Vol. 5 No. 1 (2026)

Pakistan Journal of Medical & Cardiological Review

https://pakjmcr.com/index.php/1/about

Online ISSN 3007-2387

Print ISSN 3007-2379

Clinical Outcomes and Adverse Effects of Long-Term Pantoprazole Therapy in Patients with GERD

Akhtar Ali Khan
MBBS, Bannu Medical College. Email: draakyousafzai@gmail.com & 0009-0003-3709-4768

Sheraz Khan
MBBS (China), MPH KMU Peshawar Campus Email sherazkhangmu@gmail.com

Muhammad Nouman Iqbal*
State Life Health Insurance (Sehat Card) Email: noumaniqbal0213@gmail.com

Nauman Khan Bakht
Gajju Khan Medical College,Swabi , Pakistan.
Email: naumankhanbakht123@gmail.com

Awais Ahmed Uttra
Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, 90110, Hat Yai, Thailand Email: awaisutra@yahoo.com

Afnan Ali Shah
House Officer,DHQ Medical Teaching Institute, Bannu
Email: afnanalishah88@gmail.com &cOrcid:0009-0000-8648-6504

Muhammad Yasir Khan
Nowshera Medical College Nowshera QHAMC Nowshera
Email: khanmuhammadyasir016@gmail.com

Author Details

Keywords: Gastroesophageal Reflux Disease; Pantoprazole; Proton Pump Inhibitors; Long Term Therapy; Adverse Effects; Hypomagnesemia; Vitamin B12 Deficiency.

Received on 25 June 2025
Accepted on 10 July 2025
Published on 16 July 2025

Corresponding E-mail & Author*:

Muhammad Nouman Iqbal*
State Life Health Insurance (Sehat Card) Email: noumaniqbal0213@gmail.com

Abstract

Introduction: Gastroesophageal reflux disease (GERD) is a persistent illness that is often treated with proton pump inhibitors in the long run. Pantoprazole is used extensively as an effective, safe therapy, but there are still worries about the adverse effects of long-term treatment. The goal of this study was to compare clinical outcomes and adverse experiences of protracted pantoprazole treatment in the GERD patients.

Methodology: The study was a prospective observational cohort study that was carried out during a period of twelve months. Two hundred and twenty patients who had received at least six months of pantoprazole therapy were recruited with 208 of the patients following the regimen. Symptom scores and endoscopic findings when applicable were used to measure the clinical outcomes. Laboratory indices such as serum magnesium, vitamin B12 and creatinine were assessed at the baseline and after six

months. Paired t-test, Chi-square test, and multivariate logistic regression were utilized and $p \leq 0.05$ was regarded as statistically significant.
Results: The mean GERD symptom score was significantly reduced (7.8 ± 1.6 to 2.9 ± 1.3, $p < 0.001$) and 80.8% of patients had sustained symptom control. The recovery was observed on the mucosal in 80.4 percent of patients considered. All in all, 27.9% had developed one or more adverse effects, most of which were hypomagnesemia (11.5%), and vitamin B12 deficiency (9.1%). The independent predictors of adverse effect were: therapy duration more than 12 months (AOR 2.41, $p = 0.004$), and age more than 50 years (AOR 1.89, $p = 0.041$).
Conclusion: Pantoprazole proved to be an effective long term symptom controlling treatment on GERD but long term treatment had some quantifiable side effects and must be closely monitored and reassessed periodically.

Introduction

Gastroesophageal reflux disease (GERD) is a chronic, recurrent, condition which is associated with the backward flow of the gastrointestinal contents in the esophagus resulting in irritating symptoms and/or complications. It is among the prevalent gastrointestinal disorders in the world with an increasing prevalence in the Western and Asian societies [1]. The clinical manifestation is between the common symptoms of heartburn and regurgitation to the extra-esophageal symptoms, including chronic cough, laryngitis, and asthma-like symptoms. When acid is constantly exposed, it leads to erosive esophagitis, peptic strictures, and Barretts esophagus that can lead to the development of esophageal adenocarcinoma [2]. As a chronic condition, GERD often necessitates chronic medical treatment to bring about the symptomatic control and healing of the mucosa.

