Risky Business: Kicking the PPI Habit
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Pharmacist
Rush University Medical Center

Conflict of Interest
I have no actual or potential conflict of interest to disclose.

Objectives
Pharmacists/Technicians
• Describe the proposed risks of proton pump inhibitor prophylaxis in hospitalized patients.
• Recall the level of evidence with the proposed risks of proton pump therapy.
• Explain strategies to minimize proton pump inhibitor use in hospitalized patients.

Which of the following are associated with proton pump inhibitors?
A. Acute kidney injury
B. Clostridium difficile associated diarrhea
C. Community acquired pneumonia
D. All of the above

According to a study by Hammond et al, histamine-2 receptor antagonists had which of the following superior outcomes?
A. Improved patient mortality
B. Decreased cost
C. Increased complications
D. Decreased complications

Mortality Data
Risk of death among users of PPIs: a longitudinal observational cohort of US veterans

• Background
  • Previous studies observational or meta-analysis:
    - Dementia
    - Hypo-magnesemia
    - Clostridium difficile associated diarrhea
    - Osteoporosis related fracture: hip & spine
    - Community acquired pneumonia
    - Cardiovascular events


Risk of death among users of PPIs: a longitudinal observational cohort of US veterans

• Background continued
  • Impairment in proteostasis: increased oxidative stress, endothelial dysfunction, telomere shortening (low level evidence)
  • Rationale for study: previous studies may pose mortality risk
  • Purpose of study: association of PPI and mortality with prolonged use.


Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

• Primary cohort


Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

• Secondary cohorts
  1. PPI users vs. H2 users
  2. PPI users vs. no acid suppressive therapy

• Outcomes
  • Primary: Time to death
  • Covariates: Extensive (demographic, # Scr measurements, comorbid cardiovascular conditions, GI conditions that would require acid suppressive therapy)


Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

• Results:
  • Baseline: PPI group was older, more comorbid conditions, GIB
  • PPI/risk of death: increased PPI vs. H2RA (HR 1.25, 1.23 - 1.28)
  • PPI/risk of death without GI indication: increased PPI vs. H2 (HR 1.24, 1.21 - 1.27) – lower risk cohort


Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

• Conclusions: association of death and PPI exists
  • Without possible indication
  • Duration increases association
  • Limitations
    • Study design: having Rx does not mean compliance long term/obtain OTC
    • Population studied: older, veterans, US – external validity concern
    • Outpatient setting over a few years – external validity concern
    • ?? Cause of death
  • Pharmacokinetic interaction

• Strengths
  • US veterans health system data – robust

Risk of death among users of PPIs: a longitudinal observational cohort study of US veterans

• Take a moment with the person next to you.
• Does this article change practice?
• How can health-systems pharmacists be better stewards of PPIs at your institution?

Dementia

Dementia Risk

• Prospective cohort in Germany in 7 years
• Purpose was to examine association of PPIs and dementia incidence
• PPI prescription users HR= 1.44 [95% CI, 1.36-1.52], highest with esomeprazole, males and as age increases
• Mechanisms proposed by authors:
  • Crosses BBB
  • Previous trial of mice/lab model, Aβ increased – sign of dementia
  • ? B12 deficiency

Dementia Risk – Other study does not confirm risk

• Finnish case-control study
• Purpose was to examine association of PPIs and confirmed Alzheimer’s disease
• PPI use was not associated in this study with confirmed Alzheimer’s disease at 3 or >3 years OR 1.03, 95% CI (1.00-1.05), OR 0.99, (95% CI 0.94-1.04)

Use of Gastric Acid–Suppressive Agents and the Risk of Community-Acquired Clostridium difficile–Associated Disease

• 2 case control studies in UK through 10 years
• First major study assessing risk of C diff in community setting
• Purpose: assess association of PPIs with community associated C diff
• Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>27%</td>
<td>15%</td>
<td>3.9 (3.4-4.4)</td>
</tr>
<tr>
<td>H2RA</td>
<td>25%</td>
<td>15%</td>
<td>1.3 (0.9-1.9)</td>
</tr>
</tbody>
</table>

• Similar to hospitalized based studies
• Note case definition: + C diff or clinical diagnosis

Clostridium difficile-associated diarrhea


Continuous PPI Therapy and Associated Risk of Recurrent C diff Infection

- Retrospective cohort in two Quebec hospitals
- Purpose was to evaluate if PPI use was associated with risk of C diff recurrence, risk of C diff if not an evidence based indication and compliance with discontinuing PPIs
- Continuous PPI use (pantoprazole/lansoprazole)

McDonald et al. JAMA Int Med. 2015; 175(5): 784-91.

