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Original article

Serum magnesium and proton-pump inhibitors use: a cross-sectional study☆

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ABSTRACT

Objective: The aim of this study was to evaluate the association of serum magnesium levels with proton pump inhibitors (PPIs) use and other factors.
Methods: This was a cross-sectional study of 151 patients admitted with acute diseases in the Internal Medicine Division of the Hospital de Clinicas de Porto Alegre, after the exclusion of conditions that are commonly associated with hypomagnesemia: diarrhea; vomiting; chronic alcohol use; severely uncompensated diabetes mellitus; and chronic use of laxatives, diuretics or other drugs causing magnesium deficiency.
Results: All patients had normal serum magnesium levels. Serum albumin and creatinine levels were positively associated with serum magnesium levels, after adjusting for confounders. There was no difference between mean serum magnesium levels of PPI users and non-users, nor between men and women; there was also no correlation among age, serum phosphorus, and potassium levels with serum magnesium levels. Limitations of this study include the absence of an instrument for measuring adherence to PPI use and the sample size.
Conclusion: The association of PPI use and hypomagnesemia is uncommon. Congenital defects in the metabolism of magnesium may be responsible for hypomagnesemia in some patients using this drug class.

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Magnésio sérico e uso de inibidores de bomba de prótons: estudo transversal

Palavras chave:
Magnésio
Inibidores da bomba de prótons

RESUMO

Objetivo: O objetivo desse estudo foi verificar a associação do nível sérico do magnésio com o uso de inibidores de bomba de prótons (IBP) e outros fatores.
Métodos: Realizou-se estudo transversal com 151 pacientes admitidos com doenças agudas no serviço de medicina interna do Hospital de Clínicas de Porto Alegre. Foram excluídos aqueles pacientes com condições usualmente relacionadas à hipomagnesemia: diarréia;

☆ Study conducted at Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

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vômitos; diabéticos agudamente descompensados; uso crônico de laxantes, álcool, diuréticos ou outros fármacos relacionados.

Resultados: Todos os pacientes apresentaram níveis normais de magnésio. Albumina e creatinina sérica se associaram positivamente com os níveis de magnésio sérico, após ajuste para fatores confundidores. Não houve diferença no nível sérico de magnésio em usuários ou não-usuários de IBP ou entre homens e mulheres. Não houve correlação com idade, nível sérico de fósforo e potássio. As principais limitações desse estudo foram a ausência de instrumento para medir a adesão aos IBPs e o tamanho da amostra.

Conclusão: A associação do uso de IBP e hipomagnesemia é rara. Defeitos congênitos no metabolismo do magnésio devem ser responsáveis pelo surgimento de hipomagnesemia em usuários de dessa classe de fármacos.

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Introduction

The most potent drugs available to reduce gastric acid secretion are the proton pump inhibitors (PPIs).[1] PPIs selectively and irreversibly inhibit the gastric H^+/K^+ ATPase. As this is the final step of acid secretion, this drug class has proved to be more effective than other anti-secretory drugs.[2] These drugs are widely used, and they are generally safe and effective. However, there are recent reports associating PPI use and magnesium deficiency.[3–10]

Magnesium is essential for the function of more than 300 cellular enzymes. Its deficiency can be accompanied by hypocalcemia, hypokalemia, and serious neuromuscular and cardiovascular problems.[11]

On March 2, 2011, the Food and Drug Administration (FDA) issued a Drug Safety Communication informing the public that prescription PPI drugs may cause low serum magnesium levels if taken for prolonged periods of time.[12] Nevertheless, there is little knowledge about this association. Thus, the aim of this study was to evaluate the prevalence of hypomagnesemia in patients with no other factors commonly associated to low serum magnesium, admitted to the emergency room of the Internal Medicine Division of the Hospital de Clinicas de Porto Alegre (HCPA), a tertiary care facility in Southern Brazil. Factors associated to serum magnesium levels were also studied.

