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Gastrointestinal Tract

Proton pump inhibitor use for 12 months is not associated with changes in serum magnesium levels: a prospective open label comparative study

Elton Bahtiri[1], Hilmi Islami[1], Rexhep Hoxha[1], Afrim Gashi[2], Kujtim Thaçi[3], Çağla Karakulak[4], Shpetim Thaçi[5], Hasime Qorraj-Bytyqi[1]

[1]Department of Pharmacology, Prishtina University School of Medicine, Prishtina, Kosovo
[2]Department of Rheumatology, Prishtina University School of Medicine, Prishtina, Kosovo
[3]Department of Biochemistry, Prishtina University School of Medicine, Prishtina, Kosovo
[4]Department of Pharmacology, İstanbul University Cerrahpaşa School of Medicine, İstanbul, Turkey
[5]Department of Preclinical Studies, Prishtina University School of Medicine, Prishtina, Kosovo

ABSTRACT

Background/Aims: Proton pump inhibitors (PPIs) are a widely used class of drugs because of a generally acceptable safety profile. Among recently raised safety issues of the long-term use of PPIs is the increased risk of developing hypomagnesemia. As there have been very few prospective studies measuring serum magnesium levels before and after PPI therapy, we aimed to prospectively assess the potential association between PPI therapy for 12 months and the risk of hypomagnesemia as well as the incidence of new-onset hypomagnesemia during the study. In addition, the association of PPI therapy with the risk of hypocalcemia was assessed.

Materials and Methods: The study included 250 patients with normal serum magnesium and total calcium levels, who underwent a long-term PPI treatment. Serum magnesium, total calcium, and parathormone (PTH) levels were measured at baseline and after 12 months.

Results: Of the 250 study participants, 209 completed 12 months of treatment and were included in the statistical analysis. The Wilcoxon signed rank test showed no statistically significant differences in serum magnesium levels between measurements at two different time points. However, there were statistically significant differences in serum total calcium and PTH levels in PPI users.

Conclusion: Stable serum magnesium levels were demonstrated after 12 months and no association between PPI use and risk of hypomagnesemia was shown in the general population. Significant reductions of serum total calcium levels were demonstrated among PPI users; nevertheless, further research is required before recommending any serum calcium and PTH level monitoring in patients initiated on long-term PPI therapy.

Keywords: Magnesium, calcium, parathormone, proton pump inhibitors

Original Article

INTRODUCTION

Proton pump inhibitors (PPIs) are a widely used class of medications for the treatment of acid-related disorders and prevention of nonsteroidal anti-inflammatory drugs (NSAIDs)-induced gastropathy (1-3). Generally, PPIs are considered to have an excellent efficacy profile accompanied by an acceptable safety profile in the short-term (4). Nevertheless, there are important safety issues with the long-term use of PPIs (5,6). One of them hat has been extensively studied in recent years is the observed association of the increased risk of hypomagnesemia among individuals who are long-term PPI users (7-16). The vast majority of the available data suggest interference with active or passive intestinal absorption of magnesium, but the prevalence and the mechanism(s) of PPI-induced hypomagnesemia have not yet been definitely established (17-19). As there are several PPIs clinically available, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole, there is an ongoing debate on whether hypomagnesemia should be considered a class effect of PPIs or not (20). To date, there have been very few, if any, prospective studies measuring serum magnesium levels before and after PPI therapy. Thus, the aims of this

Address for Correspondence: Hasime Qorraj-Bytyqi E-mail: hasime.qorraj@uni-pr.edu
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study were to prospectively assess the potential association between a PPI therapy for 12 months and the risk of hypomagnesemia as well as the incidence of new-onset hypomagnesemia during the study. In addition, the association of PPI therapy with the risk of hypocalcemia was assessed.

MATERIALS AND METHODS

Study Design and Population

The study design and recruitment process are described in detail elsewhere (21). They are briefly summarized here. This 12-month prospective, comparative study recruited participants from two hospitals, situated in the Republic of Kosovo and was conducted from April 2013 to July 2014. The study protocol was approved by the local ethics committee of the Faculty of Medicine, University of Prishtina (approval number 1699, date 11.05.2012) and followed the guidelines of Declaration of Helsinki. All participants gave written informed consent.

