Proton Pump Inhibitors: How bad could they be?

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Objectives for Pharmacists

At the end of this presentation PHARMACISTS should be able to:
• Describe the overutilization of proton pump inhibitors (PPIs) in current practice
• List clinical indications for use of PPIs in the outpatient and inpatient setting
• Interpret treatment guidelines when providing justification for use of PPIs
• Review risks associated with PPIs and develop evidence-based education for healthcare providers
• Recognize impact from pharmacist-driven protocols for PPI use

Objectives for Pharmacy Technicians

At the end of this presentation PHARMACY TECHNICIANS should be able to:
• Recognize the overutilization of proton pump inhibitors (PPIs) in current practice
• Explain the mechanism of action of PPIs
• List PPIs available over-the-counter
• Recall 3 clinical indications for PPI use
• Identify 3 risks of PPI therapy
PPI Statistics and Cost

- The use of PPIs continues to increase
- Over 114 million prescriptions for PPIs filled each year
- 15.3 million people on PPIs 2013
- Account for a significant proportion of pharmaceutical health-care costs
  - ~ $14 billion in sales
- Retrospective cohort study at a single center academic hospital found:
  - Annual costs for stress ulcer prophylaxis (SUP) $12,000 annually
  - Could have been prevented with adherence to proper guidelines for SLIP

Acid Production:

Mechanism of Action:
PPIs on the Market

**Prescription Only:**
- Rabeprazole (Aciphex)
- Dexlansoprazole (Dexilant)
- Pantoprazole (Protonix)

**Available Over-the-Counter:**
- Omeprazole (Prilosec)
- Sodium Bicarb (Zigred)
- Esomeprazole (Nexium)
- Lansoprazole (Prevacid)

FDA Approved Indications for Acid-Suppressive Therapy

- GERD
- H. pylori
- Zollinger-Ellison Syndrome
- ICU patients on mechanical ventilation
- Healing and maintenance of erosive esophagitis
- Healing and risk reduction of NSAID-induced peptic ulcer

Guidelines for Use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendation</th>
<th>Note</th>
</tr>
</thead>
</table>
| GERD
- Erosive vs. Non-Erosive
  - PPI once daily x 4-12 weeks
  - Erosive: 8-12 weeks
  - Non-erosive: 4 weeks |
| H. Pylori
- PPI x 10-14 days
- Duration dependent on primary or sequential therapy |
| Hypersecretory Conditions
- Daily PPI therapy
- Treat as long as clinically indicated |
| Stress Ulcer Prophylaxis
- Daily PPI therapy
- Must consider indication for use |
| Management of Bleeding Ulcer
- Acute: IV PPI therapy after hemostasis
  - Maintenance: Daily PPI
- NSAID induced consider discontinuation of offending agent in addition to healing PPI therapy

- Appropriate considerations for long-term therapy

American College of Gastroenterology
Stress Ulcer Prophylaxis – Indication

- Coagulopathy or patients requiring mechanical ventilation > 48 hours
- A history of GI ulceration or bleeding within 1 year before admission
- ≥2 risk factors for clinically significant bleeding:
  - Sepsis
  - ICU stay > 1 week
  - Occult bleeding lasting 6 days or more
  - Use of high-dose corticosteroids (>250 mg per day of hydrocortisone or the equivalent)
- Recent meta-analysis showed PPIs superior to H2RAs in preventing clinically important and overt GI bleeding in ICU patients
  - RR 0.39; 95% CI (0.21-0.71); P = 0.002

Overutilization of PPIs

- Inpatient setting — often a result of inappropriate stress ulcer prophylaxis (SUP) in non-intensive care unit patients and failure to discontinue SUP prior to discharge
- Ambulatory care setting — often a result of failure to re-evaluate the need for continuation of therapy or insufficient use of on-demand and step-down therapy
- PPIs have few immediate and tangible side effects…
  - Headache, diarrhea, and dyspepsia in <2% of users

Potential Risks of Use

- Fractures
- Electrolyte abnormalities
- *C. difficile* infections
- Incident dementia
Timeline of Discovered Risks

PPI Use and Fractures

Proposed Mechanism

- Acidic environment is needed for absorption of calcium
  - Decrease in serum calcium → Secondary hyperparathyroidism → Increased bone resorption
- Increased gastrin levels and hyperplasia of the enterochromaffin-like cells (ECL cells) in the gastric lumen
  - Promoting osteoclastogenesis

Clinical Impact

- Hip fractures are a major cause of morbidity and mortality
  - 329,000 persons are hospitalized annually with hip fractures in the US
  - Mortality rate ~5-10% within the first month, and 20% within the first year
  - In those survived, ~20% will require nursing home care

