Stress Ulcer Prophylaxis in the ICU: Proton-pump Inhibitors

Grand Rounds
Monday August 9th, 2010
Edward Jones, M.D., M.S.
Overview

- Background & history
- Who needs intervention
- What treatment is available
- Literature review
- Why proton-pump inhibitors are superior
- Questions & comments
Stress related mucosal injury

- Harvey Cushing – early 1900s
- Hans Selye – “stress ulcer” 1936
- Charles Lucas – GI Bleeds -1971
- Paul Hastings – Acid Suppression - 1978

How is the mucosa damaged?

- Ischemic injury + gastric acid
  - Rat studies – gastric blood flow w/ hemorrhage
  - Decreased BP by 40%: lesions
  - Lesion rose in dose dependent fashion, up to 10x, with addition of gastric acid
- Multifactorial – re-perfusion, oxidative stress & oxygen radicals, decreased microcirculation

Who is at risk?

**COOK ET AL. NEJM. 1994 – PROSPECTIVE MULTICENTER COHORT STUDY:**

- Overall 1.5% bleeding rate
  - Respiratory Failure
  - Coagulopathy

**ELLISON. CRIT CARE MED. 1996. – MULTICENTER COHORT STUDY IN 6 VA HOSPITALS:**

- Overall 8% bleeding rate, Mortality 49%
  - Acute hepatic failure
  - Prolonged NGT
  - Alcoholism
  - Renal failure
  - H. Pylori IgA
What does the data say?

**LEVEL I**
- All patients with:
  - Mechanical ventilation
  - Coagulopathy
  - Traumatic Brain Injury
  - Major Burn Injury

**LEVEL II**
- ICU patients with:
  - Multi-trauma
  - Sepsis
  - Acute renal failure

Prophylaxis – which drugs?

- Prophylaxis: reduce mortality by up to 50%

- What are the options?
  - Proton-Pump Inhibitors
  - Sucralfate
  - Histamine-2Receptor Antagonists
  - Others: Misoprostol, Antacids, Early feeding

Cook. JAMA. 1996
What are the drawbacks?

- Acid suppression – increased risk of infection?
  - Nosocomial pneumonia
  - *C. Dificile* diarrhea

- Altered vitamin/mineral/electrolytes

- Drug-Drug interactions
  - H2RA – known cytochrome P450 inhibitors

- Side effects/drug characteristics
Overview

- Background & history
- Who needs prophylaxis
- What treatment is available
- Literature review
- Why proton-pump inhibitors are superior
- Questions & comments
Why are PPIs better?

  - Prospective, randomized trial of 67 patients

<table>
<thead>
<tr>
<th></th>
<th>Ranitidine</th>
<th>Omeprazole</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress ulcer bleed</td>
<td>11 (31%)</td>
<td>2 (6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>5 (14%)</td>
<td>1 (3%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Clinically significant bleeding, secondary to stress ulcers, occurred at a statistically significant more frequent rate in those patients receiving ranitidine as compared to omeprazole. Nosocomial pneumonia also occurred more frequently in patients given ranitidine; however, the difference was not statistically significant.

Prospective, double-blind
Non-inferiority study of omeprazole vs. cimetidine in 359 patients

Table 2. Results in the intent-to-treat population

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole Oral Suspension (n = 178)</th>
<th>Intravenous Cimetidine (n = 181)</th>
<th>Confidence Interval for the Difference in Rates, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant bleeding, n (%)</td>
<td>7 (3.9)</td>
<td>10 (5.5)</td>
<td>-100.0, 2.8°</td>
</tr>
<tr>
<td>Any overt bleeding, n (%)</td>
<td>34 (19.1)</td>
<td>58 (32.0)</td>
<td>-21.9, -4.0°</td>
</tr>
<tr>
<td>Inadequate pH control, n (%)</td>
<td>32 (18.0)</td>
<td>105 (58.0)</td>
<td>-49.2, -30.9°</td>
</tr>
</tbody>
</table>

Any overt bleeding included both end point and non-end point bleeding. Inadequate pH control was defined as two consecutive gastric pH determinations of ≤4 at least 1 hr apart on any given day of treatment; tabulated patients experienced inadequate pH control at least once during the trial. The difference in rates was calculated as omeprazole-cimetidine.

°Noninferiority analysis, one-sided 97.5% confidence interval; °two-sided 95% confidence interval, p = .005; °two-sided 95% confidence interval, p < .001.