Regularly active subjects aged 18-65 years, with degenerative joint disease involving mainly the small joints of the hands, and complaints of pain and swelling starting during the preceding year, attending Rheumatology or Orthopedic Clinics, and on treatment with NSAIDs that were initiated in PPIs as protective long-term maintenance therapy were enrolled in the study. In addition, subjects had to have magnesium and total calcium serum levels equal to or higher than 0.66 mmol/L and 2.25 mmol/L, respectively. Those taking magnesium, calcium, and vitamin D supplements as well as contraceptives within the last 6 months, acid-suppressing agents, estrogen therapy, bisphosphonates, and glucocorticoids within the last 1 year, and concomitant use of diuretics, anticoagulants, or anticonvulsants were excluded. Subjects were also not included in the study if they had confirmed malabsorption diseases or neoplastic diseases during the last 5 years, had history of renal diseases, thyroid diseases, and cardiovascular diseases. Pregnant or breastfeeding women and women planning pregnancy were also not included. Control group consisted of healthy participants or participants with diseases and treatments not mentioned in the exclusion criteria and with no opioid and/or NSAID treatments or gastrointestinal risk factors present.

The study population originally consisted of 250 participants, of whom 200 subjects were patients treated with orally taken forms of PPIs registered in the Republic of Kosovo, and 50 subjects that were not treated with PPIs belonged to the control group. Subjects that were initiated in standard or comparable doses of PPIs were further subdivided into four groups, each of them consisting of 50 participants: first group (n=50) was treated with omeprazole (20 mg/day), second group (n=50) with esomeprazole (20 mg/day), third group (n=50) with lansoprazole (30 mg/day), and fourth group (n=50) with pantoprazole (40 mg/day). Participants in the control group were matched to each PPI treatment group.

During the 12-month follow-up, the patients were contacted every 3 months by telephone to assess the adherence to PPIs and potential adverse events. All study subjects with serum magnesium levels of <0.66 mmol/L and serum total calcium levels of <2.25 mmol/L at the 12-month follow-up visit underwent clinical examination to assess the presence of the symptoms of hypomagnesemia and/or hypocalcemia. Healthy subjects were contacted by telephone after 12 months.

Serum Measurements

The serum magnesium, total calcium, and parathormone (PTH) levels were measured before and at 12 months after the initiation of PPIs therapy. Fasting blood samples for the measurement of the serum total calcium, magnesium, and PTH levels were drawn from the antecubital vein at 8 AM. Blood samples were centrifuged and the serum was separated within 1 h.

Serum total calcium and magnesium concentrations were simultaneously determined using an automated analyzer, COBAS Integra 400 Plus (Roche Diagnostics, Switzerland). The intra- and inter-assay coefficients of variation (CVs) were less than 4.5% for all of the assays performed. Serum PTH concentrations were determined using Elecsys 2010 system (Roche Diagnostics, Switzerland). The intra- and inter-assay CVs were 5.4% and 4.7%, respectively. Hypomagnesemia was defined as serum levels of <0.66 mmol/L, hypocalcemia was defined as serum total calcium levels of <2.25 mmol/L, and hyperparathyroidism was defined as >65 pg/mL.

Statistical Analysis

Continuous variables are presented as means±standard deviations and medians and categorical variables as proportions. Baseline values of continuous variables were compared using Mann-Whitney U test or Kruskal-Wallis test as appropriate, whereas proportions (percentages) were compared using Chi-square test. Wilcoxon signed-rank test was used to evaluate the differences between pre- and post-treatment measurements. Statistical Package for the Social Sciences 16 was used to conduct all analyses (SPSS Inc; Chicago, IL, USA). All *p*-values were two-sided and were considered significant if <0.05.

RESULTS

A total of 209 participants completed 12 months of follow up so only their baseline results were included in the statistical analysis. The reasons for withdrawal from the study are described in detail elsewhere, some of which were noncompliance with the study protocol, refusal to continue taking medication, lost to follow-up, and pregnancy (20). The characteristics of study participants at baseline are listed in Table 1. Mean age was 50.59 years, and 25.4 % (n=53) of participants were men. No statistically significant differences in baseline characteristics were observed between PPI users and non-users, except higher serum PTH levels in non-users [38.26±15.23 (SD) vs. 47.28±22.15 (SD), p=0.005]. The results of Wilcoxon signed rank test summarized in Tables 2 and 3 show that serum magnesium levels remained

