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Pharmacotherapy for Acid/Peptic Disorders

Mitchell L. Schubert[a]

Departments of Medicine, Medical College of Virginia, and McGuire Veterans Affairs Medical Center, Richmond, Virginia

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In the 1970s, the identification of the histamine H_2-receptor by Black and the subsequent development of histamine H_2-receptor antagonists revolutionized our understanding and treatment of acid/peptic disorders. More recently, the identification of hydrogen-potassium-stimulated adenosine triphosphatase (H^+/K^+-ATPase) as the proton pump of the parietal cell and the recognition of the prominent role of *Helicobacter pylori* in the pathogenesis of duodenal and gastric ulceration have heralded a new revolution in our understanding and treatment of these disorders. Substituted benzimidazole compounds (omeprazole, lansoprazole and pantoprazole) that covalently bind to and inactivate the proton pump allow complete and prolonged inhibition of acid secretion. Not only can peptic ulcers now be healed more rapidly with proton pump inhibitors, but refractory ulcers have all but disappeared. Eradication of *H. pylori* with antibiotics offers, for the first time, a permanent cure for most duodenal and many gastric ulcers.

PROTON PUMP INHIBITORS

The pathogenesis of acid/peptic disorders (duodenal ulcer, gastric ulcer and reflux esophagitis) involves an imbalance between aggressive (e.g., acid, pepsin, *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs) and defensive (e.g., epithelial cell integrity, mucus, bicarbonate and mucosal blood flow) factors. Although an important role has been established for *H. pylori* in the development of duodenal and gastric ulcer, it should be emphasized that gastric acid still remains central to the pathogenesis of these disorders and Schwartz's dictum, "no acid — no ulcer," remains valid. These disorders can be completely healed and remission maintained with antisecretory therapy [1]. Furthermore, in patients with duodenal ulcer disease, peak acid secretion remains elevated even after eradication of *H. pylori* [2].

With the recent introduction of PPIs[b] into clinical practice, acid inhibitory therapy for peptic ulcer disease has come a full circle. That is, we went from intensive four times per day dosing of H_2 antagonists in the 1970s to twice daily, and eventually a single daily dose in the 1980s, with equivalent healing rates. The use of PPIs has ushered a return to aggressive acid inhibitory therapy. PPIs are being touted as first-line therapy for acid/peptic disorders and are being used in higher and higher doses. Such an approach is warranted in severe gastroesophageal reflux disease, in which it has been shown that acute healing at eight weeks correlates with the duration in hours that the intragastric pH is maintained above 4.0 [3]. PPIs suppress daytime, nighttime and especially meal-stimulated acid secretion more effectively than H_2 antagonists and, thus, yield higher healing rates for erosive and ulcerative esophagitis. After eight to 12 weeks, 74 to 96 percent of omeprazole-treated patients with esophagitis are healed compared with 28 to 66 percent of patients

[a]*To whom all correspondence should be addressed:* Mitchell L. Schubert, M.D., McGuire VAMC, Code 111N, Division of Gastroenterology, 1201 Broad Rock Boulevard, Richmond, VA 23249. Tel: (804) 675-5457; (Fax): (804) 675-5359.
[b]*Abbreviations:* PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug.

treated with H_2 antagonists [4]. Once healed, omeprazole, 20 mg/day, is more effective in preventing relapses, with 77 to 89 percent remaining in remission at twelve months compared with 25 to 46 percent of those taking 150 mg ranitidine twice daily [5, 6].

