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Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors

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SUMMARY

This review examines the evidence for the development of adverse effects due to prolonged gastric acid suppression with proton pump inhibitors. Potential areas of concern regarding long-term proton pump inhibitor use have included: carcinoid formation; development of gastric adenocarcinoma (especially in patients with *Helicobacter pylori* infection); bacterial overgrowth; enteric infections; and malabsorption of fat, minerals, and vitamins.

Prolonged proton pump inhibitor use may lead to enterochromaffin-like cell hyperplasia, but has not been demonstrated to increase the risk of carcinoid formation. Long-term proton pump inhibitor treatment has not been documented to hasten the development or the progression of atrophic gastritis to intestinal metaplasia and gastric cancer, although long-term studies are required to allow definitive conclusions. At present, we do not recommend that patients be tested routinely for *H. pylori* infection when using proton pump inhibitors for prolonged periods. Gastric bacterial overgrowth does increase with acid suppression, but important clinical sequelae, such a higher rate of gastric adenocarcinoma, have not been seen. The risk of enteric infection may increase with acid suppression, although this does not seem to be a common clinical problem with prolonged proton pump inhibitor use. The absorption of fats and minerals does not appear to be significantly impaired with chronic acid suppression. However, vitamin B_{12} concentration may be decreased when gastric acid is markedly suppressed for prolonged periods (e.g. Zolllinger–Ellison syndrome), and vitamin B_{12} levels should probably be assessed in patients taking high-dose proton pump inhibitors for many years.

Thus, current evidence suggests that prolonged gastric acid suppression with proton pump inhibitors rarely, if ever, produces adverse events. Nevertheless, continued follow-up of patients taking proton pump inhibitors for extended periods will provide greater experience regarding the potential gastrointestinal adverse effects of long-term acid suppression.

INTRODUCTION

Proton pump inhibitors are being used with increasing frequency, particularly to treat patients with gastro-oesophageal reflux disease (GERD). The widespread use of the proton pump inhibitors has led to concern about the consequences of profound acid suppression for patients, particularly when these agents are used chronically. A variety of potential gastrointestinal effects associated with long-term proton pump inhibitor therapy have been assessed.

First, pronounced acid suppression has been shown to lead to elevated serum gastrin in many individuals.[1–4] Three key observations have caused concerns related to proton pump inhibitor-induced hypergastrinaemia:

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(i) lifelong suppression of gastric acid (with proton pump inhibitors or by other methods) is associated with the formation of gastric enterochromaffin-like cell carcinoids in rats;[5–8] (ii) gastric carcinoids have occurred in patients with type-A (gastric body-predominant) chronic atrophic gastritis as well as in patients with Zollinger–Ellison syndrome when it is associated with multiple endocrine neoplasia-1, both of which are conditions in which there is marked hypergastrinaemia;[9–15] and (iii) gastrin exerts trophic effects in the gastrointestinal tract, raising the possibility that elevated serum gastrin could promote neoplastic growth in areas such as the stomach or colon.[16, 17]

Secondly, the appreciation of *Helicobacter pylori* infection and its associated gastric mucosal changes have raised concerns about the effects that long-term proton pump inhibitor treatment may have on the gastric mucosa in individuals with *H. pylori* infection. Thirdly, chronic low-acid states may lead to gastric bacterial overgrowth, raising concerns regarding the potential presence of a greater number of bacteria capable of producing nitrosamines, which may be carcinogenic.[18, 19] Fourthly, acid suppression may increase the risk of enteric infection. Finally, it has also been suggested that low-acid states can lead to diminished absorption of fats, minerals, and vitamins. This review explores the aforementioned potential adverse effects of long-term proton pump inhibitor use.

GASTRIN, ENTEROCHROMAFFIN-LIKE CELL HYPERPLASIA, AND GASTRIC ENTEROCHROMAFFIN-LIKE CELL CARCINOIDS

The physiologic effects of gastrin

Gastrin, which is secreted by antral G cells, has two main physiologic functions: (i) the stimulation of gastric acid secretion, either directly by acting on the parietal cells or indirectly by stimulating histamine release from enterochromaffin-like cells; and (ii) trophic effects on both the parietal cells and enterochromaffin-like cells of the gastric mucosa.[20]

The trophic effects of gastrin regulate normal gastric mucosal growth by mediating the division of stem cells, which differentiate into surface epithelial cells, parietal cells, and enterochromaffin-like cells.[21, 22] In contrast to the secretory effects of gastrin, which occur almost immediately, the trophic effects take place more slowly.[23] Rat enterochromaffin-like cells that are exposed to gastrin release histamine within minutes; within hours, histidine decarboxylase, the enzyme that regulates histamine synthesis, is activated. Conversely, exposure to gastrin for a prolonged period ranging from hours to days is required for rat enterochromaffin-like cells to show enlargement of the endoplasmic reticulum and golgi area and increased cell size. Gastrin exposures lasting weeks can induce enterochromaffin-like cell hypertrophy and hyperplasia.[23]

The release of gastrin is mediated by a number of events, including the presence of an ingested meal in the gastric lumen, antral distention, vagal stimulation, and neural and endocrine stimulation.[20] A negative-feedback inhibition mechanism resulting from high intragastric acidity regulates gastrin release.[20, 21, 24] Hydrochloric acid secreted by parietal cells in response to circulating gastrin inhibits its further release from antral G cells, mainly by causing release of somatostatin (Figure 1).[20] Interruption of this negative feedback mechanism results in hypergastrinaemia. This interruption can be due to a number of influences. Diseases

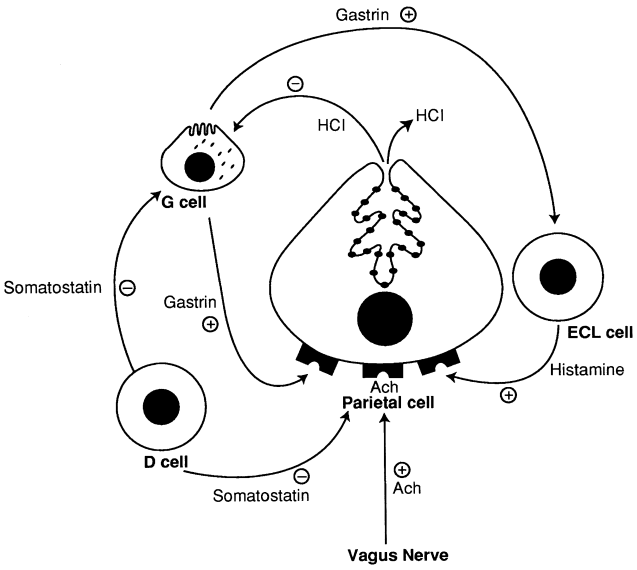

Figure 1. Acid production by the parietal cell. Gastric acid (HCl) is produced by parietal cells in response to gastrin, either directly by stimulation of the parietal cell or indirectly via stimulating histamine release from enterochromaffin-like cells. Another source of gastric acid stimulation is from acetylcholine (Ach), a neurotransmitter produced by the vagus nerve. High levels of gastric acid will cause somatostatin release from D cells; somatostatin will inhibit gastrin production from gastrin cells (G cells). Somatostatin also has a negative inhibitory effect on acid secretion via the parietal cell. When gastric acid is low, gastrin release will be stimulated.