Table 1. Baseline characteristics of the study population

	All (n=209)	PPI users (n=167)	PPI non-users (n=42)	p[a]
Age (years)	50.59±10.61 (52.00)	50.83±10.53 (53.00)	49.64±10.98 (50.00)	0.440
Female/Male	156/53	125/42	31/11	0.890
BMI (kg/m²)	29.09±5.02 (28.72)	29.04±5.13 (28.58)	29.27±4.65 (29.91)	0.717
Parathormone (10-65 pg/mL)	40.07±17.17 (37.86)	38.26±15.23 (36.39)	47.28±22.15 (43.46)	0.005
Total calcium (2.25-2.75 mmol/L)	2.45±0.17 (2.44)	2.46±0.16 (2.45)	2.44±0.19 (2.41)	0.606
Magnesium (0.66-1.07 mmol/L)	0.83±0.09 (0.80)	0.83±0.09 (0.80)	0.82±0.09 (0.80)	0.832

All variables are presented as mean±SD (Median) and as proportions, as appropriate.
BMI: Body mass index; PPI: proton pump inhibitor
[a]p values of Mann-Whitney U or chi-squared test, as appropriate

Table 2. Twelve-month changes in biochemical parameters according to PPI use

Groups	Variables	Before treatment	After treatment	Wilcoxon test	
		Mean±SD (Median)	Mean±SD (Median)	Z-score	p
PPI users (n=167)					
	Parathormone	38.26±15.23 (36.39)	44.77±18.51 (41.94)	-4.617	<0.001
	Total calcium	2.46±0.16 (2.45)	2.37±0.18 (2.40)	-4.650	<0.001
	Magnesium	0.83±0.09 (0.80)	0.82±0.09 (0.83)	-0.902	0.367
PPI non-users (n=42)					
	Parathormone	47.28±22.15 (43.46)	43.60±16.11 (39.67)	-0.925	0.355
	Total calcium	2.44±0.19 (2.41)	2.39±0.15 (2.36)	-1.351	0.177
	Magnesium	0.82±0.09 (0.80)	0.82±0.08 (0.81)	-0.525	0.599

All variables are presented as mean±SD (Median)

stable in all study groups and subgroups, with no statistically significant differences between measurements at two different time points. Nevertheless, after 12 months of treatment, the mean serum total calcium levels dropped from 2.46±0.16 (SD) to 2.37±0.18 (SD) (Z=-4.650, p<0.001) in PPI users. When analysis was focused on individual PPI drugs, it was shown that the mean serum total calcium levels dropped from 2.45±0.19 (SD) to 2.35±0.19 (SD) in participants taking esomeprazole (Z=-2.469, p=0.014), from 2.46±0.15 (SD) to 2.39±0.16 (SD) in participants taking lansoprazole (Z=-2.139, p=0.032), and from 2.47±0.16 (SD) to 2.38±0.17 (SD) in participants taking pantoprazole (Z=-2.651, p=0.008). During the follow-up period, a reduction in mean serum total calcium levels was observed in participants taking omeprazole, but the changes did not reach statistical significance (Z=-1.931, p=0.053). Changes in serum levels of total calcium were accompanied by a statistically significant increase in serum PTH levels in omeprazole-, esomeprazole-, and pantoprazole-treated patients (Z=-2.054, p=0.040; Z=2.870, p=0.004; Z=-2.332, p=0.020, respectively). Serum levels of PTH and total calcium and magnesium in the control group were not statistically different at 12 months of follow-up (Z=-0.925, p=0.355; Z=-1.351, p=0.117; and Z=-0.525, p=0.599, respectively); nevertheless, a tendency toward lower serum total calcium levels was observed even among subjects in the control group.

At the end of the study, the incidence of new-onset hypomagnesemia in the whole study population was 3.8%, with six cases (3.6%) that developed among PPI users and two cases (4.8%) among non-users (3.6% vs. 4.8%, p=0.724); the incidence of new-onset hypocalcemia in the whole study population was 22.5%, with 41 cases (24.6%) among PPI users and six cases (14.3%) among non-users (24.6% vs. 14.3%, p=0.154), whereas the incidence of new-onset hyperparathyroidism in the whole study population was 22%, with 11 cases (11.4%) among PPI users and three cases (7.1%) among non-users (11.4% vs. 7.1%, p=0.218).

DISCUSSION

Data analysis of the predominantly middle-aged participants included in our study reveals stable serum magnesium levels in all study groups and subgroups throughout the 12 months of treatment. These findings are in disagreement with the experimental model of Bai et al. (22) which predicts that PPI therapy for 12 months could lead to an 80% depletion of magnesium stores in the body. Furthermore, after 12 months of treatment, mean serum total calcium levels significantly dropped in patients on esomeprazole, lansoprazole, and pantoprazole therapy. These changes in serum calcium levels were accompanied by statistically significantly increased serum levels of PTH. There was a tendency toward a decrease in serum total calcium levels in patients on omeprazole therapy, but it did not reach statistical significance. As far as PPI-induced hypomagnesemia is reported to be associated with hypocalcemia and hypoparathyroidism (23), the presence of increased PTH levels in these treatment groups is another evidence to suggest no changes in magnesium status after 12 months of therapy. We hypothesize that hypocalcemia played a role in the development of secondary hyperparathyroidism; nevertheless, we cannot rule out the possibility of other factors causing the secondary hyperparathyroidism (i.e., vitamin D deficiency or renal disease) that we were not able to assess in this study.