Healing rates for duodenal and gastric ulcer correlate with the degree and duration of 24-hr acid suppression as well as the length of treatment. For duodenal ulcer, suppression of 24-hr and nocturnal acid secretion appears to be most important. Conventional doses of H_2 antagonists maintain intragastric pH at or above 3 for about 10 hours, which is six to seven hours less than that which can be achieved with single daily doses of 20 mg omeprazole or 15 mg lansoprazole. Accordingly, duodenal ulcers heal more rapidly on standard doses of PPIs than on H_2 antagonists, with complete healing at four and eight weeks, respectively. Thus, depending upon price, it may be more cost-effective to treat duodenal ulcers for four weeks with a PPI instead of eight weeks with an H_2 antagonist [7, 8]. In contrast to duodenal ulcer, the most important parameter for healing of gastric ulcer appears to be length of treatment, with 85 to 95 percent of both omeprazole- and ranitidine-treated ulcers healed at eight weeks [7, 9, 10]. Thus, for gastric ulcer, eight-week therapy with an H_2 antagonist may be more cost-effective.

HELICOBACTER PYLORI

H. pylori is associated with chronic type B gastritis, duodenal and gastric ulcer, and gastric adenocarcinoma and lymphoma. Eradication of *H. pylori* with antimicrobial agents prevents relapse of duodenal and gastric ulcer and causes regression of primary, low-grade B cell lymphoma of the stomach. It remains to be determined whether eradication is indicated in patients with non-ulcer dyspepsia, hyperplastic gastric polyps or a family history of adenocarcinoma of the stomach.

The "gold standard" regimen for eradication of *H. pylori* consists of bismuth and metronidazole plus either amoxicillin or tetracycline for two weeks. Another triple therapy regimen, consisting of metronidazole, clarithromycin and omeprazole, each given twice daily, shows promise with preliminary studies also showing a 90 percent eradication rate. Problems with triple therapy include: 1) resistance to metronidazole (25 percent in the U.S.; higher elsewhere), 2) high side-effect profile (25 to 35 percent) including antibiotic-associated diarrhea and colitis, 3) poor compliance due to the large number of tablets to be ingested daily (up to 16 tablets/day) and 4) induction of antibiotic resistance, not only in *H. pylori* but in other colonizers such as *Streptococcus*, *Staphylococcus*, *H. influenza*, and *Enterococcus*. None of the present regimens are ideal. Dual therapies, e.g., omeprazole plus amoxicillin, previously extolled as the treatment of choice for eradication of *H. pylori,* have now fallen into disrepute with unacceptably low eradication rates of 45 to 80 percent [11]. The search for a simple, inexpensive, well-tolerated, selective, yet effective regimen continues.

Successful eradication is generally accepted as inability to detect the organism in gastric biopsy material (rapid urease test, histology or culture) four weeks after completion of antibiotic therapy. When patients have been re-evaluated at twelve months, recurrence has been noted in 11 to 19 percent [12, 13]. DNA fingerprinting techniques indicate that recurrence of *H. pylori* after apparently successful treatment is mainly attributable to recrudescence of persistent infection rather than reinfection. During a four-week treatment of duodenal ulcer patients with omeprazole, there is a significant reduction in the number of patients with *H. pylori* in the antrum and a significant increase in those with *H. pylori* only in the fundus [14]. Thus, a greater number of persistent infections at four weeks may be detected if fundic, in addition to antral, biopsies are obtained. It is possible that our present definition of eradication may need to be revised and more sensitive techniques developed to assess residual infection.

MANAGEMENT STRATEGIES

The National Institutes of Health Consensus Development Conference on *H. pylori* recommended that patients with documented duodenal or gastric ulcer and infection with *H. pylori* be treated with antimicrobial agents in an attempt to eradicate the organism, whether on first presentation with the illness or on recurrence [15]. A more recent cost-comparison, using decision analysis, supports the notion that initial therapy with antibiotics plus an antisecretory agent provides the lowest costs per symptomatic cure [16]. Confirmation of *H. pylori* eradication is probably not necessary in patients with noncomplicated peptic ulcer disease but is mandatory in patients with previous ulcer complications.