affecting the gastric mucosa such as chronic atrophic gastritis and pernicious anaemia can cause pronounced hypergastrinaemia. In addition, surgical procedures, including vagotomy or resection of the acid-secreting portion of the stomach, and the administration of acid-inhibiting drugs including H_2-receptor antagonists (H_2-RAs) and proton pump inhibitors all can result in varying degrees of hypergastrinaemia.[24]

Enterochromaffin-like cell hyperplasia, hypergastrinaemia, and gastric carcinoid formation in rats

In rats, sustained hypergastrinaemia has been shown to be a major contributor to the development of gastric enterochromaffin-like cell carcinoids.[25–27] This finding forms the basis of the gastrin hypothesis, which suggests that hypergastrinaemia, occurring as a result of acid suppression, results in enterochromaffin-like cell hyperplasia, which can ultimately lead to the development of enterochromaffin-like cell carcinoids.[25]

Several studies support the gastrin hypothesis in rats; the results of these studies are summarized in Table 1.[25–29] These studies indicate that in rats, sustained hypergastrinaemia induced by suppression of gastric acid, whether through proton pump inhibitor or H_2-RA therapy, infusion with exogenous gastrin, or partial corpectomy, can result in enterochromaffin-like hyperplasia, in a dose-dependent manner, and may lead to gastric carcinoid formation.[25–27, 29] Female rats appear to have a greater propensity to develop carcinoids than male rats, suggesting that a gender-related event may contribute to carcinoid formation in rats.[26] enterochromaffin-like cell hyperplasia that results from omeprazole treatment in rats can be reversed upon cessation of therapy and is significantly reduced by the simultaneous administration of the gastrin receptor-antagonist proglumide.[30, 31]

While the gastrin hypothesis is well supported by studies in rats, analogous findings have not been demonstrated in other species. Mice treated for 18 months with omeprazole had no gastric carcinoids in a study in which carcinoids developed in 63 out of 360 rats that received the identical dosage regimen (i.e. 40–400 μmol/kg) for 2 years.[26] Moreover, a spontaneous increase in enterochromaffin-like cell density was observed in aged rats in this study but not in mice.[26] Further support for a specific predisposition toward gastric carcinoid formation in rats comes from the

Table 1. Effects of long-term acid inhibition on rat enterochromaffin-like cells

Ref.	*n*	Treatment/dose	Duration	Result
25	40 female control 75 female experimental	partial corpectomy	124 weeks	Plasma gastrin levels elevated 10-fold All those with elevated gastrin also had marked hyperplasia of enterochromaffin-like cells 26 out of 75 had enterochromaffin-like cell carcinoids
26	240 control, 120 experimental/dose level	omeprazole 40, 125, and 400 μmol/kg/day	2 years	Sustained hypergastrinaemia; development of enterochromaffin-like cell carcinoids in 63 out of 360 treated rats Control animals did not develop enterochromaffin-like cell carcinoids
27	50 female control, 100 female experimental	ranitidine 2 g/kg/day or placebo	2 years	Three-fold increase in plasma gastrin levels throughout study Pronounced hyperplasia associated with ranitidine Enterochromaffin-like cell carcinoids in 18 of 100 treated rats
28	10 per group	lansoprazole 135, 200 μmol/kg/day or omeprazole 400 μmol/kg/day	10 weeks	All 3 treatments increased plasma gastrin levels 11-fold after 2 h Density of enterochromaffin-like cells increased by 2–5-fold
29	10 per dose level	exogenous gastrin (Leu15)-gastrin-17 1.2 and 2.4 nmol/kg/h	28 days	Approximate 50% increase in enterochromaffin-like cell density at the higher dose

finding that long-term administration of omeprazole in species with lower gastric enterochromaffin-like cell densities, including dogs, guinea pigs, and hamsters, as well as humans, has not resulted in the formation of enterochromaffin-like cell carcinoids.[32–34]

Enterochromaffin-like cell hyperplasia, hypergastrinaemia, and gastric carcinoid formation in humans

The formation of carcinoids in some rats treated with acid-suppressive therapy led to concern that a similar situation could arise in humans who were treated on a long-term basis with these agents. In fact, humans can exhibit enterochromaffin-like cell hyperplasia in response to low gastric acid conditions; however, enterochromaffin-like cell carcinoid formation is very rare. Differences between the rat and human stomach may explain this. First, as with other species previously mentioned, humans have a much lower density of enterochromaffin-like cells than do rats; rat enterochromaffin-like cells comprise approximately 65% of the entire gastric mucosal endocrine cell population, whereas human enterochromaffin-like cells comprise only 35%.[35, 36] In addition, rats demonstrate a relatively greater increase in serum gastrin levels in response to inhibition of gastric acid secretion than do humans.[32]

In humans, gastric enterochromaffin-like cell carcinoids most often arise in a background of type A, or autoimmune, gastric body-predominant, chronic atrophic gastritis (with or without pernicious anaemia) where there is marked, long-standing hypergastrinaemia (> 500 pg/mL).[9, 37–40] Enterochromaffin-like cell carcinoids have also been reported in patients with multiple endocrine neoplasia-1 and Zollinger–Ellison syndrome.[15, 40] Few patients with Zollinger–Ellison syndrome who lack the multiple endocrine neoplasia-1 gene develop enterochromaffin-like carcinoids, suggesting that a complex process including a predisposing genetic condition is required for carcinoid formation.[15] Another type of gastric enterochromaffin-like cell carcinoid, the so-called sporadic carcinoid, presents without any background of gastropathy and usually occurs with normal or, at most, mildly elevated serum gastrin levels (< 250 pg/mL).[37, 40]

Gastric carcinoids that occur in a background of hypergastrinaemia have a particularly benign behaviour.[40, 41] They are slow-growing and rarely malignant; distant metastases are infrequent.[41, 42] Many of these carcinoids can be treated with local endoscopic excision, or with antrectomy which leads to a reduction in serum gastrin and frequently to remission.[11, 43] In contrast, sporadic gastric enterochromaffin-like carcinoids arising in non-hypergastrinaemic patients are commonly malignant, with more aggressive behaviour.[40, 42]

Thus it appears that severe, long-standing hypergastrinaemia coupled with other factors such as the genetic abnormality of multiple endocrine neoplasia-1, or the severe type A autoimmune chronic atrophic gastritis can produce gastric enterochromaffin-like cell carcinoids in humans. Hypergastrinaemia alone, however, has not been documented to induce carcinoid formation in humans. This observation is consistent with findings in clinical trials of long-term proton pump inhibitor use, which are reviewed in the next section.

