Axing Prophylaxis: PPI stress ulcer prophylaxis in ventilator-assisted patients in the ICU

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DOCTOR OF PHARMACY CANDIDATE 2018
UNIVERSITY OF UTAH
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Objectives

- Review rationale behind stress ulcer prophylaxis in ventilator assisted patients
- Discuss the agents currently used for stress ulcer prophylaxis in the ICU setting
- Recognize risks associated with PPI use in SUP
- Evaluate recent studies regarding the necessity of PPIs for SUP
- Evaluate whether patients should or should not receive SUP with PPI
Abbreviations

• SUP – Stress ulcer prophylaxis
• ICU – Intensive care unit
• PPI – Proton pump inhibitor
• H$_2$RA – Histamine 2 receptor antagonist
• NG – Nasogastric
• VAP – ventilator associated pneumonia

• GCS – Glasgow Coma Score
• BSA – Body surface area
• PRBC – Packed red blood cells
Interest in Topic

https://www.alanizmarketing.com/clients/university-of-utah-healthcare/
What causes stress ulcers?

Stress ulcers occur when there is a decrease in GI mucosal perfusion

- Many risk factors, not all related to mechanical ventilation
  - Mechanical ventilation >48 hours
  - Spinal cord injury
  - Multiple traumas
  - Hepatic failure
  - Thermal injuries >35% BSA
  - Head injury with GCS < 10

- History of ulcers/bleeding in last year
  - Sepsis/septic shock
  - > 1-week ICU stay
  - Corticosteroid treatment
Stress ulcer prophylaxis guidelines

Stress ulcer prophylaxis should be initiated in all patients who are expected to require >48 hours of mechanical ventilation

- ASHP has stated that the decision regarding selection of specific agents for SUP should be left up to each individual institution

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2760176/
Current treatment options

**PPIs**
- Considered more effective at preventing GI bleeding than H$_2$RAs

**Antacids**

**Sucralfate**

**H$_2$RAs**
University Hospital - MICU

Patient census
• Approximately 500 mechanically ventilated patients in FY 2017
• Average of 3.5 days on mechanical ventilation

Treatment – started for all mechanically ventilated patients
• Pantoprazole IV 20 – 40 mg, Daily or BID
• Omeprazole suspension 20 – 40 mg, Daily or BID
Risks associated with PPI use

**Ventilator associated pneumonia**

- Increased gut pH limits the body’s defense mechanism against colonization of bacteria
- Increased pressure at esophageal sphincter
- Increased retrograde movement of gastric content leading to risk of aspiration

[Image: Gastroesophageal Reflux]
Risks associated with PPI use

C. Difficile

• Acid secretion acts as defense mechanism against C. Diff
• Suppression of acid leads to increased colonization of C. Diff or its spores
• Definite association has not been established, but cannot be ruled out

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3124633/
Controversy

New data, presented in the July issue of Critical Care Medicine, suggest that the risk associated with use of PPIs may not outweigh the bleeding risk associated with stress ulcers in mechanically ventilated patients
Questions
Stress ulcer prophylaxis in patients being weaned from the ventilator in a respiratory care center: A randomized control trial

Objective
• Investigate the efficacy of SUP and the incidence of VAP in patients being weaned from mechanical ventilators in a respiratory care center

Study Design
• Prospective, randomized, non-blinded trial performed at the Far Eastern Memorial Hospital, New Taipei City, Taiwan
Study population

• Patients were selected from all admissions to the respiratory care center from June 1, 2009 to February 29, 2012
• All admitted patients were considered difficult to wean off mechanical ventilation
  • Difficult to wean was described as failure to be weaned off of mechanical ventilation 48-72 hours following resolution of the underlying disease process
Exclusion criteria

- Pregnant
- < 18 years old
- Allergy to lansoprazole
- Active upper GI bleed
- Use of PPIs or H₂RAs 1 week prior to enrollment
Lin 2016

758 patients admitted to RCC

534 patients were excluded due to recent or current use of PPI or H2 blockers or patients expired before enrollment.

224 patients screened for potential participants

104 patients were excluded due to no informed consent.

120 patients randomized

Group A
Lansoprazole OD
n = 60

Group B
Control
n = 60

Table 1: Distributions of baseline characteristics in two groups of patients.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Group A (n = 60)</th>
<th>Group B (n = 60)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>38 (63.3)</td>
<td>37 (67.2)</td>
<td>0.850</td>
</tr>
<tr>
<td>Age</td>
<td>66.7 ± 16.8</td>
<td>64.8 ± 18.6</td>
<td>0.652</td>
</tr>
<tr>
<td>NSAID</td>
<td>6 (10.0)</td>
<td>6 (10.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6 (10.0)</td>
<td>13 (21.7)</td>
<td>0.080</td>
</tr>
<tr>
<td>Steroid</td>
<td>3 (5.0)</td>
<td>4 (6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>11 (18.3)</td>
<td>6 (10.0)</td>
<td>0.191</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1.78 ± 1.26</td>
<td>1.55 ± 1.31</td>
<td>0.322</td>
</tr>
<tr>
<td>Operation within last months</td>
<td>33 (55.0)</td>
<td>35 (58.3)</td>
<td>0.713</td>
</tr>
</tbody>
</table>