The use of acid pump inhibitors (PPIs) has led to a paradigm shift in the treatment of disorders associated with acid secretion in the stomach with the addition of potent and sustained reduction of acid secretion in the stomach. Pantoprazole is one of them because it is effective, with a good pharmacokinetic profile, and relatively fewer risks of drug-4 interactions [2, 3]. Pantoprazole permanently insensitizes the enzyme system of H +/K + -ATPase of the gastric parietal cells, thus inhibiting basal and stimulated secretion of gastric acid. It is typically used in the treatment of erosive esophagitis, as a prophylaxis of NSAID-induced gastropathy, Zollinger-Ellison syndrome, and in the management of GERD as maintenance therapy. Within clinical practice, most patients continue to be placed on pantoprazole over prolonged periods which is likely to be longer than the treatment period initially prescribed [4, 5].

Although the short-term use of PPI therapy can be said to be safe and best, there has been an alarm on the long term use of these agents. The chronic acid inhibition can be changing the gastric physiology, intestinal microbiota and nutrient absorption [6]. The adverse effects of prolonged PPI use have been proposed to include hypomagnesemia, vitamin B12 deficiency, iron malabsorption, an increased risk of enteric infections (including Clostridioides difficile), community-acquired pneumonia, and possible renal complications including acute interstitial nephritis and chronic kidney disease [7, 8]. Also, the extent of potential association with fractures associated with osteoporosis, dementia, and cardiovascular events is still debated, but the causal relation in many of these is still uncertain [9, 10].

Nevertheless, long-term use of pantoprazole regardless of frequent review of indication or dose remains extensively prescribed. Over-the-counter supplies and the trend of empirical prescribing are common clinical practices in most of the clinical environments, especially in the low and middle-income nations, leading to prolonged use without systematic observation. Furthermore, a great part of the existing evidence on the safety of long-term use of PPI is based on non-homogeneous populations, retrospective, or a study of PPI as a drug group, but not on the specific medication of

pantoprazole. Reported outcomes are not consistent and conclusive findings are often restricted by confounding factors.

Clinical advantages and the possible side effects of the treatment with pantoprazole used long-term among patients with GERD are crucial to the successful management of the condition, as well as to reduce unnecessary exposure and to inform the evidence-based prescribing. Nonetheless, long-term clinical outcome and safety profile of pantoprazole are not especially assessed in studies to date, especially in the specific GERD groups, especially in regional groups where the practice of prescription and comorbidity prevalence may vary.

Hence, the given study is expected to assess the clinical outcomes and adverse events related to the long-term use of panto-razole among patients with GERD and determine the effectiveness of this medication in the context of the long-term control of the symptoms and the frequency and pattern of the adverse events within the context of the long-term use of this medication.

Methodology

Study Design and Setting

This study was designed as a prospective observational cohort study to assess the clinical outcomes and adverse effects of long-term pantoprazole therapy in patients with gastroesophageal reflux disease (GERD). The study was conducted in the Department of Gastroenterology and General Medicine at DHQ Hospital Bannu, a tertiary care teaching hospital affiliated with Bannu Medical College, Bannu, Pakistan, over a twelve-month period from February 2025 to January 2026.

Study Population

The population of the study included adult patients with the diagnosis of GERD and with a minimum of six consecutive months of taking pantoprazole before their inclusion and scheduled to continue with the therapy as the maintenance treatment. The diagnosis of GERD was made by using clinical manifestations and endoscopic results when available and response to acid suppression treatment according to conventional clinical guidelines.