Proton pump inhibitor therapy, hypergastrinaemia, and gastric enterochromaffin-like cell carcinoids in humans

Gastrin levels associated with pernicious anaemia are generally much higher than those seen with proton pump inhibitor therapy. In a study of 131 patients with pernicious anaemia, the mean serum gastrin level was 1197 pmol/litre (range: 10–7500 pmol/litre; normal limit < 55 pmol/litre).[10] In Zollinger–Ellison syndrome, about 60% of patients have serum gastrin levels greater than 500 pg/mL (normal limit < 100 pg/mL).[44] In contrast, long-term use of proton pump inhibitor therapy generally results in a two- to fourfold increase in serum gastrin levels.[32] Patients receiving long-term treatment with omeprazole, lansoprazole, pantoprazole, or H_2-RA therapy generally have serum gastrin values less than 250 pg/mL, and only rarely exhibit levels greater than 500 pg/mL.[45–49]

The increase in serum gastrin levels seen during proton pump inhibitor therapy is associated with considerable inter- and intrasubject variation. This variation was observed in a study of 31 patients with reflux oesophagitis resistant to H_2-RAs who had received omeprazole 20 mg to 40 mg daily for at least 1 year (mean, 2 years).[50] There was an eightfold variation in serum gastrin levels among patients treated with omeprazole 20 mg, and an intra-individual variation of up to sixfold. Most patients had at least a twofold variation, regardless of whether their initial gastrin level was greatly elevated or near normal.[50]

The rise in serum gastrin levels during proton pump inhibitor therapy has been associated with gastric enterochromaffin-like cell hyperplasia or redistribu-

tion, but not with neoplastic changes.[39, 49] The results of studies in which these parameters were assessed are summarized in Table 2. The studies with periods of evaluation up to 4–5 years are summarized below.

Changes in gastric enterochromaffin-like cell growth were qualitatively assessed in 36 peptic ulcer disease patients who had received omeprazole 40 mg daily for 4 years.[4] Increases in different stages of hyperplasia were observed, and the percentage of patients with normal enterochromaffin-like cell pattern decreased from 77% at baseline to 50% at 4 years. In a study of 91 patients with reflux oesophagitis who were treated with omeprazole 40 mg q.d.s. for healing followed by maintenance with omeprazole 20 or 40 mg q.d.s. for up to 4 years, enterochromaffin-like cell hyperplasia

Table 2. Effects of long-term acid inhibition on human enterochromaffin-like cell

Ref.	*n*	Diagnosis	Drug/dose	Duration of drug therapy	Findings
4	221	Peptic ulcer disease	omeprazole/40 mg daily	Up to 4 years	Increase in enterochromaffin-like cell hyperplasia No neoplastic changes
46	42	Reflux oesophagitis or duodenal ulcer disease	lansoprazole 30 mg to 60 mg initially; up to 120 mg	30 months	11 patients developed enterochromaffin-like cell hyperplasia No neoplastic lesions
47	88	Peptic ulcer disease	pantoprazole 40–80 mg to heal, pantoprazole 40 mg daily	6 months to 3 years	Increase in enterochromaffin-like cell density No neoplastic changes
48	122	Reflux oesophagitis or peptic ulcer disease	omeprazole 40 mg to heal, omeprazole 20 mg daily	Mean 13 months	Increase in enterochromaffin-like cell hyperplasia of 11–19% No neoplastic changes
49	91	Reflux oesophagitis	omeprazole 40 mg to heal, omeprazole 20 mg or 40 mg	Up to 5 years	Enterochromaffin-like cell hyperplasia increased 17.5% No neoplastic changes
51	98	Reflux oesophagitis	omeprazole 40 mg to heal, omeprazole 20 mg daily; ranitidine 300 mg b.d. to heal, ranitidine 150 mg b.d.	12 months	Diffuse hyperplasia of enterochromaffin-like cells in four omeprazole patients and one ranitidine patient No neoplastic changes
52	119	Reflux oesophagitis	omeprazole 20 mg to heal, omeprazole 20 mg daily or omeprazole 20 mg 3 days/wk or ranitidine 150 mg b.d.	12 months	Slight increase in enterochromaffin-like cell hyperplasia in omeprazole and ranitidine group No neoplastic changes
53	448	Peptic ulcer disease or reflux oesophagitis	omeprazole 40 mg to heal, omeprazole 20 mg daily	Up to 4 years	28% developed enterochromaffin-like cell hyperplasia No neoplastic changes
54	74	Peptic ulcer disease	omeprazole 20–80 mg	Up to 5 years	Increase in enterochromaffin-like cell hyperplasia No neoplastic changes
55	392	Reflux oesophagitis	omeprazole 20–40 mg to heal, omeprazole 10 mg or 20 mg or ranitidine 150 mg b.d.	12 months	Increase in enterochromaffin-like cell hyperplasia of 6% in both ranitidine and omeprazole groups No neoplastic changes
56	105	Reflux oesophagitis	omeprazole 40 mg to heal; omeprazole 20 mg or 40 mg	3–8 years (mean 5 years)	Increase in enterochromaffin-like cell hyperplasia Decrease in percentage of patients with normal enterochromaffin-like cell growth No neoplastic changes

increased from 2.5% at baseline to 20% at 4 years; neoplastic changes did not occur.[49]

Enterochromaffin-like cell changes were also studied in 448 peptic ulcer patients who were treated with omeprazole for up to 4 years.[53] In the 202 patients who had received omeprazole for at least 330 days, the prevalence of hyperplasia increased slightly, from 3% at baseline to approximately 10% at final biopsy. A study of 74 patients resistant to ranitidine therapy and treated with omeprazole 20–80 mg daily for up to 5 years demonstrated an increase in enterochromaffin-like cell volume density from 0.36% of the total mucosa at baseline to 0.74% at 5 years.[54] There was a decrease in the percentage of patients with a normal endocrine cell growth pattern from 64% at baseline to 33% at 5 years, and an increase in the percentage of patients with various stages of enterochromaffin-like cell hyperplasia.

