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Comparing the Long Term Use of H2 Antagonists (H2RAs) and Proton Pump Inhibitors (PPIs) and the Incidence of Colitis

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Abstract

- Medications for GERD may affect the colonic mucosa.
- H2RAs ranitidine, cimetidine , famotidine reduce acid secretion by 70%.
- PPIs omeprazole, pantoprazole, lansoprazole, esomeprazole and rabeprazole block H+ pump and reduce HCl by 80 to 95%.
- Diarrhea is often the most common adverse event.
- H2RAs and PPIs interfere with GI physiology by altering intestinal pH.
- Microcytic colitis causing chronic diarrhea and colonic inflammation is a significant complication risk after the > 4-8 week use of H2RAs and PPIs.
- Microcytic colitis has increased concurrent to the use of PPIs and H2RAs.
- Microscopic colitis is associated with ranitidine (Zantac) and lansoprazole (Prevacid), omeprazole (Prilosec) and esomeprazole (Nexium) use.

Introduction

- Microscopic colitis is a significant complication risk following the > 4-8 week use of certain H2RAs and PPIs.
- Clinicians seek a medication that is specific, selective, and effective for the treatment of GERD sparing the inflammatory SEs of the intestine.
- Improved awareness and increased use of treatments that cause microscopic colitis are some of the causes of more frequent diagnosis.
- The drugs associated with microscopic colitis are proton pump inhibitors (PPIs) and histamine 2 receptor-antagonists (H2RAs).
- The recommended duration of PPI therapy for mild-moderate peptic ulcer disease and dyspepsia is 4-8 weeks.
- Esophagitis , Barrett's esophagus and Zollinger-Ellison syndrome may require continuous therapy when upon withdrawal relapse is likely.
- Purpose is to investigate whether the use of PPIs and H2RAs are associated with the histological changes observed in microscopic colitis.

Statement of the Problem

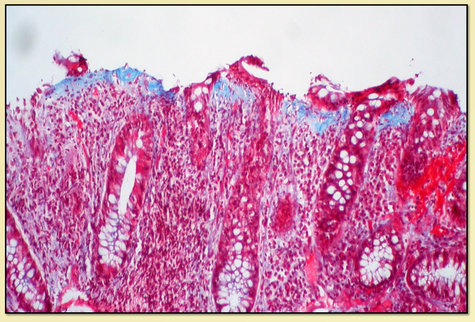
- Effective and evidenced based treatments are being chosen with good safety profiles and low incidence of side effects.
- This study discusses increased IELs ,inflammation of the colonic mucosa, alterations in intestinal barrier function and unfavorable mucosal immune activation induced with certain H2RAs and PPIs.
- Healthcare providers may need to improve the oversight and education given to GERD patients who are treated with long term H2RA and PPI therapy to decrease the incidence of colonic inflammation.

Research Question

- In patients with GERD receiving treatment, is there a statistical difference in efficacy of treatment/incidence of colitis when using H2RAs or PPIs?
- In treating patients with GERD, do H2RAs or PPIs cause colitis?

Literature Review

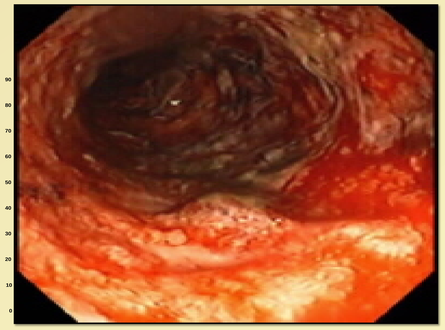
- PPIs reduce acid secretion by inhibiting the hydrochloric acid (proton) secreting pump (H+/ K+ ATPase) in the stomach and are anti- secretory agents.
- PPIs enter the parietal cell, bind to the proton pump, resulting in an irreversible pump inactivation reducing the amount of H+ that is pumped into the stomach lumen. The binding is irreversible, the effects of PPIs persist until new pumps are synthesized.
- Concerns of small and large bowel dysbiosis , microcytic, collagenous and lymphocytic colitis secondary to long term PPI use (>4-8 weeks) are raised.
- Diarrhea was reported in clinical trials and observational data of lansoprazole users.
- Lansoprazole is a highly effective PPI, has been well tolerated with minimal serious adverse events. Diarrhea is reported in approximately 3% to 8% of study patients.
- In collagenous colitis and lymphocytic colitis related to lansoprazole, with both clinical (cessation of diarrhea) and histological improvement upon cessation of this medication.
- The most potent medications that suppress gastric acid are PPIs. They have been associated with dysbiosis or microbial colonization of the normally sterile upper gastrointestinal tract (stomach, duodenum, jejunum and ileum), with altered gastrointestinal flora , posing an increased susceptibility to infectious gastroenteritis.



