CASE REPORTS
A Case Series of Proton Pump Inhibitor–Induced Hypomagnesemia

Ewout J. Hoorn, MD, PhD,1 Joost van der Hoek, MD, PhD,1 Rob A. de Man, MD, PhD,2 Ernst J. Kuipers, MD, PhD,1,2 Clemens Bolwerk, MD,3 and Robert Zietse, MD, PhD1

Proton pump inhibitor (PPI)-induced hypomagnesemia has been recognized since 2006. Our aim was to further characterize the clinical consequences and possible mechanisms of this electrolyte disorder using 4 cases. Two men (aged 63 and 81 years) and 2 women (aged 73 and 62 years) had been using a PPI (esomeprazole, pantoprazole, omeprazole, and rabeprazole, 20–40 mg) for 1–13 years. They developed severe hypomagnesemia (magnesium, 0.30 ± 0.28 mEq/L; reference, 1.40–2.10 mEq/L) with hypocalcemia (calcium, 6.4 ± 1.8 mg/dL), relative hypoparathyroidism (parathyroid hormone, 43 ± 6 pg/mL), and extremely low urinary calcium and magnesium excretion. One patient was admitted with postanoxic encephalopathy after a collapse likely caused by arrhythmia. The others had electrocardiogram abnormalities (prolonged QT interval, ST depression, and U waves). Concomitant hypokalemia (potassium, 2.8 ± 0.1 mEq/L) was considered the trigger for these arrhythmias. Hypomagnesemia-induced kaliuresis (potassium excretion, 65 ± 24 mEq/L) was identified as the cause of hypokalemia. This series of PPI-induced hypomagnesemia shows that this is a generic effect. It also indicates that hypomagnesemia may occur within 1 year of PPI therapy initiation and can have serious clinical consequences, likely triggered by the associated hypokalemia. A high index of suspicion is required in PPI users for unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms.


INDEX WORDS: Adverse drug reaction; arrhythmia; hypocalcemia; hypokalemia.

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The 4 cases are described next and in Table 1 (showing all laboratory values).

from the Departments of1 Internal Medicine and2 Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam; and3 Gastroenterology, Reinder de Graaf Gasthuis Delft, The Netherlands.


Address correspondence to Ewout J. Hoorn, MD, PhD, PO Box 2040–Rm D-405, 3000 CA Rotterdam, The Netherlands. E-mail: ejhoorn@gmail.com

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Case 1

A 63-year-old man was admitted to the hospital after he had fallen out of bed and lost consciousness for ~10 minutes. He had a medical history of gastric hemorrhage caused by peptic ulcer disease, myocardial infarction, atrial fibrillation, and partial colectomy (3.9 inches) because of adenomas. He used lisinopril, bisoprolol, atorvastatin, a coumarin derivative, and esomeprazole (20 mg/d). At presentation, he had atrial fibrillation (ventricular rate, 113 beats/min), and severe hypomagnesemia (potassium, 2.8 ± 0.1 mEq/L) was considered the trigger for these arrhythmias. Hypomagnesemia-induced kaliuresis (potassium excretion, 65 ± 24 mEq/L) was identified as the cause of hypokalemia. This series of PPI-induced hypomagnesemia shows that this is a generic effect. It also indicates that hypomagnesemia may occur within 1 year of PPI therapy initiation and can have serious clinical consequences, likely triggered by the associated hypokalemia. A high index of suspicion is required in PPI users for unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms.


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This led to a parallel increase in serum magnesium and potassium levels within 3 months. Serum magnesium and potassium levels have remained normal since. During hypomagnesemia and hypokalemia, an electrocardiogram (ECG) showed new and prominent U waves, which disappeared after correction of the electrolyte disorders.