Methods

A cross-sectional study was designed. The study was approved by the local ethics committee, and patients were included after informed consent. Blood and urine samples were collected in the morning, after a fast of at least four hours. Data such as age, gender, use of PPI, and use of other medications were obtained from medical charts. Patients with diarrhea or vomiting, chronic alcohol use, and severe uncompensated diabetes mellitus were excluded, as well as patients with chronic use of laxatives, diuretics, and other drugs that could cause magnesium deficiency, such as amphotericin B, aminoglycosides, and cyclosporine.

Serum and urine were kept at -70 °C until biochemical measurements in the same assay run. Serum and urinary magnesium levels were measured by a method based on reaction with blue xilidil. The magnesium ions react with blue xilidil in an alkaline medium to form a water soluble purple/red complex. The increase in absorbance of the blue xilidil at 505/694 nm is proportional to the concentration of magnesium in the sample. The measurement was performed on the device Advia® 1800, with normal range for serum magnesium: 1.3-2.7 mg/dL.

Serum calcium, phosphorus, potassium, creatinine, albumin, and urine creatinine levels were measured according to the HCPA routine.

Factors possibly associated with serum magnesium levels were evaluated through Student's t-test or the Mann-Whitney test, and Pearson's and Spearman's correlation coefficients, when indicated. Results were considered as statistically significant when $p < 0.05$. Multiple linear regression was used to isolate possible confounding variables. All analyses were performed using the Statistical Package for Social Sciences (SPSS), version 17.0.

Results

From September, 2010 to June, 2011 approximately 800 patients were admitted to the emergency room. Of these, around 635 patients had exclusion criteria, 14 patients refused to participate, and 151 patients were included in the study. The baseline data are described in Table 1. Their ages ranged from 17 to 94 years.

All patients had normal serum magnesium levels. Omeprazole was the only PPI used in all patients treated with this drug

Table 1 – Baseline characteristics of patients using PPI and non-users (n = 151).

	PPI (n = 56)	No PPI (n = 95)	p
Age (years)	62.0(52.3/72.0)	54.0(41/66)	0.11
Gender (n M/n F)	29/27	48/47	0.88
Serum magnesium (mg/dL)	1.97 ± 0.20	2.00 ± 0.25	0.33
Serum potassium (mEq/L)	4.51 ± 0.47	4.39 ± 0.48*	0.34
Serum calcium (mg/dL)	8.53 ± 0.74	8.54 ± 0.59	0.27
Serum phosphorus (mg/dL)	3.30(2.53/3.68)	3.39(2.53/3.68)	0.12
Serum albumin (g/dL)	3.70 ± 0.52	3.80 ± 0.43	0.21
Serum creatinine (mg/dL)	0.88 ± 0.35	0.86 ± 0.49	0.42

M, male; F, female.
Data are shown as mean ± standard deviation or median (P25/P75).
* n = 92.

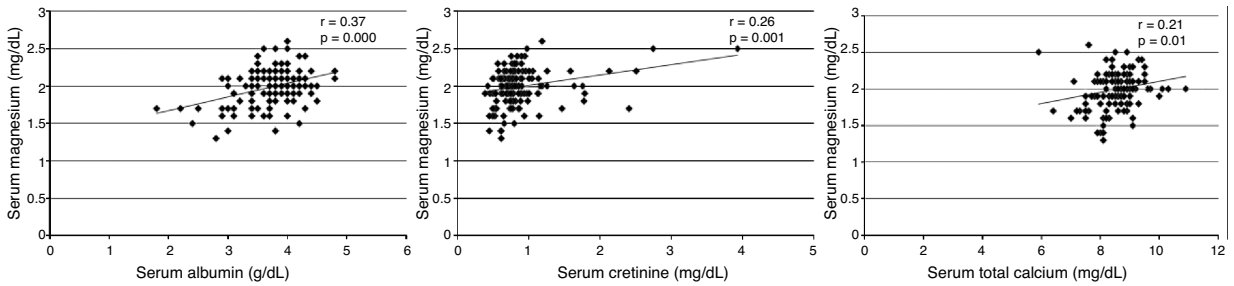

Fig. 1 – Relationship among serum magnesium, albumin, creatinine (mg/dL) and calcium levels. Pearson coefficients are shown.

class, and was administered as a single dose 30 minutes before breakfast. 42 patients received 20 mg and 14 received 40 mg. The reasons for PPI use included chronic gastritis with *H. pylori* positive culture, dyspeptic symptoms, gastroesophageal reflux disease, peptic duodenal ulcer, dyspepsia, gastritis, epigastric pain, and esophageal hiatus hernia.

