Proton Pump Inhibitors- Questions & Controversies
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Disclosure Information

Proton Pump Inhibitors: Questions & Controversies
Farah Kablaoui

I have no financial relationship to disclose
AND
I will not discuss off label use and/or investigational use in my presentation
Learning Objectives

- Review pharmacokinetics and mechanism of action of PPI class
- Discuss and analyze literature on multiple questions and controversies
- Recognize the pharmacist role in utilizing PPI’s
Proton Pump Inhibitors Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage, mg</th>
<th>IV</th>
<th>Half-life (hr)</th>
<th>Liver Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>10, 20, 40</td>
<td>Yes</td>
<td>0.5</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>15, 30</td>
<td>Yes</td>
<td>1.7</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20, 40</td>
<td>Yes</td>
<td>2-3</td>
<td>CYP2C19, CYP3A4</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20</td>
<td>No</td>
<td>2-5</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20, 40</td>
<td>Yes</td>
<td>1.5</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Dxlansoprazole</td>
<td>30, 60</td>
<td>No</td>
<td>1-2, 4-5</td>
<td>CYP2C19, CYP3A4</td>
</tr>
</tbody>
</table>

By Vaccinationist - PubChem, Public Domain
Treatment Indications

- Zollinger-Ellison Syndrome
- Acute upper GI bleed
- Erosive esophagitis
- Helicobacter pylori treatment
- Gastric or duodenal ulcer
- Gastroesophageal Reflux Disease (GERD)
Stress Ulcer Prophylaxis
SUP Pathophysiology

Stress Ulcer

- Splanchnic hypo-perfusion \(\rightarrow\) superficial lesions at the proximal stomach bulb

Peptic Ulcer

- Corrosive action of pepsin \(\rightarrow\) deep lesions in the duodenum
<table>
<thead>
<tr>
<th>Stress Ulcer Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients on mechanical ventilation for &gt;48 hours</strong></td>
</tr>
<tr>
<td><strong>Coagulopathy defined as platelet count &lt;50, INR &gt;1.5 or PTT 2x baseline</strong></td>
</tr>
<tr>
<td><strong>Traumatic head injuries with a GCS &lt;10 or inability to follow simple commands</strong></td>
</tr>
<tr>
<td><strong>Burns affecting &gt;35% total BSA</strong></td>
</tr>
<tr>
<td><strong>Major trauma with an Injury Severity Score &gt;16</strong></td>
</tr>
<tr>
<td><strong>Spinal cord injury</strong></td>
</tr>
<tr>
<td><strong>Partial hepatectomy</strong></td>
</tr>
<tr>
<td><strong>Solid organ transplantation perioperatively in the ICU setting</strong></td>
</tr>
</tbody>
</table>
## SUP Risk Factors- Two of the following

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>ICU stay &gt;7 days</td>
<td></td>
</tr>
<tr>
<td>Occult bleeding lasting more than 6 days</td>
<td></td>
</tr>
<tr>
<td>High dose steroids with a daily dose greater than:</td>
<td></td>
</tr>
<tr>
<td>• 250 mg of hydrocortisone</td>
<td></td>
</tr>
<tr>
<td>• 50 mg of methylprednisolone</td>
<td></td>
</tr>
<tr>
<td>• 60 mg of prednisone</td>
<td></td>
</tr>
<tr>
<td>• 10 mg of dexamethasone</td>
<td></td>
</tr>
</tbody>
</table>

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- Multicenter, stratified, parallel-group, placebo-controlled, blinded clinical trial
- N=3298
  - Pantoprazole (n=1645)
  - Placebo (n=1653)
- Setting: 33 ICUs in Europe
  - 2016-2017
- Analysis: Intention-to-treat
- Primary Outcome: Mortality at 90 days
- Secondary Outcome: Any clinically important events

# Pantoprazole in Patients at Risk for GI Bleeding in the ICU

## Inclusion Criteria
- ≥18 years old
- Admitted to medical or surgical ICU for an acute condition
- ≥1 risk factor for clinically important GI bleeding:
  - Shock, use of anticoagulant agents, RRT, MV (expected to last >24 hours), any history of liver disease, or any history of or ongoing coagulopathy
  - Acute and chronic coagulopathy

