Severe Hypomagnesemia with Long-Term Use of a Proton Pump Inhibitor: A Case Report

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Summary
Hypomagnesemia is a rare, though likely under-recognized, adverse effect of long-term use of proton pump inhibitors (PPIs), one of the most commonly prescribed classes of medications in North America. Hypomagnesemia can cause potentially life-threatening neurologic abnormalities, cardiac arrhythmias, and secondary electrolyte disorders. In this manuscript we present the case of a long-term PPI user who presented with an episode of decreased level of consciousness. He was found to have severe hypomagnesemia with avid renal retention of magnesium, secondary hypocalcemia with an inappropriately normal parathyroid hormone level, and hypokalemia. His serum magnesium and other electrolyte abnormalities rapidly corrected with cessation of PPI use and electrolyte supplementation. Given the propensity for patients with hypomagnesemia associated with PPI use to go unrecognized until they present with severe symptomatic hypomagnesemia, we recommend that patients being started on a PPI for an intended long-term course have baseline testing of serum magnesium and monitoring of magnesium on an annual basis, or sooner, if they develop symptoms.

Résumé
L’hypomagnésémie est un effet indésirable rare, quoique probablement sous-décelé, qui découle de l’usage prolongé d’inhibiteurs de la pompe à protons (IPP), l’une des classes de médicaments les plus fréquemment prescris en Amérique du Nord. L’hypomagnésémie peut causer des anomalies neurologiques, de l’arythmie cardiaque et des troubles secondaires de l’équilibre electrolytique pouvant entrainer la mort. Le présent document porte sur le cas d’un utilisateur à long terme d’IPP présentant une diminution du niveau de conscience. On a diagnostiqué chez celui-ci une sévère hypomagnésémie, accompagnée d’une très forte rétention rénale pour le magnésium, d’une hypocalcémie secondaire montrant un niveau contre toute attente normal de l’hormone parathyroïde, en plus d’une hypokaliémie. Le taux de magnésium sérique et les autres anomalies électrolytiques sont rapidement revenus à la normale avec la suppression de l’IPP et un apport complémentaire d’électrolytes. Compte tenu de la propension à ne pas déceler l’hypomagnésémie chez les patients faisant un usage prolongé d’IPP tant que ceux-ci ne présentent pas une hypomagnésémie symptomatique sévère, nous recommandons que les patients qui commencent à prendre un IPP dans une optique de long terme soient soumis à un contrôle du niveau de base de leur magnésium sérique, puis que leur taux de magnésium soit vérifié sur une base annuelle ou plus rapidement advenant l’apparition de symptômes.
Case Report
A 70-year-old man presented to the emergency department following a 10-minute episode of decreased level of consciousness. During this period, the patient gasped for air, stared blankly, and was unresponsive to verbal commands. There was no incontinence, tongue biting, focal neurologic signs, or tonic-clonic activity. Prior to this episode the patient was well. His medical history included a myocardial infarction with angioplasty, hypertension, gastroesophageal reflux disease (GERD), and a remote cholecystectomy. His home medications included atorvastatin, ramipril, metoprolol, nitroglycerin spray, and omeprazole 20 mg daily, the latter of which he had been taking for the past 8 years. He did not drink alcohol.

Initial examination, including a cardiovascular, respiratory, abdominal, and neurologic exam, did not reveal any abnormalities. The patient was afebrile and had no history of recent illness, vomiting, or diarrhea. Initial blood work showed marked electrolyte disturbances, with severe hypomagnesemia, hypocalcemia, and hypokalemia, as shown in Table 1. Serum parathyroid hormone (PTH) was within the normal range, representing a state of relative hypoparathyroidism given the patient’s degree of hypocalcemia. Urinary electrolytes showed high renal retention of magnesium with a fractional excretion of 0.11%.

The patient’s omeprazole was discontinued upon hospital admission and substituted with ranitidine, an H2 receptor antagonist (H2RA). He initially received IV MgSO4, which rapidly corrected the serum magnesium. This was followed by oral supplementation with 10.4 mmol of elemental magnesium, three times daily, starting on the second day of admission. On the third day of admission, the patient’s serum magnesium dropped slightly and he was given another dose of IV MgSO4. By the fourth day, his magnesium remained within the normal range. His calcium was supplemented orally with 500 mg of elemental calcium, four times daily. His serum calcium gradually increased and was normal at the time of discharge on Day 4. See Figure 1 for a graphic trend of the patient’s serum electrolytes and the course of electrolyte supplementation.

A work-up for other potential causes of episodic decreased level of consciousness, such as acute coronary syndrome, pulmonary embolism, cardiac arrhythmia, seizure disorder, and cerebral vascular accident, were pursued and were negative. Troponin-T was within the normal range. An electrocardiogram (EKG) showed no sign of ischemia or infraction, and a 24-hour holter monitor showed no significant arrhythmias. Computed tomography (CT) scan of the head was normal, as was an electroencephalogram (EEG). CT scan of the chest with pulmonary embolism (PE) protocol showed no sign of pulmonary embolism or any other significant abnormality. The patient had no further episodes of decreased level of consciousness during his admission.