The influence of *H. pylori* infection on enterochromaffin-like cells in patients receiving long-term proton pump inhibitor therapy has also been explored. In an open-label study, 109 Dutch patients with reflux oesophagitis were treated with omeprazole 20 or 40 mg o.d. for an average of 5 years.[56] In this study, no dysplasia of enterochromaffin-like cells was observed; the incidence of enterochromaffin-like cell hyperplasia was 9% at both the baseline and final visits for *H. pylori*-negative patients but increased from 15% at baseline to 31% at the final visit in *H. pylori*-positive patients. In a study of 42 patients with either reflux oesophagitis or peptic ulcer disease who were resistant to H_2-RAs and who were treated with lansoprazole for 5 years, increases in both enterochromaffin-like cell density and linear/micronodular hyperplasia were seen in 11 patients.[46]

Hyperplasia has been shown to be concentrated among *H. pylori*-positive patients, particularly those showing atrophic changes and severe inflammation of the gastric mucosa.[45, 53, 56] The inflammation- and atrophy-dependent clustering of endocrine cells can lead to histological patterns which are diagnosed as linear and micronodular 'hyperplasia';[38, 45] this may indicate either an actual increase in mucosal enterochromaffin-like cells (i.e. true hyperplasia) or a redistribution of enterochromaffin-like cells due to clustering which mimics hyperplasia (i.e. pseudohyperplasia).[38, 39, 45, 54]

In summary, the modest elevations in gastrin seen with long-term proton pump inhibitor treatment may result in gastric enterochromaffin-like cell hyperplasia or redistribution with clustering, primarily in patients with *H. pylori* infection. However, long-term proton pump inhibitor therapy alone has not been documented to induce enterochromaffin-like cell neoplasms.

ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA

H. pylori *gastritis*

Chronic gastritis can be attributed to infection with *H. pylori* in nearly all cases.[57, 58] However, the clinical consequences of this infection are variable. Many patients with *H. pylori* gastritis remain asymptomatic, while 10–15% develop peptic ulcer during their lifetime.[59, 60] Another, much smaller sub-group (approximately 1% of all infected individuals world-wide), will develop gastric cancer.[61] On the basis of epidemiologic studies linking *H. pylori* with gastric adenocarcinoma, the International Agency for Research on Cancer, a division of the World Health Organization, has classified *H. pylori* as a Group I (definite) carcinogen.[62] Concern has been raised regarding the possibility that proton pump inhibitor therapy may hasten the development of atrophic gastritis and its progression to intestinal metaplasia and carcinoma in *H. pylori*-positive subjects.[45, 49, 53, 54, 56]

Classifying gastritis

There are many classification schemes for gastritis. The Sydney–Houston system for the histological assessment of chronic gastritis, agreed upon by specialists in the field, allows careful description of morphologic details and more appropriate correlation with clinical patterns.[63] The main clinico-pathologic forms resulting from recent studies based on this or similar systems are: (i) diffuse antral-predominant active gastritis associated with duodenitis and duodenal ulcer; (ii) gastritis not associated with either ulcers or with clinically significant symptoms; (iii) multifocal atrophic gastritis, which is associated with gastric ulcer and, when severe and confluent, with gastric adenocarcinoma; and (iv) diffuse chronic atrophic gastritis of the corpus (type A) associated with pernicious anaemia and gastric carcinoids.[40, 58, 63, 64, 68, 73]

Diffuse antral predominant gastritis is characterized by diffuse inflammation of the antrum. Focal intestinal metaplasia may be present in the antrum in 10–30% of these patients, but is less frequent and far less extensive than that seen in association with proximal gastric

ulcer.[58, 64] Inflammation of the body (oxyntic gland mucosa) is mild or even absent in diffuse antral-predominant gastritis, despite histologically demonstrable *H. pylori* infection; intestinal metaplasia of the body is almost never seen.[58, 65–68] Since extensive intestinal metaplasia is the most widely accepted precursor of gastric adenocarcinoma, it is not surprising that patients with antral predominant gastritis have a low cancer risk.[69] Because the oxyntic glands remain intact, and because there is no deterioration of these glands with time, acid secretion can remain normal in these patients throughout the ageing process.[61, 63, 70, 71]

Gastritis with no ulcers and no clinically significant symptoms may belong to Correa's 'sub-clinical gastritis', or Rubin's 'non-ulcer pangastritis' sub-group.[64, 65] This sub-group has an inactive or moderately active slowly progressive pangastritis with little intestinal metaplasia; the risk of gastric adenocarcinoma in these individuals should be low. Non-ulcer sub-clinical pangastritis is seen in more than 90% of the usually asymptomatic individuals infected with *H. pylori* who do not have an ulcer.[58, 65, 69] This kind of clinically and histologically indistinct gastritis should be separated from multifocal atrophic gastritis or at least the more severe cancer-associated form of multifocal atrophic gastritis also referred to as progressive intestinalized pangastritis showing confluent, extensive areas of atrophy and intestinal metaplasia.[64, 65]

In most cases, gastritis that is associated with achlorhydria, hypergastrinaemia, pernicious anaemia, and gastric carcinoids shows diffuse, total atrophy of the oxyntic glands with hyperplasia of foveolae and immature glandular necks (pseudo-pyloric metaplasia), with or without true pyloric metaplasia or intestinal metaplasia. Type A or 'autoimmune' chronic atrophic gastritis typically spares the antrum, where gastrin cell hyperplasia is regularly found.[9, 10, 38, 40]

There has been much discussion regarding what should be considered atrophic gastritis;[63–65, 69] this has lead to the use of different criteria in different studies.[54, 56, 58, 72] It seems appropriate to separate true gland atrophy, meaning loss of gland bodies, from the displacement of retained glands by an extensive, compact inflammatory infiltrate, better diagnosed as 'interstitial gastritis'.[58] However, this is not always easy in small biopsies, especially when histological sections are not well-orientated and when dealing with focal gland loss. In the case of interstitial gastritis with or without minute foci of atrophy, *H. pylori* eradication is usually followed by restoration of mucosal glandular integrity.

Clinically relevant atrophic gastritis, significantly associated with adenocarcinoma (i.e. severe, confluent, multifocal atrophic gastritis) or with pernicious anaemia and gastric carcinoids (type A chronic atrophic gastritis), should be separated from clinically irrelevant foci of non-confluent gland atrophy, which may be found in patients with all forms of *H. pylori* gastritis, including sub-clinical and ulcer-associated gastritis.[53–56, 58] Extensive sampling of both antral and corpus mucosa is required to distinguish these two forms of atrophic gastritis from chronic gastritis with focal or even multifocal non-confluent atrophy.[73] So far, there is no convincing evidence that intestinal metaplasia regresses following eradication of *H. pylori*; however, restoration of oxyntic glands seems possible in cases of focal or multifocal (but not diffuse) non-intestinalized atrophy.