None of the study subjects with hypomagnesemia, defined as serum magnesium levels of <0.66 mmol/L, developed symptoms. On the other hand, nine subjects with hypocalcemia, defined as serum total calcium levels of <2.25 mmol/L, developed

Table 3. Twelve-month changes in biochemical parameters according to study subgroups

Groups	Variables	Before treatment	After treatment	Wilcoxon test	
		Mean±SD (Median)	Mean±SD (Median)	Z-score	p
Omeprazole group (n=42)					
	Parathormone	40.21±15.43 (39.58)	48.26±30.73 (41.88)	-1.751	0.080
	Total Ca	2.44±0.13 (2.45)	2.36±0.19 (2.40)	-1.931	0.053
	Mg	0.81±0.09 (0.80)	0.81±0.10 (0.84)	-0.233	0.815
Esomeprazole group (n=41)					
	Parathormone	36.38±12.61 (36.13)	41.35±12.53 (42.91)	-2.054	0.040
	Total calcium	2.45±0.19 (2.45)	2.35±0.19 (2.34)	-2.469	0.014
	Magnesium	0.83±0.08 (0.80)	0.82±0.07 (0.84)	-0.551	0.581
Lansoprazole group (n=42)					
	Parathormone	38.61±18.36 (33.81)	45.06±17.57 (42.03)	-2.870	0.004
	Total calcium	2.46±0.15 (2.45)	2.39±0.16 (2.42)	-2.139	0.032
	Magnesium	0.84±0.10 (0.90)	0.83±0.08 (0.84)	-0.632	0.527
Pantoprazole group (n=42)					
	Parathormone	37.80±14.18 (34.39)	46.72±19.75 (39.95)	-2.332	0.020
	Total calcium	2.47±0.16 (2.46)	2.38±0.17 (2.21)	-2.651	0.008
	Magnesium	0.83±0.08 (0.80)	0.82±0.08 (0.83)	-0.311	0.756
Control group (n=42)					
	Parathormone	47.28±22.15 (43.46)	43.60±16.10 (39.67)	-0.925	0.355
	Total calcium	2.44±0.19 (2.40)	2.39±0.15 (2.36)	-1.351	0.117
	Magnesium	0.82±0.10 (0.80)	0.82±0.07 (0.81)	-0.525	0.599

All variables are presented as mean±SD (Median)

mild symptoms (predominantly numbness and tingling sensations and muscle cramps); nevertheless, it should be mentioned that no cases of hypocalcemic emergencies or severe hypocalcemia, such as tetany, seizures, or arrhythmias, were witnessed.

Several studies support our assertion that, in the absence of other risk factors (concomitant drug use or diseases), prolonged PPI use is not associated with clinically significant hypomagnesemia. A case-control study performed by Koulouridis et al. (8) assessed the relationship between PPI use and hypomagnesemia in hospitalized patients and found that out-of-hospital treatment with PPIs is not associated with hypomagnesemia at the time of admission to the hospital [odds ratio (OR)=0.83, p=0.2]; they report no differences in results even after taking into account the type or the dose of PPIs. Similarly, Danziger et al. (9) performed a large, retrospective study on the data of hospitalized patients in intensive care unit, by comparing PPI users with users of H2 receptor antagonists or non-users of acid suppressing agents and found that PPI users had significantly lower serum magnesium levels only in patients concomitantly taking thiazide diuretics, whereas no significant association was demonstrated between PPI use and changes in serum magnesium levels in non-diuretic patients (OR=0.92; p=0.35). Consistent with these findings, Zipursky et al. (10) concluded an increased risk of hypomagnesemia in PPI users receiving diuretics (adjusted OR=1.73; 95% CI 1.11-2.70) but no significant risk in those not receiving diuretics. To further support our assertions are findings of a recent study of Sharara et al. (11), who concluded the lack of association between chronic PPI use and hypomagnesemia.

