Appropriate Use of Proton Pump Inhibitors (PPIs)

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Disclosures

• I have no actual or potential conflicts of interest to report in relation to this presentation
Objectives

• Evaluate potential risks associated with proton pump inhibitors

• Describe appropriate use of proton pump inhibitors in hospitalized patients

• Determine when to discontinue proton pump inhibitors
Proton Pump Inhibitors: U.S. Food and Drug Administration-Approved Indications and Dosages for Use in Adults (August 2013).
FDA Approved Indications

• Gastro-Esophageal Reflux Disease

• Prevention or healing of Ulcers

• H. Pylori Eradication

• Hypersecretory conditions
  • Zollinger-Ellison syndrome
Over The Counter PPIs-Heartburn

- Omeprazole
  - Prilosec OTC®
  - Zegerid OTC®
- Lansoprazole
  - Prevacid 24HR®
- Esomeprazole
  - Nexium 24HR®

• Maximum 14 days within 4 months
• Lowest Available dose once daily
Short Term Adverse Reactions

- Headache
- Diarrhea
- Nausea
- Vomiting
- Flatulence
Heartburn drugs tied to greater mortality

These Heartburn Drugs Are Linked to a Higher Risk of Early Death

Some heartburn drugs linked with higher risk of death

Heartburn drugs tied to increased risk of early death, study says
Which of the following have been associated with long term use of PPIs?

a) Pneumonia
b) C. Difficile
c) Dementia
d) Bone Fractures
e) All of the above
Dementia Risk

**Mechanism:** reduction in B12 absorption and amyloid plaque development

- Largest German Insurer conducted cohort study using inpatient and outpatient data in elderly (≥75)
- PPI use associated with 44% increase in dementia
- Needs Further evaluation

Pneumonia Risk

**Mechanism:** Increased gastric PH allows bacterial growth in upper GI

- Hospital acquired pneumonia
  - Hospitalized, Ventilated patients at greatest risk
  - NNH=111 for Non-ICU hospitalized patients
- Community acquired pneumonia
  - Case Control suggested NNH=226
  - Meta-analysis and pooled analysis showed no increased risk

Chronic Kidney Disease Risk

**Mechanism**: Potentially due to recurrent AKI or hypomagnesemia

- Cohort study in patients 45-64 years old and GFR >60
- PPI associated with increased CKD risk HR=1.45
- Additional Studies needed to establish causality
- H2 receptor blockers not associated with CKD

C. Difficile Risk

**Mechanism:** Increased gastric PH allows C. difficile overgrowth

- Meta analysis suggested association OR=1.74
  - Increased when PPIs used with antibiotics OR=1.96
  - H2 receptor blockers carried lower risk OR=0.71
- Associated with 42% increased risk of recurrence
- AGA recommendation
  - Do not use routine probiotics to prevent infection

Bone Fracture Risk

**Mechanism:** Interference with calcium absorption

- 7 epidemiological studies suggest potential increase risk in post menopausal women
  - At least 1 risk factor
  - Higher Doses
  - PPI Use >1 year
  - Does not affect bone mineral density

Yang et al. JAMA 2006;296:2947-53.
Bone Fracture Risk

• FDA decided against adding warning to labeling

• AGA recommends:
  • No routine BMD screening
  • Calcium intake should not exceed recommended dietary allowance

Yang et al. JAMA 2006;296:2947-53.
Freedberg et. al, Gastroenterology (2016), doj.gastro.2017.01.031
Which of the following have been associated with long term PPI use?

a) Pneumonia
b) C. Difficile Diarrhea
c) Dementia
d) Bone Fractures
e) All of the above
Inpatient Stress Ulcer Prophylaxis

• Multiple guidelines have recommendations for SUP

  • Surviving Sepsis 2016

  • Eastern Association for the Surgery of Trauma 2008

  • American Society of Health-System Pharmacist 1999
Inpatient Stress Ulcer Prophylaxis

