

LADUR Education Article

Appropriate Use of H₂-Antagonists and Proton Pump Inhibitors for Managing Gastrointestinal Disorders

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Issues

- H₂RAs and PPIs continue to play an important role in the treatment of common gastrointestinal disorders.
 - These agents have significant differences in efficacy, drug interaction, and adverse effects.
- The use of combined H₂RA and PPI therapy is irrational and adds to the cost of therapy.

Introduction

It is estimated that 20% to 40% of the adult population report heartburn on a monthly basis. Common gastrointestinal disorders such as peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD) affects a large percentage of the American population. Over 30, 000 prescriptions for histamine₂-receptor antagonists (H₂RAs) and proton pump inhibitors (PPIs) are adjudicated through the Louisiana Medicaid program each month. Clearly, the cost of treating these illnesses is substantial.

Despite advances in the understanding of the pathophysiology of PUD and GERD and the non-acid mechanisms that contribute to the development and maintenance of these disease states, H₂RAs and PPIs continue to play an important role in the treatment of these disorders. Agents from both classes, by different mechanisms, substantially reduce the production of gastric acid; however, there are significant differences in efficacy, drug interactions and adverse effects that may translate into differences in clinical outcome, patient quality of life, and the cost of therapy. Therefore, the purpose of this paper is to address the appropriate use of these agents in the treatment of common acid-related gastrointestinal disorders and thus why they should not be used concomitantly.

Pharmacology

Histamine₂-Receptor Antagonist

The class of agents commonly referred to as the H₂RAs reduce gastric secretion by competitively and selectively inhibiting the binding of histamine to the histamine-2 receptor located on the basolateral surface of the parietal cell (Figure 1).

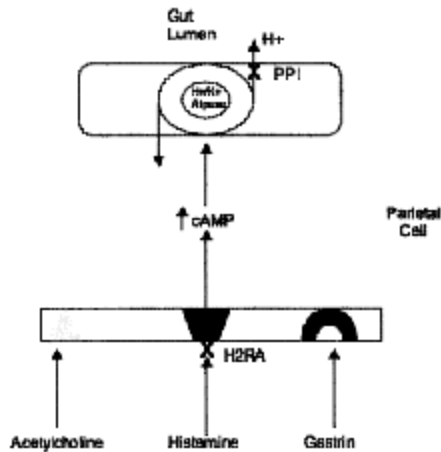


Figure 1: Schematic of acid secretion in the Gut. PPI = Proton Pump Inhibitor, H₂RA = Histamine2-Receptor Antagonist

This competitive inhibition decreases cyclic AMP production in the parietal cell resulting in decreased hydrogen ion secretion. H₂RAs cause a decrease in both basal and food stimulated acid secretion. Currently four H₂RAs are marketed, cimetidine (Tagamets), famotidine (Pepcid), nizatadine (Axid) and ranitidine (Zantac). All four agents are equally effective when used in equipotent doses (Table 1).

Table 1. Dosing of anti-secretory drugs

Drug	Treatment of Active Ulcer	Maintenance of Healed Ulcer	Mild GERD	Moderate to Severe GERD
H²-Receptor Antagonists				
Cimetidine	800mg hs	400mg hs	400mg bid	400mg qid
Famotidine	40mg hs	20mg hs	20mg bid	40mg bid
Nizatidine	300mg hs	150mg hs	150mg bid	150mg qid
Ranitidine	300mg hs	150mg hs	150mg bid	150mg qid
Proton Pump Inhibitors				
Lansoprazole	15mg q am	15mg q am	-----	30mg qd to bid
Omeprazole	20mg q am	20mg q am	-----	20mg qd to bid
Rabeprazole	20mg q am	20mg q am	-----	20mg qd to bid

These agents are rapidly absorbed, and with the exception of nizatidine, all undergo extensive first pass metabolism in the liver. All four agents are metabolized by the liver to some extent and are also eliminated renally via both

glomerular filtration and tubular secretion. Dosages need to be adjusted in hepatic failure and renal insufficiency. Cimetidine has been associated with increases in serum creatinine concentrations due to its ability to block the tubular secretion of creatinine; however, this increase in serum creatinine does not appear to be clinically relevant.

In general, the H₂RAs are well tolerated and severe adverse effects are uncommon. Headache, lethargy, thrombocytopenia, confusion, depression and hallucinations have been reported. CNS effects such as confusion are more common with larger doses, when the dosage of the drug is not decreased in patients with renal insufficiency, and in elderly patients. Cimetidine has antiandrogenic effects and may cause impotence and gynecomastia.

