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ORIGINAL ARTICLE

Short-Term Effect of High-Dose Pantoprazol on Serum and Urinary Magnesium Levels

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SUMMARY

Background: **Proton pump inhibitor (PPI) induced hypomagnesemia is a completely unexplained issue and cases are still being reported. Long-term use is the main factor, but there are a few articles stating that it may also emerge with short-term use. We aimed to evaluate the changes of serum and urine magnesium levels during short-term high dose pantoprazol treatment.**

Methods: **The serum and 24-hour urine magnesium levels of 58 patients were evaluated during the course of 2 days. Of 58 patients, 25 were allowed oral intake on the 3rd day of hospitalization and thus, 24-hour urine for 3 days was collected from 33 patients.**

Results: **There were no significant differences in the mean levels of serum magnesium and the median levels of urine magnesium. When the magnesium levels were evaluated by age over and under 60 years, the baseline serum magnesium level was significantly higher than the 1st level in patients aged ≥ 60 years ($p = 0.029$). The 3rd day serum magnesium level was significantly higher than the baseline and 1st day levels in those aged < 60 years ($p = 0.049$).**

Conclusions: **We showed that plasma levels and urinary excretion of magnesium did not change significantly during high-dose pantoprazol treatment. It can be hypothesized that magnesium levels are not affected by PPIs in short-term usage. Age and other contributing factors may have more impact on PPI induced hypomagnesemia. Patients aged over 60 years might be handled carefully under proton pump inhibitors treatment.**

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INTRODUCTION

Magnesium is an electrolyte not as well-known as other electrolytes but which has many vital functions in the human body. It is essential and has to be consumed regularly in the diet to prevent deficiency [1]. The normal level of serum magnesium is very low (1.8 to 2.3 mg/dL) and is often ignored in clinical practice. However, magnesium deficiency may cause many mortal conditions such as fatal arrhythmias and seizure [2,

3]. Proton pump inhibitors (PPIs) are one of the most commonly prescribed drugs in the world. The association of PPIs and hypomagnesemia first appeared in 2006 in a case report by Epstein et al. [4]. Increasing subsequent reports of cases prompted the Food and Drug Administration (FDA) to release a "drug safety warning" in 2011 [5]. However, the mechanism or pathways by which PPIs lead to hypomagnesemia is not yet fully known.

Normal homeostasis of magnesium is ensured mainly by the balance between intake, absorption, and excretion in the gastrointestinal and renal systems [6]. It is absorbed in the small and large bowels with complex passive and active transport mechanisms. The active transport of magnesium occurs more distally in the cecum and large bowel [6,7] by proteins within the enterocyte apical membrane, identified as transient receptor potential melastatins (TRMP) 6 and 7 [8]. The excretion of magnesium primarily occurs through gastrointestinal and renal routes. Approximately 80% of absorbed plasma magnesium is filtered through the glomerular membrane in the kidneys [9]. The vast majority of filtered magnesium is reabsorbed in the thick ascending loop of Henle (TAL) via a paracellular pathway mediated by tight junction proteins of the claudin family. Claudin 16 and 19 are the most important members for magnesium reabsorption and mutations of these proteins have been shown to lead to renal magnesium wasting in *in vitro* studies [10]. Ten percent of filtered magnesium is reabsorbed in the distal convulated tubule (DCT). The DCT determines the final urinary magnesium concentration and no reabsorption takes place beyond this segment [11]. Magnesium reabsorption in the DCT occurs in a transcellular pathway through TRPM6 and TRPM7 transporters [11].

Inhibition of intestinal absorption by active [12] or passive [3] ways are the speculated mechanisms for the PPI-induced hypomagnesemia. Although renal magnesium wasting has been another suggested mechanism previously, studies on this issue reported that renal systems were not responsible for PPI-induced hypomagnesemia [13,14]. Since high-dose intravenous PPI therapy for three days following successful endoscopic hemostasis is the current guideline recommendation for upper gastrointestinal hemorrhage (GIH), our aim was to evaluate changes in serum and urine magnesium levels in patients hospitalized for upper GIH during high-dose pantoprazol treatment and no oral intake [15]. Thus, our goal was to identify the purely renal role in magnesium equilibrium under high-dose intravenous PPI treatment.