Case 3

A 62-year-old woman with a history of Barrett esophagus (medication was omeprazole, 40 mg/d) presented in 1999 with diarrhea and a serum magnesium level of 0.38 mEq/L (0.19 mmol/L). Giardiasis was diagnosed and treated, after

| Table 1. Characteristics of 4 Patients With PPI-Induced Hypomagnesemia |
|---------------------------------|---------------|---------------|---------------|---------------|
| Case 1                          | Case 2        | Case 3        | Case 4        |
| **Clinical and drug data**      |               |               |               |
| Age (y)/sex                     | 63/man        | 73/woman      | 62/woman      | 81/man        |
| PPI                             | Esomeprazole  | Pantoprazole   | Omeprazole,   | Esomeprazole  |
| PPI dose (mg)                   | 20            | 40            | 20            | 20            |
| Duration of use (y)             | 11            | 1             | 13            | 3             |
| CYP2C19 genotype*               | *1/*1         | *1/*2         | *1/*2         | *1/*2         |
| Likelihood of adverse drug reaction* | Probable     | Probable      | Probable      | Probable      |
| Symptoms                        | Possible arrhythmia | U wave    | Prolonged QT interval, ST depression | Prolonged QT interval |
| Serum values (reference range)* |               |               |               |
| Mg2+/H11001 (1.40-2.10 mEq/L)*  | 0.06–1.88     | 0.68–1.68     | <0.16–1.80    | 0.26–1.58     |
| K+/H11001 (3.5-5.1 mEq/L)       | 2.8           | 2.8           | 2.7           | 3.0           |
| Ca2+/H11001 (8.8-1.6 mg/dL)     | 7.8           | 11.5*a       | 7.1           | 4.4           |
| PTH (13-69 pg/mL)               | 38            | 49            | 40            | 47            |
| 25-hydroxyvitamin D3 (20-54 ng/mL) | 16          | 10            | 24            | 22            |
| 1,25 dihydroxyvitamin D3 (15-70 pg/mL) | 38          | 43            | 26            | 15            |
| eGFR (mL/min/1.73 m²)           | 59            | 82            | 82            | 15            |
| Urinary and fecal excretion*    |               |               |               |
| Mg2+/H11001 (mEq/L or mEq/d)    | 0.14 (spot), 1.0 (24 h) | 0.4 (spot), 0.4 (24 h) | <0.2 (24 h) | 0.12 (spot), 0.2 (24 h) |
| K+/H11001 (mEq/L or mEq/d)      | 93 (spot)     | 43 (spot), 62 (24 h) | 68 (24 h)    | 35 (spot)     |
| Ca2+/H11001 (mg/dL or mg/d)     | 0.4 (spot)    | 0.6 (spot), 2.0 (24 h) | <1.2 (24 h) | 0.12 (spot), 2.8 (24 h) |
| Transtubular K⁺ gradient⁹        | 6.6           | 11.2          | —             | —             |
| FEMg (%)                       | 1.2           | 1             | 0.2           | 0.8           |
| Fecal Mg2+/H11001 (mEq/L)       | —             | —             | 44.9          | —             |

Note: Conversion factors for units: GFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667; magnesium in mEq/L to mmol/L, x0.5; calcium in mg/dL to mmol/L, x0.2495; PTH in pg/mL to pmoL/L, x0.1061; 25-hydroxyvitamin D₃ in ng/mL to nmol/L x 2.496; 1,25 dihydroxyvitamin D₃ in pg/mL to pmoL/L, x 2.6. No conversion necessary for potassium in mEq/L and mmol/L.

Abbreviations and definitions: Ca²⁺, calcium; CYP2C19, cytochrome P450, family 2, subfamily C, polypeptide 19; eGFR, estimated glomerular filtration rate; FEₘg, fractional excretion of Mg²⁺; K⁺, potassium; Mg²⁺, magnesium; PPI, proton pump inhibitor; PTH, parathyroid hormone.

*CYP2C19*† refers to the wild-type allele, CYP2C19*2 is a single-nucleotide change from G to A in exon 5 of CYP2C19.