Progression of atrophic gastritis and intestinal metaplasia

Proton pump inhibitor, H_2-RA, or antacid treatment of *H. pylori*-positive patients definitely increases inflammation in the corpus while decreasing inflammation in the antrum.[52, 74, 75] In addition, the question of whether long-term proton pump inhibitor treatment in *H. pylori*-infected patients accelerates the development of atrophic gastritis has been raised.[45, 53, 54, 56] Since extensive gastric atrophy in the presence of intestinal metaplasia has been closely tied to an increased risk of gastric adenocarcinoma, the clinical significance of this question is considerable. Unfortunately, results in the available literature on this subject are contradictory, primarily because studies have not been designed at the outset to observe the effects of long-term acid suppression on atrophic gastritis and most have not assessed *H. pylori* status. Further complicating the analysis of the present data are the variable definitions of 'atrophic gastritis' from study to study, as well as the fact that data from these studies are largely based on biopsy sampling which is probably insufficient to discriminate between clinically important 'true' chronic atrophic gastritis (body-restricted type A chronic gastritis or severe, progressive, intestinalized multifocal atrophic gastritis) and chronic gastritis which is slowly progressive with limited non-confluent intestinalization (and has a low risk of progression to carcinoma).

Results of some studies have shown that long-term proton pump inhibitor therapy has no effect on the

progression of atrophic gastritis. In one study, 57 patients with reflux oesophagitis were maintained on omeprazole either daily, on alternate days, or every 3–5 days for an average of 4 years.[76] No atrophic gastritis was observed with any of the omeprazole regimens. However, *H. pylori* status was not reported in this study. In another study, patients with duodenal ulcer were randomly assigned to receive 1 year of double-blind maintenance therapy with either omeprazole 20 mg daily or placebo.[77] There were no significant histological changes in the biopsy specimens taken at 6 and 12 months compared with baseline, and no increase in atrophic gastritis was detected in either treatment group.

Conversely, an increase in atrophic gastritis has been reported in a number of studies. The incidence of atrophic gastritis was shown to increase in an open-label study of 74 patients with ranitidine-resistant oesophageal, gastric, or duodenal ulcerations who were treated with omeprazole 20–80 mg daily for up to 5 years.[54] In this study, 56 patients had baseline gastritis assessments; atrophic corpus gastritis increased from 1.8% at baseline to 20.8% ($n = 24$ at 5 years); *H. pylori* infection was not determined in this trial. In another study, 448 patients with duodenal, gastric, or anastomotic ulcer or reflux oesophagitis received omeprazole 40 mg daily until healing, followed by a maintenance dose of 20 mg daily for up to 4 years.[53] The prevalence of atrophic corpus gastritis increased steadily over the 4-year period from 1% to 19%. However, patients were not tested for the presence of *H. pylori* infection at baseline and the sample size had fallen from 268 patients at baseline to 57 patients at final assessment. In an open-label study of 91 patients with reflux oesophagitis who were refractory to H_2-RAs, an increased incidence of atrophic gastritis was reported.[49] The subjects received omeprazole 40 mg daily until healed, followed by a maintenance dose of 20 or 40 mg daily for up to 64 months. At baseline, 1% demonstrated corpus atrophic gastritis vs. 25% at final biopsy. The initial *H. pylori* status of the patients was not determined.

A study by Kuipers *et al.* suggested that maintenance therapy with a proton pump inhibitor could result in an acceleration of the development of corpus atrophic gastritis in *H. pylori*-positive patients.[56] This study was a comparison of two cohorts. One cohort comprised 109 Dutch patients with severe reflux oesophagitis who were refractory to H_2-RA therapy. These patients received 20–40 mg omeprazole o.d. to maintain oesophageal healing; the average age of this group was 62 years. The second 'control' cohort comprised 137 Swedish patients (although biopsy material was available for only 72) treated with fundoplication for reflux oesophagitis; the mean age of the surgical group was 53 years. Patients in both cohorts underwent endoscopy and biopsy before treatment, at 1 year, and every 2 years thereafter; they were followed for approximately 5 years.

The investigators determined that, among patients treated with omeprazole, none of whom had signs of atrophy at baseline, corpus atrophic gastritis had developed by the final visit in 18 out of 59 *H. pylori*-positive patients and in two of 46 *H. pylori*-negative patients. Among those treated with fundoplication, atrophic gastritis of the corpus had not developed by the time of final biopsy in any of the 31 *H. pylori*-positive or 41 *H. pylori*-negative patients. Based on these findings, the authors concluded that maintenance therapy with a proton pump inhibitor could result in an acceleration of the development of atrophic gastritis if the patients were *H. pylori*-positive. They suggested that *H. pylori* diagnostic testing and treatment be considered in patients who require chronic acid suppressive therapy.

Several features of this study limit the conclusions that can be drawn from it. First, this was not a randomized, controlled trial designed to assess the effects of proton pump inhibitor therapy and *H. pylori* status on atrophic gastritis. Rather, the investigators reported on two cohorts that were undergoing different treatments for reflux oesophagitis. In addition, the two cohorts in the study were from different countries, which may have had varying inherent risks of gastric atrophy. Furthermore, the mean age of the omeprazole-treated group was 9 years older than that of the surgical group, and atrophic gastritis increases with advancing age.[53, 58, 63, 72, 78] Development of intestinal metaplasia was not observed in the omeprazole-treated patients in this study. Therefore, it may have been, as Rubin suggests, that what was observed in this study was not progressive intestinalized pangastritis (i.e. severe, confluent intestinalized multifocal atrophic gastritis), which carries an increased risk of gastric adenocarcinoma, but the more slowly progressive gastritis, non-ulcer pangastritis or sub-clinical pangastritis, which may develop multiple foci of oxyntic gland atrophy but relatively limited intestinal metaplasia, and which poses little or no cancer risk.[58, 64, 65, 73]

One randomized, controlled study evaluated the effect of long-term proton pump inhibitor treatment and the progression of corpus mucosa gastritis.[79] In this study, patients with chronic reflux disease who were considered candidates for surgery were treated with omeprazole 20–40 mg daily until healed and then received either omeprazole 20 or 40 mg daily, or anti-reflux surgery. They were then followed for a median of 3 years; two corpus biopsies were obtained at yearly intervals. At final biopsy, eight out of 33 *H. pylori*-positive omeprazole-treated patients and six out of 38 *H. pylori*-positive surgical patients who had no atrophy at baseline and had follow-up biopsies available, developed atrophy ($P = 0.39$). None of the 105 *H. pylori*-negative patients treated with omeprazole and four out of 76 *H. pylori*-negative surgical patients without atrophy at baseline had atrophy at their final biopsy. Only two out of 38 *H. pylori*-positive omeprazole and two out of 44 *H. pylori*-positive surgical patients without baseline intestinal metaplasia developed this finding at the final biopsy. The authors concluded that acid suppressive therapy with omeprazole for 3 years does not facilitate the development of gastric atrophy or intestinal metaplasia in *H. pylori*-positive patients with GERD.

