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Research Article

RELATIONSHIP BETWEEN PROTON-PUMP INHIBITOR USE AND LOWER BLOOD MAGNESIUM LEVELS

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ABSTRACT

Objective: The aim of this study was to determine whether and to what degree proton-pump inhibitor (PPI) use affects blood magnesium levels.

Methods: We performed a cross-sectional comparative study with consecutive sampling technique from June to October 2016. This study compared blood magnesium levels of patients using PPIs (lansoprazole and omeprazole) with those of patients not taking PPIs. The total sample was 184 patients. Data collected included questionnaires and medical records. Statistical analysis was performed with the unpaired *t*-test, Mann–Whitney U-test, and one-way analysis of variance.

Results: The average magnesium level in patients using PPIs was 2.08±0.21 mg/dL, whereas the average magnesium level in patients not using PPIs was 2.27±0.38 mg/dL, a statistically significant difference ($p<0.001$). Magnesium levels were significantly lower in patients using PPIs for >1 year and in patients using omeprazole ($p<0.05$).

Conclusion: Blood magnesium levels of patients using PPIs were significantly lower than those who did not use PPIs. Decreased levels of magnesium in patients using PPI are affected by PPI type and the duration of PPI use - >1 year. Thus, the long-term use of PPIs may lead to decreased levels of magnesium. Therefore, monitoring the levels of magnesium is important in patients using PPIs for a long term to avoid the risk of hypomagnesemia.

Keywords: Blood magnesium levels, Lansoprazole, Omeprazole, Proton-pump inhibitors.

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INTRODUCTION

A recent review of the United States Federal Drug Administration (US FDA) adverse event reporting system from 2004 to 2009 summarized 216 hypomagnesemia events related to omeprazole or esomeprazole use [1]. Consequently, the US FDA issued a warning in 2011, announcing that the long-term use of all proton-pump inhibitors (PPIs) could result in severe hypomagnesemia [2]. In several case reports and case series, it was already noted that PPI-induced hypomagnesemia primarily occurs in patients who use PPIs for a long period (i.e., ≥3 months) [3]. PPI-related hypomagnesemia was first reported by Epstein, McGrath, and Law in 2006 [4].

PPI-associated hypomagnesemia can cause a range of symptoms, including tremors of the extremities, convulsions (40%), muscle cramps and spasms (20%), weakness and lethargy (30%), tetany (17%), loss of consciousness, numbness, anxiety, hallucinations, agitation (20%), dizziness, and nausea (36%) [5].

PPIs are widely used by patients who receive antihypertensives, antidiabetics, analgesics, antibiotics, anticonvulsants, antiemetics, statins, and psychiatric drugs to suppress dyspepsia associated with the use of these drugs [6]. Some of the PPIs used in Indonesia are esomeprazole, omeprazole, lansoprazole, and pantoprazole. Omeprazole and lansoprazole are more often prescribed to patients because they are included in the national formulary. The purpose of this study was to determine whether and to what degree PPI use affects blood magnesium levels.

METHODS

We performed quantitative research using a cross-sectional comparative study. Approval was obtained from the Ethics Committee of the medical faculty of the University of Indonesia and the Research Department of Dr. Cipto Mangunkusumo National General Hospital. A comparative study was conducted on two populations: A group of patients using PPIs and another group of patients not using proton PPIs. The total sample in this study was 184 patients (92 in each group). We collected data using questionnaires and medical records. Statistical analysis was performed using the unpaired *t*-test and one-way analysis of variance (ANOVA). Patients who dropped out of the study were excluded from the study. Inclusion criteria were as follows: (a) Patients who used a PPI for 3 months or more and patients who use a PPI and had no history of PPI use and (b) patients who were willing to participate in this research.

RESULTS AND DISCUSSION

Comparison of blood magnesium levels between PPI users and non-users

Using an unpaired t-test, we found that the blood magnesium level in patients using PPIs was significantly lower than that in non-users. The mean blood magnesium levels in the patients are shown in Table 1.

Assessment of potential confounding variables contributing to patient blood magnesium levels

The majority of participants in both the groups were female and <60 years of age. Diuretics were the only other class of drugs used by the participants. The majority of patients in both the groups did not have diabetes mellitus (DM). Differences in the mean blood magnesium level based on gender, age, and DM status were not statistically significant by the Mann–Whitney U-test (Table 2). The results of the Mann–Whitney U-test for the use of diuretics indicated the meaningful differences between the mean blood magnesium levels in patients using diuretics ($p=0.007$).