*According to the Naranjo et al⁷ scale.

*Measured at nadir serum magnesium levels.

*During and after discontinuation of PPI therapy.

*The patient also had primary hyperparathyroidism.

*The 6-variable MDRD (Modification of Diet in Renal Disease) Study equation was used to estimate GFR.

*Spot reading given in mEq/L (for Mg²⁺ and K⁺) and mg/dL (for Ca²⁺); 24 h measurement given in mEq/d (for Mg²⁺ and K⁺) and mg/dL (for Ca²⁺).

*Calculated as (serum osmolality x urine K⁺)/(urine osmolality x serum K⁺), where osmolality is expressed in mOsm/kg and other values are expressed in mEq/L.

*Calculated as (serum creatinine x urine Na⁺)/(urine creatinine x serum Na⁺) x 100, where all values are expressed in mmol/L.
which serum magnesium level increased to 0.76 mEq/L (0.37 mmol/L). However, hypomagnesemia persisted between 1999 and 2008 (mean serum magnesium, 0.72 mEq/L [0.35 mmol/L], for which she received ad hoc intravenous magnesium supplementation. In 2003 and 2005, she was admitted with severe and symptomatic hypomagnesemia (magnesium < 0.16 mEq/L [<0.08 mmol/L]), hypocalcemia (calcium < 8.4 mg/dL [<2.1 mmol/L]), and hypokalemia (potassium < 2.7 mEq/L [<2.7 mmol/L]). The latter admission was in intensive care because of ECG abnormalities (2-mm ST depression, prolonged corrected QT interval of 390-491 ms). Aldosterone level was normal (6.8 ng/dL [0.19 mmol/L]). Her ECG normalized after correction of hypokalemia and hypocalcemia, although hypomagnesemia persisted. Further analysis using a video capsule and double-balloon enteroscopy showed intestinal lymphangiectasia. Conversion of omeprazole to rabeprazole therapy decreased serum magnesium levels from 1.00 to 0.76 mEq/L (0.50 to 0.38 mmol/L). After discontinuation of PPI therapy, serum magnesium level normalized within 2 weeks and has remained normal ever since. Currently, she uses famotidine and gastrozine.

Case 4

An 81-year-old man was admitted for antibiotic treatment of a urinary tract infection. He had a history of vascular disease, including myocardial infarction, transient ischemic attack, and stent repair for an abdominal aneurysm, which had led to end-stage renal disease. He used acebutolol, simvastatin, calcium, ion-exchange resin (because of previous hyperkalemia), and esomeprazole (20 mg/d). On admission, hypomagnesemia, hypocalcemia, and hypokalemia were discovered. An ECG showed extrasystoles and a prolonged QT interval (463 ms; 20% higher than previous recordings). The electrolyte disorders and ECG abnormalities disappeared within 3 weeks after discontinuing PPI therapy and supplementation of calcium and magnesium, and values have remained normal after withdrawal of the latter 2.

Other causes of hypomagnesemia were absent in all 4 patients, including family history of genetic electrolyte disorders, diarrhea or vomiting, and use of alcohol, laxatives, or diuretics.

**DISCUSSION**

This series of 4 patients with PPI-induced hypomagnesemia, hypocalcemia, and hypokalemia adds several new and clinically relevant points.

According to the scale of Naranjo et al,7 the likelihood that the PPIs caused hypomagnesemia was “probable” (Table 1). All cases had additional pathologic states that could have contributed to the degree of hypomagnesemia (partial colectomy,8 diabetes mellitus,9 intestinal lymphangiectasia,10 and ion-exchange resin). However, it seems very unlikely that these factors alone caused hypomagnesemia because they were still present after normalization of serum magnesium levels. Our series confirms that PPI-induced hypomagnesemia constitutes a generic effect because it was caused not only by omeprazole and esomeprazole (as reported previously3-6), but also by pantoprazole and rabeprazole (Table 1). This type of adverse drug reaction probably should be classified as “non–dose related” (type B) or “time-related” (type D).11 No electrolyte disorders were seen during short-term PPI treatment (days),12,13 and 3 of the previous cases used PPIs for ≥ 6 years.4,5 However, case 2 and 2 previous cases3,6 illustrate that PPI-induced hypomagnesemia can occur after 1 year of use.

