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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.

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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*

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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.

Table 2 | Association between acid suppression therapy and serum magnesium concentration

	Proton-pump inhibitors		H_2 receptor antagonists		No acid-suppressive medications
	β-Coefficient ± s.e.	*P*-value	β-Coefficient ± s.e.	*P*-value	Reference
Unadjusted model	0.007 ± 0.004	0.12	0.007 ± 0.008	0.41	—
Model I[a]	− 0.011 ± 0.004	0.01	− 0.005 ± 0.008	0.53	—
Model II[b]	− 0.012 ± 0.004	0.005	− 0.008 ± 0.007	0.30	—
Stratified analysis[c]					
Diuretic use ($n = 3286$)	− 0.028 ± 0.007	<0.001	− 0.009 ± 0.013	0.50	—
No diuretic use ($n = 8204$)	− 0.003 ± 0.005	0.61	− 0.008 ± 0.009	0.38	—

Abbreviation: H_2, histamine-2.
Reference category is those on no acid-suppressive medications. β-Coefficients ± s.e's and *P*-values are provided for each variable.
[a]Model I includes age, gender, ethnicity, and renal function.
[b]Model II includes all variables in Model I and the addition of systolic blood pressure, heart rate, temperature, serum calcium, serum phosphate, serum glucose, hematocrit, diuretic use, and 30 comorbidities.
[c]Stratified analysis: when entered into Model II, a multiplicative interaction term between proton-pump inhibitor (PPI) and diuretic use was significant ($P = 0.03$), and the analysis is presented stratified by diuretic exposure. An interaction term between H_2RA use was not significant.

Table 3 | Baseline characteristics of diuretic users

	Proton-pump inhibitors ($n = 1034$)	H_2 receptor antagonists ($n = 229$)	No acid-suppressive medications ($n = 2023$)	*P*-value[a]
Age, mean (s.d.), years	70.6 (13.8)	71.3 (13.2)	71.4 (13.8)	0.29
Male, no. (%)	513 (49.6)	115 (50.2)	1084 (53.6)	0.10
Ethnicity, no. (%)				
White	776 (75.1)	173 (75.6)	1506 (74.4)	0.35
African American	117 (11.3)	26 (11.4)	219 (10.8)	0.35
Hispanic or Latino	36 (3.5)	6 (2.6)	46 (2.3)	0.35
Asian	18 (1.7)	2 (0.87)	34 (1.7)	0.35
Other	23 (2.2)	4 (1.8)	41 (2.0)	0.35
Unknown	64 (6.2)	18 (7.9)	177 (8.8)	0.35
Past medical history, no. (%)				
Hypertension	425 (41.1)	98 (42.8)	868 (42.9)	0.63
Diabetes	344 (33.3)	77 (33.6)	648 (32.0)	0.74
Congestive heart failure	391 (37.8)	81 (35.4)	636 (31.4)	0.002
Liver disease	123 (11.9)	16 (7.0)	91 (4.5)	<0.001
Renal failure	55 (5.3)	14 (6.1)	102 (5.0)	0.78
Metastatic cancer	39 (3.8)	11 (4.8)	82 (4.1)	0.77
Alcohol abuse	49 (4.7)	9 (3.9)	66 (3.3)	0.14
Psychoses	33 (3.2)	2 (0.9)	54 (2.7)	0.09
Vital signs, mean (s.d.)				
Temperature, °C	36.8 (0.60)	36.7 (0.56)	36.8 (0.58)	0.50
Systolic blood pressure, mm Hg	120.0 (18.2)	120.4 (16.8)	119.3 (17.0)	0.43
Heart rate, /min	73.9 (13.3)	73.9 (13.7)	73.5 (12.8)	0.70
Laboratory values on admission, mean (s.d.)				
Magnesium, mg/dl	1.96 (0.42)	2.0 (0.39)	2.0 (0.41)	0.002
Calcium, mg/dl	8.66 (0.82)	8.74 (0.85)	8.72 (0.80)	0.15
Phosphate, mg/dl	3.76 (1.32)	3.78 (1.14)	3.74 (1.23)	0.82
Creatinine, mg/dl	1.57 (1.28)	1.45 (1.08)	1.44 (1.10)	0.008
Ratio of 24 h/baseline serum creatinine	0.97 (0.23)	1.02 (0.28)	1.01 (0.31)	<0.001
Glucose, mg/dl	156.4 (92.0)	153.8 (97.9)	162.1 (113.2)	0.25
Hematocrit, %	33.4 (6.33)	33.5 (6.10)	34.5 (6.70)	<0.001