Because it binds to and inhibits several isozymes of the cytochrome P-450 enzyme system, cimetidine is associated with a number of drug-drug interactions. Most notably, cimetidine inhibits the metabolism of theophylline, warfarin, phenytoin, and drugs such as cisapride that are metabolized by CYP 3A4. The other H₂RAs do not appear to cause clinically significant metabolic drug interactions, however, the resultant reduction in acid secretion may decrease the bioavailability of drugs that need an acidic environment for absorption (e.g., ketoconazole, itraconazole, ampicillin, iron salts, and digoxin).

Proton Pump Inhibitors

The PPIs suppress acid reduction by binding reversibly or irreversibly to the hydrogen potassium adenosine triphosphatase enzyme system (H⁺K⁺ ATPase or Proton Pump) that serves as the final mechanism for pumping hydrogen ions from the parietal cell into the lumen of the gut. (Figure 1) This results in potent and dose dependent inhibition of acid secretion stimulated by acetylcholine, histamine, and gastrin. (Figure 1) Currently, there are three PPIs available in the United States, omeprazole (Prilosec), lansoprazole (Prevacid), and rabeprazole (Aciphex). All three agents are basic compounds that must be protonated and metabolized to an active form. Omeprazole and lansoprazole bind irreversibly to the proton pump. Rabeprazole binding appears to be partially reversible.

Absorption of the three available PPIs ranges from approximately 30% for rabeprazole to more than 80% for lansoprazole. All three agents are metabolized hepatically through the cytochrome P-450 system with little or no parent drug eliminated renally. Thus, patients with renal impairment require no dosage adjustment; however, a dosage reduction should be considered for lansoprazole in patients with severe hepatic disease.

As with the H₂RAs, the PPIs are well tolerated and have minimal adverse effects. Adverse effects for the three available agents are similar with headache, diarrhea, nausea and abdominal pain being most common. In a small number of patients, skin rashes and eruptions have been reported. A potential complication of long-term use of these agents is prolonged hypergastrinemia and its potential

consequences. The degree of hypergastrinemia appears to be related to the extent of acid suppression. Hypergastrinemia has been associated with the development of gastric enterochromaffin-like cell (ECL) carcinoid tumors and ECL dysplasia in rats; however, no ECL dysplasia or tumors have been reported in humans receiving long-term PPIs. Nonetheless, some clinicians suggest the serum gastrin concentrations be obtained yearly in patients receiving continuous long-term PPI therapy.

Because these agents are metabolized through the cytochrome P-450 system, the potential for drug-drug interactions exists. Omeprazole may increase serum concentrations of clarithromycin, phenytoin, and some of the benzodiazepines including diazepam. Lansoprazole and rabeprazole do not appear to cause any clinically significant drug interactions involving drug metabolism. Because of the effect of these agents on gastric acidity, drugs requiring an acidic environment for absorption (e.g., ketoconazole, itraconazole, ampicillin, iron salts, and digoxin) may have decreased bioavailability when given concurrently with PPIs.

Role of Antisecretory Agents in the Treatment of Acid-Related Disorders

Numerous studies have demonstrated the efficacy of these classes of agents in the treatment of PUD, GERD and Zollinger Ellison Syndrome (ZES). Despite a more in-depth understanding of the importance of non-acid related factors in the development and maintenance of these disease states, H₂RAs and PPIs remain an important part of therapy; however, a renewed understanding exists of the appropriate role of these agents in therapy.

Peptic Ulcer Disease

In recent years we have come to understand that PUD has three primary etiologies, helicobacter pylori infection, non-steroidal anti-inflammatory (NSAID) use, and hypersecretory states such as ZES. The vast majority of patients that develop PUD not associated with NSAID use are positive for H. pylori. Based on this knowledge, the focus of treatment has shifted from the long-term control of acid-related symptoms to ulcer healing, H. Pylori eradication and prevention of relapse.

In patients who test positive for H. Pylori, it is imperative to treat with appropriate antibiotics; however, the addition of an anti-secretory agent enhances ulcer healing. In comparative trials, PPIs have been shown to be as good or better than H₂RAs with respect to ulcer healing after four or eight weeks of therapy. Because of this, a triple drug regimen (two antibiotics and an antisecretory drug) that includes a PPI is considered the gold standard for the treatment of H. pylori associated PUD. The addition of the PPI to the two antibiotics significantly increases eradication rates. Although the infection is usually eradicated after 10 to 14 days of therapy, ulcer healing is slower. Therefore, it is recommended that PPIs be continued for a total of 4 weeks of therapy and H₂RAs be continued for a total of 6 to 8 weeks of therapy. Longer durations of therapy are unnecessary

unless ulcer symptoms reoccur. If ulcer symptoms reoccur, the patient should be reevaluated for resistant or inappropriately treated H. pylori infection.

