2020 Third Annual National Conference

November 19-21, 2020

Red Rock Hotel – Las Vegas, NV

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Gastroenterology and Hepatology Advanced Practice Providers.
Proton Pump Inhibitors: Point/Counterpoint

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Disclosures

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Disclosures

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Speakers Bureau: Takeda, Clinical Area- IBD
Speakers Bureau: AbbVie, Clinical Area- IBD
PPI Use

- PPIs are one of the most widely prescribed classes of medications in the world
- Proton pump inhibitors (PPIs) inhibit H-K-ATPase, the final step of gastric acid secretion by parietal cells
  - Indicated for GERD/Barrett’s esophagus, PUD (peptic ulcer disease), NSAID/stress ulcer, H Pylori treatment, Zollinger-Ellison syndrome
How Do PPIs Work?

- Animated video – Dr Jehad Hammad
  - [https://www.youtube.com/watch?v=Fz871WjMzdU](https://www.youtube.com/watch?v=Fz871WjMzdU)
Proposed PPI Risks

- Gastric neoplasia
- Kidney disease
- Bone fractures
- Impaired absorption of micronutrients
- Dementia
- Liver disease
- Infection/GI effects

Image from reference 2.
## Gastric Neoplasia

### Point
Mechanistic studies suggest that hypoacidity and hypergastrinemia increase the risk of gastric cancer in the corpus/fundus and this was also supported by some epidemiological studies\(^1\)

### Counterpoint
- Incidence is small
- More likely are benign lesions → fundic gland polyps, black spots, cobblestone-like lesions
- Untreated H Pylori/ulcers could also result in malignancy
Kidney Disease – AIN

**Point**
- PPIs are now considered to be among the most common causes of drug-induced AIN worldwide\(^2\)
- Symptoms of n/v, malaise, maybe oligura, maybe no symptoms
- Presents 10 weeks to nine months after starting treatment, risk is not dose dependent
- Some evidence that they also increase the risk of CKD (mechanism not well understood)

**Counterpoint**
- If patient has been on PPI long term and renal function is normal, they should not be at risk for AIN
- Unclear whether they may still be at risk for CKD
Bone Health/Fracture Risk

**Point**
- PPI-induced hypochlorhydria can augment osteoclastic activity, thereby decreasing bone density\(^4,5\).

**Counterpoint**
- The absorption of water-soluble calcium salts or calcium in dairy products are NOT impacted by PPI-induced hypochlorhydria.
- Suggestion that gastric hypoacidity affects bone metabolism negatively, however, the recent data from a randomized trial\(^3\) suggest that PPIs do not increase fracture risk.
Impaired Absorption of Micronutrients

Point

• B12 deficiency – increased risk in observational studies\textsuperscript{6}

• Many studies have suggested an increased risk and that hypomagnesemia develops in a proportion of PPI users\textsuperscript{7}

• A large case-control study found PPI use to be associated with an increased risk of iron deficiency\textsuperscript{8}

Counterpoint

• B12 deficiency not reproduced in other studies

• Hypomagnesemia is rare and it seems that mainly patients who already use a diuretic are at risk\textsuperscript{7}

• The magnitude of reduced iron absorption is most likely small in most individuals and the clinical importance has been questioned\textsuperscript{1}
Dementia

Point
• Some studies have found a significant association between use of PPIs and incident dementia\(^9\)

Counterpoint
• Increased risk of dementia has not been reproduced in other epidemiological studies\(^10,11\)
Liver Disease

**Point**
- PPIs appear to increase the risk and severity of HE in cirrhosis patients, thought to be due to SIBO\(^{12}\)
- Some evidence for increased r/o SBP, liver cancer as well\(^{13,14}\)

**Counterpoint**
- Epidemiological evidence is limited for the influence of PPIs on the pathogenesis of liver diseases including cancer (but bacterial overgrowth and altered bacterial composition are indeed well-documented)\(^1\)
**Infection/GI effects**

**Point**
- A 2017 meta-analysis of 50 observational studies found that PPI use was significantly associated with an increased risk of *C. difficile* infection (relative risk [RR] 1.3; 95% CI 1.1-14). The risk of *C. difficile* infection appears to be greater with PPIs as compared to H2 receptor antagonists\(^{15}\)
- SIBO and altered bacterial composition also well-noted
- Increased risk of microscopic colitis, other enteric infections

**Counterpoint**
- Use of probiotics may decrease risk of diarrhea, SIBO – [Bacillus subtilis (B. subtilis) and Enterococcus faecium (E. faecium) 500mg TID]\(^{16}\)
Proposed PPI Risks

- Gastric neoplasia
- Kidney disease*
- Bone fractures
- Impaired absorption of micronutrients*
- Dementia
- Liver disease
- Infection/GI effects*
Many patients have appropriate indications for long-term PPI use that may outweigh the risks discussed.

However, a large proportion of PPI users without indication have no benefits to outweigh any risk of side effects.

Some of the potential side effects may have an incubation time of years or even decades the risks and benefits of starting long-term PPI use should be carefully considered.

Take-Home Points
References

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6829383/