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

taking acid-suppressive therapies ($P = 0.002$). In multivariable analysis of those on diuretics (Table 2), PPI use was associated with a 0.028 (± 0.007) mg/dl lower serum magnesium concentration. In diuretic naive individuals, PPI use was not associated with a change in serum magnesium concentration. There was no association between H_2RA use and serum magnesium concentration in either diuretic or non-diuretic group. An interaction term between H_2RA use and diuretic use was not significant ($P = 0.9$).

Relationship of PPI use to hypomagnesemia

We next assessed whether PPI use was related to frank hypomagnesemia, defined as a serum magnesium concentration <1.6 mg/dl. In a fully adjusted analysis, neither PPI nor H_2RA exposure was associated with hypomagnesemia. However, diuretic use again significantly modified the effect of PPI exposure on magnesium concentrations ($P<0.001$). As seen in Table 4, PPI use was associated with a 54% increased odds of hypomagnesemia in diuretic users compared with diuretic users not taking acid-suppressive therapy. PPI use was not associated with an increased risk of hypomagnesemia among patients not taking diuretics.

Effect of different types of diuretics on the association between PPI exposure and magnesium levels

Given the modifying effect of diuretics, we then assessed whether the type and number of diuretic medications further influenced the association between PPI exposure and magnesium concentrations. As seen in Table 5, the effects of PPI exposure on magnesium concentrations were similar in individuals taking any type of single diuretic agent, although the association was strongest in those taking a loop diuretic. The effect of PPI exposure on magnesium concentrations was not altered by the use of multiple diuretics. H_2RA exposure was not associated with differences in magnesium concentrations in any group.

Acid-suppressive medication and phosphate

To test the specificity of our analysis, we also evaluated PPI use and serum phosphate. Similar to magnesium, phosphate concentrations are affected by nutritional intake, diuretic use, and renal function, yet should not be affected by PPI or H_2RA use. Neither PPI nor H_2RA use was associated with serum phosphate levels, regardless of diuretic use (interaction term P-values both >0.05), in whole cohort analysis or in the subset of diuretics users (all P-values >0.05).

DISCUSSION

In this large hospital-based cross-sectional study, PPI exposure before admission was associated with lower serum magnesium concentrations in those patients concurrently using diuretics. The combination of diuretic and PPI exposure was associated with an almost 55% increased odds of hypomagnesemia compared with those on diuretics who were not taking acid-suppressive medications. PPI use was not associated with magnesium in diuretic naive individuals.

Although the risk of hypomagnesemia has been suggested by smaller observational studies, this study is the first to our knowledge to provide an analysis between PPI use and magnesium concentrations in a large sample, and supports the notion that PPI use may lead to hypomagnesemia in susceptible individuals.

The mechanism as to how PPI use may lead to hypomagnesemia is not certain. Magnesium homeostasis depends on the balance between intestinal absorption and renal excretion. Intestinal absorption occurs through two major pathways: active and passive. Active transcellular transport across the apical lumen occurs via the channel transient receptor potential melastatin 6.[33] Passive movement down a concentration gradient occurs paracellularly,

Table 4 | Association between acid suppression therapy and hypomagnesemia[a]

	Proton-pump inhibitors			H_2 receptor antagonists			No acid-suppressive medications	
	Cases, *n* (%)	Odds ratio (95% CI)	*P*-value	Cases, *n* (%)	Odds ratio (95% CI)	*P*-value	Cases, *n* (%)	Ref.
Study population[b]	405 (15.3)	1.10 (0.96–1.25)	0.18	94 (14.3)	0.97 (0.76–1.23)	0.81	1362 (16.6)	—
Diuretic use ($n=3286$)	161 (15.6)	1.54 (1.22–1.95)	<0.001	17 (7.4)	0.63 (0.36–1.03)	0.07	223 (11.0)	—
No diuretic use ($n=8204$)	244 (15.2)	0.92 (0.78–1.09)	0.35	77 (18.0)	1.14 (0.85–1.49)	0.39	1139 (18.4)	—

Abbreviations: H_2, histamine-2; Ref., reference category.
Reference category is those on no acid-suppressive medications.
[a]Adjusted analysis using all variables from Model II, with magnesium dichotomized at <1.6 mg/dl.
[b]A multiplicative interaction term between proton-pump inhibitor (PPI) and diuretic use was significant ($P<0.001$). A multiplicative interaction term between histamine-2 receptor antagonist (H_2RA) and diuretic use was also significant ($P=0.01$).

