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Long Term Proton Pump Inhibitor Use and Gastrointestinal Cancer

David Y. Graham, M.D. and
Professor of Medicine and Molecular Virology and Microbiology, Michael E. DeBakey VA Medical Center, Baylor College of Medicine, 2002 Holcombe Blvd. Houston, Texas 77030, dgraham@bcm.tmc.edu

Robert M. Genta, M.D.
Clinical Professor of Pathology and Medicine (Gastroenterology), University of Texas Southwestern Medical Center, 8400 Esters Boulevard - Suite 190, Irving, TX 75063, robert.genta@utsouthwestern.edu

Abstract

Proton pump inhibitors profoundly affect the stomach and have been associated with carcinoid tumors in female rats. There is now sufficient experience with this class of drugs to allow reasonable estimation of their safety in terms of cancer development. Long term proton pump inhibitor use is associated with an increase in gastric inflammation and development of atrophy among those with active *Helicobacter pylori* infections. The actual risk is unknown but is clearly low. However, it can be markedly reduced or eliminated by *H. pylori* eradication leading to the recommendation that patients considered for long term proton pump inhibitor therapy be tested for *H. pylori* infection and if present, it should be eradicated. Oxyntic cell hyperplasia, glandular dilatations, and fundic gland polyps may develop in *H. pylori*-uninfected patients, but these changes are believed to be reversible and without significant cancer risk.

Introduction

The stomach is a tightly regulated organ that serves many functions, including that of a protective barrier to ingested pathogens. By the early 1900's gastric cancer was known to be closely related to gastritis and gastric atrophy. Much of the stomach's protective powers can be attributed to the secretion of acid and pepsin; it was commonly believed that the normal stomach was generally sterile, especially during fasting, and that this was a direct result of the presence of its low pH. In contrast, the inflamed and atrophic stomach was found to contain a wide variety of bacteria, including some species that were normal residents of the lower gut. This change was also associated with an increased bacterial load in the small intestine, which was thought to adversely affect its function (1). Correa proposed a role for the bacteria colonizing the atrophic stomach in the induction of carcinogens, thus providing a hypothesis that unified the structural and physiologic changes that created the background for gastric cancer (2). The potential role of bacteria and yeast in gastric carcinogenesis has remained an active area of investigation and continues to elicit interest as new potential mediators are being identified.

H_2-receptor antagonists were introduced in the mid 1970's. Their ability to reliably reduce gastric acidity prompted inquiries regarding whether they might also promote gastric

Corresponding author: David Y. Graham, M.D. Michael E. DeBakey Veterans Affairs Medical Center, RM 3A-320 (111D), 2002 Holcombe Boulevard, Houston, TX 77030, Phone: 713-795-0232, FAX: 713-790-1040, dgraham@bcm.tmc.edu.

colonization and enhance the risk of gastric cancer (1). However, since this class of drugs is unable to continuously maintain the gastric pH at levels sufficiently low (*e.g.*, above pH 4) to allow bacterial overgrowth, concerns regarding gastric carcinogenesis subsided. The question resurfaced less than a decade later following the introduction of the more potent proton pump inhibitors (PPIs) and remains incompletely answered to this day (1). The issue became even more complicated when it was discovered that in the majority of instances gastric inflammation and the resulting atrophy were one outcome of infection with the bacterial pathogen *Helicobacter pylori* (3). Even among those with *H. pylori* infection acid secretion varied in relation to the pattern of gastritis with high acid secretion and duodenal ulcer being related to an antrum-predominant gastritis, and gastric ulcer and gastric cancer being associated with inflammation involving both the antrum and corpus (pangastritis). The focus of therapy with anti-secretory agents also changed from duodenal ulcer to gastroesophageal reflux disease, which appears to be increasingly associated with *H. pylori*-uninfected stomachs.

To completely understand the potential role of PPIs in altering gastric physiology one must understand their effects on both the normal and the *H. pylori*-infected stomach, in which PPI effects vary with different patterns of gastric inflammation.

Effects of Proton-pump Inhibitors on the Gastric Mucosa

Oxyntic gland dilatation and fundic gland polyps

Experienced pathologists can generally determine whether a patient is receiving PPIs. Oxyntic glands, which are normally tight tubes with a virtual lumen lined by smooth parietal, mucous, and chief cells, become unevenly dilated and the lumen acquires a ragged lining caused by the protruding oxyntic cells, which are increased in height and project minuscule cytoplasmic protrusions into the lumen. In biopsy specimens from the corpus these changes may be observed in just a few glands or in the majority of them; consequently, the mucosa may acquire an oddly irregular aspect. Although it is usually more difficult to detect because of the inflammation, dilatation of oxyntic glands is also observed in *H. pylori*-infected mucosa.

