

# Proton Pump Inhibitors

Functional Gastroenterology Webinar One  
6-28-13  
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## To be discussed:

- Proton pump inhibitors–
  - Effects on:
    - secretion
    - gastric mucosa
    - food allergy
    - bile reflux
    - Barrett metaplasia and dysplasia
    - esophageal carcinoma
    - GI carcinoma
    - bone metabolism

## To be discussed

- Proton pump inhibitors:
  - Effects on
    - Pulmonary infections
    - GI infections
    - Nutrition
    - Lab values
  - Also:
    - Prescribing
    - Common side effects
    - Rebound hypersecretion

## Proton pump inhibitors

- Omeprazole (Prilosec)
- Esomeprazole (Nexium)
- Rapid release omeprazole (Zegarid)
  
- Lansoprazole (Prevacid)
- Dexlansoprazole (Dexilant)
  
- Rabeprazole (Aciphex)
- Pantoprazole (Protonix)

## PPIs

### ► Effect on secretion

- Blocks  $H^+/K^+$  ATPase enzyme system on the parietal cell secretory surface
- > pepsinogen
- > gastrin
- < pepsin

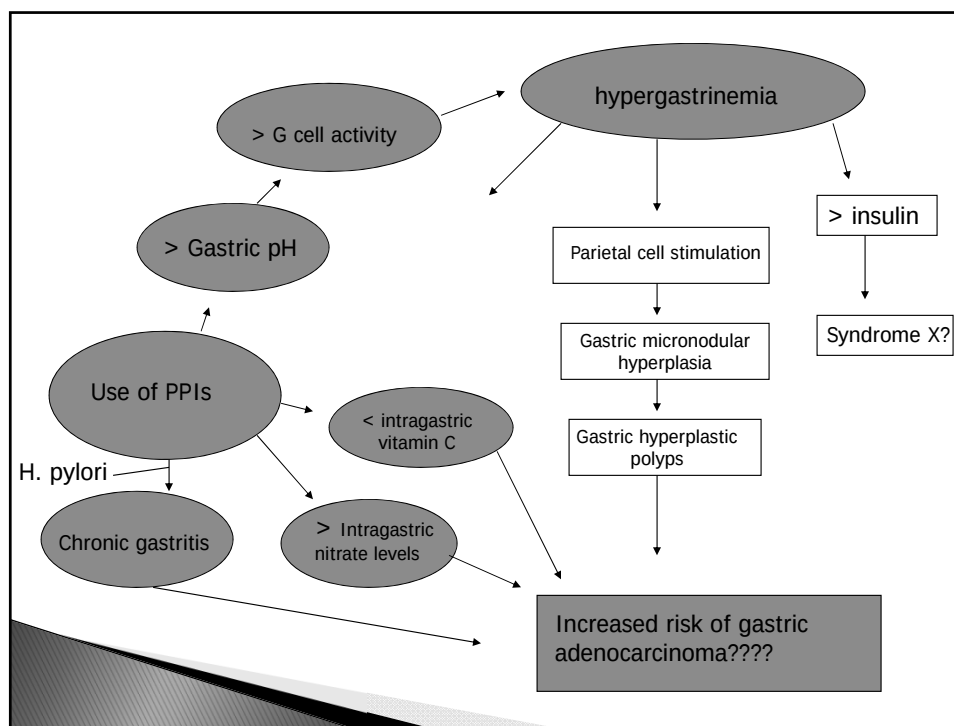
## PPIs

### ► Effect on gastric mucosa

- decreases blood flow to the antrum, pylorus and duodenal bulb
- > gastric nitrate rendering bacteria
- > nitrate in gastric juice
- > gastric bacterial overgrowth ( $pH > 3.8$ )
- > risk of viral and prion infections?
- > deconjugation of bile acids
- > gastric hyperplastic polyp formation
- < intragastric vitamin C levels