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Recurrence of CDI</th>
<th>No Recurrence of CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td># pts (%)</td>
<td>193 (25.6%)</td>
<td>561 (73.4%)</td>
</tr>
<tr>
<td>HR</td>
<td>1.5 (1.1-2)</td>
<td>- -</td>
</tr>
</tbody>
</table>

Indication for PPI use

- None (per internal med MD reviewing chart) 52.9
- Age >60 + 2 risk factors (NSAID, antiplt, anticoag, steroid, hx GIB) 20.6
- Presumed upper GIB 8.9
- Symptomatic nonulcer dyspepsia reflux disease within 3 mo 7.2
- Erosive esophagitis 6.7
- PUD – endoscopically proven 6.3
- DAPT, age <60 0.5
- Antiplaatlet + anticoagulant, age <60 0.5

3 patients had PPI discontinued if + C diff

McDonald et al. JAMA Int Med. 2015; 175(5): 784-91.

Community Acquired Pneumonia

Use of PPIs and the Risk of CAP

- Questionnaire showing acid-suppressive therapy and increase in respiratory infections
- Same author conducted case control study and concluded association with PPIs > H2RAs and CAP (as well as dose response curve)
- Purpose: confirm association between PPI therapy and CAP
- Population based case-control study in Funen, Denmark
- Cases: first admission with CAP (2000-04)
- Controls: Funen, Denmark, matched by age and sex
- Exposed to PPI during past 90d (excluded if >90d)

Gulmez et al. Arch Int Med. 2007; 167:950-955

Use of PPIs and the Risk of CAP

- Overall OR 1.5 [95% CI 1.3-1.7]
- Same association for H2RAs
- Did not find association with H2RA
- Cannot account for noncompliance

Gulmez et al. Arch Int Med. 2007; 167:950-955

Hypomagnesemia
PPIs linked to hypomagnesemia: a systematic review & meta-analysis of observational studies

- FDA warning (2011)
- Prolonged use of PPIs linked to hypomagnesemia
- Difficult to overcome with Mg supplementation, sometimes D/C required
- Cardiac consequences of low Mg levels
- Recommendation to obtain baseline and "periodic" Mg levels
- Studies controversial on hypomagnesemia and PPIs
- Purpose of meta-analysis to examine association of PPIs with hypomagnesemia


Osteoporosis

Bone Mineral Density—SWAN Study

- US cohort study of middle aged women (42-52) followed ~10 yr
- Examined PPI, H2RA, and neither medication
- No apparent baseline differences
- Compared spine, femoral and hip BMD – all differences within margin of error

<table>
<thead>
<tr>
<th>BMD change</th>
<th>Spine</th>
<th>Femur</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>-0.53 (-0.68, -0.38)</td>
<td>-0.43 (-0.54, -0.29)</td>
<td>-0.41 (-0.49, -0.27)</td>
</tr>
<tr>
<td>Non-user</td>
<td>-0.61 (-0.67, -0.55)</td>
<td>-0.46 (-0.51, -0.40)</td>
<td>-0.31 (-0.35, -0.26)</td>
</tr>
</tbody>
</table>


Fractures

<table>
<thead>
<tr>
<th>Population</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedberg et al</td>
<td>Pediatrics</td>
<td>Case-control</td>
</tr>
<tr>
<td>Agnew et al</td>
<td>Men &gt;65yr with hip fractures</td>
<td>Case-control</td>
</tr>
<tr>
<td>van der Hofstede et al</td>
<td>Females, aged 75</td>
<td>Cohort</td>
</tr>
<tr>
<td>Ding et al</td>
<td>Adult</td>
<td>Cohort</td>
</tr>
<tr>
<td>Soder et al</td>
<td>Osteoporotic women</td>
<td>Observational</td>
</tr>
<tr>
<td>Cox et al</td>
<td>Hip fracture, age 70-80</td>
<td>Case-control</td>
</tr>
<tr>
<td>Chen et al</td>
<td>PPI long-term user (≥5yr) vs HRT</td>
<td>Cohort</td>
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Adherence, duration
Subsequent only