Patients of either gender between the ages of 18 and 70 were included. Patients with a history of gastric or esophageal malignancy, prior upper gastrointestinal surgery, At least stage 4 of chronic renal disease and chronic liver disease, pregnancy, concurrent use of H2 receptor antagonists or other proton pump inhibitors, and those receiving medications known to significantly interfere with magnesium or vitamin B12 levels were excluded from the study.

Sample Size Calculation

The single proportion of the population formula was utilized to figure out the sample size.

$$n = Z^2 p (1 - p) / d^2$$

In this formula, n represented the required sample size, Z was the standard normal deviate at 95% confidence level (1.96), p was the anticipated proportion of adverse effects among long-term pantoprazole users, and d was the error margin. Based on previously published literature reporting an approximate 25% prevalence of clinically relevant adverse effects with prolonged PPI use, p was taken as 0.25 [11]. To achieve sufficient precision, the margin of error was set as 0.06.

Replacement of these values in the formula gave the minimum sample size of 200 participants. The initial calculated sample size was 220 patients after a 10 percent adjustment in consideration of patients who might drop out and/or fail to follow up on the study.

Sampling Technique
A non-probability consecutive sampling was used. Every eligible patient who came to the outpatient department or was admitted to the medical wards in the period of the study but met the criteria of admission to the study were approached and enrolled after giving informed consent until the desired sample size was realized.

Data Collection Procedure
Baseline demographic and clinical data were documented using a structured proforma after the informed consent was provided in writing. Data was recorded in terms of the age, gender, body mass index, GERD symptom duration, comorbidity, lifestyle behavior including smoking and alcohol consumption, and the period and dosage of pantoprazole use.
The assessments of clinical outcomes were in the form of symptom control, symptom recurrence, dose escalation requirement, and endoscopic healing where possible. Examining the symptom severity was done through a validated GERD symptom scoring system during the baseline and the follow up visits.
The negative outcomes were evaluated by clinical assessment and laboratory tests. The laboratory parameters were serum magnesium levels, vitamin B12 levels, hemoglobin, serum creatinine, and bone mineral density in identified high-risk patients. The patients were trailed after every three months up to a period of six months. The new symptoms that are suggestive of infection, renal impairment or metabolic abnormality were recorded.

Study Variables
Sustained clinical improvement of the GERD symptoms and adverse effects associated with the long-term use of pantoprazole were the key outcome variables. The secondary outcome variables were the changes in laboratory parameters and relationships between the duration of therapy and adverse events. Independent variables were age, gender, length of therapy, comorbid conditions and lifestyle.

Statistical Analysis
Statistical Package of Social Sciences (SPSS) version 26.0 was used to enter and analyze the data. Quantitative variables age, length of treatment and variables within laboratory were expressed as mean + standard deviation or median with interquartile range based on the distribution of data. Frequencies and percentages were used to describe such qualitative variables as gender, adverse effects, and resolution of symptoms.
Shapiro-Wilk test was used to test the normality of data. To compare the continuous variables before and after follow-ups, paired t-test was used to compare normally distributed data whereas Wilcoxon signed-rank test was used to compare non-normally distributed data. The Chi-square test or Fisher's exact where necessary were used to test the association between categorical variables. Continuous variables comparison between groups was done by the use of independent sample t-test or Mann Whitney U test.
Multivariate logistic regression analysis was conducted to determine independent predictors of adverse effects correcting the possible confounders (age, gender, duration of therapy, and comorbidities). The p-value of less than 0.05 was taken as statistically significant.

Ethical Considerations
The Institutional Ethical Review Committee of Bannu Medical College reviewed and gave their approval to the study protocol before its start. The study was conducted at DHQ Hospital Bannu. All participants gave informed consent in writing. The study was carried out in a confidential manner, and the participants were assured that they have

the right to withdraw from the study at any time without any impact on their medical care.