## Functional GI Webinar Series

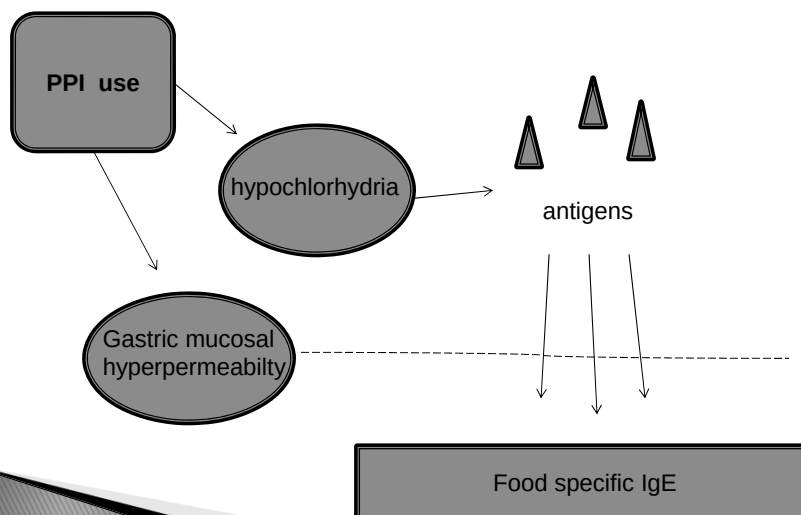
### Part 1: Proton Pump Inhibitors



## Food allergy and PPIs

- Breakdown of food antigens inhibited
- Induction of gastric hyperpermeability (Mullin JM, 2008)
- Higher food specific IgE
- > risk of eosinophilic esophagitis (Merwat SN, 2009)

## PPIs and food allergy



Am J Gastro 2001, Feb;96(2):331-337

Increased acid and bile reflux in Barrett's esophagus compared to reflux esophagitis, and effect of proton pump inhibitor therapy.

In 12% of PPI treated BE pts. bile reflux > during therapy.

**DGERD**

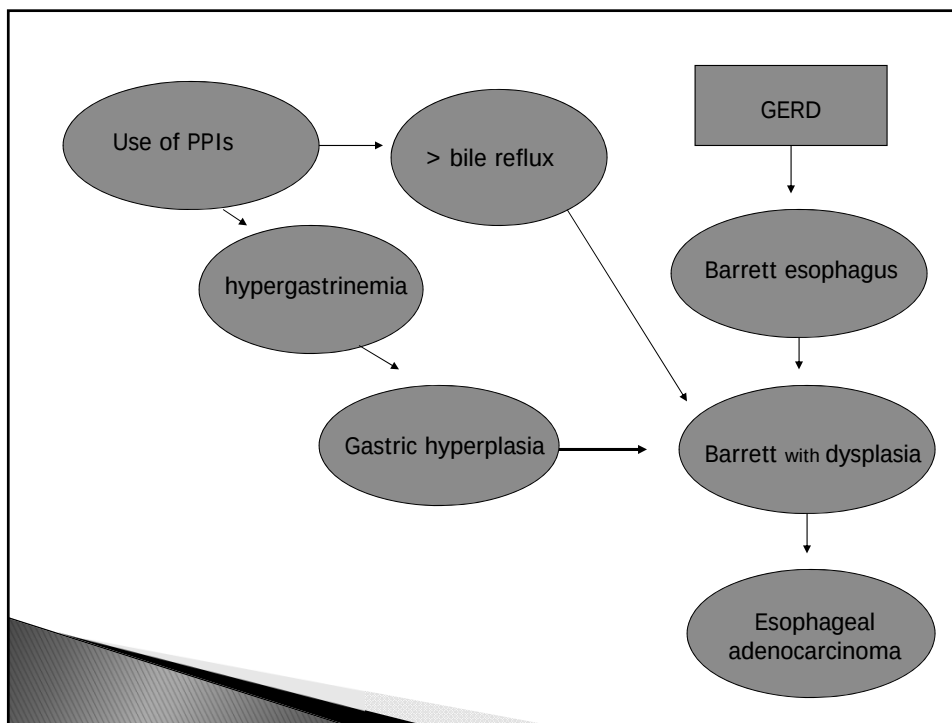
## PPIs

### ► Effect on Barrett's metaplasia

- It is generally assumed that the use of PPIs removes the acid influence on the distal esophagus, thereby decreasing the risk of esophageal carcinoma in Barrett's esophagus

BUT....

- The presence of gastric hyperplastic polyps may increase the rate of esophageal dysplasia



Best Pract Res Clin Gastroenterol. 2004;18 Suppl:47-53.