## Exclusion Criteria
- Contraindication to PPI therapy
- Receiving acid-altering therapy prior to enrollments
- Diagnosis of PUD during current hospital admission
- Pregnant
- Organ transplant
- Withdrawal of active therapy

Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- Results:
  - Mortality at 90 days 31.1% vs. 30.4% (RR 1.02; 95% CI 0.91-1.13; P=0.76)

- Any clinically important events
  - Any: 21.9% vs. 22.6% (RR 0.96; 95% CI 0.83-1.11)
  - GI bleeding: 2.5% vs. 4.2% (RR 0.58; 95% CI 0.40-0.86)
  - Pneumonia or C. difficile infection: 16.8% vs. 16.9% (RR 0.99; 95% CI 0.84-1.16)
Pantoprazole in Patients at Risk for GI Bleeding in the ICU

- **Discussion**
  - Mortality
  - Inclusion criteria
  - SUP was statistically significant in reducing GI bleeding
  - Nutrition

- **Conclusion**
  - Pantoprazole should be used in select patients with highest risk of bleeding
  - More studies need to be conducted prior to changing practice
SUP in ICU patients receiving EN: Systematic review and meta-analysis

Inclusion: RCTs, ICU patients receiving EN
  • Intervention - patients receiving any pharmacologic SUP, regardless of dosage, frequency and duration
  • Control - patients receiving placebo or no prophylaxis

• Outcomes - GI bleeding, overall mortality at the longest available follow up, HAP, length of ICU stay, duration of MV and C. diff. infection
• Searched PubMed, Embase, and the Cochrane database from inception through 30 Sep 2017
Results: 7 studies (n = 889 patients)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statistic</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Bleeding</td>
<td>RR 0.80</td>
<td>0.49 - 1.31</td>
<td>0.37</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>RR 1.21</td>
<td>0.94 - 1.56</td>
<td>0.14</td>
</tr>
<tr>
<td>C diff</td>
<td>RR 0.89</td>
<td>0.25 – 3.19</td>
<td>0.86</td>
</tr>
<tr>
<td>LOS in ICU</td>
<td>MD 0.04 days</td>
<td>-0.79 – 0.87</td>
<td>0.92</td>
</tr>
<tr>
<td>Duration of MV</td>
<td>MD -0.38 days</td>
<td>-1.48 – 0.72</td>
<td>0.50</td>
</tr>
<tr>
<td>Subgroup Analysis for PPI (n= 527)</td>
<td>RR 0.4</td>
<td>0.21 – 1.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Conclusion:

- Pharmacologic SUP in patients on EN offered no beneficial effect on the incidence of GI bleeding and other clinically important outcomes
- Larger RCTs needed to confirm findings
EN as SUP in critically ill patients: A randomized controlled exploratory study

- Investigated whether early EN alone may be sufficient prophylaxis against stress-related gastrointestinal (GI) bleeding in mechanically ventilated patients
- Prospective, double blind, randomized, placebo-controlled, exploratory study that included mechanically ventilated patients in medical ICUs of two academic hospitals
- Pantoprazole IV + early EN were compared to placebo + early EN as SUP
- Incidences of clinically significant and overt GI bleeding were compared in the two groups
EN as SUP in critically ill patients: A randomized controlled exploratory study

Results

- Treatment group n= 55; placebo n= 47

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt GI Bleed, n (%)</td>
<td>1 (1.82)</td>
<td>1 (2.13)</td>
<td>0.99</td>
</tr>
<tr>
<td>Significant GI Bleed, n</td>
<td>1 (1.82)</td>
<td>1 (2.13)</td>
<td>0.99</td>
</tr>
<tr>
<td>(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of CDI, n (%)</td>
<td>1 (1.82)</td>
<td>3 (6.38)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Conclusions:

- No benefit of pharmacologic SUP when early EN is initiated in critically ill, MV patients in the medical ICU
- Results add to the growing evidence supporting the protective role of early EN in ICU
Do we need PPI’s for Dual Anti-Platelet? & Is the Interaction Real?
Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

- **Objective:** Examine the interaction using a well-controlled study design in a population of participants free of confounders.