The treatment and prevention of NSAID induced ulcers is somewhat more problematic than those caused by H. Pylori infection. Either a PPI or an H₂RA (but not a combination of both) may be used to promote ulcer healing. Continuation of the NSAID during the ulcer treatment phase will delay healing. If the NSAID must be continued, PPIs may be more effective than H₂RAs in promoting healing. If H₂RA therapy is selected, a higher daily dose or a longer treatment period (12 weeks instead of 8) may be necessary. Gastric ulcers may require higher doses of anti-secretory agents and a longer duration of therapy. The most effective method of preventing recurrent NSAID induced PUD is the discontinuation of the NSAID; however, this course of action is often not feasible. Misoprostol (Cytotec) is the only agent that is approved by the FDA for preventing NSAID induced ulcers, but clinical trials with both H₂RAs and PPIs have shown them to be effective in preventing ulcers in patients on chronic NSAID therapy. More recent studies have shown that PPIs may be superior to H₂RAs at standard doses in patients with NSAID ulcers.

The combination of a PPI and H₂RA for the treatment of PUD has never been shown to be more effective than either agent alone. Based on the pharmacologic profile of these two classes of agents, this combination is irrational and may put the patient at higher risk for adverse effects or drug interactions than if an appropriate trial of a single agent is used.

Based on the available data and standards of practice, antisecretory maintenance therapy is not indicated in most patients with PUD. A single treatment regimen with 4 weeks of a PPI or 8 weeks of a H₂RA is usually sufficient to treat most patients. Higher doses of a PPI (e.g., omeprazole 40mg/day) are often effective in treating ulcers unresponsive to standard therapy. In patients with refractory ulcers, other factors such as patient compliance, NSAID use, heavy smoking, or gastrin secreting tumors should be examined.

Gastroesophageal Reflux Disease

A number of factors contribute to the development and continuance of GERD. The disease itself can vary from intermittent heartburn to debilitating esophagitis. Unlike PUD, GERD can be a chronic disease that requires prolonged therapy. Recent guidelines from the American College of Gastroenterology present a step plan for its treatment. Initial and chronic therapy should always involve lifestyle modifications. The use of patient directed therapy with over-the-counter (OTC) antacids and H₂RAs is appropriate in most patients. OTC H₂RAs appear to be particularly effective when used prior to activities that precipitate reflux. Patients should be reminded to let their pharmacist and physician know that they are taking these agents.

For patients with more severe GERD or those who have symptoms despite patient directed therapy, acid suppression therapy with either a PPI or H₂RA (but not both) is usually effective in relieving symptoms and healing esophagitis. Therapy may be initiated with low dosages of H₂RAs (OTC doses, ranitidine 75mg BID) and escalated until symptoms are controlled. Alternatively therapy may be initiated with once or twice daily PPI therapy (omeprazole 20mg QD or BID) and then decreased to the lowest effective dose. High doses of H₂RAs (e.g., ranitidine 300mg BID) may often be necessary to control GERD symptoms. Although promotility agents (e.g., cisapride [Propulsid]) may provide some benefit to patients with esophageal motility disorders, PPIs appear to be more effective. Divided daily doses of H₂RAs appear to be more effective than single daily doses in the treatment of GERD.

Because GERD is a chronic disease, long-term therapy may be necessary. Chronic therapy should be titrated to the lowest effective dose and lifestyle modifications should be stressed. Sufficient data to support the use of the combination of the promotility agents and an anti-secretory agent in the treatment of GERD is not available. The use of high dose PPIs alone is more efficacious and cost effective than a combination of a H₂RA and cisapride (Propulsid). As with the treatment of PUD, the combination of a PPI and a H₂RA is irrational and should not be used. H₂RA are the drug of choice for maintenance of mild esophagitis; however, patients with moderate to severe esophagitis should be maintained on a PPI.

Zollinger Ellison Syndrome (ZES)

ZES is a rare disorder that often presents as recurrent and refractory PUD and/or GERD. This painful syndrome is caused by one or many gastrin producing tumors that cause extreme hypersecretion of acid. In the case of a single tumor, resection is often the treatment of choice; however, even after resection, a large percentage of patients will continue to have acid hypersecretion. PPIs are the anti-secretory agent of choice. High dosages are usually necessary with the average omeprazole treatment dose approaching 60-80mg/day and dosages as high as 160mg/day of omeprazole or lansoprazole may be necessary. The PPI dose should be titrated to a basal hydrogen ion secretion of 10mEq/hr or less. H₂RAs may be effective in some patients but extremely high doses (1.2-6grams/day) may be necessary. Cimetidine should not be used in this population due to its anti-androgenic effects.

Conclusions

Acid-related gastrointestinal disorders are common and the use of H₂RAs and PPIs are effective in treating these disorders when used appropriately. However, new understanding of these disease states has altered what is considered the appropriate use of these agents. PPIs, the most potent class of anti-secretory agents, may be the drugs of choice in most patients. Single agent anti-secretory therapy is appropriate in all patients. The combination of conventional anti-secretory agents adds to cost of therapy without enhancing healing.

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