http://www.kidney-international.org

see commentary on page 553

Proton-pump inhibitor use is associated with low serum magnesium concentrations

John Danziger[1], Jeffrey H. William[1], Daniel J. Scott[2], Joon Lee[2], Li-wei Lehman[2], Roger G. Mark[2], Michael D. Howell[1], Leo A. Celi[1,2] and Kenneth J. Mukamal[1]

[1]*Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA and* [2]*Massachusetts Institute of Technology, Harvard-MIT Division of Health Sciences and Technology, Boston, Massachusetts, USA*

Although case reports link proton-pump inhibitor (PPI) use and hypomagnesemia, no large-scale studies have been conducted. Here we examined the serum magnesium concentration and the likelihood of hypomagnesemia (<1.6 mg/dl) with a history of PPI or histamine-2 receptor antagonist used to reduce gastric acid, or use of neither among 11,490 consecutive adult admissions to an intensive care unit of a tertiary medical center. Of these, 2632 patients reported PPI use prior to admission, while 657 patients were using a histamine-2 receptor antagonist. PPI use was associated with 0.012 mg/dl lower adjusted serum magnesium concentration compared to users of no acid-suppressive medications, but this effect was restricted to those patients taking diuretics. Among the 3286 patients concurrently on diuretics, PPI use was associated with a significant increase of hypomagnesemia (odds ratio 1.54) and 0.028 mg/dl lower serum magnesium concentration. Among those not using diuretics, PPI use was not associated with serum magnesium levels. Histamine-2 receptor antagonist use was not significantly associated with magnesium concentration without or with diuretic use. The use of PPI was not associated with serum phosphate concentration regardless of diuretic use. Thus, we verify case reports of the association between PPI use and hypomagnesemia in those concurrently taking diuretics. Hence, serum magnesium concentrations should be followed in susceptible individuals on chronic PPI therapy.

Kidney International (2013) **83,** 692–699; doi:10.1038/ki.2012.452; published online 16 January 2013

KEYWORDS: diuretics; electrolytes; gastrointestinal medications; mineral metabolism

Correspondence: *John Danziger, Department of Medicine, Division of Nephrology, Beth Israel Deaconess Medical Center, 185 Pilgrim Road, Farr 8, Boston, Massachusetts 02215, USA. E-mail: jdanzige@bidmc.harvard.edu*

Received 18 July 2012; revised 23 October 2012; accepted 26 October 2012; published online 16 January 2013

Although proton-pump inhibitors (PPIs) are extremely widely used, with over 100 million US prescriptions in 2007,[1] increasing attention has focused on the adverse effects of this class of medicine, including respiratory infections,[2] renal failure,[3,4] *Clostridium difficile* colitis,[5,6] hip fractures,[7] and drug–drug interactions.[8] Recently, a potential association between chronic PPI use and hypomagnesemia has been reported. Approximately 30 cases of severe hypomagnesemia in patients on PPI therapy have been identified in the literature, with symptoms ranging from cardiovascular instability to neuroexcitability, including tetany and seizures.[9–20] In light of these case reports and others from the Adverse Event Reporting System, the US Food and Drug Administration released a 'drug safety communication' in March 2011 regarding the risk of PPI-induced hypomagnesemia. They suggested that health care professionals should consider obtaining baseline and periodic follow-up serum magnesium levels for those patients expected to be long-term PPI users, particularly among those on diuretics and other medicines that could predispose to hypomagnesemia.[21]

Magnesium, as the second most common intracellular cation, is important in a wide range of cellular functions, including protein synthesis, enzymatic reactions, and the regulation of ion channels. The classic symptoms of severe hypomagnesemia include tetany, convulsions, bradycardia, hypotension, and death.[22–24] Even mild hypomagnesemia may be clinically important and has been associated with cardiovascular and total mortality,[25] possibly through effects on left ventricular size,[26,27] hypertension,[28,29] endothelial function,[30] and insulin resistance.[31]

Beyond case reports and a case series,[32] little is known about the potential effect of PPI use on magnesium concentrations, with no large-scale data currently available. This lack of robust data is particularly important given the costs associated with surveillance of magnesium levels among patients taking PPIs and the potential risks of hypomagnesemia.

To address these questions, we examined the association of acid-suppressive medication use with serum magnesium concentrations in a large sample of patients admitted to a single medical center in whom information on current

outpatient medication use and admission serum magnesium levels was available. Given that the indications for PPI and histamine-2 receptor antagonist (H_2RA) use are similar, we compared both PPIs and H_2RA users to those not taking acid-suppressive medications.