Results

The number of patients enrolled in the study was 220. The 12 patients were lost in the course of follow-up leaving the study with 208 patients who completed and were included in the final analysis. The average age of the participants was 45.8 ± 12.6 years. Most patients (58.2%) belonged to the age group of 31-50 years. Males (56.7% and females (43.3%) included 118 and 90 individuals, respectively, as the study population. The mean duration of GERD symptoms prior to enrollment was 3.4 ± 1.8 years. The median duration of pantoprazole therapy before study entry was 8 months (IQR: 6–14 months). The most common comorbidities observed were hypertension in 62 (29.8%) patients and type 2 diabetes mellitus in 48 (23.1%) patients.

The average GERD symptom duration before enrolment was 3.4 ± 1.8 years of duration. The median length of time on the pantoprazole therapy prior to study entry was 8 months (IQR: 6-14 months). The reason was that the most prevalent comorbidities were hypertension in 62 (29.8%) patients and type 2 diabetes mellitus in 48 (23.1%) patients.

Table 1: Baseline Demographic and Clinical Characteristics (n = 208)

Variable	**Frequency (n)**	**Percentage (%)**
Age Group (years)		
18–30	32	15.4
31–50	121	58.2
51–70	55	26.4
Gender		
Male	118	56.7
Female	90	43.3
Comorbidities		
Hypertension	62	29.8
Diabetes Mellitus	48	23.1
Obesity (BMI ≥30)	54	26.0
Smokers	46	22.1

The baseline mean score of GERD symptoms was 7.8 with a standard deviation of 1.6. Six months of further treatment with pantoprazole observed a significant reduction in the average score of symptoms to 2.9 ± 1.3. As the data on the symptom score was normally distributed (Shapiro Wilk $p>0.05$), a paired t-test was used. The decrease in the symptom score was also significant ($t = 32.14$, $p < 0.001$).

Prolonged control of symptoms in 168 (80.8%) of the patients was attained. Symptom reoccurrence with a need to increase the dose was seen in 26 (12.5%) patients and ongoing moderate symptoms despite treatment were experienced by 14 (6.7%) patients. Among 92 patients who underwent baseline and follow-up endoscopy, mucosal healing was documented in 74 (80.4%) patients.

