Prevalence of Hypomagnesemia Associated with Proton Pump Inhibitor Therapy in Children with Cystic Fibrosis (HAPPIT Study)

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Background
- Up to 80% of cystic fibrosis (CF) patients have gastroesophageal reflux (GER), with proton pump inhibitors (PPI) considered treatment of choice for moderate to severe GER
- Since 2006, > 30 case reports published implicating hypomagnesemia as a rare potentially serious side effect of PPI
- Potential complications of hypomagnesemia include: Other electrolyte abnormalities, muscle cramps, tetany, abnormal cardiac rhythm, and seizures
- Concomitant proarrhythmic medications commonly used in CF patients: macrolides, prokinetic agents, azole antifungals
- CF team in British Columbia Children’s Hospital (BCCH) aims to address uncertainties around whether children with CF receiving PPI should undergo routine serum magnesium (Mg) monitoring

Objectives
Primary: Prevalence of hypomagnesemia in CF patients receiving PPI compared to CF patients not receiving PPI
Secondary: Severity of the hypomagnesemia
Interventions initiated and/or clinical complications

Methods
Design: Retrospective cohort study approved by institutional research ethics board
Inclusion criteria for cohort group:
- Diagnosis of CF, received medical care at BCCH CF Clinic, received a PPI between Jan 2008 - July 2012, ≥ 1 serum Mg measured at BCCH
- Same inclusion criteria for control group, except:
  - No previous documented use of PPIs
Exclusion Criteria:
- Serum Mg excluded if drawn when patient receiving oral/IV diuretics or IV amphotericin
Statistical Analysis: Descriptive statistics. Prevalence of hypomagnesemia by risk ratios (RR) at 95% confidence interval
Sample size: 42 cohorts and 84 controls to provide 80% power to detect a RR of 2 for hypomagnesemia

Definitions
Hypomagnesemia:
- <0.66 mmol/L in patients <2 mos
- <0.78 mmol/L in patients between 2 mos to 12 yrs
- <0.74 mmol/L in patients greater than 12 yrs

Proton pump inhibitor (PPI):
- Omeprazole, pantoprazole, esomeprazole, rabeprazole, dexlansoprazole

Results

<table>
<thead>
<tr>
<th>Table 1: Patient Characteristics</th>
<th>Cohort (n=42)</th>
<th>Control (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age, years (median (range))</td>
<td>8.3 (0.2-17)</td>
<td>8.0 (0.1-18)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>Number of serum Mg per year per patient (median (range))</td>
<td>1.8 (0.4-22.2)</td>
<td>1.0 (0.04-4.6)</td>
</tr>
<tr>
<td>Hospitalized when serum Mg drawn (%)</td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td>Aminoglycoside use when serum Mg drawn (%)</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Pancreatic Insufficiency (%)</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>Glucose Intolerance (%)</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>History of Bowel Resection (%)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Celiac Disease (%)</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Patients with Hypomagnesemia Events

<table>
<thead>
<tr>
<th>Cohort (n=84)</th>
<th>Control (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesemia</td>
<td>10</td>
</tr>
<tr>
<td>Cohorts (n=20)</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Mg supplements initiated (n)</td>
<td>1</td>
</tr>
<tr>
<td>Adverse events + chronic Mg supplementation initiated (n)</td>
<td>1</td>
</tr>
</tbody>
</table>

Adverse events reported at the time of low magnesium level:
- Cohort: 1 QTc prolongation, 1 dysesthesia/paresthesia
- Control: 1 cardiac arrhythmia
- All patients were receiving other medications concomitantly that were felt to be responsible for the adverse events
- None resulted in discontinuation of the PPI

Limitations
- Retrospective review design
- Unable to meet calculated sample size → Risk of type II error
- Confounders leading to hypomagnesemia are prevalent in the CF population
- Baseline characteristics indicate more severe CF disease in the cohort group

Conclusions
- This is the first study to our knowledge to explore hypomagnesemia associated with PPIs in children with or without CF
- No statistically significant difference in the prevalence of hypomagnesemia between the cohort and control group, although sample size not achieved
- The risk factors and clinical significance of hypomagnesemia associated with PPI in children with CF are unclear
- Routine monitoring of serum Mg in children with CF receiving PPI may not be needed at this time

Figure 1: Patients with ≥ 1 Hypomagnesemia Events

RR 1.43; 95% CI 0.88-2.32

Figure 2: Box Plot of Serum Magnesium Levels

All Mg Levels
Low Mg Levels

Cohort (n=324) | Control (n=203) | Cohort (n=84) | Control (n=33)