Table 5 | Effect of diuretic type on association between acid suppression therapy and serum magnesium concentrations

	Serum magnesium concentration (mg/dl)				
	Proton-pump inhibitors		H_2 receptor antagonists		No acid-suppressive medications
	β-Coefficient ± s.e.	*P*-value	β-Coefficient ± s.e.	*P*-value	Ref.
Thiazide diuretics ($n=994$)	−0.027 ± 0.015	0.07	−0.013 ± 0.028	0.63	—
Loop diuretics ($n=1631$)	−0.030 ± 0.010	0.003	−0.004 ± 0.018	0.80	—
Other diuretics ($n=89$)	−0.026 ± 0.055	0.63	−0.084 ± 0.133	0.54	—
Multiple ($n=572$)	−0.033 ± 0.018	0.06	−0.033 ± 0.030	0.27	—

Abbreviations: H_2, histamine-2; Ref., reference category.
Reference category is those on no acid-suppressive medications within each diuretic class. β-Coefficients ± s.e's and *P*-values are provided for each variable.

modulated by the tight junction proteins claudin-16 and claudin-19,[34] and is postulated to be the major route of magnesium absorption. Renal excretion primarily depends on tubular reclamation in the proximal tubule and thick ascending limb via paracellular absorption,[35] with some active absorption in the distal convoluted tubule.[36] Diuretics, by affecting the electrochemical gradient within the tubular lumen, inhibit tubular magnesium reclamation.[35,36]

Emerging clinical and basic scientific data suggest that PPIs inhibit intestinal absorption rather than causing renal wasting. In a case series of hypomagnesemic patients on PPI therapy,[12] urine magnesium levels were appropriately low. Furthermore, repletion with intravenous magnesium rapidly corrected serum concentrations, whereas for many,[9,11] but not all,[13] oral magnesium seemed to have less of an effect. Recent cell culture data suggest that PPIs may impair passive magnesium absorption across intestinal epithelial cells.[37] Although H_2RA use affects the pH of the gastric epithelium, H_2RA use has not been associated with hypomagnesemia, suggesting a pH-independent mechanism. Our study results also support this distinction.

Although the observed effect size of PPI exposure on magnesium concentration is modest, it may reflect larger differences in magnesium homeostasis that are clinically important. Because magnesium is primarily stored within the skeleton,[38] magnesium efflux from the bone may maintain serum concentrations, despite a net negative balance. In a manner similar to net acid retention seen in chronic kidney disease, where despite a loss of renal hydrogen excretion, serum bicarbonate levels are maintained by efflux of bicarbonate from the bone, PPI exposure may lead to a net negative magnesium balance with modest changes in serum magnesium concentration. Chronic magnesium egress may induce bone mineral loss, potentially explaining the association between long-term PPI use and osteoporosis in several observational studies,[39,40] although not confirmed by others.[41,42] Carefully designed balance studies are needed to further address whether PPI exposure affects net magnesium homeostasis independently of serum concentrations.

Given the remarkable popularity of PPIs and the relative paucity of reported cases of hypomagnesemia, our findings should be contextualized. It is possible that rare genetic variants in magnesium transport channels or cell junction proteins might account for the observed cases reports of profound hypomagnesemia, with less generalizability to the larger population. However, it is also plausible that chronic PPI use decreases intestinal magnesium absorption in all individuals, yet net changes in magnesium balance are prevented by compensatory upregulation of renal tubular magnesium reclamation. It is possible that only in those with diuretic-induced impairment of renal magnesium reclamation that a negative magnesium balance ensues.

There are several important limitations of our analysis. Given the observational nature of the study, causality cannot be established between PPI exposure and serum magnesium concentration. In addition, as our sample is comprised of critically ill patients, generalizability to the outpatient population is uncertain. However, the majority of subjects in this analysis were admitted through the Emergency Department, where labs are typically drawn upon arrival and reflect pre-hospitalization values. Magnesium levels of patients transferred from outside facilities were not likely to represent a true initial serum magnesium level and were therefore excluded. In addition, our findings are strengthened by accounting for illness-associated predictors of magnesium.