MATERIALS AND METHODS

The study included 58 patients hospitalized with a diagnosis of upper GIH in the Gastroenterology Clinic of our hospital between January 2016 and September 2016. Hemodynamically unstable patients, patients with concomitant disease involving the lungs, kidneys, liver or heart, patients previously treated with diuretics and medications containing magnesium, and patients with a history of hypomagnesemia were excluded. The follow-up and treatment protocols of the patients were not changed by the authors and management of the patients was undertaken according to endoscopic findings and follow-up visits by primary physicians. None of the patients included in the study were permitted oral intake and the pantoprazol infusion was started at a dose of 8 mL/hour as hospitalisation was because of upper GIH. Patients with oral intake on the first day were also excluded from the study. After providing written informed consent, all patients collected 24-hour urine for magnesium excretion. The serum magnesium levels of all patients were measured before PPI treatment (baseline level) and daily serum and 24-hour urinary magnesium concentrations were measured in all participants until they were permitted oral intake. The study protocol was conducted in accordance with the ethical principals stated in the Declaration of Helsinki and was approved by the local Research Institutional Ethics Committee (reference, 73/11).

Statistical analysis

Statistical analyses were done using the Statistical Package for Social Sciences v. 21.0 software (IBM SPSS Statistics for Windows, version 21.0. released 2012, IBM Corp., Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD), number (n), percentage (%), and median (minimum-maximum) values, where appropriate. The Friedman test and the Wilcoxon Signed Ranks test were used for comparison of quantitative variables with non-normal distribution where measurements were repeated over time while the paired *t*-test was used for comparison of the means of two related groups with normal distribution. Repeated measures ANOVA was used to investigate the effect of time on the serum magnesium levels, and mixed-design ANOVA was applied to determine the interaction between gender and serum magnesium level over time. The Mauchly test was used to test whether data met or failed the assumption of sphericity, and degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity when this assumption was not met. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Evaluation was done on 13 female and 45 male patients with a mean age of 51.05 years. Twenty-four-hour urine was collected for 2 days from all patients, although 25 of the 58 patients were allowed oral nutrition on the 3rd day of hospitalization thus only 33 patients collected 24-hour urine for three days (Table 1). No significant differences were determined in the mean levels of baseline nor on the 1st, 2nd, and 3rd days of serum magnesium of all the patients included in the study (1.94

Table 1. Daily serum and urinary magnesium levels of patients.

Magnesium Levels (mg/dL)	Baseline (n = 58)	1st Day (n = 58)	2nd Day (n = 58)	3rd Day (n = 33)	p_1	p_2
Serum, mean (SD)	1.94 (0.19)	1.88 (0.2)	1.94 (0.18)	1.97 (0.18)	0.152 $^{+}$	0.097 *
Female, mean (SD) (n = 13)	2.03 (0.16)	1.95 (0.17)	1.98 (0.25)	-	0.560 $^{+}$	-
Male, mean (SD) (n = 45)	1.89 (0.19)	1.86 (0.21)	1.91 (0.21)	-		
Urine, median (min-max)	-	43.1 (2.47 - 142)	47.75 (1.4 - 171)	37.54 (2.67 - 151)	0.342 $^{++}$	0.168 **
Female, median (min-max)	-	33 (22 - 91.5)	46.59 (2.35 - 76.8)	31.6 (20.0 - 69.44)	-	0.115 **
Male, median (min-max)	-	50.31 (2.47 - 142)	47.75 (1.4 - 171)	41.48 (2.67 - 151.0)	-	0.540 **

$^{+}$ **Baseline - 1st, 2nd Day,** * **Baseline - 1st, 2nd, 3rd Day,** $^{++}$ **- 1st, 2nd Day,** ** **- 1st, 2nd, 3rd Day.**

Table 2. Daily serum and urinary magnesium levels of patients according to age under and over 60 years age.