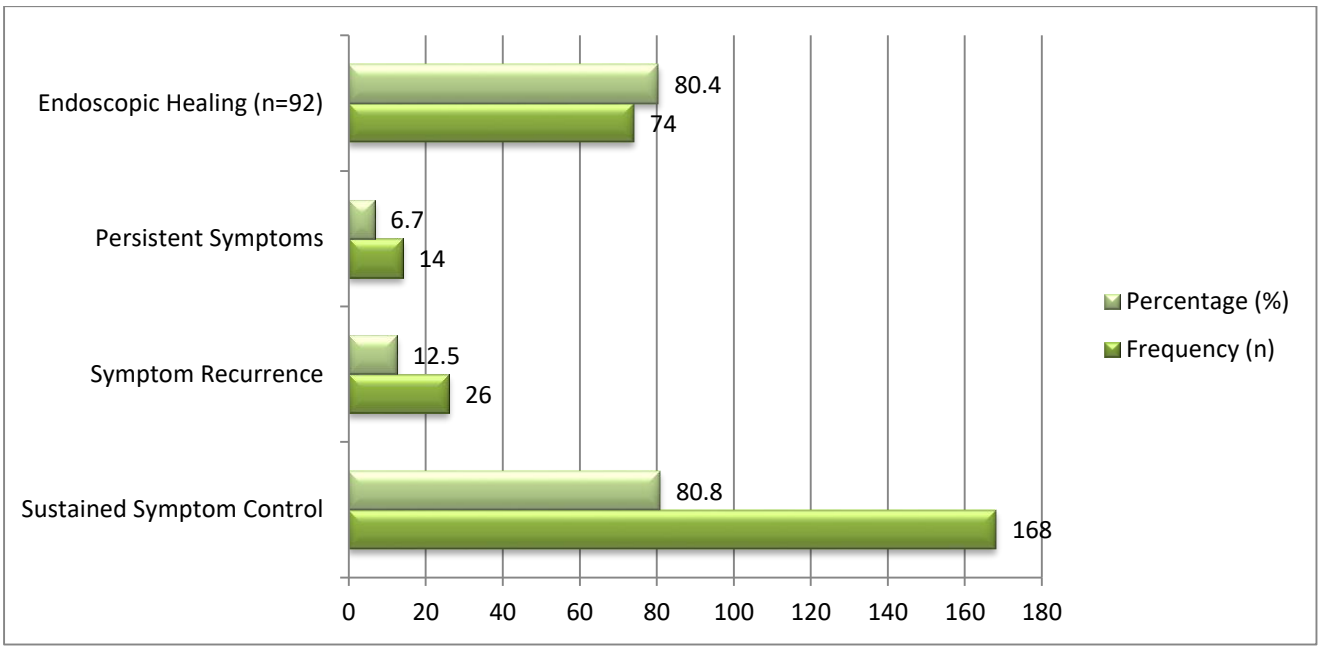

Figure 1: Clinical Outcomes After Six Months of Follow-Up (n = 208)

The levels of serum magnesium were found to be reduced mildly yet significantly between the baseline (1.92 = 0.21 mg/dl) and follow-up (1.81 = 0.24 mg/dl). As data were normally distributed, paired t-test was applied and demonstrated statistical significance ($t = 5.84$, $p < 0.001$). Vitamin B12 levels decreased from a baseline mean of 412 ± 136 pg/mL to 356 ± 128 pg/mL at follow-up. This reduction was statistically significant (paired t-test, $t = 6.11$, $p < 0.001$).

Serum creatinine showed no statistically significant change (baseline 0.93 ± 0.18 mg/dL vs follow-up 0.96 ± 0.21 mg/dL; paired t-test, $p = 0.082$).

Table 2: Comparison of Laboratory Parameters Before and After Therapy (n = 208)

Parameter	Baseline (Mean ± SD)	Follow-up (Mean ± SD)	Test Applied	p-value
Serum Magnesium (mg/dL)	1.92 ± 0.21	1.81 ± 0.24	Paired t-test	<0.001
Vitamin B12 (pg/mL)	412 ± 136	356 ± 128	Paired t-test	<0.001
Serum Creatinine (mg/dL)	0.93 ± 0.18	0.96 ± 0.21	Paired t-test	0.082

Overall, 58 (27.9%) patients developed at least one clinically relevant adverse effect during follow-up. Hypomagnesemia was the most frequent adverse effect reported as it was seen in 24 (11.5%) patients. Vitamin B12 deficiency was identified in 19 (9.1%) patients. Enteric infections occurred in 9 (4.3%) patients, while 6 (2.9%) patients developed acute interstitial nephritis.

The association between duration of pantoprazole therapy (>12 months vs ≤12 months) and adverse effects was analyzed using the Chi-square test. A significantly higher frequency of adverse effects was observed in patients with therapy duration >12 months ($\chi^2 = 8.72$, $p = 0.003$).

