A Case of Severe Hypomagnesemia with Long-term Use of a Proton Pump Inhibitor

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Learning Objectives

To understand the association between severe hypomagnesemia and use of proton pump inhibitors including the proposed mechanism of action and consequences
Outline

- An Interesting Case
- Proton Pump Inhibitors
- Hypomagnesemia
  - Link to PPI use
  - Consequences
  - Hypothesized Mechanism
- Key Points
An Interesting Case

- 70 yo M presented with an episode of decreased LOC at home lasting ~10min
  - Gasp for air
  - Gaze fixed ahead
  - Unresponsive to verbal commands
  - No incontinence, tongue biting, focal neurologic signs, or tonic-clonic activity
  - Fully alert and responsive on arrival to ED
Past Medical History

- 2005: MI with angioplasty
- Hypertension
- Gastroesophageal reflux disease
- Remote cholecystectomy
- Smoker
- Non-drinker

Medications

- Atorvastatin 20mg daily
- Ramipril 5mg daily
- Metoprolol 25mg daily
- Nitroglycerin spray PRN
- Omeprazole 20mg daily
  - Started in 2005 after MI for gastric protection with dual anti-platelet therapy
Physical Examination

- Afebrile with stable vital signs
- Cardiovascular, respiratory, abdominal, and neurological exams all unremarkable upon arrival at the ED
- Initial labs .......
## Laboratory Results

<table>
<thead>
<tr>
<th></th>
<th>Measured Value</th>
<th>Normal Range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>141</td>
<td>133 - 145</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3</td>
<td>3.3 - 5.1</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>79</td>
<td>50 - 120</td>
<td>μmol/L</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>6.6</td>
<td>3.3 - 11.0</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.26 !</td>
<td>0.65 - 1.05</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.66</td>
<td>2.10 - 2.55</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>36</td>
<td>33 - 48</td>
<td>g/L</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>29</td>
<td>13 - 54</td>
<td>ng/L</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>66.8</td>
<td>80 - 200</td>
<td>nmol/L</td>
</tr>
</tbody>
</table>

**Fractional Excretion of Mg = 0.11% → GI Loss**
Clinical Course

- Omeprazole stopped
  - Substituted with Ranitidine

- Electrolytes supplemented

- Investigations:
  - hsTn-T, ECG & 24 hr Holter
  - EEG
  - CT head
  - CT PE

All negative/normal
Potassium Supplementation (40 mmol)
Calcium Supplementation (500mg)
Oral Magnesium Supplementation (10.4 mmol)
IV Magnesium Supplementation (2g)
Why is This Important?

- PPIs are one of the most commonly prescribed classes of medications
- 65.7 million US prescriptions for omeprazole in 2012
  - 7th most commonly prescribed
- Nexium (esomeprazole) was the 6th most prescribed drug in Canada in 2010
  - Over 3.9 million prescriptions
- Hypomagnesemia can have severe consequences


Consequences of Hypomagnesemia

- Weakness
- Tremor
- Tetany
- Carpopedal Spasm
- Chvostek’s and Trousseau’s sign
- Seizures
- Coma

- Nausea
- Anorexia

- Wide QRS
- Nonspecific T-wave changes
- Prolonged QT
- PVCs
- Ventricular tachycardia
- Torsade de pointes
- Ventricular fibrillation
- Enhanced digitalis toxicity

- Secondary electrolyte disturbances
  - Hypocalcemia
  - Inappropriately normal or low PTH
  - PTH resistance
- Hypokalemia

Images: [http://seksyensatu.blogspot.ca/]; [http://howshealth.com/hypocalcemia/]
[http://healthmaven.blogspot.ca/2011_07_31_archive.html]
PPI Mechanism

- Inhibit gastric acid release from gastric parietal cells
- Irreversibly block hydrogen potassium adenosine triphosphatase enzyme system
Absorption of Magnesium

- Active transport via saturable TRPM6 & 7 channels
- Passive paracellular transport (low affinity)

*MTransient receptor potential cation channel, subfamily M, member 6 & 7
Effect of PPIs on Mg$^{2+}$ Absorption

- PPIs reduce intestinal luminal pH (opposite to effect in the gastric lumen)
  - Decrease pH by 0.5

- Inhibition of H$^{+}$K$^{+}$-ATPase in the pancreatic duct plasma membrane
  - Reduced proton secretion into the interstitium
  - Reduced HCO$_3^-$ secretion into the pancreatic duct
  - Reduction in pH

Effect of PPIs on Mg$^{2+}$ Absorption

- TRPM6/7 channels contain ionized glutamic and aspartic acid side chains
  - Critical for magnesium absorption
- Side chain ionization is sensitive to pH
Summary: PPI’s and Mg$^{2+}$ Absorption

- Proton pump inhibitors impair intestinal absorption of magnesium via reduced active transport through TRPM6/7
- PPIs decrease intestinal luminal pH
- Reduced fraction of ionized TRPM6/7 channels at lower pH
- Ionized TRPM6/7 channels critical for transport of Mg$^{2+}$ across apical surface of enterocytes
Key Points/Recommendations

- Consider proton pump inhibitors in your differential for hypomagnesemia
  - It is a rare, though perhaps under recognized, serious adverse effect associated with all proton pump inhibitors

- Long-term use can cause severe magnesium depletion and secondary electrolyte disturbances

- For patients starting on a PPI for a long-term course
  - Measure baseline serum magnesium
  - Monitor serum magnesium on an annual basis (or sooner if symptoms develop)
Acknowledgements

- Dr Paul Gibson


IMS Institute for Healthcare Informatics. Declining medicine use and costs: For better or worse? a review of the use of medicines in the united states in 2012, May 2013.

