PROTON PUMP INHIBITORS: SHOULD THEY BE IN THE WATER?

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Background
- Risk of developing cancer
- Medical complications
- Pregnancy
- Drug Interactions

How effective is PPI therapy and is it better than other available agents for GI related diseases?

Mechanism of Action
Effective Therapy: Mucosal Healing

PPIs Superiority Over H₂RAs
- Control basal and food produced acid secretion to a much greater degree
- Produce longer lasting acid suppression
- Tachyphylaxis not observed

Faster Improvement of Symptoms

PPIs Recommended Over H₂RAs
- Empiric treatment of GERD
- Endoscopy negative reflux disease
- H. pylori eradication

- Esophageal strictures
- Ulcerations
- Functional dyspepsia
- Barrett’s esophagus
Combining PPIs and H$_2$RAs?

What About Rebound Acid?

Overuse of PPIs – Outpatient Experience

How would I answer .....

- PPIs are the most potent inhibitor of gastric acid secretion
- Much more efficacious in terms of mucosal healing and symptom relief than H$_2$RAs
- One of the most commonly prescribed drug classes in primary care, but there is an associated high rate of inappropriate usage
I read on the internet that PPIs can cause cancer. Are PPIs associated with an increased risk of cancer?

Potential for Malignant Transformation – Role of Gastrin

- Gastrin has growth promoting properties
  - Zollinger-Ellison syndrome patients have increased proliferation of rectal mucosa
  - Hypergastrinemia leads to an increase in colorectal adenomas in transgenic mice

- Possible carcinogenic properties of gastrin
  - Increased gastrin levels associated with a 4-fold increase in CRC

PPIs and Colonic Polyps

- PPIs do not affect the frequency or size of adenomatous polyps
Do PPIs Increase the Risk of Colorectal Cancer?

- No link between CRC and PPI usage has been established
- Prolonged use of PPIs has not been shown to increase the risk of CRC
- Higher and more frequent PPI dosing does not increase one's risk for developing CRC

PPIs and Carcinoids

- Life-long use of Omeprazole is associated with the formation of ECL-like cell carcinoids in rats
  - Rats have higher gastrin levels in response to PPI therapy compared to humans
  - Lower density of ECL cells in humans
- Hyperplasia of ECL cells noted in 10-30% of chronic PPI users, but precancerous mucosal changes have not been associated with PPI use
- Invasive carcinoid has not been reported in humans

PPIs and Fundic Gland Polyps

- PPI maintenance therapy is strongly correlated with the development of fundic gland polyps
  - Increase in prevalence from 8% to 35% after 1 year of PPI use
  - Rare case reports of dysplasia
  - Not necessary to remove or perform surveillance
How would I answer .....  

- No clear association between PPI use and the development of many GI cancers  
- PPI users have an increased prevalence of fundic gland polyps  
  - No increased risk of dysplasia except in FAP patients  
- No change or recommendations for cancer surveillance in chronic PPI users  

Are PPIs associated with an increased risk of bone fractures?  

Acid and Bones – What’s the Connection?  

- Acidic environment aids in the release of ionized calcium from insoluble calcium salts  
  - Ca^{2+} carbonate disintegration and dissolution is a pH dependent process  
- PPIs can act on bones independent of calcium absorption  
  - Inhibit osteoclastic H^+\textbackslash K^+ ATPase pumps  
  - Hypergastrinemia enhances bone resorption via parathyroid gland hyperplasia  

PPI Therapy and Fracture Risk  

- Short term use of PPIs has been modestly linked to an increased fracture risk  
  - British study demonstrated an increased risk with each consecutive year of PPI therapy (OR 1.2 – 1.6 over 1-4 years)  
  - Kaiser study illustrated that the risk of hip fracture increased by 30% in people who used PPIs for > 2 years  
- Strength of association was higher with increasing doses of PPI therapy  
  - H_2 RA therapy also had positive, but weaker association with hip fracture
PPI Therapy and Fracture Risk – Long Term Use

But Not So Fast.....

- Risk of having a bone fracture while on PPI therapy is modified if there are other pre-existing fracture risk factors

- PPI use not associated with the development of osteoporosis at the hip or lumbar spine
  - No significant decrease in BMD

- Only retrospective, case control studies performed to date
  - Residual confounding or effect modification may be present

How would I answer .....