**The challenges of Barrett's -- suppression, symptoms or surveillance.**

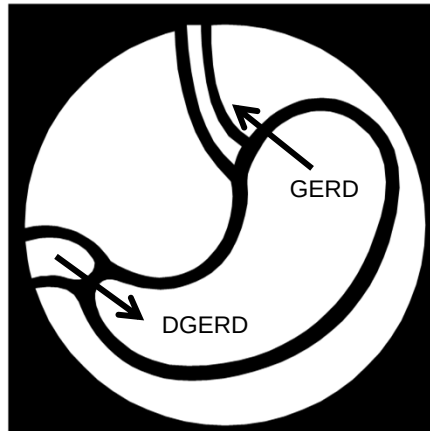
Playford RJ.

Barrett's esophagus is a metaplastic change related to esophageal reflux of acidic gastric contents. Its presence is associated with an increased risk of adenocarcinoma. The data behind our current clinical strategies are, however, based on limited evidence. This document considers the sort of information that should be discussed with patients to allow them to make their own choices regarding therapeutic strategies.

## **PPIs & Barrett esophagus**

- Effects on esophageal carcinoma
  - There is thought that PPIs while decreasing the effect of acid reflux on the distal esophagus, may > the risk of duodenal gastroesophageal reflux while simultaneously increasing deconjugation of bile.

## GERD and DGERD



### **PPIs and Barrett esophagus – *reflux controlled in only 1/3 of patients***

Arch Surg. 2004 May;139(5):547-51.

- ▶ **Persistent acid and bile reflux in asymptomatic patients with Barrett esophagus receiving proton pump inhibitor therapy.**
- ▶ **CONCLUSIONS:** Despite symptom control with PPIs, both acid reflux and bile reflux were controlled in only one third of patients. Post-therapeutic monitoring of acid and bile reflux is recommended in future clinical trials of PPI treatment vs laparoscopic antireflux surgery.

### **Gastric Cancer. 2004;7(1):31–5.**

Lanzoprazole promotes gastric carcinogenesis in rats with duodenogastric reflux.

- ▶ Gastric cancers occurred significantly more often in lanzoprazole-treated rats (50%) compared with controls (27%).

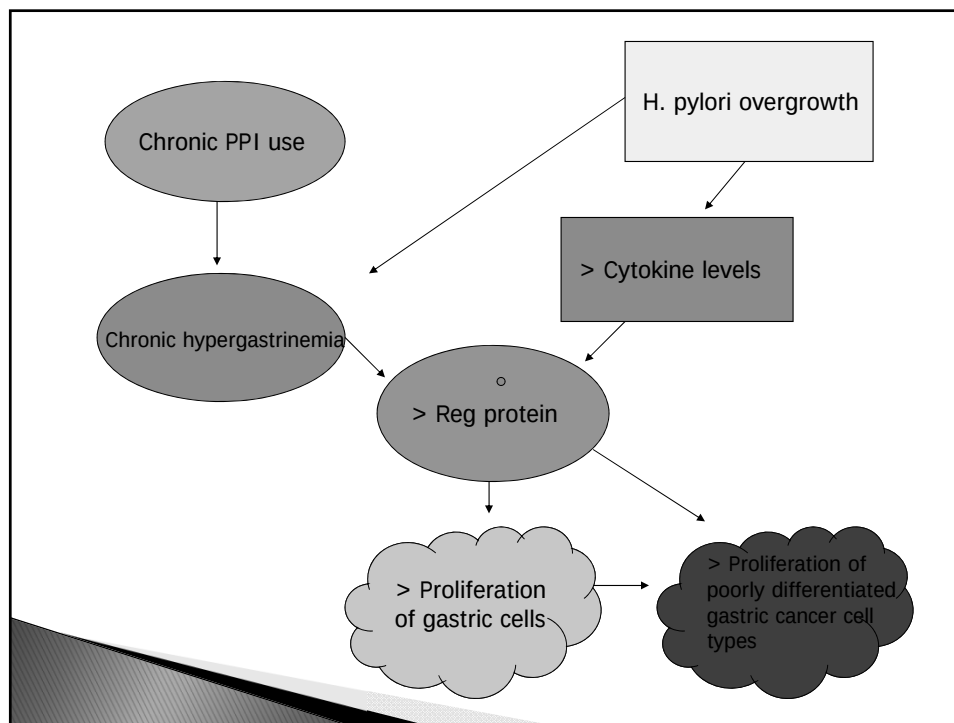
**CONCLUSION:** Lanzoprazole given orally enhances the carcinogenic effect of duodenogastric reflux in rats.