Although MIMIC-II is an exceedingly rich data set and we captured many markers of illness severity, unmeasurable preadmission confounders likely exist. We neither had information regarding length of illness before presentation, nor information about preceding nutritional intake. However, PPI use seemed to have no effect on phosphate, the other major nutritionally dependent mineral. In addition, although we included terms for both initial serum creatinine and change in creatinine over the first 24 h of hospitalization, our model likely does not fully capture the effect of renal function on magnesium given known limitations of creatinine-based estimates of kidney function.[43] However, because unmeasured renal dysfunction should lead to higher magnesium concentrations, and given the higher prevalence of renal dysfunction observed among patients taking PPIs, this residual confounding would tend to lead to an underestimate of the true association between PPI use and hypomagnesemia.

In addition, it is likely that there was misclassification in exposure to acid-suppressive medication use and other medications that do not require a prescription. Many forms of magnesium supplementation may not have been recorded as a preadmission medication. In addition, PPIs became available without a prescription during the study period, likely reducing the consistency with which they were reported in admission records. However, if misclassification of PPI use is unrelated to serum magnesium levels, then this would likely bias our findings toward a false finding of no association.

Finally, as we measured PPI use solely through the identification of the medication on a preadmission medication list, we were unable to establish the dose or duration of its use. Given the potential importance of the chronicity of PPI use on serum magnesium, further studies that include this information are clearly needed.

In summary, we found that, among a large sample of critically ill patients, magnesium levels on admission were lower among patients in whom both PPI and diuretic use was documented beforehand. Our findings support the current Food and Drug Administration advisory suggesting that PPI use can lead to hypomagnesemia in susceptible individuals. Further data from well-designed prospective studies are needed to inform clinical decision-making regarding monitoring and replacement of magnesium among patients who take these widely used medications.

MATERIALS AND METHODS

Study population

We used the MIMIC-II (Multiparameter Intelligent Monitoring in Intensive Care) research database, a joint venture managed by researchers from the Laboratory for Computational Physiology at Massachusetts Institute of Technology and the Department of Medicine at the Beth Israel Deaconess Medical Center (BIDMC).[44] BIDMC is a large, urban academic medical center. The database contains high temporal resolution data from clinical systems, including lab results, electronic documentation, and bedside monitor trends and waveforms, for all patients admitted to a BIDMC ICU between 2001 and 2008. Use of the MIMIC II database has been approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology.

MIMIC-II contains data from 24,581 adult patients who were admitted to surgical or medical ICUs at BIDMC. On the basis of ICD-9 codes assigned at discharge, we excluded individuals with conditions likely to influence PPI use and magnesium levels, including acute and chronic diarrheal illnesses, chronic inflammatory bowel disease, malabsorptive conditions, end stage renal disease, preeclampsia, and primary hyperparathyroidism ($n = 2639$). Another 5526 patients were excluded because of the lack of an identifiable medication section in the initial History and Physical examination upon admission to the hospital. Because we could not account for medication exposure or magnesium administration while hospitalized at other institutions, 3413 patients transferred from other medical facilities were excluded. In addition, we excluded 27 patients with missing comorbidity data and 1486 individuals who did not have magnesium levels measured on admission, leaving a final sample of 11,490 unique patients. The first hospitalization with an ICU stay was used for all patients.

Medication exposure and outcome

PPI or H_2RA exposure was defined as any PPI or H_2RA listed as a preadmission medication. We developed a Natural Language Processing (NLP) algorithm that searched discharge summaries for a discrete home medication section within the History and Physical examination performed on admission. Of those with an identifiable section, the NLP then processed the medications to find individual entries of PPIs, H_2RAs, and diuretics. We performed a validation of the NLP algorithm by formal physician examination of the discharge summaries of 100 random cases that included patients in five different groups: (1) patients with no identifiable home medication section on the discharge summary, (2) those taking PPIs, (3) those taking H_2RAs, (4) those taking both classes, and (5) patients taking neither class. Among these 100 patients, we identified one false-positive case (containing the phrase 'patient has not been taking: cimetidine') and no false negatives.