Despite these data, the mechanism of PPI-induced hypomagnesemia is elusive. We tested the hypothesis that PPI-induced hypomagnesemia occurs predominantly in poor metabolizers of PPIs, which was not the case (Table 1, genotyping as described previously14). PPI-induced hypomagnesemia likely is caused by gastrointestinal magnesium loss (very low urinary magnesium excretion), although fecal magnesium was determined in only 1 patient. Possible explanations for hypocalcemia could be parathyroid hormone resistance (no frank hypoparathyroidism) or gastrointestinal calcium loss (despite normal 1,25 dihydroxyvitamin D levels), which also would explain the hypocalciuria (Table 1).

In the first case, hypomagnesemia-induced hypokalemia was analyzed further, showing renal potassium loss because of an aldosterone-like effect (high transtubular potassium gradient), but without actual aldosteronism (normal renin and aldosterone levels). This implies that renal potassium loss is determined primarily by a tubular process and is independent of circulating aldosterone. The current concept of hypomagnesemia-induced hypokalemia is that normal intracellular magnesium levels inhibit the renal outer medullary potassium channel (ROMK; encoded by the KCNJ1 gene).14 Low intracellular magnesium levels are believed to relieve this inhibition, thereby causing ROMK-mediated potassium secretion.15 Five of the 7 previous cases had hypokalemia3-6 (Drs Cundy and Epstein, personal communication, July and October 2009).

Previous hypotheses for PPI-induced hypomagnesemia have postulated a role for decreased active magnesium transport in the colon, which is mediated primarily through the ion channels.
TRPM6 and TRPM7 (transient receptor potential melastatin 6 and 7, respectively).\textsuperscript{4,16} Changes in intestinal pH or a heterozygous carrier state for TRPM6 or TRPM7 have been proposed as explanations for perturbed transport through these channels\textsuperscript{3}; however, confirmative studies are lacking. Cundy and Dissanayake\textsuperscript{4} showed that PPI-induced hypomagnesemia can still be corrected with very high magnesium supplementation, suggesting the passive transport pathway for magnesium to be intact. However, because PPIs are absorbed in the stomach and small intestine, metabolized in the liver, and excreted largely by the kidneys, their local effect in the colon appears limited. Alternatively, PPIs may exert an effect on the gastrointestinal system after entering the circulation, as shown previously.\textsuperscript{17}

The clinical importance of PPI-induced hypomagnesemia is illustrated by the arrhythmia and/or ECG abnormalities observed in our 4 patients. These potentially serious complications have not been reported in any except 1 of the previous cases.\textsuperscript{3-6} Although hypomagnesemia, hypocalcemia, and hypokalemia are well-recognized causes of ECG abnormalities and arrhythmia, hypokalemia seems to be the most important.\textsuperscript{18} Yelamanchi et al\textsuperscript{19} showed an association between QT interval prolongation and hypokalemia, but not hypomagnesemia and hypocalcemia. Kingston et al\textsuperscript{20} found no ECG abnormalities in 20 patients with isolated severe hypomagnesemia. This also was supported by the observation that ECG abnormalities disappeared after correction of hypokalemia, whereas hypomagnesemia and sometimes also hypocalcemia persisted.

In conclusion, we report 4 additional cases of PPI-induced hypomagnesemia and show that this is a generic effect that can develop after 1 year of use and can have serious clinical consequences (arrhythmia and ECG abnormalities) that may be triggered by concomitant hypokalemia caused by renal potassium loss. A high index of suspicion is warranted in PPI users with unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms.

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