### **Dig Dis Sci. 2005**

- ▶ There are reports indicating development of ECL cell carcinoids after long-term treatment with proton pump inhibitors.
- ▶ These ECL cell carcinoids may give rise to gastric carcinomas of diffuse type, which have increased during the last decades.
- ▶ Therefore, long-lasting iatrogenic hypergastrinemia induced by potent inhibitors of acid secretion may be expected to increase the occurrence of gastric carcinomas in the future.

## Gastric cancer

- ▶ According to this Danish study the incidence of gastric cancer is directly related the number or PPI prescription refills and duration of use (Poulsen AH, 2009)



## PPIs

- Risk of colon cancer may be increased with PPI use



Br J Cancer. 2002 Aug 27;87(5):567-73.

**Potential role of endocrine gastrin in the colonic adenoma carcinoma sequence.**

**Conclusion:** Hypergastrinemia may promote proliferation of human colonic adenomas that express CCK-2 receptor isoforms.

## PPIs and bone

- ▶ Women over age 50 who take PPIs for more than a year have a 44% increased risk of hip fracture.
- ▶ Long term high dose use increases hip fracture by 245% (Geller JL, 2007)
- ▶ Women's health initiative data showed a modest association between PPI use and >spine, forearm, wrist and total fracture (Gray SL, 2010)

## PPIs and hip fracture

- ▶ In 2010 the FDA revised the labeling of all PPIs to include the increased risk of fractures of the hip, wrist and spine.
- ▶ From FDA Drug Safety Communication  
<http://www.fda.gov/Drugs/DrugSafety/PostMarketDrugSafetyInformationforPatientsandProviders/ucm213206.htm>

## PPI and pneumonia

- ▶ Herzig SJ, 2009 found a 30% increased risk of hospital acquired pneumonia in patients started on PPIs.
- ▶ Eurich DT, 2010 found that elderly patients—when started on PPIs in the hospital—have **nearly double the risk** of developing recurrent community-acquired pneumonia.

*JAMA*. 2004;292:1955–1960.

Laheij RJ et al, Risk of Community-Acquired Pneumonia and Use of Gastric Acid-Suppressive Drugs

**Conclusion:** Current use of gastric acid-suppressive therapy was associated with an 1.89 risk ratio for community-acquired pneumonia.

H2 receptor antagonists had a 1.62 RR.

## PPIs and Clostridium difficile

- ▶ PPI usage in hospitalized pts. Significantly increases the risk of C. difficile diarrhea (Kim JW, 2010.)
- ▶ A Harvard study found it to be dose dependant (Howell MD, 2010.)
- ▶ Taking statin drugs with PPIs may increase the risk even without recent antibiotic use (McGuire T, 2009.)

## PPIs and other GI infections

- ▶ Increased risk of Campylobacter enteritis (Leonard J, 2007)
- ▶ Increased risk of viral gastroenteritis in children treated for GERD (Canani RB, 2006)

## Acute interstitial nephritis (AIN)

- ▶ Raza MN et al, Acute tubulointerstitial nephritis, treatment with steroid and impact on renal outcomes. Nephrology 2012 Nov;17(8):748–53.
- ▶ Conclusions: NSAIDS were the #1 cause of drug induced AIN.
- ▶ PPIs were the second most common drug category.

