PROTON PUMP INHIBITORS: SHOULD THEY BE IN THE WATER?

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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 offer more rapid relief of heartburn related symptoms

- 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 H₂RAs?

- Day 1
- Day 7
- Day 28

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median pH &lt;4</th>
</tr>
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<tbody>
<tr>
<td>No Rx</td>
<td>99.3%</td>
</tr>
<tr>
<td>Omeprazole 20 mg BID</td>
<td>42.8%</td>
</tr>
<tr>
<td>Omeprazole 20 mg BID &amp; Ranitidine 300 mg QHS</td>
<td>32.3%</td>
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*P<0.05 vs Omeprazole 20 mg BID

**What About Rebound Acid?**

- Start of therapy
- Cessation of therapy
- Mean symptom score

Niklasson et al. Dyspeptic symptom development after discontinuation of a proton pump inhibitor. *AJG* 2010; 105: 1534

**Overuse of PPIs – Outpatient Experience**

- Prescribed PPI
- Inappropriate PPI Prescription

- Walker (2001)
- Balabanoglu (2006)
- Mallory (2007)
- Leyp-Neumard (2007)
- Scaglioni (2009)

**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 H₂RAs
- 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 enterochromaffin-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
- Invasive carcinoid has not been reported in humans who have been on long term PPI therapy

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
  - $\text{Ca}^{2+}$ carbonate disintegration and dissolution is a pH dependent process
- PPIs can act on bones independent of calcium absorption
  - Inhibit osteoclastic $\text{H}^+$/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 1.22 – 1.59 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
- $\text{H}_2$ RA therapy also had positive association with hip fracture
PPI Therapy and Fracture Risk – Long Term Use

- All osteoporosis-related fractures
- Hip and vertebral fractures
- Hip fractures

Risk of having a hip fracture while on PPI therapy disappears if one does not have pre-existing 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 osteoporotic risk factors and fall risk in long term PPI users

But Not So Fast.....

- Risk of having a hip fracture while on PPI therapy disappears if one does not have pre-existing risk factors

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  - No significant decrease in BMD

- Only retrospective, case-control studies performed to date
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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

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

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
  - \( \leq 7 \) days \( \text{OR} 4.0 \)
  - 7-30 days \( \text{OR} 1.6 \)
- Elevated PPI dosage strongly associated with developing CAP
Nutritional Deficiencies

- **Vitamin B12**
  - Reduced gastric acidity impairs activation of pepsinogens
  - 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 and possible 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 or subgroup of patients susceptible to developing CAP while on PPIs may explain some of the findings

Are PPIs safe during pregnancy?

PPIs and 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

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 1.39)
  - 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 Plavix). What medications should I be worried about?

### Plavix “Resistance” Theory

**Diagram showing the interaction between Clopidogrel and Proton-pump inhibitors (PPIs).**

- **Clopidogrel** undergoes a first-step oxidation by CYP450, followed by a second-step oxidation by CYP450, leading to active metabolites.
- **PPIs** inhibit CYP450 enzymes, reducing the formation of active metabolites.

### PPIs and Plavix: The Story Begins

- Anti-platelet properties of Plavix are reduced in the presence of PPIs.
- PPIs and Plavix are commonly prescribed together.
- Case-control studies suggest an increase in adverse events associated with concomitant Plavix 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 Plavix “Resistance”: Ulcer Disease

- Prospective, randomized controlled trial assessing whether PPIs prevent recurrent peptic ulcers/ulcer complications in patients on Plavix:
  - Patients on Plavix 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 Plavix (75mg)/Esomeprazole (20mg) or Plavix alone for 6 months.

*Hsu et al. Esomeprazole with Clopidogrel Reduces Peptic Ulcer Recurrence Compared with Clopidogrel Alone in Patients with Atherosclerosis. Gastroenterology 140: 791-798.*
Challenging Plavix “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 Plavix “Resistance”: COGENT Study

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

Bhatt DL, Cryer BL et al. Clopidogrel with or without Omeprazole in Coronary Artery Disease. NEJM 2010; 363: 1909-1917

Available data on combined Plavix 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 protective

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

How would I answer.....
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 Plavix co-administration:
  - Recent RCTs show it to be safe and helps to reduce the risk of GI bleeding.