The issue of acceleration of atrophic gastritis in *H. pylori*-positive patients treated long-term with a proton pump inhibitor was addressed by a Food and Drug Administration Gastrointestinal Advisory Committee meeting.[80] This panel reviewed the available data on the incidence and prevalence of atrophic gastritis and intestinal metaplasia in *H. pylori*-infected patients who had been treated with omeprazole or lansoprazole for prolonged periods. The Committee concluded that there was no documentation of an increase in atrophic gastritis in patients who had received prolonged proton pump inhibitor therapy and they did not recommend treatment for *H. pylori* prior to long-term proton pump inhibitor therapy. However, they suggested the need for additional studies designed to specifically investigate this issue.

In summary, an increase in the rate of development of body 'atrophic gastritis' has been reported with proton pump inhibitor therapy as well as with ranitidine and vagotomy.[46, 49, 53, 55, 81] However, there is no documentation that long-term pharmacologic or surgical acid suppression produces the multifocal atrophic gastritis with extensive intestinal metaplasia that is associated with an increased risk of gastric adenocarcinoma.[65, 79, 80] Acid suppression increases inflammatory cell infiltration of the gastric corpus in those infected with *H. pylori* and thus may cause separation of gastric glands and apparent atrophy. In addition, gastritis activity is enhanced, and with prolonged (> 1 year) treatment, focal gland atrophy is likely to appear in a minority of cases. Further studies with longer follow-up, careful *H. pylori* evaluation, and more critical assessment of gland atrophy and intestinal metaplasia are warranted before definitive conclusions can be made. At present, however, testing for *H. pylori* in patients who require long-term acid suppression is not recommended, as an increased risk of serious effects beyond those known to occur independently with *H. pylori* infection has not been demonstrated.

Hypergastrinaemia and gastric adenocarcinoma

Circumstantial evidence would suggest that it is possible for long-term therapy with proton pump inhibitors to lead to the development of gastric adenocarcinoma. This evidence comes from two sources. First, patients with pernicious anaemia have been reported to develop gastric adenocarcinoma at higher rates than the general population;[82] hypergastrinaemia has been implicated as a possible cause. Secondly, decreased gastric acidity has been shown to increase rates of bacterial overgrowth, leading to an increase in N-nitrosamines;[83] these compounds have been linked to gastric adenocarcinoma in humans.[83] The issue of bacterial overgrowth and N-nitrosamine formation will be addressed later in this review.

An increased risk of gastric adenocarcinoma in patients with pernicious anaemia has not been demonstrated conclusively. A Danish study involving 114 patients with achlorhydria with or without pernicious anaemia revealed an incidence of gastric cancer four to six times that expected, based on Danish Cancer Registry records.[84] Another Danish study showed that the prevalence of pernicious anaemia in 877 patients with gastric cancer was 2.2% compared with an expected prevalence in the general population of 0.3%.[85] Conversely, in a study performed at the Mayo Clinic, 152 patients with pernicious anaemia were followed for more than 1550 patient years with no increased risk in the development of gastric adenocarcinoma.[86]

If there is an increased risk of gastric adenocarcinoma in patients with pernicious anaemia, it is not clear whether this risk is mediated by gastrin, or some other manifestation of pernicious anaemia itself, or of the associated type A chronic atrophic gastritis. Experience in

other conditions does not suggest a relationship between hypergastrinaemia and gastric adenocarcinoma. An increased risk of gastric adenocarcinoma may result from antrectomy (low gastrin state), but not vagotomy (high gastrin state).[87, 88] In patients with Zollinger–Ellison syndrome, the risk of gastric adenocarcinomas is not increased, despite long-standing hypergastrinaemia.[32] The association between non-endocrine gastric cancer and hypergastrinaemia is therefore not clear. The use of proton pump inhibitors or of other antisecretory agents has not been associated with an increase in cancer risk.[32]

Hypergastrinaemia and colon cancer

Hypergastrinaemia has also been implicated as a risk factor for colon cancer. A number of lines of evidence may support this association. First, persistent hyperproliferation of the normal colonic mucosa may be a precursor of colon carcinogenesis, and gastrin may be trophic for the normal colonic mucosa. In addition, colon cancer cells can exhibit a growth response to gastrin. Furthermore, some interventions that cause hypergastrinaemia can promote chemically induced colon cancers in animal models. In some, but not all, case-control studies, it has been reported that hypergastrinaemia occurs more commonly in patients with colon cancer.[4, 89–96]

Animal studies. Animal studies provide contradictory data with regard to the effects of gastrin on the normal colon. Pentagastrin increased synthesis of DNA, RNA, and protein from colonic mucosal scrapings of fasted animals in one study, and reversed an antrectomy-induced reduction in these parameters in another.[97, 98] In addition, the ability of proglumide, a receptor antagonist, to block the pentagastrin effect suggests an interaction with receptors of gastrin or cholecystokinin.[99] Conversely, gastrin or pentagastrin infusion had no effect on colonic growth in fed rats.[100, 101] Similarly, hypergastrinaemia induced by long-term omeprazole treatment did not have a trophic effect on the colons of fed rats.[101]

The growth of certain mouse colon cancer cells, which are known to be responsive to gastrin, was increased in mice made hypergastrinaemic by the administration of exogenous gastrin.[102] In another study, the growth of mouse cancer cells was not significantly increased by the administration of omeprazole, while in yet another study, omeprazole therapy, given at doses that raised gastrin concentrations sixfold, reduced the proliferative rate of experimentally induced colon cancers.[103, 104]

Carcinogen-induced colon cancer models also suggest that the effect of hypergastrinaemia on promotion of tumour growth in the colon is greatly dependent on how the hypergastrinaemia is induced. Hypergastrinaemia induced by antral exclusion promoted chemically induced colon cancers.[105] However, the exogenous administration of gastrin did not increase tumour formation in nitrosamine models of colon cancer.[106] Omeprazole or ranitidine-induced hypergastrinaemia had no effect on colonic mucosal growth or on methylazomethanol-induced carcinogenesis.[107] Indeed, the administration of omeprazole at doses producing a nine- to tenfold increase in serum gastrin concentrations was found to significantly decrease the number of colon cancers induced by azoxymethane.[108] Furthermore, a report of elevated serum gastrin concentrations in rats with colon cancer induced by the carcinogen azoxymethane suggests the possibility that an increased gastrin concentration may be the result of the tumour.[109]

Thus, studies in animal models demonstrate that exogenous gastrin may increase the proliferative rate of normal colonic mucosa of fasted, but not of fed animals, and that the underlying cause of hypergastrinaemia may be a critical factor in promoting carcinogenesis. There is no evidence in pre-clinical studies, however, that antisecretory therapy is a risk factor for the induction of colon cancer.