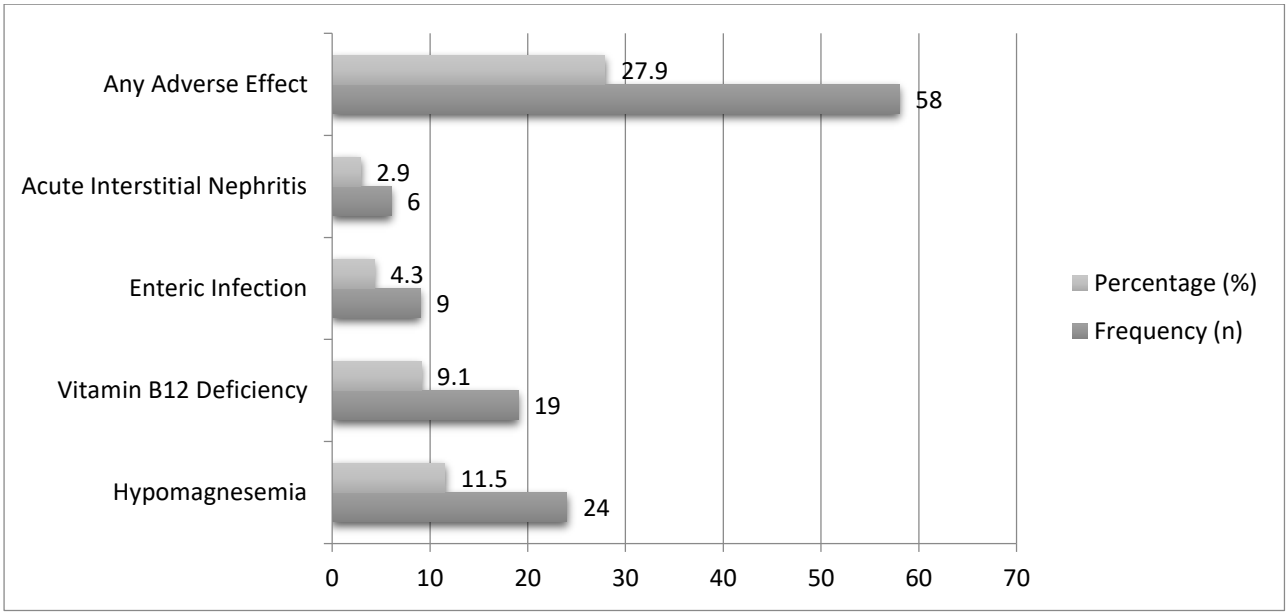

Figure 2: Distribution of Adverse Effects (n = 208)

Chi-square analysis showed a statistically significant association between age >50 years and development of adverse effects ($\chi^2 = 6.41$, $p = 0.011$). No statistically significant association was found between gender and adverse effects ($\chi^2 = 1.12$, $p = 0.289$).

Patients with diabetes mellitus had a higher frequency of adverse effects compared to non-diabetics (37.5% vs 24.1%), and this association was statistically significant ($\chi^2 = 4.38$, $p = 0.036$).

Table 3: Association of Selected Variables with Adverse Effects

Variable	Adverse Effects Present n (%)	Adverse Effects Absent n (%)	p-value
Age >50 years	24 (41.4%)	31 (20.7%)	0.011
Male Gender	35 (30.8%)	83 (55.3%)	0.289
Diabetes Mellitus	18 (37.5%)	30 (20.0%)	0.036
Therapy >12 months	29 (45.3%)	35 (23.3%)	0.003

Multivariate logistic regression was performed to identify independent predictors of adverse effects. The variables used in the model were age above 50 years, diabetes mellitus, therapy more than 12 months and obesity.

Duration of therapy >12 months emerged as an independent predictor of adverse effects (Adjusted Odds Ratio [AOR] 2.41, 95% CI: 1.32–4.38, p = 0.004). Age above 50 years was also found statistically significant (AOR 1.89, 95% CI: 1 02-3.49, p = 0.041). The borderline significance of diabetes mellitus did not affect the results of the adjustment (AOR 1.67, 95% CI: 0.92-3.01, p = 0.084).

The **Table 4: Multivariate Logistic Regression for Predictors of Adverse Effects**

Variable	Adjusted Odds Ratio (AOR)	95% CI	p-value
Age >50 years	1.89	1.02–3.49	0.041
Diabetes Mellitus	1.67	0.92–3.01	0.084
Therapy >12 months	2.41	1.32–4.38	0.004
Obesity	1.28	0.71–2.29	0.398

Discussion

The current research evidence revealed that prolonged treatment with pantoprazole was very effective in the attainment of durable symptom management in GERD patients with over four-fifths of the cases exhibiting critical clinical outcomes. There was

statistically significant and significant improvement in the symptoms of GERD scores at the end of six months, and significant endoscopic mucosal healing rates. Nonetheless, almost a third of patients experienced at least one of the clinically significant adverse effects that occurred in the course of follow-up with hypomagnesemia and vitamin B12 deficiency being the most common ones. The factors that were found to be significant predictors of adverse events were increasing age and therapy duration over twelve months.