Magnesium Levels (mg/dL)	Baseline	1st Day	2nd Day	3rd Day	p
≥ 60 years age, Serum, median (min-max) (n = 10)	2 (1.8 - 2.3)	1.9 (1.6-2)	1.9 (1.7-2)	2 (1.6 - 2.1)	0.029 $^{+}$
<60 years age, Serum, mean ± SD (n = 23)	1.91 (0.19)	1.89 (0.21)	1.95 (0.19)	1.98 (0.18)	0.049 *
≥ 60 years age, Urine, median (min - max)(n = 10)	-	31.9 (18 - 82.8)	34.8 (2.35 - 91.84)	27.35 (2.67 - 62)	0.741
< 60 years age, Urine, median (min - max)(n = 23)	-	55.3 (2.47 - 142)	49.85 (1.4 - 171)	46.54 (18 - 151)	0.157

$^{+}$ **- Baseline serum magnesium level was significantly higher than the 1st day level,** * **- Third day serum magnesium level was significantly higher than the baseline and 1st day levels.**

(0.19) vs. 1.88 (0.20) vs. 1.94 (0.18), p = 0.152, vs. 1.97 (0.18), p = 0.097). There were no significant differences in the median levels of 1st, 2nd, and 3rd days of urinary magnesium of all patients (43.10 (2.47 - 142.0) vs. 47.75 (1.40 - 171.0), p = 0.342, vs. 37.54 (2.67 - 151.0), p = 0.168) (Table 1, Figure 1, Figure 2).

There was no significant change in serum and urine magnesium levels of patients according to gender (Table 1).

The change in serum and 24-hour urine magnesium levels of 33 patients were evaluated by age over and under 60 years. The baseline median serum magnesium level was significantly higher than the 1st day level in patients aged ≥ 60 years (day 1: 2.0 (1.8 - 2.3) vs. day 2: 1.9 (1.6 - 2.0) vs. day 3: 1.9 (1.7 - 2.0) vs. day 4: 2.0 (1.6 - 2.1), p = 0.029). There was a statistically significant effect of time on serum magnesium levels of patients, and LSD corrected post hoc test showed that the 3rd day mean serum magnesium level was significantly higher than the baseline and 1st day levels in the group aged < 60 years (1.91 (0.19) vs. 1.89 (0.21) vs. 1.95 (0.19) vs. 1.98 (0.18), p = 0.049). In both groups, no significant change was determined in the 24-hour urine magnesium levels (Table 2).

DISCUSSION

Decreased gastrointestinal absorption or increased renal wasting are two default mechanisms for proton-pump-induced hypomagnesemia. The results of this study showed no significant change in serum and urinary

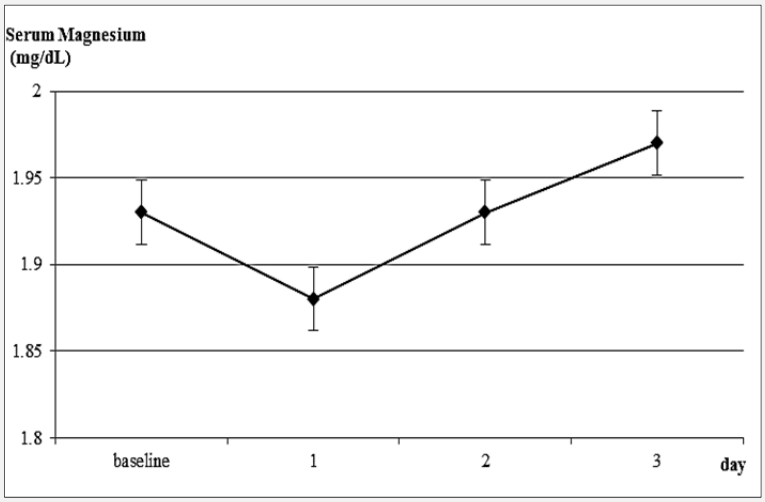

Figure 1. Daily changes of serum magnesium levels.

