ICU Stress Ulcer Prophylaxis: Non-PPI Methods

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Surgical Grand Rounds
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Outline

• History
• Therapeutic Options
• Current Usage
• Efficacy Data
• Adverse Drug Effects
• Cost
• Recommendations
History: Why do we care?

- Sentinel paper from Dr. Eiseman and our institution

- Incidence: 11%

- Medical therapy:
  - Iced saline lavage
  - Antacid
  - NG suction and blood replacement

- Surgical therapy:
  - Vagotomy and pyloroplasty
  - Gastric resection (generous)
  - Treatment of underlying factor causing stress (undrained pus)

Eiseman and Hayman NEJM 1970
History: Why do we care?

- Critically ill patients in 2009:
  - Stress-related mucosal damage 75-100%
  - Occult bleeding 15-50%
  - Clinically overt bleeding if no prophylaxis 5-25%
  - Clinically significant bleeding 0.6-4%
  - Confers a mortality of almost 50%
Therapeutic Options

• H2-receptor antagonists (Cimetidine, Ranitidine, Famotidine)
  – Blocks histamine receptor on parietal cells
• PPI (Omeprazole, lansoprazole, pantoprazole)
  – Irreversible H/K ATPase pump inhibitor
Therapeutic Options

• Misoprostol
  – Synthetic PGE$_1$ analog
• Sucralfate
  – Sucrose/aluminum hydroxide salts
  – Coats the gastric mucosa
• Antacids (aluminum and magnesium hydroxide)
  – Neutralize gastric acid and inactivate pepsin’s proteolytic activity
• Enteral feeding
Current Usage

• Survey of 188 Level 1 trauma centers in the US
• 119 surveys returned (63%)
• 86% said they use stress ulcer prophylaxis in the majority of trauma patients
• Of those, 71% said that H2 blockers were most popular

Barletta et al, Critical Care 2002
H2 Blockers vs: PPI

• Meta-analysis of 7 RCTs
• 936 patients
• Combine efficacy and safety information for randomized trials: PPIs vs H2 blockers
  – UGI Bleeding
  – Pneumonia
  – Mortality
• IV and oral formulations

Lin, Crit Care Med 2010
H2 Blockers vs: PPI

- No statistically significant difference in upper GI bleed

Lin, Crit Care Med 2010
H2 Blockers vs: PPI

- No statistically significant difference in rates of pneumonia

Lin, Crit Care Med 2010
H2 Blockers vs: PPI

- No statistically significant difference in rates of mortality

Lin, Crit Care Med 2010
Antacids vs. H2 Blockers

• Meta-analysis
• 42 randomized trials, 4409 patients
  – Examined antacids, H2 blockers, sucralfate and prostaglandins
• Antacids vs H2 blockers: included 14 studies
• Looking for: overt bleeding, clinically important bleeding and mortality

Antacids vs. H2 Blockers

• Antacids vs placebo:
  – Overt bleeding - OR 0.40 (95% CI 0.20-0.79)

• H2 blocker vs placebo – overt bleeding:
  – OR 0.29 (95% CI 0.17-0.45)

• H2 blocker vs Antacids – overt bleeding:
  – OR 0.56 (95% CI 0.16-0.97)

Sucralfate vs H2 Blockers

- Multicenter, randomized, blinded, placebo controlled
- 1200 pts on mechanical ventilation
- Assigned to either:
  - Ranitidine + sucralfate placebo
  - Ranitidine placebo + sucralfate

Cook et al, NEJM 1998
Sucralfate vs. H2 Blockers

- Rates of bleeding:
  - Ranitidine – 1.7%
  - Sucralfate – 3.8%
  - Relative risk: 0.44 (95% CI 0.21-0.92)

- No significant difference in rates of VAP (19 vs 16% p = 0.19) or mortality (23.5 vs 22.8% p = 0.79)

Cook et al, NEJM 1998
Enteral Nutrition

• Animal models: enteral nutrition increases GI blood flow, decreases macroscopic lesions

• Continuous administration of intragastric enteral nutrition to critically ill pts increases gastric pH
  – More likely to raise gastric pH to >3.5
    • Compared to no nutrition (OR 4.5)
    • Compared to antacids, H2 blockers or PPIs (OR 2.04)

MacLaren et al, Ann Pharm 2001
Adverse Effects: Pneumonia

- Retrospective review
- 887 CT patients receiving stress ulcer prophylaxis (pantoprazole vs ranitidine)
- Examine rates of nosocomial pneumonia
- Rates of upper GI bleeding:
  - 0.8% in pantoprazole group
  - 0.2% in ranitidine group

Miano et al, Chest 2009
Adverse Effects: Pneumonia

- Increased rates of nosocomial pneumonia in PPI group
- OR 6.6 (95% CI 2.9-14.9)

Miano et al, Chest 2009
Adverse Effects: *C difficile*

- Systematic literature review
- Included observational studies
- 12 studies included, 2948 pts with *C difficile*
- Examined association between acid suppression therapy and enteric infections

Leonard et al, Am J GI 2007
Adverse Effects: *C. difficile*

**H2 Blockers**

**PPIs**

Increased risk of *C. difficile* infection with PPIs.

OR 1.94 (95% CI 1.37 to 2.75)

Leonard et al, Am J GI 2007
Protonix IV requires refrigeration, has limited stability, is twenty times more expensive per day ($20 per 40 mg IV versus $0.49 per 20 mg famotidine IV) and is more complex to administer, requiring filtration with the filter placed below the site.
Conclusions

• H2 blockers are as effective or more effective than other non-PPI alternatives.
• H2 blockers are as clinically as effective as PPIs.
• H2 blockers confer a lower risk of pneumonia and *C difficile* infection.
• H2 blockers are at WORST 25% of the cost of PPIs.
Recommendations:

• In coagulopathic, intubated patients with either TBI or major burns
  – H2 Blocker until extubated or for 7 days
• Consider use of prophylaxis in critically ill patients with:
  – Acute hepatic failure
  – Prolonged NG tube
  – Alcoholism
  – Renal failure
• Appropriate monitoring of critically ill patients
• Feed’em if possible
• DO NOT send the patients to the floor with stress ulcer prophylaxis
References:

Enteral Nutrition

• Burn patients:
  – 181 burn pts total
  – Prospective randomized studies
  – Antacid therapy, continuous elemental enteral nutrition, or combination
  – No difference in bleeding rates

MacLaren et al, Ann Pharm 2001
Cost

The cost is as following:

(1) Average number of days on IV PPI = 4.5;
(2) Acquisition costs of PPIs vary among institutions as a result of purchasing contracts, and cost was estimated on the basis of price provided by the pharmacy of the hospital [4];
(3) Price of IV PPI (40 mg vial) = 7.5 USD;
(4) Total number of non indicated PPI injections = 2445;
(5) Estimated cost of medication = 18337 USD.
Cost

• Retrospective study
• Primary outcome: appropriateness of use of PPI
  – Per American GI Association guidelines
• 1472 pts received IV PPI
  – Randomly selected 75% - 1104 chart reviewed
  – 713 pts received IV PPI for stress ulcer prophylaxis
  – In 68.5% of those, PPI were not indicated

Perwaiz et al, J Clin Med Res 2010