The confirmed rate of the sustained symptom control corresponds to the already proven efficacy of proton pump inhibitors in the maintenance of GERD remission [11]. Symptom control rates of 70-85 have always been reported in large-scale clinical trials and long-term maintenance studies, and this is consistent with the 80.8% rate in this study [12]. Equally, mucosal healing reported in the past endoscopic follow up studies have ranged between 75 and 90, which supports the therapeutic efficacy as observable in the current studies [13].

The total proportion of adverse effects (27.9%), in this cohort is within the range of those that are found in observational studies that consider prolonged exposure to PPI. A number of population-based studies have determined hypomagnesemia and vitamin B12 deficiency as prevalent metabolic effects of long-term chronic acid suppression, especially in the context of more than one year [14, 15]. The statistically significant decrease of serum magnesium and vitamin B12 in this research also conforms to the biological plausibility of the condition of impaired intestinal absorption as the result of persistent inhibition of the acid.

The long-term duration of therapy and increased rate of adverse events are also related to longitudinal data that indicates the cumulative risk of adverse events with long-term exposure to PPI [15]. On the same lines, previous literature has pointed to old age as a risk factor of metabolic disturbances and renal complications probably because physiological reserve is lower and polypharmacy occurs. The absence of strong correlation between gender and negative effects in this study is as well in conformity with other studies before that reported that sex-based variations do not always affect PPI-related complications [16].

Renal outcomes in there were no statistically significant findings in this investigation. change in mean serum creatinine during the follow-up period, although a small proportion developed acute interstitial nephritis. This can be equated to the reports that although serious renal events are not very frequent, they happen in vulnerable patients [15]. The comparatively low rate of enteric infections is also in line with the previous research which reported relative but clinical significant rises in the risk of infection with the continued use of acid blockers [17].

Limitations and Future Suggestions:

There were some limitations of this study. The findings are limited to generalizability of the results to larger groups as the study was a single-center observational study. The follow-up period, though adequately long to identify short- to intermediate-term adverse effects, perhaps may have been not sufficiently long to identify unusual or delayed events like osteoporosis-related fractures or progression of chronic kidney disease. Certain outcomes based on a laboratory parameter, and not on a clinical endpoint, could not be completely avoided, and unmeasured confounding variables could not be completely ruled out. Also, the study lacked a control group who did not get pantoprazole to determine causality.

Future studies must consider a multicenter randomized or comparative cohort study with prolonged follow-ups to help outline causal association between long-term use of pantoprazole and negative consequences. Risk profiles would further be established by stratified analyses in terms of dosage, genetic factors and burden of comorbidity. The use of control groups and standardized monitoring protocols would be more compelling evidence on the development of guidelines. Additional research on how to deprescribe

and on step-down therapy methods would also assist in streamlining both the long-term management of GERD and reducing the time to unwarranted exposure.

Conclusion

Pantoprazole was found to be effective in the long-term of control of symptoms and mucosal healing of GERD patients. Nonetheless, a significant percentage of patients experienced adverse effects that were related to metabolism and renal, especially the individuals who were older than 50 years and had undergone over-a-year therapy. The results indicate that the clinical and laboratory monitoring, risk evaluation at the individual level, and rational prescribing in the course of long-term use of pantoprazole should be periodically carried out.

References

Castellana C, Pecere S, Furnari M, Telese A, Matteo MV, Haidry R, Eusebi LH. Side effects of long-term use of proton pump inhibitors: practical considerations. Polskie Archiwum Medycyny Wewnetrznej. 2021;131(6):541-9.