- Identification of modifiable risk factors would be of substantial benefit
  - Prevents invasive interventions, prolonged rehabilitation, and unnecessary costs

Observational Studies Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Fracture</th>
<th>OR</th>
<th>95% C.I.</th>
<th>Duration of PPI</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. 2006</td>
<td>Hip</td>
<td>1.22</td>
<td>(1.15-1.30)</td>
<td>1 year</td>
<td>Increased risk of hip fractures in H2RA with &gt; 1 year use compared to PPI users</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.65</td>
<td>(1.80-3.90)</td>
<td>&gt; 1 year with high dose 4 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.59</td>
<td>(1.39-1.80)</td>
<td>&gt; 1 year</td>
<td></td>
</tr>
<tr>
<td>Corley et al. 2010</td>
<td>Hip</td>
<td>1.30</td>
<td>(1.21-1.41)</td>
<td>&gt; 2 years</td>
<td>Fracture risk decreased after discontinuation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.41</td>
<td>(1.21-1.64)</td>
<td>&gt; 2 years with high dose</td>
<td></td>
</tr>
<tr>
<td>Targowinik et al. 2008</td>
<td>All</td>
<td>1.92</td>
<td>(1.16-3.18)</td>
<td>≥ 7 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>1.62</td>
<td>(1.02-2.58)</td>
<td>&gt; 5 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>4.55</td>
<td>(1.68-12.9)</td>
<td>&gt; 7 years</td>
<td></td>
</tr>
</tbody>
</table>

Fracture Risk After Discontinuation

<table>
<thead>
<tr>
<th>Corley et al. 2010</th>
<th>User Status</th>
<th>Interval Since Last Prescription</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Use</td>
<td>-</td>
<td>-</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt; 2 Year Supply</td>
<td>All users</td>
<td>All persons &gt; 2 years PPI supply</td>
<td>1.30 (95%CI 1.21-1.39)</td>
</tr>
<tr>
<td>Current vs. Former Users</td>
<td>Current</td>
<td>Prescription in last year</td>
<td>1.30 (95%CI 1.21-1.41)</td>
</tr>
<tr>
<td></td>
<td>Recent</td>
<td>Last prescription 1-4.9 years prior</td>
<td>1.24 (95%CI 0.90-1.72)</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>Last prescription 2-9 years prior</td>
<td>1.09 (95%CI 0.64-1.85)</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>Last prescription 3-5.9 years prior</td>
<td>0.49 (95%CI 0.27-1.28)</td>
</tr>
</tbody>
</table>
What Was Learned

Meta-analysis including the 3 discussed studies:
- Modest increase in risk for hip fracture
- Increase in spine and any-site fractures
- Appeared risk related to dose and duration of acid suppression; possibly reversible
- H2RAs were not associated with fracture risk

PPI Use and Hypomagnesaemia

Proposed Mechanism

- Reduced intestinal absorption of magnesium
  - Direct mechanism unclear
- PPI-induced inhibition of transient receptor potential melastatin-6 (TRPM6) and TRPM7 channels
  - Kinase channel responsible for the homeostasis of magnesium levels
  - TRPM6 located in kidney, lung, cecum and colon
  - TRPM7 distributed ubiquitously


Clinical Impact

• Observed in more than half of critically ill patients and is associated with increased mortality

• Increased morbidities including greater need for ventilator support, prolonged mechanical ventilation, more frequent sepsis, hypocalcemia, and hypoalbuminemia

• Symptoms typically seen at Mg < 1.0 mEq/L (1.5 - 2.5 mEq/L)
  • Neuromuscular manifestations
  • Cardiopulmonary manifestations
  • Mental status changes

• Cofactor for homeostasis of calcium, sodium, and potassium

Hypomagnesaemia in the General Population

Evaluated PPI or H2RA users compared to no acid-suppressive users

• Hypomagnesaemia defined as ≤ 1.14 mEq/L

• Use of PPIs were associated with lower serum Mg²⁺ levels
  • OR 2.00, 95% CI (1.36-3.93)
  • -0.022 mEq/L (-0.032 to -0.014) p < 0.001

• Duration-of-use analysis of PPI use showed increased risk mainly present in participants with the longest duration of use
  • Risk tripled compared to non-users – those with use > 6 months
    • OR 2.99, 95% CI (1.73-5.15)


• Lower serum Mg²⁺ levels were also seen in H2RA users compared to those with no use
  • OR 2.00, 95% CI (1.08-3.72)
  • -0.018 mEq/L (-0.032 to -0.002) p = 0.02

• Duration-of-use analysis of H2RA use was also associated with increased risk, compared to no use – use > 111 days
  • OR 2.55, 95% CI (0.99-6.58)