Some of the dilated glands may acquire a cystic aspect, resulting in the histopathologic appearance of an empty cavity lined by flattened parietal and chief cells; these cavities may become large enough to become visible to the endoscopist, making the transition to a fundic gland polyp. Fundic gland polyps were described in the 1970s by the German pathologist Kurt Elster (4), who considered them to represent hamartomatous lesions. They are commonly present in patients with the familial adenomatous polyposis syndrome, where they may develop foci of dysplasia and acquire a prevalently adenomatous appearance with its inherent risk of malignant progression (5). In contrast, sporadic fundic gland polyps that occur in conjunction with PPI intake are considered generally benign lesion that typically regress if PPIs are discontinued (6-9). Interestingly, fundic gland polyps arise only exceptionally in *H. pylori*-infected stomachs. For example, in a study of more than 6,000 patients with fundic gland polyps we found concurrent *H. pylori*-gastritis in only 29 patients and *H. pylori* organisms were present on the polyp itself in only two patients (Lash and Genta, abstract submitted).

ECL-cell, G-cell hyperplasia, and hypergastrinemia

Enterochromaffine-cell-like cells (ECL cells) are distributed throughout the oxyntic mucosa where they participate in the regulation of acid production. Gastrin-producing cells (G-cells) are endocrine-type cells confined to the gastric antrum. In response to acid suppression G-cell increase their production of gastrin in an attempt to promote acid secretion. Gastrin stimulates acid secretion in two mechanisms: by direct action on the parietal cell's basolateral membrane CCKB receptors and indirectly by affecting the ECL cell's CCKB receptors with respond by releasing histamine which stimulates parietal cell acid secretion by binding to the parietal cell's

basolateral histamine$_2$ (H_2) receptor. The increased stimulation of parietal cells results in the hypertrophy and hyperplasia described in the previous section; the stimulation of ECL cells induces their hyperplasia, the initial step of a sequence that may progress to the formation of aggregates of ECL-cells that, depending on their size and shape, are known as linear hyperplasia, micro-carcinoids, and carcinoids.

The normal range of serum gastrin levels depends on the method and laboratory, but is generally below 150 pg/mL. Very high levels of gastrin (*e.g.*, >400 pg/mL) were considered indicative of the Zollinger-Ellison syndrome or end-stage atrophic gastritis, where the gastric corpus has lost most or all the parietal cells and antral G-cells secrete ever increasing quantities of gastrin in a futile attempt to stimulate acid secretion. Chronic use of H_2-receptor antagonists or PPIs is typically associated with a slight increase in serum gastrin. However, about 20–25% of chronic PPI users develop modest degrees of hypergastrinemia (200–400 pg/mL) (10). Approximately 1% per year develop significant hypergastrinemia (>400 pg/mL) (vide infra). This significant hypergastrinemia is much more frequent in patients with *H. pylori* infection than in uninfected subjects with a previously normal stomach.

Effect of PPIs on the *H. pylori*-infected gastric mucosa

In the late 1980's it was noted that PPI use was associated with an improvement in *H. pylori*-associated antral inflammation. In 1989 Unge *et al.* examined both the antrum and corpus and observed that PPI use was associated with a reversible improvement in antral inflammation and *H. pylori* density, whereas *H. pylori* density in the corpus either increased or was unchanged (11). Subsequent histologic studies by Stolte and Bethke reported that *H. pylori* were not detected histologically in either the antrum or corpus in 34% of 154 PPI users, were absent from the antrum and decreased in the corpus in 31%, and decreased in both the antrum and corpus in 35%. In no instance were *H. pylori* found only in the antrum (12). Later studies in which histology has been combined with quantitative culture confirmed that PPIs use is associated with a change in the distribution of gastric inflammation with improvement in antral histology and worsening and deepening of the corpus inflammation to include the proliferative zone (13). These changes have been attributed to alteration in local pH as *H. pylori* are killed at pH's below 4 and above 8, are able to survive but not replicate at pH's between 4 and 6, and only replicate at pH's between 6 and 8 (14). The pH of acid within an actively secreting pit is below 1 making colonization of actively secreting pits difficult or impossible for *H. pylori*.

Overall, these results are consistent with the observations of Kuipers *et al.* suggesting that PPI use was associated with an increased risk of development of atrophic gastritis, the acknowledged primary risk factor for development of gastric cancer (15-18). Their landmark studies prompted a number of additional investigations; although the final word has yet to be written, most agree that PPI use in *H. pylori*-infected patients is associated with an increase in corpus inflammation and atrophy (eg, (17;19-23)).