Needs Prophylaxis

• Mechanical ventilation
• Coagulopathy
  • Platelets <50k
  • INR >1.5
  • aPTT >2x normal
• Traumatic brain injury
• Major burn injury

Rhodes et al. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486–552
Inpatient Stress Ulcer Prophylaxis

Needs Prophylaxis if multiple present

• Extended ICU stay
• Sepsis
• Multiple Trauma
• History of GI bleed
• High Dose Corticosteroids
  • 250 mg hydrocortisone equivalent
Inpatient Stress ulcer Prophylaxis

- PPIs, H2 receptor blockers, Sucralfate considered equally effective

- Discontinue when risk factors no longer present or at discharge

Rhodes et al. Critical Care Medicine: March 2017 - Volume 45 - Issue 3 - p 486–552
De-prescribing Definition

• Discontinue PPI

• Taper PPI

• Decrease Dose of PPI

• Switch to H2 receptor Blocker

• Stop PPI and Use on Demand
  • Daily until symptoms resolve

Haastrup et al. Family Practice, Volume 31, Issue 6, 1 December 2014, Pages 625–630
Who should continue PPI

• Refractory GERD

• Barrett’s esophagus

• Hypersecretory Conditions (Zollinger-Ellison)

• High Risk for NSAID Induced Ulcer

Freedberg et. al, Gastroenterology (2016), doi:gastro.2017.01.031
Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm

Why is patient taking a PPI?
If unsure, find out if history of endoscopy, if ever hospitalized for bleeding ulcer or if taking because of chronic NSAID use in past, if ever had heartburn or dyspepsia

- Mild to moderate esophagitis or GERD treated x 4-8 weeks (esophagitis healed, symptoms controlled)
- Peptic Ulcer Disease treated x 2-12 weeks (from NSAID; H. pylori)
- Upper GI symptoms without endoscopy; asymptomatic for 3 consecutive days
- ICU stress ulcer prophylaxis treated beyond ICU admission
- Uncomplicated H. pylori treated x 2 weeks and asymptomatic
- Barrett's esophagus
- Chronic NSAID users with bleeding risk
- Severe esophagitis
- Documented history of bleeding GI ulcer

Recommend Deprescribing

Strong Recommendation (from Systematic Review and GRADE approach:
- Decrease to lower dose (evidence suggests no increased risk in return of symptoms compared to continuing higher dose), or
- Stop and use on-demand (daily until symptoms stop) 1/10 patients may have return of symptoms)

Monitor at 4 and 12 weeks

If verbal:
- Heartburn
- Regurgitation
- Dyspepsia
- Epigastric pain

If non-verbal:
- Loss of appetite
- Weight loss
- Agitation

Use non-drug approaches
- Avoid meals 2-3 hours before bedtime; elevate head of bed; address if need for weight loss and avoid dietary triggers

Manage occasional symptoms
- Over-the-counter antacid, H2RA, PPI, alginate pn (ie. Tums*, Rolaid*, Zantac*, Olex*, Gaviscon*)
- H2RA daily (weak recommendation – GRADE; 1/5 patients may have symptoms return)

If symptoms relapse:
- If symptoms persist x 3 – 7 days and interfere with normal activity:
  1) Test and treat for H. pylori
  2) Consider return to previous dose

Continue PPI or consult gastroenterologist if considering deprescribing
Case

KS is admitted with a suspected upper GI bleed. She was started on a pantoprazole IV infusion in the ER. The endoscopy reveals a high risk bleeding ulcer. What is the best course of action?

a) Continue pantoprazole infusion for 72 hours total
b) Switch to pantoprazole 40 mg IV q 12 hours
c) Stop pantoprazole infusion
d) Hospice
# Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