- B12 deficiency and the use of H2RAs or PPIs for twelve months or more.
- The use of both PPI and clopidigrel was associated with an increased risk of death or rehospitalization, revascularization surgery for ACS compared with that of clopidigrel alone without PPI.
- Prolonged gastric acid inhibitor -induced hypochlorhydria has been correlated as a risk factor for severe gastrointestinal infections.
- The causative role of lansoprazole suggest that lansoprazole related lymphocytic colitis takes longer to develop and resolve, implicating significant mucosal damage .

Discussion

- Microcytic colitis causing chronic diarrhea and chronic colonic inflammation continues to be a statistically significant complication risk with extended use (4-8 weeks) of certain H2RAs and PPIs.
- Among the drugs associated with microscopic colitis are H2RAs; ranitidine (Zantac) and proton pump inhibitors, lansoprazole (Prevacid), omeprazole (Prilosec), and esomeprazole (Nexium).
- Diarrhea is one of the most frequently reported adverse events during the long term use of PPIs. The diarrhea was most commonly loose and occurred on average 4.4 times per day ranging from 4-9 times per day.



- Multiple case studies suggest a causal relationship between microscopic colitis and lansoprazole, omeprazole and esomeprazole treatment, due to the temporal association of exposure, resolution of symptoms and normalization of histopathology upon drug withdrawal, and the immediate recurrence of disease with histologic abnormalities upon drug re-exposure.
- PPIs are therapeutically more effective than H2RAs in the treatment of gastroesophageal reflux disease, have a higher risk profile, increased ADRs and are more broadly implicated in microscopic colitis.
- Microcytic colitis causing chronic diarrhea and chronic colonic inflammation continues to be a significant complication risk with the extended use of certain PPIs (lansoprazole (Prevacid), omeprazole (Prilosec) and esomeprazole (Nexium) and the H2RA (ranitidine (Zantac)).
- PPIs have the physiological and functional potential to interfere with gastrointestinal physiology by virtue of altering intestinal pH.
- PPIs can also interact with mechanisms and sites of action, other than that of gastric H+/K+ ATPase. Colonic epithelial cells also express proton pumps, which are involved in maintaining local electrolyte balance.
- Several bacteria including *Heliobacter pylori* and *Strep pneumoniae*, as well as fungi such as *Candida albicans* contain H+/K+ plus ATPase in their plasma membranes, which are highly similar to human plasma membranes.
- PPIs can influence a wide variety of microbial growth, including bacteria and fungi, by inhibition of H+/K+ ATPase.

Applicability to Clinical Practice

- H2RAs and PPIs are widely prescribed worldwide by physicians and can be purchased over-the-counter by patients.
- In 2010, 53.4 million US prescriptions for the generic antacid medication Prilosec (omeprazole) not including OTC sales.
- PPIs interfere with gastrointestinal physiology by virtue of altering intestinal pH.
- Hydrochloric acid is required for the breakdown and digestion of food. Although considered safe, long-term use has raised safety concerns.
- Potential adverse drug reactions include *Clostridium difficile* infection, dysbiosis, changes in autoimmunity, bone fractures, respiratory infections, B12, and iron malabsorption, malabsorption syndromes, watery diarrhea, enteric infections, small bowel bacterial overgrowth, inflammatory bowel disease, such as microscopic colitis, hypergastrinemia, including rebound secretion of hydrochloric acid and carcinoid tumors.
- Successful GERD management includes lifestyle and behavior modification as first line, prior to adding H2RAs or PPIs.
- In high-risk populations, such as the elderly, acid reducing medications are short-term solutions (2-8 weeks).
- Patient education in avoiding GERD triggers can decrease the frequency and incidence of GERD, esophagitis, peptic ulcer disease and dyspepsia.

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