A provocative cost-effectiveness analysis challenges the NIH recommendation that both the presence of an ulcer and *H. pylori* infection be documented before antibiotic medications intended to eradicate the organism be prescribed [17]. Although endoscopy precisely guided diagnosis and treatment and, thus, reduced the number of patients exposed to unnecessary antibiotics, it was almost twice as costly as empiric antisecretory and antibiotic therapy per patient treated ($1584 vs. $818) or per ulcer cured ($8045 vs. $4155). In a prospective trial in Denmark, comparing empiric H_2 antagonists to immediate endoscopy [18], 65 percent of empirically-treated patients with dyspepsia eventually required endoscopy. At this rate of recurrent symptoms, the cost-effectiveness advantage of empiric antibiotic therapy will be minimal. In this environment of competitive managed care, the onus is squarely on us, as gastroenterologists, to bring down the cost of esophagogastroduodenoscopy. At less than $500, initial endoscopy becomes the most economical strategy.

Although it is an important consideration, cost-effectiveness should not be the overriding factor influencing our decision processes. It should be noted that only a minority of patients, less than 10 percent, presenting to their primary-care physicians with upper abdominal complaints have an ulcer; most have gastroesophageal reflux disease or nonulcer dyspepsia, conditions that do not respond to antimicrobial therapy. Even in patients with documented peptic ulcer disease, not all ulcers are due to *H. pylori* — a large proportion are non-steroidal anti-inflammatory drug (NSAID)-induced. It is not reasonable to expose such a large number of patients unnecessarily to the risks of triple antibiotic therapy and to burden society with increasing numbers of antibiotic resistant organisms. Multidrug resistant mutations of *Streptococcus*, *Staphylococcus* and *Enterococcus* are already inflicting increasing morbidity and mortality on our patients.

THEORETICAL CONCERNS: HYPERGASTRINEMIA

Gastrin is the major hormonal stimulant of gastric acid secretion and is a mucosal growth factor. In the antrum, the secretion of gastrin is regulated via a feedback mechanism, whereby an increase in luminal acidity stimulates somatostatin secretion, which, in turn, attenuates gastrin secretion. Accordingly, a decrease in luminal acidity, such as that induced by PPIs, decreases somatostatin and, thus, increases gastrin secretion. In general, the level of hypergastrinemia is proportional to the duration and degree of acid suppression. Infection with *H. pylori* also increases gastrin secretion, both basal and meal-stimulated, possibly by decreasing antral somatostatin release [19, 20]. Although the current evidence suggests that the hypochlorhydria and hypergastrinemia observed during PPI therapy have little or no clinical significance, at least up to 10 years follow-up, it should be noted that the risk of cancer in patients with gastric resection or pernicious anemia increases only after a latency of decades. Furthermore, it has been shown that endogenous hypergastrinemia, induced by fundectomy, increases the spread of human colon carcinoma transplanted into the colon of athymic rats [21]. Although most patients on PPIs have

only moderate increases in fasting serum gastrin levels, in about 25 percent of patients, gastrin levels increase to over 500 pg/ml [22]. For patients maintained on long-term PPIs, it seems prudent to check a fasting serum gastrin level at six months to one year. If marked hypergastrinemia (greater than 400 to 500 pg/ml) is found, it would seem reasonable to reduce the dose of the drug and perhaps check for the presence of *H. pylori*, a gastric emptying disorder or Zollinger-Ellison Syndrome.

Adenocarcinoma of the proximal stomach has the most rapidly rising incidence of any cancer in the United States. The increase began around 1980, and the slope appears to mirror the use of potent antisecretory drugs. Prolonged acid suppression, besides inducing hypergastrinemia, may predispose to gastric malignancy by inducing intragastric bacterial overgrowth leading to increased gastric nitrite and N-nitroso levels and by spreading *H. pylori* infection from the antrum to the body and fundus of the stomach with a hastening of the development of the precancerous conditions of atrophy and intestinal metaplasia [23]. Perhaps patients requiring long-term acid-suppressive therapy, such as those with severe esophagitis, should be tested for *H. pylori* and, if positive, have the organism eradicated.

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