RESULTS

Patient admission characteristics

Of the 11,490 unique intensive care unit (ICU) admissions from 2001 to 2008, we documented PPI use in 23% ($n = 2632$) before admission, compared with 6% ($n = 657$) on a H_2RA. As seen in Table 1, PPI users tended to be older, had worse renal function, and had a higher prevalence of comorbidities than those on neither medication.

Relationship of PPI use to magnesium concentrations

As shown in Table 2, baseline unadjusted magnesium concentrations did not differ by type of acid-suppressive medication. However, after adjusting for patient demographics and renal function (Model I), and in the fully adjusted model (Model II), PPI exposure was significantly associated with lower magnesium concentrations compared with those not taking acid-suppressive therapy, in a model adjusted for diuretic use. Age and renal function were both important independent confounders that accounted for the change in directionality of the effect of PPIs on magnesium concentrations. We did not find a significant association between H_2RA exposure and magnesium concentration in either model, although the s.e's for this less prevalent exposure were comparatively larger.

Diuretic use significantly modified the effect of PPI exposure on magnesium concentrations ($P = 0.03$ for multiplicative interaction term). As seen in Table 3, diuretic users were similar in age, gender, ethnicity, and presence of comorbidities, regardless of PPI or H_2RA exposure, but had significantly worse renal function. In unadjusted analysis of diuretic users, those on a PPI medication had significantly lower magnesium concentrations than those not

Table 1 | Baseline characteristics by acid suppression medication

	Proton-pump inhibitors ($n = 2632$)	H_2 receptor antagonists ($n = 657$)	No acid-suppressive medications ($n = 8201$)	*P*-value[a]
Age, mean (s.d.), years	67.8 (15.4)	66.9 (15.9)	61.1 (19.2)	<0.001
Male, no. (%)	1403 (53.3)	368 (56.3)	4796 (58.5)	<0.001
Ethnicity, no. (%)				
White	2022 (76.8)	496 (75.5)	6054 (73.8)	<0.001
African American	245 (9.3)	61 (9.3)	682 (8.3)	<0.001
Hispanic or Latino	79 (3.0)	19 (2.9)	292 (3.6)	<0.001
Asian	59 (2.2)	14 (2.1)	225 (2.7)	<0.001
Other	52 (2.0)	10 (1.52)	244 (3.0)	<0.001
Unknown	175 (6.7)	57 (8.7)	704 (8.6)	<0.001
Past medical history, no. (%)				
Hypertension	1009 (38.4)	253 (38.5)	2749 (33.5)	<0.001
Diabetes	749 (28.5)	184 (28.0)	1671 (20.4)	<0.001
Congestive heart failure	623 (23.7)	143 (21.8)	1215 (14.8)	<0.001
Liver disease	210 (8.0)	36 (5.5)	331 (4.0)	<0.001
Renal failure	164 (6.2)	41 (6.2)	255 (3.1)	<0.001
Metastatic cancer	158 (6.0)	41 (6.2)	382 (4.7)	0.010
Alcohol abuse	120 (4.6)	22 (3.4)	555 (6.8)	<0.001
Psychoses	95 (3.6)	30 (4.6)	330 (4.0)	0.46
Vital signs, mean (s.d.)				
Temperature, °C	36.8 (0.59)	36.8 (0.57)	36.9 (0.60)	<0.001
Systolic blood pressure, mm Hg	119.8 (17.5)	120.5 (16.6)	120.1 (16.8)	0.60
Heart rate, /min	75.4 (13.6)	76.0 (13.1)	76.1 (13.5)	0.067
Laboratory values on admission, mean (s.d.)				
Magnesium, mg/dl	1.93 (0.41)	1.93 (0.38)	1.91 (0.40)	0.24
Calcium, mg/dl	8.61 (0.83)	8.65 (0.88)	8.57 (0.87)	0.004
Phosphate, mg/dl	3.68 (1.28)	3.66 (1.14)	3.58 (1.17)	<0.001
Creatinine, mg/dl	1.50 (1.52)	1.34 (1.22)	1.22 (1.20)	<0.001
Ratio of 24 h/baseline serum creatinine	0.99 (0.31)	1.06 (0.60)	1.01 (0.34)	<0.001
Glucose, mg/dl	153.1 (90.5)	154.6 (92.8)	152.2 (98.3)	0.77
Hematocrit, %	33.6 (6.4)	34.5 (6.3)	35.5 (6.7)	<0.001
Diuretic use, no. (%)	1034 (39.3)	229 (34.9)	2023 (24.7)	<0.001

Abbreviation: H_2, histamine-2.
[a]*P*-values reflect across-group differences.