- Some data to suggest that long-term PPI use is associated with an increase risk of fracture
  - Only retrospective, case-control studies have examined this question
  - Divided conclusions among the published studies

- Important to ensure that your patient needs to be on a long-term PPI and that the lowest possible dose is used

- Assess for other fracture risk factors and fall risk in long term PPI users

A friend told me not to take my PPI for too long because it increases my risk for infection. Is this true?
PPIs and Enteric Infections

- PPI use is associated with increased bouts of gastroenteritis
  - *Campylobacter* and *Salmonella* infections more common
  - 5-fold risk of developing gastroenteritis if PPI dose is doubled
  - Elderly appear to be at a higher risk

Leonard et al. Systematic review of the risk of enteric infection in patients taking acid suppression. AJG 2007; 102: 2054

PPIs and *Clostridium Difficile*

- Modest increase in risk of having *C. difficile* infection while on PPI therapy
- Only observational studies
- Temporal and dose dependent effects are unclear and not included in published data

Leonard et al. Systematic review of the risk of enteric infection in patients taking acid suppression. AJG 2007; 102: 2054

PPIs and Respiratory Infections

- Intestinal pathogens colonize oral space and gain access to the lower respiratory tract secondary to decreased acid production
- Proton pumps present in human laryngeal seromucinous and lung mucus glands
- PPIs may inhibit the function of PMNs and the activity of natural killer cells


Community Acquired Pneumonia

- Modest increase for developing CAP (OR 1.3)
- Association strongest with recent PPI use
  - ≤ 7 days OR 4.0
  - 7-30 days OR 1.6
- Elevated PPI dosage strongly associated with developing CAP
Nutritional Deficiencies

- Vitamin B12
  - Reduced gastric acidity impairs activation of pepsinogen
  - May impair absorption in elderly or in patients taking high doses of PPI
  - Evidence does not justify routine screening

- Magnesium
  - Multiple case reports of hypomagnesium in the literature
  - Unclear mechanism of action or risk factors
  - High index of suspicion for symptomatic patients

How would I answer .....

- Increased risk with some bacterial infections
  - Campylobacter and Salmonella gastroenteritis
  - C. difficile colitis
  - Elderly appear to be at an increased risk

- Small risk for developing CAP
  - Greatest risk with higher doses and within the first week of initiating therapy
  - Confounding among studies may explain some of the findings

Are PPIs safe during pregnancy?

- Variety of conditions during pregnancy may require PPIs
- PPIs in animal studies do cross the placenta
- Safety demonstrated in multiple small studies
  - No increased risk of spontaneous abortions
  - No increased risk of pre-term delivery

Congenital Malformations & In Utero Exposure to PPIs

<table>
<thead>
<tr>
<th>Study on Subcategory</th>
<th>Log (Adjusted OR) (SE)</th>
<th>Adjusted OR (random) 95% CI</th>
<th>Weight %</th>
<th>Adjusted OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicklow et al.</td>
<td>0.436 (0.6028)</td>
<td>4.78 (0.48, 5.65)</td>
<td>1.55</td>
<td>4.78 (0.48, 5.65)</td>
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<tr>
<td>Kallen et al.</td>
<td>0.1570 (0.4623)</td>
<td>7.49 (1.37, 10.01)</td>
<td>1.73</td>
<td>7.49 (1.37, 10.01)</td>
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<tr>
<td>Lithi et al.</td>
<td>0.0368 (0.7750)</td>
<td>2.96 (0.33, 7.66)</td>
<td>1.17</td>
<td>2.96 (0.33, 7.66)</td>
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<tr>
<td>Ragunathan et al.</td>
<td>0.1704 (0.4730)</td>
<td>7.76 (0.88, 10.22)</td>
<td>0.98</td>
<td>7.76 (0.88, 10.22)</td>
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<tr>
<td>Mosch et al.</td>
<td>0.1003 (0.1141)</td>
<td>1.60 (0.16, 1.77)</td>
<td>1.50</td>
<td>1.60 (0.16, 1.77)</td>
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<tr>
<td>Das-Cox et al.</td>
<td>-0.0025 (0.4421)</td>
<td>6.89 (0.83, 2.21)</td>
<td>0.93</td>
<td>6.89 (0.83, 2.21)</td>
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<tr>
<td>Mobli et al.</td>
<td>0.1103 (0.1631)</td>
<td>66.60 (1.32, 1.04)</td>
<td>1.12</td>
<td>66.60 (1.32, 1.04)</td>
</tr>
</tbody>
</table>

Total (95% CI) = 100.00 (1.12 [0.08, 1.45])


Safety of PPIs in Pregnancy

- Retrospective cohort study using health registry data in Denmark (1996-2008)
  - Assessed the association between PPI exposure and risk of major birth defects in infants
  - Analyzed major birth defects detected within first year of life
  - Examined PPI exposure from 4 weeks before conception to 12 weeks of gestation

- Included 800,000 live births with nearly 5,000 PPI users

PPIs Safe in the 1st Trimester of Pregnancy

- Prevalence of PPI use during pregnancy dramatically increased over time

- No association found with PPI use in the first trimester and the development of birth defects

- Risk of birth defects increased in women taking PPIs 4 weeks before conception (OR 1.4)
  - Only Prevacid was statistically significant

How would I answer .....?