- **Materials and Methods:** 28 healthy male participants
  - Week 1: Clopidogrel 75 mg was taken daily for 1 week
  - Week 2: Addition of 1 of 3 PPIs
  - Week 3: 1 week washout period
  - Repeat with 2 other PPI’s from list:
    - Pantoprazole 40 mg, omeprazole 20 mg, rabeprazole 20 mg, esomeprazole 40 mg, lansoprazole 30 mg, or dexlansoprazole 30 mg

Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

- Endpoint: Platelet responsiveness in whole-blood samples
  - Impedance aggregometer (Normal: drug-free population ranges 6-24 Ω)
    - Normal ADP response: difference in impedance of 7 Ω

- Results:
  - No PPIs had statistically significant interaction with clopidogrel as measured by whole-blood impedance aggregation

<table>
<thead>
<tr>
<th>PPI</th>
<th>Ω (Standard error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pantoprazole</td>
<td>−9.119</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>−9.120</td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>−9.507</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>−9.185</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>−8.940</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>−9.029</td>
</tr>
</tbody>
</table>

Przeszeplewski, E et al. Journal of Stroke and Cerebrovascular Diseases, Vol. 27, No. 6 (June), 2018: pp 1582–1589
Evaluating the Effect of Six Proton Pump Inhibitors on the Antiplatelet Effects of Clopidogrel

![Graph showing responsiveness to Adenosine Diphosphate (ADP) in Clopidogrel vs. Clopidogrel + Proton Pump Inhibitors (PPIs)].

Responsiveness (Mean ± Standard Deviation) to Adenosine Diphosphate (ADP) in Clopidogrel vs. Clopidogrel + Proton Pump Inhibitors (PPIs).

- **No Drug**: n=28, 10.5 ± 2.3
- **Clopidogrel Only**: n=23, 0.6 ± 1.2
- **Dexlansoprazole + Clopidogrel**: n=10, 0.6 ± 1.4
- **Rabeprazole + Clopidogrel**: n=10, 1.3 ± 2.9
- **Esomeprazole + Clopidogrel**: n=11, 1.1 ± 1.2
- **Omeprazole + Clopidogrel**: n=9, 1.3 ± 2.4
- **Lansoprazole + Clopidogrel**: n=10, 0.8 ± 1.7
- **Pantoprazole + Clopidogrel**: n=12, 1.1 ± 2.8

Note: Drug-free range of platelet aggregation to ADP 10μM is 6-24 Ω.
Clopidogrel and the Optimization of GI Events Trial (COGENT)

Method

- Randomized, double-blind, double-dummy, placebo-controlled, phase III study
- N=3761 high-risk patients with ACS or undergoing PCI
  - Clopidogrel and omeprazole (n=1876)
  - Clopidogrel alone (n=1885)
- Setting: 393 sites in 15 countries
- Median follow-up: 106 days

## Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Occurrence</th>
<th>Hazard Ratio (CI 95%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of GI events</td>
<td>1.1% vs. 2.9%</td>
<td>0.34 (0.18 - 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite of CV events</td>
<td>4.9% vs. 5.7%</td>
<td>0.99 (0.68 – 1.44)</td>
<td>0.96</td>
</tr>
<tr>
<td>Composite of overt and occult GIB</td>
<td>0.8% vs. 2.0%</td>
<td>0.3 (0.13 – 0.66)</td>
<td>0.001</td>
</tr>
<tr>
<td>MI</td>
<td>1.2% vs. 1.5%</td>
<td>0.92 (0.44 – 1.90)</td>
<td>0.81</td>
</tr>
<tr>
<td>Revascularization</td>
<td>4.0% vs. 4.6%</td>
<td>0.91 (0.59 – 1.38)</td>
<td>0.64</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.2% vs. 0.3%</td>
<td>N/A</td>
<td>0.43</td>
</tr>
<tr>
<td>Serious ADE</td>
<td>10.1% vs. 9.4%</td>
<td>N/A</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Conclusion