Outcome

The primary outcome was the first serum magnesium level recorded within 36 h of admission to the hospital. To limit the effect of outliers, all extreme magnesium levels (0.5%) were winsorized at the 0.5 and 99.5 percentiles. In addition, to examine potentially severe hypomagnesemia, we dichotomized levels at 1.6 mg/dl in concert with our hospital laboratory reference and in keeping with previous clinical studies.[45,46]

As serum phosphate is affected by the balance of nutritional intake and renal excretion in a similar fashion to magnesium, we tested phosphate levels as a secondary outcome to ensure the specificity of observed associations.

Covariates

Demographic information included age, sex, and ethnicity, coded as White, African American, Asian, Hispanic, other, or unknown. Individual predictors of the illness severity, averaged over the first 24 h of ICU stay, included systolic blood pressure, heart rate, and temperature. On the basis of tests of model fit, we included creatinine as both a linear and centered quadratic term, along with a creatinine ratio (repeat creatinine within 24 h of admission over admission creatinine) to capture the dynamic nature of renal function in critically ill patients. Values of serum glucose, calcium, phosphate, and hematocrit were included when obtained within 36 h of admission to the hospital. All 30 comorbidities of the Elixhauser score[47] were incorporated into the model as separate, independent measures, rather than a summary index score. We encoded any type and number of oral diuretics, obtained from the admission medication list, as a binary variable. Imputed means were used for all variables with missing or implausible values: systolic blood pressure ($n = 471$), heart rate ($n = 469$), temperature ($n = 1749$), baseline serum creatinine ($n = 13$), ratio of 24 h/baseline creatinine ($n = 1043$), glucose ($n = 23$), calcium ($n = 1263$), phosphate ($n = 1261$), and hematocrit ($n = 39$).

Statistical analysis

We present baseline characteristics according to use of PPIs, H_2RAs, or neither, with group differences assessed by analysis of variance. To assess whether acid-suppressive medications were related to magnesium concentrations, we developed sequential multivariable linear regression models. Binary indicator variables were created for PPI or H_2RA use, as well as for diuretic use and all Elixhauser comorbidities. Ethnicity was included as a multicategory variable. Age, vital signs, and laboratory values were all included as continuous variables. Model I included age, gender, ethnicity, and renal function. Model II added admission vital signs, laboratory data, comorbidities, and diuretic use, as described above. Model diagnostics included visual inspection of residual plots, distribution of the residuals, and quantile plots.

Given the direct effect of diuretic use on magnesium excretion and the nature of the Food and Drug Administration alert, we tested for effect modification of the PPI and magnesium relationship by diuretic exposure. In these analyses, we used the covariates from Model II, along with a multiplicative interaction term, and in the presence of significant interaction, we present the results stratified by diuretic use. We also provide the baseline characteristics of the diuretics users stratified by use of PPIs, H_2RAs, or neither. Differences across all three groups were assessed by analysis of variance. Differences between group magnesium concentrations were assessed by the Tukey–Kramer test.

To assess the association between acid-suppressive medication use and hypomagnesemia, defined as a value less than 1.6 mg/dl, we created comparable logistic regression models. The same variables used in the multivariate linear regression were included without further dichotomization.

To characterize the effect of diuretic exposure on the association between PPI exposure and magnesium concentrations, we also examined models stratified by diuretic class (loop, thiazide, other) and those on more than one class of diuretic medications. Sensitivity analyses of the complete data set ($n = 8948$) without imputation

revealed similar results in both the linear and logistic models. In addition, exclusion of the Elixhauser comorbidity 'Fluid and Electrolyte Disorders' did not lead to meaningful differences in the results. Analysis of only those individuals admitted through the Emergency Department ($n = 9108$) revealed similar results. In addition, as the effect of PPI exposure was observed in diuretic users, we performed analyses of this subset using complete data ($n = 2358$) and using those admitted through the Emergency Department ($n = 2619$), without significant differences in the reported results. Finally, to test the specificity of our analysis, serum phosphate concentrations were used as a continuous dependent variable in multivariable analysis of the whole cohort and of the subset of diuretic users. All analyses were performed using JMP Pro (SAS Institute, Cary, NC).

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

JD and JHW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The study authors were designated in the following roles: study concept and design: JD, JHW, MDH, KJM; acquisition of data: DJS, JL, L-wL, RGM, MDH, LAC; analysis and interpretation of data: JD, JHW, DJS, JL, KJM; drafting of the manuscript and study supervision: JD, JHW; critical revision of manuscript for important intellectual content: JD, JHW, MDH, KJM; statistical analysis: JD, DJS, JL, L-wL, RGM, LAC, KJM.

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