2 months

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer history</td>
<td>4 (6.7)</td>
<td>5 (8.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>UGI bleeding history</td>
<td>1 (1.7)</td>
<td>1 (1.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>APACHE II</td>
<td>21.3 ± 6.7</td>
<td>19.9 ± 6.9</td>
<td>0.242</td>
</tr>
<tr>
<td>GCS at RCC</td>
<td>9.2 ± 3.0</td>
<td>10.1 ± 3.0</td>
<td>0.082</td>
</tr>
<tr>
<td>Rapid shallow index</td>
<td>106.3 ± 69.9</td>
<td>112.5 ± 102.9</td>
<td>0.599</td>
</tr>
<tr>
<td>(breaths/min/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.1 ± 1.5</td>
<td>10.3 ± 1.5</td>
<td>0.477</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>3.01 ± 0.50</td>
<td>2.92 ± 0.55</td>
<td>0.389</td>
</tr>
<tr>
<td>Ventilator-dependent days</td>
<td>15.8 ± 7.9</td>
<td>14.7 ± 11.4</td>
<td>0.157</td>
</tr>
</tbody>
</table>

* Comparisons between two groups: χ² test or Fisher’s exact
Lin 2016

Control group
• Lansoprazole 30 mg daily via nasogastric tube for 14 days

Treatment Group
• Withholding of all medications for the treatment or prevention of peptic ulcers
Lin 2016

Primary outcome measures
• Apparent upper GI bleeding within 2 weeks of enrollment
  • Coffee ground substance from NG aspirate
  • Fresh blood from NG aspirate
  • Passage of tarry stool

Secondary outcome measures
• Clinically significant upper GI bleeding
  • Upper GI bleeding with hemoglobin level decrease > 2 g/dl or need of a transfusion of > 2 units
  • Successful weaning
  • VAP
  • 30-day survival rate
Statistical Methods

• $X^2$ or Fisher’s exact, and Mann-Whitney U test were used to compare patients baseline characteristics
• $X^2$ or Fisher’s exact were used to compare rates of primary and secondary outcomes
• 55 patients in each group were required to achieve 80% power at a significance level of 0.05, assuming a 3% and 20% bleeding incidence in SUP and non-SUP groups respectively
### Lin 2016

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SUP (N=60)</th>
<th>No SUP (N=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients that showed signs of apparent upper GI bleeding</td>
<td>0</td>
<td>5</td>
<td>0.057</td>
</tr>
<tr>
<td>Number of patients that showed signs of significant upper GI bleeding</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- No statistical difference among other secondary outcomes
Lin 2016

**Strengths**
- Randomized
- Appropriate inclusion criteria
- Appropriate SUP therapy selection
- Met Power

**Weaknesses**
- Single center
- Non-blinded
- Endoscopy was not required to diagnose ulcer
- Questionable Exclusion criteria
Author’s Conclusion

• Stress ulcer prophylaxis with oral PPIs in patients weaning from mechanical ventilators trends to a lower, but not statistically significant incidence of apparent upper GI bleeding. There was no significant increase in the incidence of VAP in the prophylaxis group. Further large scale studies are needed to clarify the benefit of SUP in this population.
Lin 2016

Seminarian’s conclusions

• In the presented patient population, there is not significant data to support the removal of SUP therapy. However, future studies involving larger patient populations may help form more definitive recommendations.
Questions
Withholding pantoprazole for stress ulcer prophylaxis in critically ill patients: a pilot randomized clinical trial

WALEED ALHAZZANI, ET AL. CRITICAL CARE MEDICINE, 2017;45:1121-1129
Alhazzani 2017

Objective
• Investigate the efficacy and safety of withholding PPIs in critically ill patients

Study Design
• International multi-center, randomized, stratified, concealed, blinded, placebo-controlled, parallel group trial
Alhazzani 2017

Inclusion criteria

• ≥ 18 years old
• Anticipated to require > 48 hours of mechanical ventilation
Alhazzani 2017

Exclusion criteria

• 72 hours since initiating mechanical ventilation
• Prior use of PPIs due to active bleeding or increased risk of bleeding
• Use of dual antiplatelet therapy prior to randomization
• Palliative care decision to withdraw life support
• Pregnancy
• ICU physician, patient, or substitute decision maker declined trial participation
• > 2 “daily dose equivalents” of H₂RA or PPI in the current ICU admission
Alhazzani 2017

Eligible patients (n=150)
- Excluded (n= 59)
  - Physician declined (n= 16)
  - Declined to participate (n= 23)
  - No SDM (n= 3)
  - Enrolled in confounding study (n=2)
  - Other (n=15)

Randomized (n=91)