By the time of discharge on Day 4, the patient’s serum magnesium, calcium, and potassium were all within normal limits. He was discharged home on oral calcium supplementation once daily and vitamin D 2000 IU daily, as his vitamin D was found to be slightly low (see Table 1). Magnesium supplementation was stopped and he continued to take an H2RA. Twelve days post-discharge the patient’s serum magnesium and calcium remained normal. He was advised to avoid use of any proton pump inhibitors (PPIs) in the future.

Discussion
This case illustrates a long-term PPI user presenting with decreased level of consciousness in the setting of severe hypomagnesemia and secondary hypocalcemia. His hypomagnesemia quickly improved with PPI cessation and concurrent electrolyte supplementation. The serum calcium improved, with the aid of oral supplementation, as the hypomagnesemia resolved. Application of the Naranjo Scale, a validated method for estimating the probability of adverse drug reactions, to our case gives a score of 6, within the probable adverse drug reaction category (definite ≥ 9, probable 5–8, possible 1–4, doubtful ≤ 0). Of note, four of the ten questions

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<tr>
<th>Table 1. Initial Laboratory Results of a Patient Presenting with an Episode of Decreased Level of Consciousness.</th>
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<tr>
<td><strong>Measured Value</strong></td>
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<td>Hemoglobin</td>
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<td>Platelet count</td>
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<td>Sodium</td>
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<td>Random blood glucose</td>
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<td>hsTroponin-T*</td>
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<tr>
<td>Calcium</td>
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<tr>
<td>Albumin</td>
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<tr>
<td>Ionized calcium</td>
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<tr>
<td>Phosphate</td>
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<td>TSH</td>
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<td>Vitamin D</td>
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Major electrolyte abnormalities found on initial laboratory investigations included severe hypomagnesemia, hypocalcemia, and hypokalemia. Parathyroid hormone was inappropriately normal.

*High-sensitivity Troponin-T.
Hypomagnesemia with Proton Pump Inhibitor

This case highlights a serious adverse effect of PPIs that may be under-recognized due to a lack of awareness of the association between PPIs and hypomagnesemia. The case also illustrates how prompt cessation of PPI use can lead to rapid improvement in a patient’s electrolyte abnormalities and clinical condition. The remainder of this document summarizes our review of the literature for other reported cases of hypomagnesemia in association with PPI use and describes the purported mechanism of this adverse medication effect.

PPIs are some of the most commonly prescribed medications. There were 65.7 million prescriptions for omeprazole alone in the US in 2012. In Canada, Nexium (esomeprazole) was the sixth most prescribed drug in 2010, with over 3.9 million prescriptions. PPIs have long been thought by physicians to be safe, with few adverse effects; however, the longer that PPIs have been on the market, the more evidence that has come to light suggesting they may be associated with significant side effects. Adverse effects, including respiratory infections, Clostridium difficile colitis, bone fractures, and acute interstitial nephritis, have all been described. In addition, a recent association has been found between long-term PPI use and hypomagnesemia. The concern over this association and the serious consequences it may pose prompted Health Canada to release an adverse drug reaction notification in 2011, warning that prescription PPIs may cause hypomagnesemia if taken for periods of time longer than one year.

In 2006 Epstein et al. described two cases of hypomagnesemia associated with long-term PPI use, which resolved following PPI cessation. Since this publication, there have been over 30 cases described in the literature. The mechanism proposed for this adverse effect is inhibition of magnesium transport due to the PPI induced hypocalcemia. The figure below shows the serum magnesium, calcium, and potassium levels during the hospital admission and 12 days after discharge. Each dose of magnesium, calcium, and potassium is represented by a single point on the graph at the corresponding time it was given. The normal ranges are highlighted. The x-axis shows days with the day of admission set at Day 1.

PPIs achieve their therapeutic effect through potent inhibition of gastric acid release from gastric parietal cells by irreversibly blocking the hydrogen potassium adenosine triphosphatase enzyme system (H+/K+ ATPase). PPIs are commonly prescribed to treat conditions such as GERD, peptic ulcer disease, dyspepsia, and esophagitis. There are currently six PPIs available by prescription in the US and Canada, including omeprazole, lansoprazole, dexlansoprazole, esomeprazole, pantoprazole, and rabeprazole.

on the Narajo Scale were inapplicable to this case and were assigned a score of 0.

Figure 1. Graphic trend of the patient’s serum magnesium (•■•), calcium (□), and potassium (△) during the course of his hospital admission and 12 days after his discharge. The normal ranges (■) are highlighted. Also shown is the electrolyte supplementation regime that he received while in hospital. Each dose is represented by a single point on the graph at the corresponding time it was given. A single dose of IV magnesium (♦) was 2 grams, oral magnesium (◊) was 10.4 mmol of elemental magnesium, calcium (□) was 500 mg of oral elemental calcium, and potassium (△) was 40 mmol of oral elemental potassium. The x-axis shows days with the day of admission set at Day 1.
cases reported in the literature of severe hypomagnesemia in PPI users.14–16 Severe hypomagnesemia can lead to such nonspecific symptoms as weakness, tremors, tetany, and nausea, as well as potentially life-threatening complications including seizures, cardiac arrhythmias, and secondary electrolyte disturbances, such as hypocalcemia and hypokalemia. The risk of these adverse effects may be greater in patients with a history of seizure disorder, with cardiac conduction abnormalities, or who are on medications such as digoxin or diuretics. The magnitude of increased risk in these situations, however, is unclear.

