

***Helicobacter pylori*, Proton Pump Inhibitors and Gastroesophageal Reflux Disease**

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Proton pump inhibitors have become of pivotal importance for the treatment of GERD. The purpose of this paper is to review the interaction between Helicobacter pylori and PPIs in the treatment of GERD. H. pylori exaggerates the acid suppressive effects of PPIs. During treatment with these drugs, H. pylori-positive subjects thus have a higher intragastric pH than H. pylori-negative subjects. The mechanism for this phenomenon remains to be elucidated. We hypothesize that it is related to H. pylori-induced corpus gastritis, which impairs parietal cell function. The available evidence suggests that this phenomenon has no clinical relevance for the treatment of GERD. The 24-hr esophageal pH during PPI treatment does not depend on the H. pylori status, nor does the medication dose needed for maintenance therapy or the number of clinical relapses during such therapy depend on the H. pylori status. PPIs, on the other hand, also affect H. pylori. During treatment with these drugs, the pattern of bacterial colonization and associated gastritis shifts proximally. The increased gastritis of the body mucosa is associated with a more rapid development of atrophic gastritis, a condition characterized by a loss of gastric glands and associated with an increased cancer risk. For these reasons, one has to consider H. pylori eradication in infected GERD patients in need of PPI maintenance therapy.

INTRODUCTION

Proton pump inhibitors (PPIs)^b are very effective for the initial and maintenance treatment of gastroesophageal reflux disease. Recent evidence suggests that *Helicobacter pylori* infection may interact with this treatment, both with respect to efficacy as well as with respect to long term side effects. The purpose of this paper is to review the effect of *H. pylori* on PPIs, as well as the effect of PPIs

on *H. pylori* based on the present literature data.

EFFECTS OF *H. pylori* ON PROTON PUMP INHIBITORS

PPIs, H. pylori and gastric pH

In 1995, Verdú and colleagues from Switzerland showed that intragastric pH during omeprazole therapy depends on the

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^bAbbreviations: PPI, proton pump inhibitor.

H. pylori status of an individual [1]. They measured the 24-hr intragastric pH in 14 *H. pylori*-negative and 18 *H. pylori*-positive healthy volunteers both during treatment with 20 mg omeprazole and during treatment with placebo. During treatment with placebo, median 24-hr pH values did not differ between *H. pylori*-infected and -uninfected subjects (1.5 vs. 1.4). However, during treatment with omeprazole, median 24-hr pH values were higher in *H. pylori*-positive than in *H. pylori*-negative subjects (5.5 vs. 4.0). These results were subsequently confirmed in a number of different studies. The same group showed that *H. pylori* eradication resulted in a decrease of 24 hour intragastric pH during omeprazole therapy, whereas the pH during the untreated state did not change [2]. Another paper showed that the same effect also occurred in duodenal ulcer patients [3]. These measurements were performed six to eight weeks after *H. pylori* eradication. The efficacy of omeprazole in lowering intragastric pH remains permanently decreased after *H. pylori* eradication, as shown by repeated measurements one year after bacterial eradication [4]. The effect of *H. pylori* on drug-induced intragastric acid reduction is not restricted to omeprazole or proton pump inhibitors alone. In another recent study, 18 *H. pylori*-infected duodenal ulcer patients were treated with 300 mg ranitidine daily before and six to eight weeks after bacterial eradication. Before eradication, the intragastric pH during ranitidine treatment was higher than after eradication [5]. In summary, *H. pylori* infection exaggerates the effect of acid suppressing drugs on intragastric pH.

The mechanism underlying this phenomenon remains to be elucidated. Possible explanations include the hypothesis that it is due to bacterial production of ammonia buffering gastric acid, or to a direct effect of bacterial products, such as the vacuolating cytotoxin A and the acid inhibitory protein of *H. pylori*, on parietal

cell function. In our opinion, the most likely explanation is that it is related to the effect of acid suppression on the distribution of *H. pylori* gastritis. *H. pylori* prefers an acidophilic environment. The distribution of bacterial colonization and that of associated gastritis depend on acid secretion. Profound acid suppressive therapy changes the usual antral predominant gastritis pattern into a corpus predominant pattern [6]. Inflammation of the corpus mucosa impairs acid production. As such, the increase of corpus gastritis will exaggerate the acid-lowering effect of acid suppressive therapy.

The magnitude of this phenomenon increases with more profound acid suppression. In case of treatment with 300 mg ranitidine daily, *H. pylori* eradication led to a decrease of the percentage of time per 24 hours during which the intragastric pH was greater than 4.0 from 39 to 27 percent [5]. In contrast, this percentage changed from 73 to 38 during treatment with 20 mg omeprazole daily [4]. This difference between mild and profound acid suppression can be explained by the fact that more pronounced acid suppression leads to more severe corpus gastritis in *H. pylori*-infected subjects. An additional explanation could be that the effect of *H. pylori* on proton excretion is independent of acid suppression, but small, and, therefore, only measurable at higher pH due to its log scale.

