.

The findings of the present study are consistent with those of other studies documented in the extant literature. The fact that the present study was conducted in a double-blind manner, especially in the gastroenterology clinic of a tertiary healthcare institution, demonstrated that even physicians who are experts on the subject make inappropriate PPI use at a very high rate. It is recommended

that further studies of this nature be supported in order to increase awareness. The limitations of our study include the inclusion of data from only one centre, the relatively small sample size, and the evaluation of only patients hospitalised in the gastroenterology clinic.

It is also essential to consider the economic burden associated with PPI treatment. Although this study did not conduct an economic evaluation, it is clear that unnecessary medication use incurs additional financial costs that should be avoided. Numerous factors contribute to the excessive utilization of PPIs by both patients and physicians. To alleviate the financial burden, reduce the adverse effects associated with these medications, and prevent decreased compliance with other treatments due to polypharmacy, PPIs should be used only for appropriate indications and for optimal duration.

**Ethics:** *This study was approved by Mersin University Noninterventional Clinical Research Ethical Committee (Decision no: 301/2024, Date: 20.03.2024).*

**Conflict of interest:** *All authors declare no conflict of interest regarding this article.*

**Finance:** *All authors declare that no financial support regarding this article.*

## REFERENCES

1. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for the treatment of erosive gastroesophageal reflux disease: A double-blind, randomized clinical trial. *Am J Gastroenterology*. 2000;95(8):1894-9.
2. Wolfe M, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology*. 2000;118(2 Suppl 1):S9-31.
3. Shi S, Klotz U. Proton pump inhibitors: an update of their clinical use and pharmacokinetics. *Eur J Clin Pharmacol*. 2008;64(10):935-51.
4. Lassen AT. Acid-related disorders and use of antisecretory medication. *Dan Med Bull*. 2007;54(1):18-30.
5. Chiba N, De Gara C, Wilkinson J, Hunt R. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. *Gastroenterology*. 1997;112(6):1798-810.
6. Hussain S, Stefan M, Visintainer P, Rothberg M. Why Do Physicians Prescribe Stress Ulcer Prophylaxis to General Medicine Patients?. *Southern Medical Journal*. 2010;103(11):1103-10.
7. Książczyńska D, Szeląg A, Paradowski L. Overuse of proton pump inhibitors. *Pol Arch Med Wewn*. 2015;125(4):289-98.
8. Ntaios G, Chatzinikolaou A, Kaiafa G, Savopoulos C, Hatzitolios A, Karamitsos D. Evaluation of use of proton pump inhibitors in Greece. *Eur J Intern Med*. 2009;20(2):171-3.

9. Walker NM, McDonald J. An evaluation of the use of proton pump inhibitors. *Pharm World Sci*. 2001 Jun;23(3):116-7.
10. Sebastian S, Kernan N, Qasim A, O'Morain C, Buckley M. Appropriateness of gastric antisecretory therapy in hospital practice. *Ir J Med Sci*. 2003;172(3):115-7.
11. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment Pharmacol Ther*. 2003;17(12):1503-6.
12. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. *Am J Manag Care*. 2010;16(9):e228-34.
13. Sheen E, Triadafilopoulos G. Adverse Effects of Long-Term Proton Pump Inhibitor Therapy. *Dig Dis Sci*. 2011;56(4):931-50.
14. Savarino V, Dulbecco P, Savarino E. Are proton pump inhibitors really so dangerous? *Dig Liver Dis*. 2016;48(8):851-9.
15. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. *Aliment Pharmacol Ther*. 2005;21(2):149-54.
16. Metz DC, Pilmer BL, Han C, Perez MC. Withdrawing PPI therapy after healing esophagitis does not worsen symptoms or cause persistent hypergastrinemia: analysis of dexlansoprazole MR clinical trial data. *Am J Gastroenterol*. 2011;106(11):1953-60.
17. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients<sup>1</sup>. *Am J Gastroenterology*. 2000;95(11):3118-22.
18. Eid SM, Boueiz A, Paranji S, Mativo C, BA RL, Abougergi MS. Patterns and Predictors of Proton Pump Inhibitor Overuse among Academic and Non-Academic Hospitalists. *Intern Med*. 2010;49(23):2561-8.
19. Heidelbaugh JJ, Inadomi JM. Magnitude and Economic Impact of Inappropriate Use of Stress Ulcer Prophylaxis in Non-ICU Hospitalized Patients. *Am J Gastroenterology*. 2006;101(10):2200-5.