Human studies. In humans, relatively few studies have examined the effect of hypergastrinaemia on colonic proliferation, and those that have, report conflicting information. One study of a group of 23 patients with Zollinger–Ellison syndrome showed an increase in the colonic proliferation rate; however, there was no expansion of the proliferative compartment and no mucosal hyperplasia in these patients.[110] In addition, there was no correlation between proliferation rate and serum gastrin concentrations or the duration of hypergastrinaemia. Other studies have shown that patients with Zollinger–Ellison syndrome had normal colonic proliferation rates, but exhibited an expansion of the proliferative compartment.[111]

Patients with hypergastrinaemia resulting from pernicious anaemia, truncal vagotomy, gastric surgery, chronic atrophic gastritis, or Zollinger–Ellison syndrome[4, 110, 112–115] have not been shown to be at increased risk for colon cancer compared with control populations. One study did, however, report a higher incidence of colon cancer in the first 5 years after the

diagnosis of pernicious anaemia, raising the possibility that hypergastrinaemia may increase the growth rate of established colon cancers.[112] No studies designed to examine the effect of hypergastrinaemia resulting from the long-term use of proton pump inhibitors have been conducted.

Case-control studies examining the presence of hypergastrinaemia in patients with colonic adenomas and carcinomas have produced conflicting findings.[4, 89–96] The initial report of increased serum gastrin levels in patients with colonic adenomas and carcinomas has been confirmed by some subsequent studies and refuted by others.[4, 89–93] In studies showing hypergastrinaemia in patients with colonic adenomas and carcinomas, mean serum gastrin concentrations were elevated largely due to a small number of patients with very marked hypergastrinaemia.[89, 91, 93] Unfortunately, the conditions underlying the hypergastrinaemia were not identified. As previously discussed, identification of the underlying condition may be important in assessing any association between hypergastrinaemia and cancer risk. In these studies, elevated gastrin concentrations frequently returned to normal following tumour resection, suggesting that hypergastrinaemia may be the result, rather than the cause of the colon cancer.

In addition, infection with *H. pylori* may confound determinations of cancer risk in these patients. Penman *et al*. found that serum gastrin concentrations decreased after colon cancer resection only in patients who had undergone eradication of pre-existing *H. pylori* infection.[96] The authors concluded that when *H. pylori* and other confounding factors, such as age and pernicious anaemia, are taken into account, serum gastrin concentrations are not found to increase in colorectal cancer or to decrease after curative resection.

Thus, while there is conflicting evidence in humans regarding the relationship between elevated gastrin levels and colonic carcinogenesis, available information does not indicate that the prolonged use of proton pump inhibitor therapy is a risk factor for the induction or growth promotion of colon cancers.

GROWTH OF GASTRIC BACTERIA AND N-NITROSAMINE FORMATION

Bacterial colonization

The acidic gastric environment is considered an important barrier to colonization of the stomach and small intestine by ingested bacteria. Low-acid states, whether caused by gastric gland atrophy or drug-induced hypochlorhydria, may compromise this barrier, increasing bacterial colonization and making the host more susceptible to enteric infections.[18, 19]

Significant increases in bacterial concentrations have been detected in the gastric contents of healthy subjects treated with omeprazole 20–30 mg daily for 2 weeks.[116, 117] In one study, the increase in bacterial concentrations was readily reversed when antisecretory therapy was discontinued.[116] In another study involving 23 patients with peptic ulcer disease, a 6-week course of cimetidine, 1 g daily, resulted in significant increases in intragastric aerobic and nitrate-reducing bacteria.[118] Increased growth of bacteria in the duodenum was found in 56% of patients in a placebo-controlled trial in which patients received omeprazole 20–40 mg or placebo daily for 4–8 weeks.[119] In this study, bacterial counts were similar in patients receiving either dose of omeprazole, but no colonization was observed in the placebo group.

Bacterial colonization appears to depend on the degree of reduction in gastric acid.[120, 121] This was demonstrated in a prospective study of 47 patients with peptic ulcer disease; the percentage of patients with increased gastric and duodenal bacterial counts was significantly greater among those who had received 4 weeks of 20 mg omeprazole therapy daily than in those who had taken 800 mg cimetidine daily (53% vs. 17%).[122]

N-nitrosamine formation

As bacterial counts increase in the stomach, so do nitrate–reductase-positive strains that are able to convert nitrates to nitrites, which can then be converted to nitrosamines.[123] This results in an increase in the concentration of luminal nitrites and possibly N-nitrosamines. The latter compounds have been shown to be carcinogenic in experimental animal models and may contribute to the risk of gastric adenocarcinoma in man.[124] However, the production of N-nitroso compounds can also be catalysed by acid, raising questions about the relative contributions of acid and bacterial catalysis.[123]

Early studies in patients with various gastroduodenal conditions have demonstrated that cimetidine significantly increased N-nitrosamine concentrations in gastric juice.[118, 125] A study in 14 healthy subjects who received omeprazole 20 mg daily for 2 weeks revealed increased

nitrite and N-nitrosamine concentrations in the gastric juice.[117] However, in another study of 10 healthy subjects, while median bacterial concentrations were significantly increased in subjects receiving omeprazole, the concentration of N-nitrosamines after 2 weeks was not significantly different in the omeprazole-treated vs. the placebo-treated subjects.[116] A more recent prospective study of 47 patients with peptic ulcer disease showed that the nitrate, nitrite, and nitrosamine concentrations in gastric juice did not increase after 4 weeks of treatment with either omeprazole 20 mg daily or cimetidine 800 mg daily, despite increased bacterial counts.[122] Data regarding the relationship between proton pump inhibitor-induced hypochlorhydria and N-nitrosamine compounds therefore remain uncertain, and the association with cancer risk continues to be speculative. In addition, the influence of *H. pylori* infection on the carcinogenic effect of nitrosamines in the hypochlorhydric stomach requires further study.

ENTERIC INFECTIONS

Hypochlorhydria and achlorhydria have been documented to increase the risk of enteric infections (e.g. cholera, species of *Shigella* and *Salmonella*).[126–131] Thus, patients may be at increased risk of development of these infections during periods of marked acid suppression due to proton pump inhibitor therapy. Only occasional cases of enteric infections in patients taking proton pump inhibitors have been reported. A large case-control study suggested a small increase in enteric infection in patients taking proton pump inhibitors for 2 months (relative risk = 1.6; 95% CI: 1.0–2.4); patients receiving omeprazole for 1 year, however, did not have an increased risk (1.1; 95% CI: 0.7–1.9).[132]

PROTON PUMP INHIBITOR THERAPY AND ABSORPTION

The potential for proton pump inhibitor therapy to produce malabsorption has been evaluated in several studies. Issues related to fat, mineral, and vitamin B_{12} absorption have been raised.