Not significant

Hypomagnesaemia - Systematic Review

Reviewed 36 PPI-induced hypomagnesaemia (PPIH) case reports

- **Primary endpoint: PPI withdrawal and re-challenge**
  - Discontinuation of PPIs resulted in fast recovery from PPIH in 4 days and re-challenge led to recurrence within 4 days
  - Time to onset of hypomagnesaemia was highly variable and ranged from 14 days up to 13 years (mean 5.5 years)

- **Secondary endpoint: to profile the at risk patient**
  - All suffered from significant co-morbidities
  - No correlation with age or gender


What Was Learned

- Discontinuation of PPIs should result in a rapid normalization of serum magnesium levels
  - Should help exclude other causes of hypomagnesaemia

- In most cases, supplementation with electrolytes could be stopped after normal serum magnesium was obtained

- Chance to escape hypomagnesaemia by alternative acid suppressants
  - H2RAs should be attempted


- There was no information on the long-term success rate of the alternative treatment and the need for persistent electrolyte supplementation

- H2RAs were the preferable replacement therapy in PPIH and prevented recurrence of hypomagnesaemia

PPI Use and *Clostridium Difficile* Infection

**Proposed Mechanisms**
- Decreased gastric acidity could lead to inadequate sterilization of ingested organisms
- Higher gastric pH facilitates survival of ingested *C. difficile* spores
- Impairment of leukocyte function

**Clinical Impact**
- *Clostridium difficile* (C. diff) infection is a significant contributor to attributable costs, morbidity, and mortality
- ~20% of individuals with successful treatment of initial episode will experience 1 or more recurrences
- Nosocomial-acquired *C. diff* listed as "urgent threat" – CDC
- Potential inappropriate use in non-ICU patients may complicate or lengthen their stay with *C. diff* infection
Significant Additional Risk Factor

- Retrospective case-control study investigating the use of PPIs as an additional risk factor to broad spectrum antibiotics
- 170 inpatients in the UK with C. diff associated diarrhea

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>2.5</td>
<td>(1.5-4.2)</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>2.8</td>
<td>(1.5-5.2)</td>
</tr>
<tr>
<td>Cytotoxic Chemo</td>
<td>4.3</td>
<td>(1.5-11.5)</td>
</tr>
<tr>
<td>PPI + Antibiotic</td>
<td>5.4</td>
<td>(2.2-12.2)</td>
</tr>
<tr>
<td>PPI + Cytotoxic Chemo</td>
<td>15.8</td>
<td>(3.5-100.7)</td>
</tr>
<tr>
<td>PPI + Antibiotic + Cytotoxic Chemo</td>
<td>43.2</td>
<td>(5-330.4)</td>
</tr>
</tbody>
</table>

Dose Dependent Association

- Secondary analysis of data collected prospectively on 101,796 discharges from a tertiary-care center over a 5-year period
- Observed varying levels of acid-suppressive therapy classified by intensity (none, H2RA, daily PPI, >daily PPI use)
- The risk of nosocomial C. difficile increased with increased intensity of acid suppressive therapy

Risk of C. difficile Diagnosis with Level of Acid Suppression

- OR 1.54
- 95% CI (1.11-2.15)
- OR 1.74
- 95% CI (1.39-2.18)
- OR 2.36
- 95% CI (1.5-3.35)
Recurrence of C. diff Infection

754 patients with incident C. diff retrospectively evaluated for PPI exposure
Exposure = receipt of PPI at the time of initial episode of CDAD with either:
• Ongoing inpatient use 75% of days admitted
• Discharge prescription for PPI valid for 90 days after initial episode
• Recurrences were re-evaluated at the time of recurrence for valid PPI prescription from at least 48 hours before recurrence
• PPI use beyond initial episode of CDAD was associated with the risk of recurrence

Results – Recurrence in 90 Days

754 Patients

193 Recurrences

132 PPI Users

61 Non-Users

561 Without Recurrence

HR 1.5
(95%CI: 1.1-2.0)

Increased Severity

• Retrospective, single-center, cohort study, involving 41,663 patients
• PPI use associated with both increased rate and severity of hospital-acquired C. difficile infection (CDI)

<table>
<thead>
<tr>
<th>Category of C. diff</th>
<th>PPI Group with CDI</th>
<th>Control Group with CDI</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Infections</td>
<td>17,237</td>
<td>14</td>
<td>12.35</td>
<td>6.63-22.8</td>
</tr>
<tr>
<td>Severe Infections</td>
<td>17,237</td>
<td>8</td>
<td>2.27</td>
<td>0.91-5.48</td>
</tr>
<tr>
<td>Complicated Infections Only</td>
<td>17,237</td>
<td>2</td>
<td>34,078</td>
<td>15.32</td>
</tr>
</tbody>
</table>
Systematic Review