Benefits of PPIs

- Do not develop tolerance (vs. H2RAs)
- More consistent pH control (vs. H2RAs, Suc)
- More palatable (vs. Sucralfate)
- More cost effective (Lansoprazole PO vs. IV H2RAs)

Hospital-acquired pneumonia

- Herzig – JAMA, 2009 – 2219 NON-ICU patients underwent subgroup analysis to reveal an increased risk of pneumonia

- Zhou - Zhongguo Wei Zhong Bing Ji Jiu Yi Xue, 2010 - meta-analysis of randomized studies of H2RAs vs. PPIs; n=771
  - No difference 10% vs. 9.9% p=0.89
  - Stress Ulcer Bleeding 2.2% vs. 6.8% p=0.04
Increased potency

  - Meta-analysis of randomized controlled trials comparing PPIs vs. H2RAs
  - 936 patients in 7 studies
  - Equivalency of PPIs & H2RAs for bleeding, mortality and pneumonia (p=0.19, p=0.85, p=0.50)
  - Removed Levy et al. from meta-analysis
  - PPIs held pH > 6 more effectively
References

Esomeprazole vs. placebo

- Randomized trial of 764 patients in 91 EDs
- Significant reduction in
  - <72H re-bleeds
  - Re-bleed up to 30 days
  - Surgery, mortality, transfusions

Table 3. Recurrent Bleeding Rates, Mortality Rates, Surgery, and Hospital Stay

<table>
<thead>
<tr>
<th>Variable</th>
<th>Esomeprazole Group</th>
<th>Placebo Group</th>
<th>P Value</th>
<th>Absolute Risk Reduction (95% CI), percentage points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent bleeding, n (%)</td>
<td>22 (5.9)</td>
<td>40 (10.3)</td>
<td>0.026</td>
<td>4.4 (0.6 to 8.3)</td>
</tr>
<tr>
<td>Within 72 h</td>
<td>14 (4.8)</td>
<td>33 (10.4)</td>
<td>0.009</td>
<td>6.6 (1.5 to 9.8)</td>
</tr>
<tr>
<td>Within 7 d</td>
<td>27 (7.2)</td>
<td>50 (12.9)</td>
<td>0.010</td>
<td>9.7 (1.4 to 9.9)</td>
</tr>
<tr>
<td>Within 30 d</td>
<td>29 (7.7)</td>
<td>53 (13.6)</td>
<td>0.009</td>
<td>9.9 (1.5 to 10.2)</td>
</tr>
<tr>
<td>All-cause mortality within 30 d, n (%)</td>
<td>3 (0.8)</td>
<td>8 (2.1)</td>
<td>0.22</td>
<td>1.3 (−0.4 to 2.9)</td>
</tr>
<tr>
<td>Bleeding-related mortality within 30 d, n (%)</td>
<td>2 (0.5)</td>
<td>3 (0.8)</td>
<td>1.00</td>
<td>0.2 (−0.9 to 1.4)</td>
</tr>
<tr>
<td>Surgery within 30 d, n (%)</td>
<td>10 (2.7)</td>
<td>21 (5.4)</td>
<td>0.059</td>
<td>2.7 (−0.0 to 5.5)</td>
</tr>
<tr>
<td>Repeated endoscopic treatment within 30 d, n (%)</td>
<td>24 (6.4)</td>
<td>45 (11.6)</td>
<td>0.012</td>
<td>5.2 (1.1 to 9.2)</td>
</tr>
<tr>
<td>Blood transfused within 30 d</td>
<td></td>
<td></td>
<td>0.034</td>
<td>−</td>
</tr>
<tr>
<td>Total units</td>
<td>589</td>
<td>935</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean units (SD)</td>
<td>1.6 (2.5)</td>
<td>2.4 (4.5)</td>
<td>0.008</td>
<td>−</td>
</tr>
<tr>
<td>Additional hospital days due to recurrent bleeding within 30 d</td>
<td>0.008</td>
<td>−</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.8 (3.2)</td>
<td>1.3 (3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITT = intention-to-treat; PP = per-protocol.
* Esomeprazole group: ITT sample, n = 375; PP sample, n = 292. Placebo group: ITT sample, n = 389; PP sample, n = 316.

Costly continuation

- Longitudinal cost analysis of managed care system in PA
- 29,000 patients discharged after hospital stay with risk factors & given PPIs
- 69% discharged with PPI prescriptions
- $3,000,000 cost to MCO for inappropriate post-discharge PPI prescriptions

Thomas et al. Journal of Managed Care Pharmacy. 2010.