Our approach to the estimation of risk for gastric cancer would be to determine the risk of developing severe atrophic gastritis. Marked hypergastrinemia in PPI users generally identifies patients who have developed gastric atrophy. While there are few studies, the prevalence of gastric atrophy seems to be directly related to the length of the study, suggesting an incidence of approximately 1% per year among those with *H. pylori* infection (24-29). Importantly, those without known active *H. pylori* also may develop gastric atrophy while taking PPIs, suggesting that in some patients either *H. pylori* was not detected or overgrowth by non-*H. pylori* organisms may on occasion lead to the same outcome. Since approximately a quarter of PPI users develop gastrin levels in the range of 200 to 400 pg/mL, it may be possible to identify those most at risk. Measuring gastrin levels may also provide a good biomarker for prospective studies as well as to identify patients who may benefit from a reduction of PPI dose or use of an alternate approach.

How Each of these Changes Could Theoretically Relate to Cancer

Each of the PPI-induced changes outlined above could be linked to the development of cancer in the stomach and elsewhere in the gastrointestinal tract. Below we present the current evidence for each of these possibilities.

Malignant transformation of fundic gland polyps

Although long-term PPI use is associated with an up to fourfold increase in the risk of fundic gland polyps, the risk of dysplasia is negligible. In a series of 107 chronic PPI users with fundic gland polyps from the Netherlands, only one polyp was believed to have low-grade dysplasia (6). In our own series of 6,065 patients with fundic gland polyps, a single polyp was initially interpreted by the original pathologist as possibly having low-grade dysplasia. Serial sectioning and re-evaluation in a consensus conference led to the diagnosis of reactive changes, most likely related to the healing of an erosion that had occurred on the surface epithelium lining the dilated glands. We conclude that outside of familial polyposis there is no evidence suggesting a malignant potential for fundic gland polyps.

Gastric carcinoids

Although PPI or H_2-receptor antagonist-associated hypergastrinemia has been reported to cause gastric carcinoids in female rats, this has not been found in other species, including humans. After approximately 20 years of use and several billion prescriptions worldwide, gastric carcinoids have not been documented to arise in association with PPI use. In a series of 1326 patients receiving various doses of esomeprazole and followed for 6 to 12 months with serial gastric biopsies, simple, linear, or micronodular hyperplasia were detected on final biopsy in 5-12% of patients. However, there were no instances ECL cell dysplasia, carcinoids, or neoplasia (30). We conclude that the risk for carcinoids is low to absent.

Hypergastrinemia and colon cancer

It has been suggested, largely based on in vitro studies that hypergastrinemia may increase the risk of colon cancer. Recent studies have not supported that hypothesis and we conclude that this concern appears unwarranted (31;32).

Accelerated corpus atrophy

PPI use is clearly associated with a low risk of development of gastric atrophy. The risk of developing gastric cancer among those with gastric atrophy is in the range of 500 to 1000 per 100,000 per year (33). Thus, the maximum rate would be in the range of 1/10,000 users per year among *H. pylori* infected individual and would be difficult or impossible to separate from “naturally occurring” *H. pylori*-associated gastric cancer. Eradication of *H. pylori* would reduce the risk remarkably. Clearly, the risk of developing atrophy is very low to non-existent among those without *H. pylori* infections and can be reduced by *H. pylori* eradication among those with active *H. pylori* infections.

Conclusions

PPI use in those with *H. pylori* infection

Since inflammation of the oxyntic mucosa is believed to be not only a precursor of atrophy, but also an independent risk factor for gastric cancer, it is now generally agreed that *H. pylori*-positive subjects who are candidates for long-term acid suppression, *H. pylori* eradication is indicated. However, because, because PPI use is associated with a reduction in the *H. pylori* bacterial load and, therefore, the diagnosis may be difficult because testing by histology, rapid urease tests, culture, urea breath testing or stool antigen testing can all be

negative. Histology is especially likely to be negative in the antrum, and it is important that the endoscopist take samples from the gastric angle and corpus and for the pathologist to be sensitive to the presence of gastric inflammation. One approach it to substitute an H_2-receptor antagonist for the PPI as H_2-receptor antagonists have no effect on *H. pylori* growth in the stomach and, therefore, testing would be accurate. A two week period of H_2-receptor antagonist substitution should be sufficient. The alternative is to do serologic testing. Because of the high likelihood of a false positive when testing in a low pretest probability condition such as gastroesophageal reflux disease, positive results should be confirmed using a test for active infection (*i.e.*, one of those listed above). False negatives in this instance would be rare and a negative value can be taken at face value.

