ACTA ABP BIOCHIMICA POLONICA

Vol. 64, No 3/2017
499–501
https://doi.org/10.18388/abp.2017_1505

Regular paper

Short-term proton pump inhibitor treatment may cause hypomagnesaemia in critically ill patients – a pilot study

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Many studies have suggested a link between long-term PPI treatment and hypomagnesaemia, though none of them investigated the short-term exposure in high-risk patients. We sought to investigate this issue in 90 critically ill patients. We assessed serum Mg concentrations, necessity of Mg supplementation, PPI dose, duration of PPI therapy and route of administration. In multiple analysis we found that Mg supplementation (positive effect/p=0.03) and enteral route of PPI administration (negative effect/p=0.02) had significant impact on Mg concentration. Although the deleterious relationship between short-term PPI treatment and Mg concentration was found, further studies should be provided to confirm this interesting effect.

Key words: proton-pump inhibitors, hypomagnesaemia, critically ill

Received: 12 January, 2017; revised: 28 February, 2017; accepted: 04 April, 2017; available on-line: 24 June, 2017

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Abbreviations: Mg, Magnesium; IPP, Proton-pump inhibitor; ICU, Intensive Care Unit; SAPS, Simplified Acute Physiology Score; CRRT, continuous renal replacement therapy

INTRODUCTION

Many studies have suggested a link between long-term PPI treatment and hypomagnesaemia (Park *et al,* 2014; Zipursky *et al.,* 2014; Kieboom *et al.,* 2015; Toh *et al.,* 2015). This effect is more pronounced when the exposure lasts at least 6 months while PPI dose seems to be of low importance. PPI-induced hypomagnesaemia is thought to be caused by Mg intestinal malabsorption, probably due to inhibition of TRPM6 and -7 active transport channels (Bai *et al.,* 2012).

PPIs are frequently used in ICU for stress ulcer prevention or treatment, although this indication still remains uncertain (Krag *et al.,* 2016). Hypomagnesaemia in critically ill patients may induce potentially fatal complications, including hypoparathyroidism, ventricular arrhythmias, coronary artery vasospasm or even sudden cardiac death (Epstein *et al.,* 2006; Hoorn *et al.,* 2010; El-Charabaty *et al.,* 2013). Therefore, we sought to verify the association between short-term treatment with PPI and serum Mg concentration in the ICU environment.

MATERIALS AND METHODS

This observational study included 90 consecutive patients hospitalized in the multidisciplinary ICU in 2015. Serum Mg concentrations, necessity of Mg supplementation, PPI dose, duration of therapy and route of its administration were assessed. SAPS II score was calculated. The results were adjusted to the fact of CRRT use. Serum magnesium level was measured by colorimetric method based on reaction with xylidyl blue in an alkaline medium with addition of EGTA.

Patient confidentiality was ensured as the dataset was fully anonymised. Approval of the Ethics Committee was not necessary because the project was non-interventional and did not extend beyond routine laboratory sampling. Informed consent was obtained from conscious patients.

The statistical analysis was based on the procedures available in the licensed MedCalc (v14) software. Quantitative variables are presented as mean with standard deviation (those normally-distributed) or median with interquartile range (IQR) (skewed distribution). All variables were tested for normal distribution using the Shapiro-Wilk test. Qualitative variables are presented as percentage. Between-group differences were evaluated with the chi-squared test. Student's t-test or U Mann-Whitney test were used for quantitative data. Correlation was determined by the use of Spearman rank coefficient (R). Multiple regression was used to verify findings from bivariate analyses. The p-value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study group are listed in Table 1. Mean serum Mg concentration was 0.96±0.17 mmol/l and was higher in patients who underwent CRRT (CRRT+1.0±0.17 mmol/l *vs.* CRRT – 0.94±0.16 mmol/l; p=0.04). Mg supplementation was necessary due to hypomagnesaemia in 50 subjects via a continuous infusion with mean dose of 2 g per day. Those subjects requiring Mg supplementation had higher Mg level (Suppl+ 0.99±0.19 mmol/l *vs.* Suppl– 0.92±0.13 mmol/l; p=0.04). PPIs were started on admission and used among all patients for 10 (IQR 5-21) days with a daily dose of 55 (IQR 40-70) mg. None of subjects received H2-blockers, calcium channels blockers, β-blockers nor thiazides as potential confounders. No symptoms of hypomagnesaemia were present after the first dose of PPIs. We found that patients with PPIs given intravenously only (PPI_{IV}) had higher Mg level compared to those who were treated intravenously and enterally (PPI_{PO}) (PPI_{IV} 1.02±0.17 *vs.* PPI_{PO} 0.93±0.16; p=0.02) (Fig. 1). There was no correlation between Mg level and PPI dose (All: R=0.05; p=0.6/PPI_{IV}: R=–0.21; p=0.2/PPI_{PO}: R=0.05; p=0.7). No correlation was found between PPI therapy duration and Mg level (R=–0.11; p=0.3) as well. Mul-