Fat absorption

The relationship between bacterial overgrowth and fat absorption has been investigated in healthy, elderly subjects who had confirmed bacterial overgrowth related to either atrophic gastritis or a 10-day course of omeprazole 40 mg daily.[133] All subjects were monitored while receiving a standard diet that provided 100 mg of fat daily. The study showed no evidence of fat malabsorption; 72-h faecal fat levels were within normal limits in all subjects in both study groups.

Mineral bioavailability

Intragastric pH is generally believed to affect mineral bioavailability, with gastric acid increasing the release of minerals from organic food matrices and maintaining metal ions in solution. The effects of inhibition of gastric acid secretion on mineral bioavailability have been investigated in a placebo-controlled trial of 13 healthy subjects, eight of whom received omeprazole 40 mg daily for 7 days prior to the study.[134] While omeprazole treatment resulted in an increased intragastric pH, there were no significant changes in the intestinal absorption of calcium, phosphorus, magnesium, or zinc as measured using a whole gut lavage technique. The investigators concluded that deficiencies due to malabsorption of these minerals were unlikely to occur during the clinical use of omeprazole. In addition, serum iron and ferritin levels have been monitored during 6–48 months of continuous omeprazole therapy in 34 patients with peptic ulcer disease.[135] Serum iron and ferritin concentrations were decreased in two and three patients, respectively, but in each case, the decreases were attributed to medical conditions rather than to omeprazole therapy.

Vitamin B_{12} absorption

There has been concern that antisecretory therapy may result in vitamin B_{12} malabsorption. Ingested vitamin B_{12} is protein-bound, and its release from food is facilitated by the presence of gastric acid. The vitamin can then bind to R proteins in the stomach before passing into the duodenum. Pancreatic enzymes in the duodenum split this complex to form a complex of vitamin B_{12} with intrinsic factor, which then undergoes absorption in the small intestine.[136]

The possible effects of antisecretory therapy on vitamin B_{12} absorption have been studied in several short- and long-term trials involving both healthy subjects and patients with acid-related disorders. In a study that investigated the effect of cimetidine on the uptake of protein-bound cyanocobalamin, the excretion of radio-

active cyanocobalamin decreased from 2.3% to 0.2% after a morning dose of cimetidine 300 mg.[137] Macuard *et al.* reported that treatment of healthy subjects with omeprazole 20 mg or 40 mg daily for 2 weeks resulted in decreased vitamin B_{12} absorption as measured by a modified Schilling test.[138] Cyanocobalamin absorption was reduced from 3.2% to 0.9% in those who received 20 mg omeprazole, and from 3.4% to 0.4% in those who received 40 mg omeprazole. The investigators therefore recommended the monitoring of cyanocobalamin levels in patients who receive long-term omeprazole therapy.

In another study of 34 patients receiving long-term omeprazole therapy, all of them maintained serum vitamin B_{12} concentrations that were constant and within normal limits during the initial 3 years of treatment.[137, 139] With longer duration of therapy, however, a small but significant downward trend in serum vitamin B_{12} levels was evident.[135] In another study, investigators reported no decrease in serum vitamin B_{12} levels in 25 patients who were receiving omeprazole 20–60 mg daily for a median of 56 months.[140]

The effect of long-term antisecretory therapy on vitamin B_{12} levels was also studied in 131 patients with Zollinger–Ellison syndrome who were taking either omeprazole ($n = 111$; mean follow-up 4.5 years, range 0.2–12) or an H_2-RA ($n = 20$; mean follow-up 10 years, range 3–17).[141] Eight patients developed subnormal serum vitamin B_{12} levels during the period of follow-up, and vitamin B_{12} levels correlated with the degree of acid suppression. The investigators suggested monitoring serum vitamin B_{12} levels in patients with Zollinger–Ellison syndrome who were being maintained on proton pump inhibitors.

In summary, acid suppression may decrease protein-bound vitamin B_{12} absorption. Over years, some patients may show a decrease in vitamin B_{12} levels, and profound acid suppression over many years (as in Zollinger–Ellison syndrome) may lead to subnormal vitamin B_{12} levels on occasion. Whether any patients develop clinical vitamin B_{12} deficiency is uncertain, but greater experience with marked acid suppression for a decade or more will provide greater information on this topic.

CONCLUSIONS

Lifelong hypergastrinaemia, whether induced by a proton pump inhibitors or other acid suppressive therapy, may lead to gastric enterochromaffin-like cell carcinoid formation in rats. These findings, however, have not been documented in humans. While long-term treatment with proton pump inhibitors may elevate gastrin moderately and may even lead to enterochromaffin-like cell hyperplasia, no neoplastic changes directly attributable to proton pump inhibitor treatment have been reported after more than a decade of use. When gastric enterochromaffin-like cell carcinoid formation occurs in humans, it does so under circumstances in which there is both marked hypergastrinaemia and an additional factor, such as the coexistent genetic abnormality in patients with multiple endocrine neoplasia-1. Furthermore, elevation of serum gastrin induced by proton pump inhibitors has not been documented to increase the risk for adenocarcinomas of the stomach or colon.

Long-term studies designed to assess whether proton pump inhibitor therapy accelerates the development of atrophic gastritis in *H. pylori*-positive patients are not available. A cohort study suggested this possibility, while a randomized, controlled study showed no influence of proton pump inhibitor treatment. An increased risk of intestinal metaplasia or gastric carcinoma in *H. pylori*-positive patients has not been documented. At present, we do not recommend routine *H. pylori* diagnostic testing and treatment in patients on long-term proton pump inhibitor therapy. However, further studies to answer this question are required before definitive conclusions on this issue can be drawn.

Suppression of gastric acid does appear to increase gastric and/or duodenal bacterial growth and has the potential to increase the risk of enteric infections. However, the role of proton pump inhibitor therapy in the production of N-nitrosamine compounds remains unclear, and no association of antisecretory therapy with gastric cancer has been identified.

Fat and mineral bioavailability appears to be unaltered by proton pump inhibitor therapy. However, absorption of protein-bound vitamin B_{12} levels can be impaired by proton pump inhibitor therapy, and profound acid suppression for many years might lead to vitamin B_{12} levels dropping below normal in some patients.

In conclusion, current evidence suggests that prolonged acid suppression due to proton pump inhibitor use rarely, if ever, produces adverse events. Nevertheless, continued follow-up of patients taking proton pump inhibitors for extended periods will provide greater experience regarding the potential gastrointestinal adverse effects of long-term acid suppression.

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