**Table 1. Characteristics of Studies Included in the Meta-analysis**

<table>
<thead>
<tr>
<th>Source</th>
<th>PPI</th>
<th>Dose, Route, and Frequency of Intermittent PPI</th>
<th>Cumulative Dose of Intermittent PPI, mg</th>
<th>Type of Study</th>
<th>Stigmata of Recent Hemorrhage</th>
<th>Endoscopic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriulli et al, 2008</td>
<td>Omeprazole (n = 330); pantoprazole (n = 144)</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority</td>
<td>Spurting, 50; oozing, 155; NBVV, 166; clot, 103</td>
<td>Epinephrine; epinephrine with bipolar/argon plasma coagulation; epinephrine with clips</td>
</tr>
<tr>
<td>Chan et al, 2011</td>
<td>Omeprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Equivalence</td>
<td>Spurting, 8; oozing, 46; NBVV, 39; clot, 29</td>
<td>Epinephrine; epinephrine with heater probe; epinephrine with clips</td>
</tr>
<tr>
<td>Chen et al, 2012</td>
<td>Omeprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority</td>
<td>Spurting, 12; oozing, 71; NBVV, 117; clot, 0</td>
<td>Epinephrine with heater probe</td>
</tr>
<tr>
<td>Choi et al, 2009</td>
<td>Pantoprazole</td>
<td>40 mg/d IV</td>
<td>120</td>
<td>Superiority for pH difference</td>
<td>Spurting, NS; oozing, NS; NBVV, NS; clot, NS</td>
<td>Epinephrine with argon plasma coagulation with or without clips</td>
</tr>
<tr>
<td>Hsu et al, 2010</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 6 h</td>
<td>560</td>
<td>Superiority</td>
<td>Spurting, 12; oozing, 40; NBVV, 52; clot, 16</td>
<td>Epinephrine with bipolar; bipolar</td>
</tr>
<tr>
<td>Hung et al, 2007</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>320</td>
<td>Superiority of PPI infusion to no treatment</td>
<td>Spurting, 11; oozing, 52; NBVV, 26; clot, 13</td>
<td>Epinephrine; epinephrine with heater probe</td>
</tr>
<tr>
<td>Jang et al, 2006</td>
<td>Pantoprazole</td>
<td>40 mg PO every 12 h</td>
<td>400</td>
<td>Uncertain</td>
<td>Spurting, 2; oozing, 4; NBVV, 13; clot, 0</td>
<td>Epinephrine; argon plasma coagulation; clips</td>
</tr>
</tbody>
</table>

### Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>PPI Dose</th>
<th>Treatment</th>
<th>Endpoints</th>
<th>Comparator</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Javid et al. (2009)</td>
<td>Omeprazole (n = 36); pantoprazole (n = 35); rabeprazole (n = 35)</td>
<td>Bolus: 80 mg PO once, then 40 mg PO every 12 h; bolus: 80 mg PO once, then 80 mg PO every 12 h; bolus: 80 mg PO once, then 40 mg PO every 12 h</td>
<td>320, 520, 320</td>
<td>Noninferiority for pH difference</td>
<td>Spurting, 17; oozing, 20; NBVV, 53; clot, 0; Epinephrine with heater probe</td>
</tr>
<tr>
<td>Kim et al. (2012)</td>
<td>Rabeprazole</td>
<td>20 mg PO every 12 h</td>
<td>120</td>
<td>Noninferiority</td>
<td>Spurting, 10; oozing, 29; NBVV, 44; clot, 23; Epinephrine; epinephrine with monopolar; epinephrine with clips; epinephrine with monopolar and clips</td>
</tr>
<tr>
<td>Sung et al. (2012)</td>
<td>Esomeprazole</td>
<td>40 mg PO every 12 h</td>
<td>240</td>
<td>Superiority</td>
<td>Spurting, NS; oozing, NS; NBVV, NS; clot, NS; Epinephrine with sclerotherapy</td>
</tr>
<tr>
<td>Ucbilek et al. (2013)</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>320</td>
<td>Uncertain</td>
<td>Spurting, NS; oozing, NS; NBVV, NS; clot, NS; Epinephrine with bipolar; epinephrine with clips</td>
</tr>
<tr>
<td>Yamada et al. (2012)</td>
<td>Pantoprazole</td>
<td>Bolus: 80 mg IV once, then 40 mg IV every 12 h</td>
<td>240</td>
<td>Superiority</td>
<td>Spurting, 13; oozing, 3; NBVV, 6; clot, 5; Epinephrine; epinephrine with monopolar and clips</td>
</tr>
<tr>
<td>Yuksel et al. (2008)</td>
<td>Pantoprazole</td>
<td>40 mg IV every 12 h</td>
<td>240</td>
<td>Uncertain</td>
<td>Spurting, 7; oozing, 60; NBVV, 30; clot, 0; Epinephrine with heater probe</td>
</tr>
</tbody>
</table>