Table 1. Baseline characteristics of subjects

Variable	Value
Demographics	
Number of patients	90
Male gender	66%
Age [years]	64 ± 13
SAPS II [points]	53 (39-67)
Chronic obstructive pulmonary disease	19%
Coronary heart disease	69%
Arterial hypertension	68%
Diabetes mellitus	22%
Obesity	40%
ICU-related data	
Length of stay [days]	12 (6-27)
Mortality	41%
Primary ICU admission diagnosis	
Respiratory failure	25%
Circulatory failure	54%
Neurological disorders	5%
Sepsis	6%
Multi-organ failure	10%

ICU, intensive care unit; SAPS, Simplified Acute Physiology Score

tiple regression analysis proved that Mg supplementation (p=0.03) and enteral route of PPI administration (p=0.02) had statistically significant influence on Mg concentration (Table 2).

DISCUSSION

Up to our knowledge, this is the first investigation showing significant effect of short-term PPI use on Mg level in ICU patients. This interesting observation gives additional evidence that critically ill subjects should receive intravenous PPI treatment to prevent accidental hypomagnesaemia. Otherwise, enteral PPI treatment must be accompanied by Mg supplementation.

Molecular mechanisms of magnesium transporters action, including the pH-dependent regulation of transient receptor potential melastatin transporters in the enterocytes, were proposed to explain the effect of PPI on magnesium reabsorption, but may be only a small part of a more complicated interplay of molecular biology, pharmacology, and genetic predisposition, especially in critically ill subjects with multiple comorbidities and poly-drug therapy (William *et al.,* 2016).

Recent meta-analysis showed that long-term PPI use may increase the risk of hypomagnesaemia with

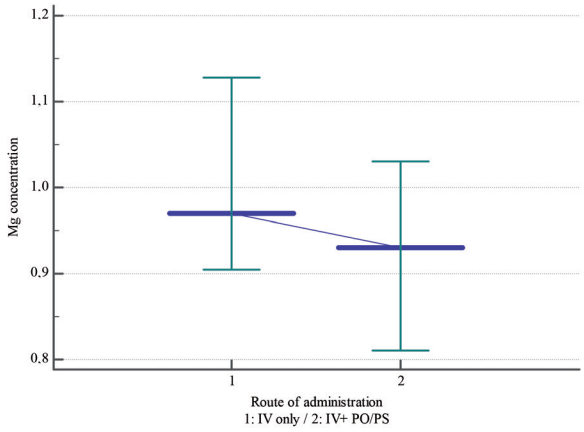

Figure 1. Serum magnesium concentration vs route of proton-pump inhibitor administration

OR=1.775 (95%CI 1.077–2.924) (Park *et al.,* 2014). However, significant heterogeneity among the included nine studies (p<0.001) prevented the authors from reaching definitive conclusions. Due to novelty of our pilot study the comparability with other observations is limited. Danziger and coworkers (2016) in a single-centre observational study covering 11 490 ICU patients found that the risk of hypomagnesaemia was 54% higher in patients who reported PPI use prior to admission but only if they were treated with diuretics.

One ought to remember that in critically ill patients PPI-induced hypomagnesaemia may be interfered by numerous confounders such as demographic data, use of loop diuretics, parenteral and enteral nutrition. Moreover, an attempt should be made to assess the impact of PPIs given prior to ICU admission. William and Danziger suggested that despite the increasing prevalence of this highly popular class of acid secretion inhibitors, and despite the potential significant risks associated with magnesium depletion, including cardiac arrhythmias and seizures, there are no well-designed studies to delineate the nature of this observed association (William *et al.,* 2016). Taken together, it is necessary to verify the impact of short-term high-dose PPI use on Mg concentration in a prospective randomised manner.

CONCLUSION

Our preliminary data show that even short-term high-dose enteral PPI treatment may cause hypomagnesaemia in critically ill patients.

Conflicts of interests

There are no conflicts of interests regarding this study.

Table 2. Multiple regression analysis for Mg concentration as the dependent variable

Independent variables	Coefficient of regression ± standard deviation	*P* value
Route of PPI administration	–0.09±0.04	0.02
PPI dose (per mg)	0.0001±0.0001	0.9
Need of Mg supplementation	0.08±0.03	0.03
CRRT use	0.07±0.04	0.06

CRRT, continuous renal replacement therapy; PPI, proton-pump inhibitor

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