Multivariate linear regression was conducted on the groups, and the use of diuretics along with the use of PPIs had the most influential effect on the decrease in blood magnesium levels ($p<0.001$). Multivariate linear regression results are shown in Table 3.

Assessment of the relationship between dose and duration of PPI use with the patients' blood magnesium levels

Omeprazole was the PPI most widely used by patients in this study (51.1%). The doses of PPIs that were the most widely used were omeprazole at 20 mg/day and lansoprazole at 30 mg/day (56%). The duration of PPI use in our study was ≥366 days in 62% PPI users and between 90 and 180 days in 14.1%. The results of an unpaired t-test conducted on the type and dose of PPI were not statistically significant. One-way ANOVA test results conducted on the duration of PPI use showed that there is a statistically significant difference in the blood magnesium levels between the two groups. The results of a *post hoc* analysis showed significant differences in the blood magnesium levels in the group of patients who used PPIs for 181–365 days and those who used them for 366 days or more. Test results for the effect of the type and duration of PPI use on blood magnesium levels are shown in Table 4.

Results of a multivariate linear regression test showed that the PPI type and duration of PPI use affect the blood magnesium levels. The results of this multivariate analysis are shown in Table 5.

DISCUSSION

Our cross-sectional comparative study showed that the blood magnesium levels of patients using PPIs significantly differed from those of patients who did not use PPIs. These results are similar to those of studies conducted by Shah and Sachdeva [6]. Our study involved 92 patients who were taking PPIs and 92 patients who did not use PPIs; only one patient using PPIs had hypomagnesemia. Patients taking PPIs and who have hypomagnesemia usually show no symptoms of hypomagnesemia (asymptomatic). This result correlates with that of Hess *et al*. [7], who reported that many cases of hypomagnesemia related to the use of PPIs are asymptomatic. According to Tamura *et al*., the symptoms of hypomagnesemia that results from the long-term use of PPIs would occur if the blood magnesium levels were <1.22 mg/dL [1]. The prevalence of hypomagnesemia related to the use of PPIs is not known exactly [8,9].

Table 1: Mean blood magnesium levels based on PPI use

Group	n	Mean±SD (mg/dL)	p-value
Patients using PPIs	92	2.08±0.21	0.000
Patients not using PPIs	92	2.27±0.38	

Unpaired *t*-test, p<0.05=Significant. PPIs: Proton-pump inhibitors, SD: Standard deviation

Table 2: Mean blood magnesium levels based on gender, age, use of diuretics, and DM

Variable	n	Mean±SD (mg/dL)	p-value
Gender			
Male	76	2.17±0.31	0.645
Female	108	2.18±0.33	
Age			
≤60 years	129	2.17±0.28	0.714
>60 years	55	2.18±0.40	
Use of Diuretic			
Yes	8	1.93±0.17	0.007
No	176	2.19±0.3	
DM			
Yes	27	2.20±0.52	0.928
No	157	2.17±0.28	

p<0.05=Significant. DM: Diabetes mellitus, SD: Standard deviation

Table 3: Results of multivariate linear regression of blood magnesium levels based on group and the use of diuretics

Step	Variable	Coefficient	Coefficient correlation	p-value
Step 1	Group	0.167	0.259	0.000
	Use of diuretics	−0.166	−0.105	0.152
	Constant	1.936		0.000
Step 2	Group	0.182	0.281	0.000
	Constant	1.907		0.000

p<0.05=Significant

Our study compares the blood magnesium levels between patients taking omeprazole and those taking lansoprazole. The results showed no significant differences between the mean blood magnesium levels in patients taking omeprazole versus those taking lansoprazole. Similar results were reported by Gau *et al*. [10].

Our analysis showed significant differences in the blood magnesium levels in the group of patients who used PPIs for 181–365 days versus those who used PPIs for >366 days. This result correlates with the research by Kieboom *et al*., which states that the risk of hypomagnesemia increases when using PPIs for a long period (>6 months) [3]. Hess *et al*. suggested that the onset of hypomagnesemia resulting from the long-term use of PPIs varies from 14 days to 13 years (with an average of 5.5 years) [7].

Koulouridis *et al*. reported that hypomagnesemia associated with the long-term use of PPIs was not associated with the doses of PPIs used [11]. Our study results showed that there was no significant difference between the blood magnesium levels according to the dose of PPI used by the patient.

The results of this study showed no significant difference between males and females with respect to the blood magnesium levels. Takeda *et al*. also reported no significant difference in the blood magnesium levels between men and women [12]. Our results also showed no meaningful differences between the mean blood magnesium levels according to patient age, and similar results were reported by Lindner *et al*. in 2014 [13].