Maideen NM. Adverse effects associated with long-term use of proton pump inhibitors. Chonnam medical journal. 2023 May 25;59(2):115.

Koyyada A. Long-term use of proton pump inhibitors as a risk factor for various adverse manifestations. Therapies. 2021 Jan 1;76(1):13-21.

Pyne L, Smyth A, Molnar AO, Moayyedi P, Muehlhofer E, Yusuf S, Eikelboom J, Bosch J, Walsh M. The Effects of Pantoprazole on Kidney Outcomes: Post Hoc: Observational Analysis from the COMPASS Trial. Journal of the American Society of Nephrology. 2024 Jul 1;35(7):901-9.

Bhatnagar MS, Choudhari S, Pawar D, Sharma A. Long-term use of proton-pump inhibitors: unravelling the safety puzzle. Cureus. 2024 Jan 23;16(1):e52773.

Thurber KM, Otto AO, Stricker SL. Proton pump inhibitors: Understanding the associated risks and benefits of long-term use. American Journal of Health-System Pharmacy. 2023 Apr 15;80(8):487-94.

Kamboj AK, Patel DA, Yadlapati R. Long-term proton pump inhibitor use: review of indications and special considerations. Clinical Gastroenterology and Hepatology. 2024 Jul 1;22(7):1373-6.

Kowalewski J, Bęben D, Pyc G, Kowalewski Ł. Proton pump inhibitors-possible side effects of long-term therapy: a review. Quality in Sport. 2024 Dec 8;36:56387-.

Sakarkar P, Khan S. A Comprehensive Systematic Review of the Adverse Effects of Long-Term Proton Pump Inhibitors on the Gastrointestinal System in the Adult Population.

Arj A, ghaleh Takizadeh Z, Gilassi H, Razavizadeh M. Relationship between long-term use of proton pump inhibitor (PPI) and hypomagnesemia in patients with gastroesophageal reflux disease. Caspian Journal of Internal Medicine. 2022;13(1):107.

Lakshmisai SS, Bheemaneni RS, Nwachukwu EC, Nigam A, Sakarkar P, Khan S. A Systematic Review of the Adverse Effects of Long-Term Proton Pump Inhibitor Use on the Gastrointestinal System in the Adult Population. Cureus. 2025 Aug 20;17(8).

Novotny M, Klimova B, Valis M. PPI long term use: risk of neurological adverse events?. Frontiers in Neurology. 2019 Jan 8;9:1142.

Manolis AA, Manolis TA, Melita H, Katsiki N, Manolis AS. Proton pump inhibitors and cardiovascular adverse effects: Real or surreal worries?. European Journal of Internal Medicine. 2020 Feb 1;72:15-26.

Kim SY, Lee KJ. Potential risks associated with long-term use of proton pump inhibitors and the maintenance treatment modality for patients with mild gastroesophageal reflux disease. Journal of neurogastroenterology and motility. 2024 Oct 30;30(4):407.

Jeridi D, Pellat A, Ginestet C, Assaf A, Hallit R, Corre F, Coriat R. The safety of long-term proton pump inhibitor use on cardiovascular health: a meta-analysis. Journal of Clinical Medicine. 2022 Jul 15;11(14):4096.

Rajkumar R, Bhagyalekshmi N, Ramesh M, Pillai SR. An observational study on adverse drug reaction profile in patients on long-term treatment with proton pump inhibitors. National Journal of Physiology, Pharmacy and Pharmacology. 2022;12(4):477-80.

Nurhafidah Z, Hilmi IL, Sudarjat H. Analysis of the Side Effects of Long-Term Proton Pump Inhibitor (PPI) Use in Patients with Gastroesophageal Reflux Disease (GERD). Healthy Tadulako Journal (Jurnal Kesehatan Tadulako). 2025 Apr 30;11(2):324-35.