Acute Kidney Injury

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<tr>
<td>Cea Soriano et al</td>
<td>Hip fracture, age 40-89</td>
<td>Case-control</td>
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<tr>
<td>Lewis et al</td>
<td>PPI long-term user (≥5yr) vs HRT</td>
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Adherence, dose
### Background

- **Acute Interstitial Nephritis**
  - Usually: (+) Fever, (-) Rash, (-) Polyarthralgias; (+) Fatigue; (+) Wt loss
  - Lab: Pyuria, Hematuria, Proteinuria
  - Most commonly drug induced, can be immune-mediated

### PPIs & Acute Kidney Injury

- Retrospective nested case-control study
- Univ. Nebraska Medical Center
- Cases of AKI using multiple ICD-9 codes (quite exhaustive), 2 renal disease claims
- Renal disease OR 2.04 (1.53-2.71), NNH=303
- Most common diagnoses – acute renal failure NOS, acute renal insufficiency
- Critique – misclassification (type I error), surveillance bias, selection bias (due to other disease state/medicine)

### Pharmacoeconomics

#### Previous Literature/Scope

<table>
<thead>
<tr>
<th>Population</th>
<th>Methods</th>
<th>Findings</th>
<th>Misc</th>
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<tr>
<td>Barkun et al.</td>
<td>ICU</td>
<td>&quot;high risk&quot; for ulcer H2RA vs PPI</td>
<td>Increased bleeding with H2RA (0.6% vs 1.3%)</td>
</tr>
<tr>
<td>Heidelbaugh et al.</td>
<td>U-M Intermediate Care/General Medicine</td>
<td>Retrospective chart review 4 month for indication</td>
<td>79% had diagnosis supporting AST 22% had inappropriate SUP continued from ICU 90% discharge w/o AST</td>
</tr>
<tr>
<td>MacLaren et al.</td>
<td>ICU</td>
<td>H2RA vs PPI</td>
<td>H2RA cost savings $1001</td>
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<td>Harrold et al.</td>
<td>ICU–8 days of AST Simulation with outcomes</td>
<td>H2RA cost savings $2400 Survival benefit 3.06%</td>
<td>Complication rate 5.37 H2RA, 4.46% PPI Preferred 70.3% situations</td>
</tr>
<tr>
<td>Buckley et al.</td>
<td>Entire hospital Pre-/post- implementation of stewardship</td>
<td>20,053 = 3280 inpt costs for SUP 50% of 36.2%&lt;0.4% Annualized cost savings =$200K</td>
<td>PPI Stewardship</td>
</tr>
</tbody>
</table>
Impact of Clinical Pharmacist SUP Management Program

- Grant supported by ACCP Critical Care PRN
- Banner Health (700 bed academic medical center)
- Institutional Indications: ICU only with
  - Mechanical ventilation
  - Coagulopathy
  - Solid organ transplant
- Protocol for pharmacist to discontinue if not indicated, initiate if indicated or modify from PPI to H2RA
- If on AST prior to admission, it was continued

Impact of Clinical Pharmacist SUP Management Program

Results:

- RR of SUP days in ICU 58.3% (p<0.001)
- RR of SUP days in gen medicine 83.5%
- Rate of inappropriate SUP days 41.2% \(\rightarrow\) 6.8% (p<0.001)
- C diff, pneumonia, GIB were <1% pre-implementation and post-implementation

What may this look like at your institution

- Pair with someone and briefly discuss.

Banner Health was able to implement a stress ulcer prophylaxis management program. Which of the following was not an outcome from their program?

A. Decrease in inappropriate stress ulcer prophylaxis patient days
B. Annualized cost savings exceeding $200,000
C. Decrease in prescriptions for stress ulcer prophylaxis for discharged patients
D. Increase in gastrointestinal bleeding

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References

- McDonald EG, Milligan J, Frenette C. Continuous proton pump therapy and the associated risk of recurrent Clostridium difficile infection. JAMA Int Med. 2015; 175(5): 84-93.