Allocation
- Allocated to Pantoprazole (n= 49)
  - Received allocated intervention (n= 49)
  - Did not receive allocated intervention (n= 0)
- Allocated to Placebo (n= 42)
  - Received allocated intervention (n= 40)
  - Did not receive allocated intervention (n= 2)

Follow-Up
- Lost to follow-up (n=0)
  - Discontinued intervention (n=4)
  - Discontinued intervention (n=3)
- Lost to follow-up (n= 0)

Analysis
- Analysed (n= 49)
- Analysed (n= 42)
Patient Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pantoprazole, $n = 49$</th>
<th>Placebo, $n = 42$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>61.8 (48.4–73.5)</td>
<td>55.3 (42.4–65.6)</td>
</tr>
<tr>
<td>Females, $n$ (%)</td>
<td>22 (44.9)</td>
<td>17 (40.5)</td>
</tr>
<tr>
<td>Admission type, $n$ (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td>39 (79.6)</td>
<td>31 (73.8)</td>
</tr>
<tr>
<td>Surgical</td>
<td>2 (4.1)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Trauma</td>
<td>8 (16.3)</td>
<td>6 (14.3)</td>
</tr>
</tbody>
</table>
Alhazzani 2017

Control group
• Once daily IV infusion of 40 mg pantoprazole in 50 ml NS

Treatment group
• Once daily IV infusion of 50 ml NS
Alhazzani 2017

**Outcome measures**

- Incidence of clinically important GI bleeding, plus one of the following in the absence of other causes
  - Drop in systolic BP ≥ 20 mmHg within 24 hours of upper GI bleed
  - Orthostatic increase in pulse rate ≥ 20 BPM and a decrease in systolic BP ≥ 10 mmHg
  - A decrease in hemoglobin ≥ 2 g/dL in 24 hours
  - Transfusion of ≥ 2 units of PRBC within 24 hours of bleeding
- Incidence of VAP
- Incidence of C. Diff Infection
- ICU mortality
- ICU length of stay (days)
Statistical Methods

• Continuous data is reported as means and standard deviations or medians and interquartile ranges
• Categorical data is reported as frequencies and percentages
• Treatment effects were compared as relative risk and 95% confidence interval
• P values were calculated with Fisher exact test, with significance at p<0.05
### Alhazzani 2017

<table>
<thead>
<tr>
<th>Outcomes (# of occurrences)</th>
<th>SUP (N=49)</th>
<th>No SUP (N=42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically important GI bleeding events</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>C. Diff</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Late VAP</td>
<td>10</td>
<td>6</td>
<td>0.58</td>
</tr>
<tr>
<td>Median length of ICU stay (days)</td>
<td>12</td>
<td>8.5</td>
<td>0.299</td>
</tr>
<tr>
<td>Median length of hospital stay (days)</td>
<td>27</td>
<td>25</td>
<td>0.049</td>
</tr>
</tbody>
</table>
Alhazzani 2017

**Strengths**
- Blinded
- Randomized
- International Multi-center
- Appropriate inclusion/exclusion criteria

**Weaknesses**
- Endoscopy was not required for diagnosis of source of bleeding
- Small number of patients
Author’s conclusion

• There was no substantial absolute increase in risk of GI bleeding in the placebo group, although results were too imprecise to allow clinical inferences.

• The total body of evidence to date is well below the optimal information size, and the observed effects are associated with very wide CIs including important benefit and important harm for all major outcomes.

• The available evidence is not sufficient to confirm or refute the safety of routine administration of PPIs for SUP in the ICU.
Seminarian’s Conclusion

• Due to the small patient population the presented data is not sufficient alone to modify current standards of care. However, the results of this trial do provide a basis for larger future studies.
Questions
On the Horizon

Upcoming guidelines
• Current SUP guidelines were published in 1999
• ASHP has listed the guidelines as under revision in the last 4 weeks
• Expected release date for new guidelines Q2 2018
On the Horizon

Alhazzani 2017 – Post study Meta analysis

• 5 additional studies
• Total of 3,141 patients across
• No statistically different risk of clinically important GI bleeding, VAP, C.Diff, or mortality
On the Horizon

Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU)

• PPI vs Placebo
• Enrollment of 3,400 patients
• Expended completion date 2018

https://clinicaltrials.gov/ct2/show/NCT02467621?recrs=abdf&cond=stress+ulcer&rank=1
Final Conclusions

• Current data does not provide sufficient evidence to justify deviation from current guidelines for SUP
• The use of PPIs as SUP continues to be guideline recommended
• The information presented in these and other small studies provides a basis for future large studies to build upon
• PPIs are not a benign therapy and consideration of risk should be evaluated
Role of the Pharmacist

• Assist the medical team in initiating SUP in mechanically ventilated patients
• Monitor for adverse events associated with SUP
• As more information regarding SUP becomes available assist the medical team in adjusting therapy accordingly
• Renal adjusting SUP as necessary
• Assist in determining when to d/c therapy to decrease risk as much as possible
Questions