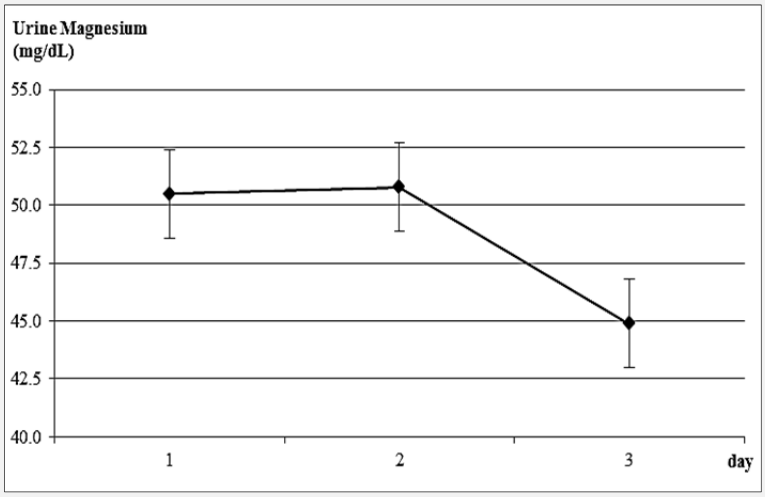

Figure 2. Daily changes of 24-hour urine magnesium levels.

magnesium levels with high-dose pantoprazole during the follow-up period. The serum magnesium levels of 58 patients showed a statistically non-significant decrease within the 1st day compared with the baseline values and then an increase up to baseline level on the 2nd day (1.94 mg/dL vs. 1.88 mg/dL vs. 1.94 mg/dL). On the 3rd day, the serum and urine magnesium levels of 33 patients were measured and the mean serum magnesium level was 1.97 mg/dL, which was just a little higher than the baseline value. Although statistically non-significant, the median urine magnesium level on the 3rd day was lower than the levels on the 1st and 2nd days (43.10 mg/dL vs. 47.75 mg/dL vs. 37.54 mg/dL). Magnesium absorption is almost passive in the intes-

tine, although active magnesium absorption is more important when dietary magnesium intake is extremely low [16,17]. In the current study, the patients had no oral or intravenous magnesium intake and were on high-dose PPI treatment. Total body magnesium was compensated by decreasing urinary wasting on the basis of these findings. However, it cannot be definitively stated whether this is a normal body compensating mechanism or the acute effect of high-dose intravenous PPIs. Two studies conducted in the 1990s prospectively evaluated the short-term effect of PPIs on intestinal absorption of electrolytes, including magnesium. Serfaty-Lacrosniere et al. tested the short-term effect of omeprazole on 13 normal participants in 1995. A control (n = 5) group and drug treatment group (n = 8) were formed and the treatment group received 40 mg/day omeprazole daily for 7 days prior to the study and during the 10 days of the study. Hydrochloric acid was applied to clarify the effect of acidity on mineral absorption after measurement of mineral values before and during omeprazole treatment. It was concluded that gastric pH changes alone did not modify the intestinal absorption of magnesium, calcium, phosphorus and zinc [18]. In another study by Jeppesen et al., 13 patients with short bowel syndrome were given 40 mg omeprazole or 150 mg ranitidine intravenously for 5 days. On the subsequent 3 days, the patients received no medications for gastric acid suppression as the control period. The intestinal absorption of sodium, potasium, calcium and magnesium was seen to be similar in the drug-free, omeprazole and ranitidine periods [19]. Similarly, in the current study, high-dose intravenous PPI was adminstered and serum magnesium levels did not changed signficantly.