<table>
<thead>
<tr>
<th>Association</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of incident <em>C. diff</em></td>
<td>1.74</td>
<td>1.47-2.05</td>
</tr>
<tr>
<td>Risk of incident <em>C. diff</em> with antibiotic use</td>
<td>1.96</td>
<td>1.03-3.70</td>
</tr>
<tr>
<td>Risk of recurrent <em>C. diff</em></td>
<td>2.51</td>
<td>1.16-5.44</td>
</tr>
<tr>
<td>Risk of H2RAs</td>
<td>0.71</td>
<td>0.53-0.97</td>
</tr>
</tbody>
</table>


What Was Learned

- Use of PPIs provides additive associated risk
- Risk associated with increased acid-suppressive therapy intensity
- Associated with risk of both incident and recurrent *C. difficile*
- Associated with risk of severity of hospital-acquired *C. difficile* infection
- Less risk associated with the use of H2RAs for *C. difficile*

PPI Use and Dementia
Proposed Mechanism

- Omeprazole and lansoprazole have been reported to cross the blood-brain-barrier
  - Able to directly affect the brain
- PPIs may be able to interact with brain enzymes
  - Observed increased Aβ levels in amyloid cell model and in the brains of mice after PPI treatment
- Association of PPI use and vitamin B12 deficiency

Clinical Impact

- Drugs that modify the risk for dementia are of interest to avoid when appropriate
  - Burden on patients, families, and the healthcare system
- In 2010, the estimated world-wide cost of dementia was $604 billion

Association with Risk of Incident Dementia

Prospective multicenter cohort using observational data from 2004-2011 in Germany

- 73,679 patients, >75 y, free of dementia diagnosis at baseline
- Aggregated data at 1 year baseline in 2004, then at 18 month intervals
- Exposure of PPI defined as: At least 1 PPI prescription per quarter of an interval
- Dementia diagnosis were considered if reported in at least 2 quarters of a 12- or 18- month interval
Results

- The use of PPIs was associated with a significant increased risk of incident dementia.
  - HR, 1.44 (95% CI, 1.36-1.52); P < 0.001
- Age-group analysis revealed that incident dementia gradually decreased with age:
  - The highest HR in the age-group of 75-79 years.
- Time-dependent Cox regression models to evaluate association:
  - Adjusted for potential confounding factors: age, sex, polypharmacy, history of stroke, depression, ischemic heart disease, or diabetes.


Dementia Free Survival

- Omeprazole and lansoprazole may cross the blood brain barrier and be able to directly effect the brain.
- PPI use may be associated with incident dementia.
- Vitamin B12 deficiency may play a role in cognitive impairment.
Final Thoughts

Pharmacists’ Impact

Studies of pharmacist-driven protocols:

- Stress-ulcer prophylaxis (SUP) — Decreased inappropriate SUP in ICU patients by 58.3% and in general ward patients by 83.5%
- Participation in interdisciplinary rounds — Use of acid-suppressants without appropriate indications decreased in the pharmacist group
  - 46.1% versus 23.9% (p=0.001)
- Decreased use in non- ICU patients — PPIs were discontinued in 66% of patients at some point during their hospital stay
  - Discontinuation included step-down to H2RA per-protocol

Step Down Therapy

- Step 1: Halve doses of PPIs for the higher dose regimen (twice-daily stepped down to once daily or 40mg decreased down to 20mg)
  - Two weeks on this step
- Step 2: Transition to every other day dosing of the PPI
  - Two weeks on this step, then discontinue therapy with the PPI
- Step 3: “On demand” dosing with an H2RA such as ranitidine or an antacid such as calcium carbonate
- Step 4: Assess how symptoms are controlled with the “on demand” H2RA and/or antacid
  - Reassess if PPI therapy is needed
**Summary**

<table>
<thead>
<tr>
<th>Associated Risk</th>
<th>PPIs</th>
<th>H2RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>Yes</td>
<td>Controversial</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Yes</td>
<td>Less likely</td>
</tr>
<tr>
<td>Dementia</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Ensuring Appropriate Use**

- Match appropriate indication upon drug utilization review
- Provider and patient education
- Create institutional guidelines for use
- Continue to reassess need for use in each patient
- Discontinue when associated risk or indication is no longer present

**Take Away Points**

- Judicious use of proton pump inhibitors is key!
- Proton pump inhibitors are not benign drugs
  - Associated risks include: Fractures, C. difficile infections, electrolyte abnormalities, and dementia
- Overuse contributes significantly to healthcare costs
- Pharmacists and technicians can have a great impact on proper education for use and decrease the risks patients face