For those without *H. pylori* infection

As noted above, the risk of developing gastric cancer in this group is believed to be extremely low. Those who have a marked response and develop consistently high intragastric pH could possibly develop bacterial overgrowth and eventually gastric atrophy. One way to prevent this would be to check serum gastrin levels at regular intervals (*e.g.*, every 5 years). Chronic PPI use must also be considered in relation to other potential risks including risk of developing gastric atrophy, vitamin B12 deficiency, and possible an increase in the risk for hip fractures, community acquired pneumonia, and pseudomembraneous colitis (34-40). Clinically, the most common indications for long term PPI use are for the management of symptomatic gastroesophageal reflux disease and for prevention of NSAID-associated upper gastrointestinal complications. While strict compliance is critical for prevention of NSAID-associated injury (41), intermittent therapy is an effective and less costly strategy for management of uncomplicated gastroesophageal reflux disease, and should also prevent sustained gastric colonization with its possible consequences (42).

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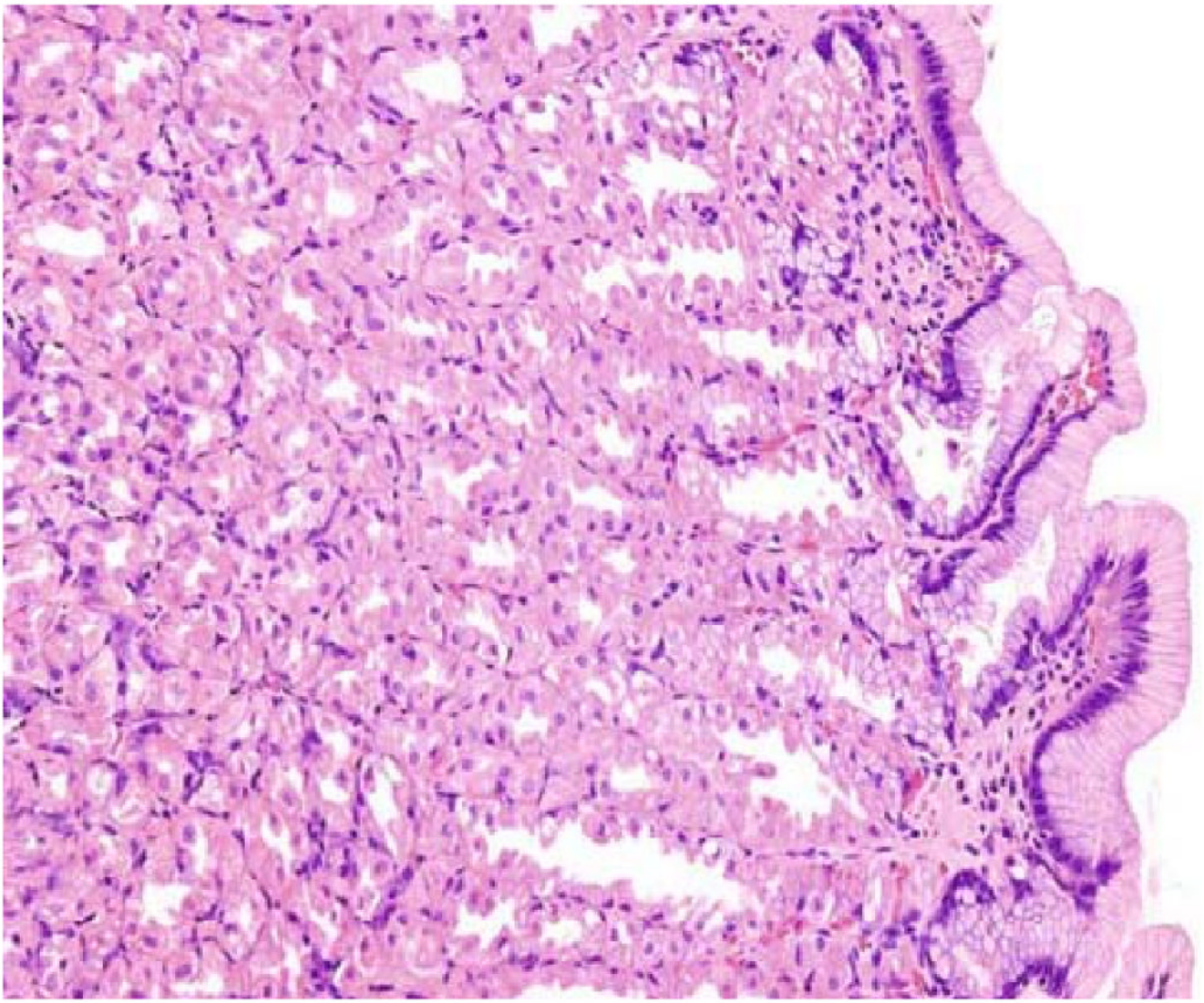

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An experienced pathologist will have no difficulty recognizing this patient as a non-*H. pylori* infected chronic PPI user: the gastric corpus is completely devoid of inflammation, but parietal cells are hyperplastic and protrude into the lumen of dilated oxyntic glands. When these dilatations become more prominent (and, therefore, endoscopically visible) they are known as fundic polyps. Hematoxylin and eosin, original magnification 20×.