**Abbreviations:** IV, intravenous; NBVV, nonbleeding visible vessel; NS, not stated; PO, orally; PPI, proton pump inhibitor.
Intermittent Vs. Continuous PPI in Patients with High Risk Bleeding Ulcers

<table>
<thead>
<tr>
<th>Source</th>
<th>Intermittent Bolus, No.</th>
<th>Continuous Infusion, No.</th>
<th>Risk Ratio (M-H, Fixed, 95% CI)</th>
<th>Favors Bolus</th>
<th>Favors Infusion</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriulli et al, 14 2008</td>
<td>19 239</td>
<td>28 243</td>
<td>0.69 (0.40-1.20)</td>
<td></td>
<td></td>
<td>43.2</td>
</tr>
<tr>
<td>Chen et al, 16 2012</td>
<td>6 101</td>
<td>7 100</td>
<td>0.85 (0.30-2.44)</td>
<td></td>
<td></td>
<td>11.0</td>
</tr>
<tr>
<td>Choi et al, 17 2009</td>
<td>3 21</td>
<td>1 19</td>
<td>2.71 (0.31-23.93)</td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Jang et al, 24 2006</td>
<td>0 19</td>
<td>2 19</td>
<td>0.20 (0.01-3.91)</td>
<td></td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>Javid et al, 20 2009</td>
<td>4 53</td>
<td>4 53</td>
<td>1.00 (0.26-3.79)</td>
<td></td>
<td></td>
<td>6.2</td>
</tr>
<tr>
<td>Kim et al, 21 2012</td>
<td>2 54</td>
<td>1 52</td>
<td>1.93 (0.18-20.60)</td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Sung et al, 25 2012</td>
<td>3 105</td>
<td>2 95</td>
<td>1.36 (0.23-7.95)</td>
<td></td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>Uc bilek et al, 26 2013</td>
<td>3 37</td>
<td>10 36</td>
<td>0.29 (0.09-0.97)</td>
<td></td>
<td></td>
<td>15.8</td>
</tr>
<tr>
<td>Yamada et al, 22 2012</td>
<td>4 13</td>
<td>5 15</td>
<td>0.92 (0.31-2.73)</td>
<td></td>
<td></td>
<td>7.2</td>
</tr>
<tr>
<td>Yüksel et al, 23 2008</td>
<td>3 49</td>
<td>4 50</td>
<td>0.77 (0.18-3.24)</td>
<td></td>
<td></td>
<td>6.2</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47 691</td>
<td>64 682</td>
<td>0.74 (0.52-1.06)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 5.96$ (P = .74) $I^2 = 0\%$
Test for overall effect: $z = 1.65$ (P = .10)

Case

KS is readmitted with a suspected upper GI bleed. She was started on a pantoprazole IV infusion in the ER. The endoscopy reveals a high risk bleeding ulcer. What is the best course of action?

a) Continue pantoprazole infusion for 72 hours total
b) Switch to pantoprazole 40 mg IV every 12 hours
c) Stop pantoprazole infusion
d) Hospice
In Summary

• Long term Use of PPIs potentially associated with serious adverse effects

• Avoid PPI when unnecessary

• Prescribe PPI when indicated

• Evaluate need for PPI prior to discharge

• De-prescribe when appropriate
THANK YOU!