Cundy et al. applied magnesium infusion testing to two patients with severe hypomagnesemia due to long-term PPIs to assess renal tubular handling and retention of parenteral magnesium load [12]. The renal excretion of magnesium remained extremely low until reaching normal blood level during the test and thus no evidence was reported of renal magnesium wasting in PPI-induced hypomagnesemia [12]. As the plasma magnesium concentration increased during the infusion test and hypomagnesemia was partially corrected by high-dose oral magnesium supplements while under PPI treatment, it was concluded that PPIs can inhibit active magnesium transport through ion channels TRMP 6 and 7 in the intestine [12]. Later, Hoorn et al. reported a case series of four patients with PPI-induced hypomagnesemia. The PPI therapy was discontinued in all patients and evaluation was made of the changes in serum values, urinary and fecal excretion of magnesium, potassium, and calcium. Gastrointestinal magnesium loss was the mechanism thought to be responsible because of very low urinary excretion of magnesium in that study [13]. Kuipers et al. evaluated a patient with PPI-induced hypomagnesemia over a period of 110 weeks using the trial and error method [20]. They reported normal renal magnesium conservation during PPI use and blamed gastrointestinal magnesium absorption as in the above-mentioned studies [20]. Most reports in literature have suggested renal magnesium conversion, similar to the current study findings. Recently, William et al. analyzed the 24-hour urinary magnesium excretion of 278 ambulatory patients which had been collected for retrospective nephrolithiasis evaluation and reported that PPI use was associated with significantly lower 24-hour urinary excretion similar to the findings in literature and of the current study [14].

Despite widespread usage, PPIs do not cause hypomagnesemia in the majority of patients. Person-specific mutations of TRMP 6/7, comorbidities such as malabsorptive conditions, dietary intake, age, medications, especially diuretics, and the duration of PPI use have been reported to be contributing risk factors for PPI-induced hypomagnesemia [8]. Hypomagnesemia is a class effect of all PPIs, for which duration of use is the main contributory factor. However, there have been different reports about usage time. In most case reports, hypomagnesemia has been diagnosed in patients on long-term PPI use [5]. In a systematic review, time to onset of hypomagnesemia was found to be highly variable and ranged from 14 days up to 13 years (mean 5.5 years) [21]. William et al. emphasized that hypomagnesemia emerged after an average of 10 - 15 years of PPI exposure [8]. However, in a community setting study by Markovits et al., an association of PPIs with hypomagnesemia was found even in the short term (< 4 months). Thus it was reported that PPI-induced hypomagnesemia should also be considered in short-term therapy [22]. In the current study, gender was not seen to have any effect on changes in serum magnesium levels. The effect of age was also evaluated on serum and 24-hour urine magnesium levels by PPIs. As the FDA warning refers to patients aged over 60 years (63 and 67 years) [5], in the current study, changes in serum and 24-hour urine magnesium levels were evaluated in patients grouped according to age as older or younger than 60 years. In the patient group aged ≥ 60 years, the serum magnesium levels on the 1st and 2nd days were significantly lower than the baseline value and increased to the level of baseline on the 3rd day. Although there was no significant change in the 24-hour urine magnesium levels in this group, there was an increase in urine magnesium excretion on the 2nd day of treatment which was not seen in the < 60 years age group. It then decreased on the 3rd day to below the level of the 1st day. Age may be an important factor for this phenomenon as the older patients in this study were seen to have a later compensatory protective response to preserve serum magnesium levels. There are conflicting findings in literature about the age effect on PPIH, and recently published articles mostly support our hypothesis. In a recent study, where the mean age of patients was 50.59 years, PPI use for 12 months was not associated with changes in serum magnesium levels [23], whereas, in a systematic review by Hess et al., the mean age of 12 published cases of PPI-induced hypomagnesemia was 67.4 years [21]. There are sufficient case reports and observational data

on this subject, although this is the first study to make a prospective evaluation of the short-term effects of high-dose PPIs on humans. The current study was larger than those of previous clinical studies. Limitations of the study could be said to be that patients more prone to hypomagnesemia were excluded and for ethical reasons there was no control group of non-oral intake for 4 days without PPI treatment.

CONCLUSION

Plasma levels and urinary excretion of magnesium did not change significantly during high-dose pantoprazol treatment in this study. Other contributing factors may have a greater impact on PPI-induced hypomagnesemia. The data of this study also suggests that there is no need to follow magnesium levels in patients hospitalized with upper GIH diagnosis while taking high-dose PPIs. Patients aged over 60 years may have a weaker magnesium preserving mechanism; therefore, they should be carefully monitored while under PPI treatment.

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Declaration of Interest:
There is no conflict of interest.

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