The use of loop diuretics and thiazide can stimulate the loss of magnesium in the kidney by decreasing the passive reabsorption of magnesium or indirectly interfere with magnesium homeostasis by inhibiting sodium reabsorption [7]. The US FDA states that the use of loop diuretics and thiazide can reduce the levels of magnesium whether used alone or in combination with other antihypertensives (angiotensin-converting enzyme inhibitors, β-blockers, and/or angiotensin receptor blockers) [2]. The present study showed meaningful differences between the mean levels of magnesium in patients using diuretics. Studies conducted by Danziger *et al*. in patients with critical conditions who used a combination of drugs with PPIs and diuretics had a larger decrease in magnesium levels [14].

DM can decrease magnesium levels. Decreased magnesium levels in patients with diabetes may be caused by a lack of intake of foods high in magnesium, the high excretion of magnesium in the kidney, deficiency/insulin resistance, decreased absorption of magnesium in the kidney, insensitivity to insulin that affects magnesium transport and glucose metabolism, metabolic acidosis (diabetic ketoacidosis), and the use of loop diuretics and thiazide [15-18]. The results of this study indicate that DM does not affect the levels of magnesium, which is similar to the results reported by Takeda *et al*. [12].

The limitations of our study are that we obtained blood magnesium level data at 1-time point (cross-sectional), and we did not analyze blood magnesium levels before and after the use of PPIs (cohort).

Magnesium absorption in the small intestine occurs by both active transport and passive absorption. Active transport mediated by the transport proteins such as transient receptor potential melastatin 6 (TRPM6) and TRPM7 is responsible for 30% of the absorption process, whereas the passive transport through the tight junctions of enterocytes is responsible for 70% of the remaining absorption [19]. An *in vitro* study conducted by Thongon and Krishnamra showed that the transport of cations that pass through the cell lining of the large intestine is greatly reduced by treatment with PPIs [20].

Table 4: Mean blood magnesium levels based on the PPI type and dose and duration of use in patients using PPIs

Variable	n	Mean±SD (mg/dL)	p-value
Type of PPI			
Omeprazole	47	2.04±0.23	0.070
Lansoprazole	45	2.13±0.18	
Dose of PPI			
Omeprazole 20 mg/day; Lansoprazole 30 mg/day	56	2.10±0.2	
Omeprazole >20 mg/day; Lansoprazole >30 mg/day	36	2.06±0.2	0.342
Duration of PPI use (days)			
90–180	13	2.13±0.25	0.020
181–365	22	2.18±0.19	
≥366	57	2.04±0.20	

Type and dose of PPI: Unpaired t-test: Duration use of PPI: One-way ANOVA test, p<0.05 was considered significant, *post–hoc* LSD test: 90–180 versus 181–365 days, p=0480, 90–180 versus ≥366 days, p=0158, 181–365 days ≥ versus 366 days, p=0.008. PPIs: Proton-pump inhibitors, SD: Standard deviation

Table 5: Results of multivariate linear regression of blood magnesium levels based on the PPI type and duration of PPI use in patients

Step	Variable	Coefficient	Coefficient correlation	p-value
Step 1	Type of PPI	0.118	0.275	0.010
	Duration use of PPI	−0.090	−0.304	0.004
	Constanta	2.135		0.000

p<0.05 = Significant, PPIs: Proton-pump inhibitors

Intracellular magnesium regulates TRPM6 activity according to pH, whereby a more acidic milieu increases TRPM6 activity [21,22]. Since PPI therapy decreases gastric hydrogen ion secretion, thereby increasing lumen pH, PPI use could potentially decrease TRPM6 activity, resulting in decreased magnesium absorption. Under the condition of magnesium deficiency, PPIs may inhibit magnesium absorption by increasing the pH of the intestinal lumen through both gastric and non-gastric antagonisms of the H^+–K^+ ATPase pump (proton pump). TRPM6/7 affinity for magnesium decreases in a higher pH environment. While this may trigger mRNA transcription of TRPM6 channels in most individuals, hypomagnesemia may develop when this compensation is incomplete or the individual has additional risk factors [23].

CONCLUSION

Blood magnesium levels of patients using PPIs were significantly lower than those in patients who did not use PPIs. Decreased levels of magnesium in patients using PPI are affected by PPI type and the duration of PPI use for >1 year. Thus, the long-term use of PPIs may lead to decreased levels of magnesium. Therefore, monitoring the levels of magnesium is important in patients using PPIs for a long term to avoid the risk of hypomagnesemia.

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CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest.

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