## PPIs are used for stress ulcer prophylaxis in ICU

- ▶ To minimize adverse outcomes, physicians should discontinue PPIs in patients when they are discharged from the ICU if there are no other indications for therapy.”
- ▶ From the EAST Practice Management Guidelines Committee

## Side effects

- ▶ CNS (7%)
  - headache
  - dizziness
  - asthenia
- ▶ GI (3%)
  - diarrhea/constipation
  - abdominal pain
  - nausea/vomiting
- ▶ Misc.
  - URI (2%)
  - rash/pruritis/alopecia
  - cough
  - back pain

## Effect on lab values

- ▶ Lansoprazole (prevacid)
  - > transaminases
  - > globulin
  - > LDH
  - hypergastrinemia
  - > creatinine
  - > alk phos
  - hyperbilirubinemia
  - eosinophilia
  - > glucocorticoids
- > or <
  - cholesterol
  - electrolytes

## Effect on lab values

- Rabeprazole (aciphex)
  - hyperglycemia
  - albuminuria
  - hypercholesterolemia
  - > transaminases
  - hyperlipidemia
  - > PSA
  - > CPK
- hypokalemia
- hyponatremia
- < or >
  - RBCs
  - WBCs
  - Platelets

## Pregnancy category

- Omeprazole – category C
  - Lansoprazole
  - Rabeprazole
  - esomeprazole
- category B

## PPI /drug interactions

- ▶ Interferes with absorption of
  - ketoconazole
  - ampicillin
  - digoxin
- ▶ May increase levels of
  - warfarin
  - clarithromycin
  - cyclosporine
  - Benzodiazepines
  - phenytoin
  - disulfuram

## Nutritional/botanical interactions of PPIs

- ▶ Calcium – disintegration and dissolution of calcium carbonate decreases from 96% at a pH of 1.0 to 23% at a pH of 6.1
- ▶ PPIs effectively reduce gastric pH to an average of 5.5 with 19% of the day spent above 6.0 (O'Connell 2005.)
- ▶ Zinc – decreased intestinal absorption

## PPIs and folic acid

- The human proton-coupled folate transporter (hPCFT) has recently been identified as a pH-dependent folic acid transporter, and mutations in this transporter have been linked to hereditary folic acid malabsorption.
- PPI drug use appears to be associated with reduced hPCFT expression in vivo (Urquhart BL, 2010)

## Magnesium deficiency

- Luk CP et al, Proton Pump Inhibitor-Associated Hypomagnesemia: What Do FDA Data Tell Us? Ann Pharmacother. 2013 Apr 30.
- All PPIs were associated with hypomagnesemia
- esomeprazole had the lowest risk and pantoprazole had the highest risk.
- The risk was higher in males and the elderly
- Hypocalcemia and hypokalemia commonly coexisted with PPI-associated hypomagnesemia.

## Nutrition and PPIs

- ▶ B12 – 72–88% reduction in levels (Termanini B, 1998.)
- ▶ Iron – iron malabsorption is especially affected in patients who are iron deficient before starting on a PPI (Sharma VR, 2004.)

## B12 deficiency

- ▶ Rozgony NR et al, Vitamin B(12) deficiency is linked with long-term use of proton pump inhibitors in institutionalized older adults. J Nutr Elder. 2010 Jan;29(1):87–99.
- ▶ B12 deficiency was increased in a group of elderly institutionalized persons taking PPIs for more than 12 months compared to those not taking PPIs.

## Botanicals and PPIs

- St. John's wort – along with PPIs have an additive effect on photosensitivity
- Cranberry juice – > absorption of B12 in patients taking PPIs

## PPIs and rebound acid

- Significant rebound acid hypersecretion lasts from 8–26 weeks after long term PPI use (Fossmark R, 2005 and Waldum HL, 1996.)

### **Dig Liver Dis. 2003 Oct;35(10):738–46.**

- “The relatively common use of acid inhibitors (proton pump inhibitors and histamine-2 receptor antagonists) in uncomplicated gastro-esophageal reflux disorders or in the prevention of non-steroidal anti-inflammatory drugs/steroid gastropathy is often unsubstantiated and should be limited to very specific situations.”

### **Weaning patients off PPIs**

- Correct underlying causes of reflux
  - Improve parasympathetic tone
  - Improve LES tone
  - Improve gastric emptying and motility
  - Improve protective factors
  - Heal esophageal erythema, erosions or ulcers
  - Heal areas of Barrett esophagus or dysplasia
  - Improve pancreatic enzyme levels

## Weaning patients off PPIs

- Decrease to the lowest dose available in prescription
- When accommodated – decrease to an every other day dosage
- Later go to an every 3<sup>rd</sup> day dosage
- Switch to an H2 receptor antagonist
- Gradually discontinue