On the other hand, some studies point out that PPI use is associated with hypomagnesemia. In this context, in a retrospective cross-sectional study comparing PPIs ambulatory users with H2RA users and non-users of acid-suppressive drugs, Markovits et al. (12) reported an association between prolonged use of PPI and hypomagnesemia. Furthermore, the authors found statistically significant PPIs-associated hypomagnesemia even with short-term use. Another retrospective, cross-sectional study of El-Charabaty et al. (13) in hospitalized patients with acute coronary syndromes who were first prescribed PPIs during the hospital stay, found significant correlation between PPI use and hypomagnesemia ($p=1.31e^{-29}$); nevertheless, this conclusion might have been confounded because the authors did not account for diuretic use. Similarly, Gau et al. (14) reported significantly lower serum magnesium levels among hospitalized adults who were using PPIs prior to admission time, thus concluding an association between PPI use and the occurrence of hypomagnesemia, whereas Janett et al. (15), in a systematical review of the literature about the association between PPIs and magnesium metabolism, concluded that PPIs may cause hypomagnesemia and thus advised switching to a histamine type 2 receptor antagonist. Findings of these studies are in line with that of a recent prospective study that demonstrated the association between prolonged PPI use and increased risk of hypomagnesemia in the general population, but the authors acknowledge as a limitation the fact that they had a single serum magnesium measurement and were unable to investigate the potential changes of serum magnesium levels after the initiation of PPI therapy (16). Nevertheless, there is an ongoing debate on whether to define hypomagnesemia as a class effect of PPIs or not. Based on their observations of reported adverse drug reactions from the Food and Drug Administration

(FDA) database, Luk et al. (20) suggested that it is a class effect of PPIs, but they reported pantoprazole to have the highest risk and esomeprazole to have the lowest risk of PPI-associated hypomagnesemia.

Although no statistically significant effect of PPI use for 12 months on serum magnesium levels was observed in this study, the small effects of PPIs on magnesium homeostasis cannot be entirely ruled out, as serum magnesium levels may not appropriately indicate body magnesium stores. Accordingly, appropriateness of PPIs use and risk stratification for PPIs-induced hypomagnesemia are clinically important and should be considered in patients with diseases and/or on therapy with drugs known to influence magnesium homeostasis or to be influenced by its changes. Despite the controversy of the data, FDA's warning from March 2011 that long-term PPI use may be associated with hypomagnesemia is still valid (24).

The focus of several studies has also been on the effects of PPI therapy on calcium absorption or homeostasis, but most of them were short-term studies yielding controversial conclusions. To the best of our knowledge, this is the first prospective study to demonstrate a significant effect of PPI therapy on calcium metabolism. Nevertheless, these findings should be interpreted cautiously, considering the tendency toward lower total serum calcium levels as well as cases of hypocalcemia after 12 months among non-users. In addition, our inability to assess vitamin D status and nutritional intake of magnesium and calcium limits the conclusion that detrimental effect on serum calcium levels is definitely attributed to PPIs.

Although O'Connell et al. (25) demonstrated a significant reduction of fractional calcium absorption of ^{45}Ca carbonate consumed under fasting condition a decade ago, two other studies assessed calcium absorption using dual-stable calcium isotopes and found no changes in fractional calcium absorption, thus concluding no effect of PPI on calcium absorption and metabolism (26,27). Similarly, a recent study of Sharara et al. (28) concluded no measurable effect of PPI intake on calcium metabolism.

The current study has strengths and limitations. The prospective design of the study performed on participants that are first-time medication users, enrollment of participants with normal serum magnesium and calcium levels, and measurements of magnesium and calcium levels before the start of treatment and 12 months thereafter are the strengths. As we did not perform sample size and power calculations, the sample size might be a limitation of the study. The inability to assess vitamin D status and nutritional intake of magnesium and calcium as well as the lack of serum albumin levels are another limitations of our study.

In conclusion, this study demonstrated stable serum magnesium levels after 12 months of PPIs use, thus failing to show an association between PPIs use and risk of hypomagnesemia. While routine screening of serum magnesium levels in patients on PPIs is likely unwarranted in general practice, clinicians should be aware of this adverse effect whenever PPIs are prescribed to patients with other therapies and conditions that may put them at risk for developing hypomagnesemia. Our study demonstrated significant reductions of serum total calcium levels among PPIs users compared with nonusers; however, the tendency toward lower total calcium serum levels as well as cases of hypocalcemia after 12 months among nonusers makes us urge further research in this field before recommending any serum calcium and PTH level measurements prior to and periodically after initiating long-term PPI therapy.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Prishtina University School of Medicine.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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