There was no difference (p = 0.59) between the mean serum magnesium levels of men (1.98 ± 0.27) and women (2.00 ± 0.19). There was no correlation between age and serum phosphorus or potassium levels with serum magnesium levels. Serum albumin, creatinine, and calcium levels were positively correlated with serum magnesium levels, as shown in Fig. 1. After multiple linear regression, only serum albumin and creatinine levels were independently associated with serum magnesium levels (Table 2).

Discussion

In this study, no patient had hypomagnesemia, although 56 were using PPIs. The prevalence of hypomagnesemia was lower than previously described in hospitalized patients, ranging from 12% to 50%.[13] This may be due to the exclusion criteria of this study, which withdrew patients with conditions or using drugs commonly associated to hypomagnesemia, such as chronic diarrhea, vomiting, use of diuretics, gentamicin, cisplatin, ciclosporin, and others.

Data from this study suggest that the association between PPI use and hypomagnesemia is uncommon. It is possible that hypomagnesemia occurs in patients with genetic susceptibility, which may become clinically evident with PPI use. Several inherited diseases were described as causing low serum magnesium. Hypomagnesemia with secondary hypocalcemia is caused by a defect in TRPM6 channel, present in the intestine and renal tubules. The loss of function of TRPM6 leads to a reduction in intestinal absorption of magnesium, also accompanied by decreased renal reabsorption of this cation.[14,15] There are other hereditary causes of hypomagnesemia that lead to renal losses, such as familial hypomagnesemia with hypercalciuria and nephrocalcinosis, where a mutation in the gene encoding claudin-16, a tight junction protein present in the kidney responsible for the paracellular transport of magnesium, decreases magnesium reabsorption. Gitelman's syndrome also affects renal transport, and is characterized by hypomagnesemia and hipokalemia. Bartter's syndrome may have mutations of various proteins, and all these mutations affect the transport of magnesium through the thick ascending loop of Henle.[16]

Table 2 – Multiple linear regression analyses of factors affecting variation of serum magnesium (n =151).

Variable	B	Beta	p
Albumin	0.157	0.319	0.001
Creatinine	0.151	0.297	0.000
Calcium	0.029	0.083	0.439

Dependent variable, serum magnesium.
B, coefficient; Beta, intercept.

The mechanism of hypomagnesemia associated with PPI use is unknown; however, there is a decrease in the intestinal absorption of magnesium and the role of the kidney it is not well established.[9] As an increase in urinary excretion of magnesium before correction of hypomagnesemia has been observed in one patient, increased urinary loss cannot be excluded.[3] Although two patients described by Cundy et al. presented increased urinary magnesium excretion only when serum magnesium levels were normal, after intravenous magnesium infusion, it could not be excluded that other drugs affecting renal magnesium handling could have contributed to their results.[9]

Serum albumin and magnesium levels were positively correlated, as expected, since 30% of magnesium circulates bound to this protein.[11] For other ions such as calcium, the calculation of total serum concentration is performed considering the albumin levels,[17] but this correction is not usually recommended for magnesium. The positive correlation between albumin and magnesium suggests that this correction should also be made for this ion in order to obtain more reliable serum values.

There was also a positive correlation between serum creatinine and magnesium levels. Serum magnesium increases in the presence of kidney damage, reflected by increased blood creatinine and decreased glomerular filtration rate. This is due to loss of the ability of the kidneys to properly excrete magnesium. This correlation was expected, since it is also true for other electrolytes.

Limitations of this study include the lack of an instrument to measure adherence to the use of PPI, and the sample

size. No patient had low levels of magnesium, so a larger sample is needed to evaluate the prevalence of this adverse effect.

Conclusion

PPI use did not affect mean serum magnesium levels in this study. The association between PPI use and hypomagnesemia is uncommon.

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Conflicts of interest

The authors declare no conflicts of interest.

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