A 2013 cross-sectional study of patients admitted to an intensive care unit showed a statistically significant association between PPI use and hypomagnesemia among those who were concurrently taking diuretics.17 This is in contrast to the results from a 2012 systematic review, in which no specific risk factors, beyond PPI use itself, were found to be correlated with hypomagnesemia in PPI users.16 In the cross-sectional study, the duration of outpatient PPI use was unknown, and patients were acutely ill with various conditions. This study is therefore not generalizable to a broader ambulatory population. Given the high prevalence of PPI users and the potential severity of hypomagnesemia, there is a need for large prospective studies to better delineate the potential causative role of PPIs on hypomagnesemia and to determine the incidence of this adverse effect.

The exact mechanism by which PPIs induce hypomagnesemia is unknown, but evidence from case reports and recent modelling studies have elucidated probable hypotheses.14–16,18 As highlighted in the systematic review by Hess and colleagues, case reports of hypomagnesemia with PPI use consistently show low renal magnesium excretion.16 These findings suggest reduced intestinal absorption as the source of magnesium loss. This is in contrast to other medications such as gentamycin, calcineurin inhibitors, cisplatin, and diuretics that all cause renal tubular wasting of magnesium.18–22

Intestinal absorption of magnesium occurs by both a passive paracellular and active transcellular mechanism.18,23 Active transport occurs through the saturable ion channels, transient receptor potential cation channel, subfamily M, members 6 and 7 (TRPM6/7), which are present on the apical surface of enterocytes.23 Results from a recent study suggest it is active, rather than passive, transport of magnesium that is primarily impaired with PPI use.16 TRPM6 and TRPM7 channels contain ionized glutamic and aspartic acid side chains that are critical for magnesium absorption. The fraction of these side chains that are ionized decreases with decreased pH. PPIs have been found to actually reduce intestinal luminal pH, opposite to their effect in the gastric lumen.24 This is thought to be due to inhibition of H+/K+ ATPase in the plasma membrane of the pancreatic duct, causing reduced proton secretion into the interstitium, which results in reduced bicarbonate secretion into the pancreatic duct and, ultimately, a reduction in pH.23

In most reported cases, the magnitude of hypomagnesemia due to PPI use was severe. Hess et al. reported a mean serum nadir of 0.22 mmol/L.16 The time to onset, or at least to detection, of hypomagnesemia with PPI use is variable, but in the vast majority of cases, it has been greater than one year. Hess et al. found a mean duration of use of 5.5 years.16

Hypomagnesemia appears to be a class effect of PPIs, with cases reported not only with omeprazole but also with esomeprazole, rabeprazole, pantoprazole, and lansoprazole.16 In each case, hypomagnesemia normalized promptly after PPI use was stopped. Hess et al. found a mean time to normalization of four days.16 Substitution with an H2RA does not cause further magnesium depletion.13,15,16 Hypomagnesemia has been found to quickly recur, within four days on average, with PPI rechallenge.13,16 Oral magnesium supplementation, while still on a PPI, has been found to fail to correct or only partially correct hypomagnesemia.13

In many cases, hypocalcemia and relative hypoparathyroidism, with slightly low or inappropriately normal PTH levels, were present in conjunction with hypomagnesemia.13–15 Hypocalcemia was typically mild to moderate.16 Mackay and Bladon observed that severe hypomagnesemia, defined as serum magnesium ≤0.54 mmol/L, was associated with hypocalcemia in 64% of cases.25

Hypocalcemia is thought to be a result of both hypomagnesemia-induced diminished synthesis and/or secretion of PTH from the parathyroid glands and peripheral PTH resistance. Anast et al. reported on impaired synthesis and/or secretion of PTH in a state of chronic severe magnesium deficiency.26 In studies of isolated perfused bone, Freitag et al. showed that hypomagnesemia may suppress G-protein activation and cyclic AMP production in response to PTH, resulting in PTH resistance and impaired PTH-induced release of calcium from bone.27

Magnesium deficiency is also frequently associated with hypokalemia that is unresponsive to potassium supplementation alone.15,16 The mechanism for this involves hypomagnesemia-induced reduced inhibition of renal outer medullary potassium channels (ROMK), causing increased ROMK activity and thus increased renal potassium excretion.28

We recommend that patients being started on a PPI for an intended long-term course have a baseline serum magnesium level drawn and have periodic monitoring of serum magnesium levels. The optimal timing for monitoring magnesium levels
is unknown, but annual monitoring (sooner if the patient develops symptoms) may be reasonable. Clinical judgement should always be applied to individual cases. Presently there are no large prospective trials to better define the necessity of or timing for magnesium monitoring. Such a study would be valuable in defining the true incidence and timing of PPI-associated hypomagnesemia. Long-term use of PPIs should be considered in the differential diagnosis for hypomagnesemia.

References