• Concomitant use of aspirin, clopidogrel, and PPIs decreased the rate of GI bleeding

• No differences in the risks of MI, cardiogenic death, and all-cause mortality

• GI benefits should be weighed against the MACE risks when prescribing PPIs to patients taking aspirin and clopidogrel

Influence of PPI on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis

• Searched PubMed, Embase, and the Cochrane Library for articles published between January 1, 2010 and April 11, 2017

• Primary endpoints MACE (defined as ACS, stent thrombosis, revascularization, stroke, and all-cause mortality) and GI bleeding (overt and occult)

• Secondary endpoints were MI, stent thrombosis, revascularization, cardiogenic death, and all-cause mortality
Influence of PPI on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis

**Results:**
- 12 studies (33,492 patients)
- 50.29% on a PPI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.17 (1.07 -1.28)</td>
<td>P= 0.001</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>0.58 (0.36 – 0.92)</td>
<td>P= 0.02</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>1.30 (1.01 – 1.68)</td>
<td>P= 0.041</td>
</tr>
<tr>
<td>Revascularization</td>
<td>1.20 (1.04 -1.38)</td>
<td>P= 0.011</td>
</tr>
<tr>
<td>MI</td>
<td>1.03 (0.87 – 1.22)</td>
<td>P= 0.742</td>
</tr>
<tr>
<td>Cardiogenic death</td>
<td>1.09 (0.83 – 1.43)</td>
<td>P= 0.526</td>
</tr>
<tr>
<td>All - cause mortality</td>
<td>1.08 (0.93 – 1.25)</td>
<td>P= 0.329</td>
</tr>
</tbody>
</table>
Conclusion

• Combination therapy resulted in decreased GI bleeding and potentially increased MACE

• GI benefits should be weighed against the MACE risks when prescribing PPIs to patients on combination

• Study had some limitations and weaknesses

• Results should be interpreted with caution
Guidelines

2017 ECS DAPT
Class of recommendation B
Level of evidence C
While the evidence that a PPI does not increase the risk of CV events was generated with omeprazole, based on drug–drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

2016 ACC/AHA DAPT
PPIs should be used in patients with a history of prior GI bleeding treated with DAPT (Class I)
Patients with increased risk of GI bleeding, including those with advanced age and those with concomitant use of warfarin, steroids, or nonsteroidal anti-inflammatory drugs, use of PPIs is reasonable (Class IIa)
Routine use of PPIs is not recommended for patients at low risk of GI bleeding (Class III: No Benefit).

Upper GI Bleeding: Continuous Infusion?
Background: Guidelines recommend an IV bolus dose of a PPI followed by continuous PPI infusion after endoscopic therapy in patients with high-risk bleeding ulcers

Purpose: To compare intermittent PPI therapy with the currently recommended bolus plus continuous-infusion PPI regimen for reduction of ulcer rebleeding

Method: Searched MEDLINE, EMBASE, and Cochrane up to December 31, 2013, and relevant abstracts from major gastroenterology scientific meetings

Results: 11 full-text articles and 2 meeting abstracts
Results

• RR 0.72 recurrent rebleeding within 7 days for intermittent vs continuous PPI administration
Intermittent vs Continuous PPI Therapy for High-Risk Bleeding Ulcers: A Systematic Review and Meta-analysis

Conclusion

- Intermittent PPI regimens are comparable to continuous PPI infusion regimens in patients with bleeding ulcers and high risk endoscopic findings.

- Greater ease of use and lower cost and resource utilization, intermittent PPI therapy should be the regimen of choice after endoscopic therapy.

- Current national and international guidelines should be revised to incorporate this new information and recommend intermittent PPI therapy.
<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress Ulcers</td>
</tr>
<tr>
<td>New Study? EN?</td>
</tr>
<tr>
<td>DAPT Interaction? Protection?</td>
</tr>
<tr>
<td>Continuous PPI</td>
</tr>
</tbody>
</table>

Give prophylaxis for the high risk patients and discontinue when possible.


• El-Kerish, K et al. Journal of Critical Care 43 (2018) 108–113


THANK YOU!

Farah Kablaoui, PharmD, BCPS, BCCCP