- PPI use during the first trimester of pregnancy does not appear to increase the risk for birth defects
  - Potential increased teratogenicity noted with PPI use and the pre-conception period
  - May need to counsel women of child bearing age who are on PPIs of this possible risk and select PPIs with better safety profile

- Lifestyle modifications and OTC antacids should still be first line approach in treating GERD during pregnancy
Doctor, I have heard a lot in the news about taking PPIs with other medications (like Clopidogrel). What medications should I be worried about?

PPIs and Clopidogrel: The Story Begins
- Anti-platelet properties of Clopidogrel are reduced in the presence of PPIs
- PPIs and Clopidogrel commonly prescribed together
- Case-control studies suggest an increase in adverse events associated with concomitant Clopidogrel and PPI usage
  - Higher number of re-admissions for myocardial infarction, unstable angina, need for revascularization, and mortality
  - Increase in adverse CV events ranged from 25-75%, but HR were small (<2)

Challenging Clopidogrel “Resistance”: Ulcer Disease
- Prospective, randomized controlled trial assessing whether PPIs prevent recurrent peptic ulcers/ulcer complications in patients on Clopidogrel
  - Patients on Clopidogrel for atherosclerotic disease (ischemic heart disease, CVA) for 2 weeks
  - Had to have a history of gastroduodenal ulcers with recent EGD showing no recurrent ulcer disease
  - *Helicobacter pylori* infection had to be eradicated
  - Received Clopidogrel (75mg)/Esomeprazole (20mg) or Clopidogrel alone for 6 months

Clopidogrel “Resistance” Theory
- Prodrug (absorbed)
- Intermediate metabolite
- Active metabolite
- Intestinal absorption
- Possible methods of interaction
- CYP450 (first step)
- CYP450 (second step)
- Platelet activation
- Platelet

Hsu et al. Esomeprazole with Clopidogrel Reduces Peptic Ulcer Recurrence, Compared with Clopidogrel Alone in Patients with Atherosclerotic Disease. *Gastroenterology.* 140:791-798

Challenging Clopidogrel “Resistance”: Ulcer Disease

Patients with reduced-function alleles of CYP2C19 had HIGHER combined cardiocerebral events than patients with full-function alleles (7.5% vs. 0).

Hsu et al. Esomeprazole with Clopidogrel Reduces Peptic Ulcer Recurrence, Compared with Clopidogrel Alone in Patients with Atherosclerosis. Gastroenterology 2011; 140: 791-798.

Challenging Clopidogrel “Resistance”: COGENT Study

- Multicenter, multi-nation RCT of patients with ACS/placement of a coronary stent and required Clopidogrel
  - Patients received Clopidogrel (75mg)/Omeprazole (20mg) or Clopidogrel/Placebo
  - All patients were taking ASA
  - 3,761 patients participated in the study
  - Patients followed for over 1 year
  - Trial stopped early


Challenging Clopidogrel “Resistance”: COGENT Study

Available data on combined Clopidogrel and PPI use is divided but …
- Observational studies show only a moderate increase in risk
- Large RCTs have shown no association in developing CV adverse events and that PPIs were GI protective

How would I answer ..... 

- Available data on combined Clopidogrel and PPI use is divided but …
  - Observational studies show only a moderate increase in risk
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What is the patient’s risk for GI bleeding on antiplatelet therapy?
- Address and modify identified risk factors for GI bleeding

Some strategies to employ
- Separate taking drugs by > 2 hours
Conclusions

- PPIs are commonly used and effective at treating a multitude of diseases and symptoms
- Risk of developing GI associated malignancies on PPI therapy is low
- Conflicting data on fracture risk, and if a risk exists, it appears to be related to the duration of time on PPI

Conclusions

- PPI usage modifies risk for infectious processes
  - Elevated risk for developing some forms of bacterial gastroenteritis
  - Evidence for CAP is less compelling
- PPI use is safe in the first trimester of pregnancy, but a risk may exist in the pre-conception phase
- Debate exists about the safety of PPI and Clopidogrel co-administration
  - Recent RCTs show it to be safe and helps to reduce the risk of GI bleeding