PPIs, H. pylori, and esophageal pH

Does the effect of *H. pylori* infection on the efficacy of acid suppressive drugs have any clinical relevance for the management of GERD? One could hypothesize that *H. pylori*-infected GERD patients require a lower dose of acid suppression than uninfected GERD patients. A meta-analysis of three clinical trials focused on disease relapse in 340 GERD patients during 12 months treatment with either ranitidine 300 mg, omeprazole 10

mg, or omeprazole 20 mg daily. In each treatment group, the relapse rate was somewhat higher among *H. pylori*-negative patients, but these differences were not significant (Carlsson, R., Astra Pharmaceuticals, Sweden, personal communication). We followed 137 GERD patients for 58 ± 15 months during treatment with omeprazole [7]. Each patient was studied by endoscopy before the start of treatment and at annual follow-up. Omeprazole was started at a dose of 20 mg daily. This dose was increased during follow-up in case of endoscopic or symptomatic relapse with steps of 20 mg. If the required daily dose surpassed 40 mg, the dosing scheme was adjusted to twice daily. Although the *H. pylori*-negative patients at baseline had more symptoms of severe GERD, in particular Barrett's esophagus, there was no difference at all for the dose of omeprazole needed in both groups. The median daily dose in both groups at the end of follow-up was 40 mg ($p = .35$) [7]. Another very large international study also focused on the efficacy of maintenance treatment with omeprazole for GERD. This study also did not observe any association between *H. pylori* status and the relapse rate or required omeprazole dose during 1496 patient years follow-up [8]. Finally, in another study, we measured 24-hr esophageal acid exposure in 30 *H. pylori*-negative and 28 *H. pylori*-positive patients with a Barrett's esophagus at baseline and during treatment with either 150 mg ranitidine twice daily or 40 mg omeprazole twice daily [9]. It appeared that *H. pylori* infection did not influence esophageal acid reflux in these patients, nor did it influence the effect of low or profound acid suppression on reflux. Although none of these studies used patients as their own controls by studying them before and after *H. pylori* eradication, they strongly suggest that *H. pylori* status does not affect the efficacy of acid suppressive therapy in the management of GERD. This means that the dose

of acid suppression does not have to be titrated upon *H. pylori* status.

EFFECTS OF PROTON PUMP INHIBITORS ON *H. pylori*

PPIs and accelerated development of atrophic gastritis

H. pylori exaggerates the effect of proton pump inhibitors on intragastric pH. On the other hand, proton pump inhibitors also have a significant effect on *H. pylori*. *H. pylori* is an acidophil with an optimum pH, which, in the presence of urea, presumably lies around 5.0. Drugs that affect acid production thus affect the intragastric distribution of *H. pylori* and thereby affect *H. pylori*-associated gastritis. Acid suppression induces an increased inflammation of the gastric body mucosa in *H. pylori*-infected subjects [6, 10]. This effect occurs at the start of therapy and persists throughout the duration of therapy [11]. The magnitude of the effect depends on the level of acid suppression. It has been observed to a limited extent during H_2 -blocker therapy [12] and is more pronounced during intake of PPIs [6, 10]. It is associated with increased epithelial cell proliferation [13].

We questioned whether the increased severity of corpus gastritis induced by acid suppressive therapy in *H. pylori*-infected patients has any clinical relevance, in particular with respect to the development of atrophic gastritis [6, 14]. The latter condition, characterized by a loss of gastric glands [15], can develop as a result of chronic active gastritis and is associated with an increased gastric cancer risk. Development of atrophic gastritis is usually a slow process. It takes approximately 20 years before one out of every three subjects with chronic gastritis has developed signs of atrophic gastritis; the annual incidence of atrophic gastritis among *H. pylori*-infected subjects varied between 1

and 3 percent in a number of cohort studies [16-18]. These studies all focused on "healthy" volunteers, i.e., subjects with a presumable normal acid production. In contrast, various cohort studies focusing on patients with a condition that impaired acid production, reported a 3.8 to 8.7 percent annual incidence of atrophic gastritis [14]. These studies focused on patients with gastric ulcer disease [19], duodenal ulcer patients after vagotomy [20, 21], or on patients treated with omeprazole for different indications [22, 23]. Although none of these studies specified results according to *H. pylori* status, the results were rather concordant and contrasted with the 1 to 3 percent annual incidence of atrophic gastritis in cohorts of subjects without specific disease or treatment. Nevertheless, there were no direct comparisons of different populations within one study available. It was also unknown whether development of atrophic gastritis in subjects with reduced acid output was also associated with *H. pylori*, or with other unidentified factors. For these reasons, we prospectively compared two populations of GERD patients [11]. One group of 105 Dutch patients was treated with omeprazole maintenance therapy and another group of 72 Swedish patients was treated with a fundoplication procedure, without any further acid suppression. Both groups were followed for five years with endoscopy and gastric biopsy sampling at regular intervals. All these specimens were evaluated by one pathologist. Development of atrophic gastritis was rare in the *H. pylori* negative patients of both treatment groups. Among the *H. pylori*-positive patients treated with a fundoplication, the upper limit of the 95 percent confidence interval for incidence of atrophic gastritis was 2.2 percent, which is fully in accordance with the findings of previous studies in patients with unsuppressed acid production [17]. In the *H. pylori*-positive group treated with omeprazole however, the annual incidence of atrophic gastritis was 6.1 percent (95 percent CI 3.8-8.8) [11]. After five years of treatment, atrophy

was thus observed in approximately one out of every three *H. pylori*-infected patients treated with omeprazole, which is in sharp contrast with the usual 20 years needed for such a prevalence of atrophy to develop. Development of argyrophil cell hyperplasia was also strongly associated with *H. pylori* and atrophic gastritis [11]. Both atrophic gastritis and argyrophil cell hyperplasia almost remained absent in the group of non-infected patients. Based on these findings and with the above-mentioned background, we concluded that profound acid suppressive therapy accelerates the natural course of *H. pylori* gastritis [11].

PPIs, H. pylori and the definition of atrophic gastritis

The main arguments against our publication [11] in particular focused on the definition of gastric atrophy, and the difference in mean age and country of origin of the two cohorts in our study. We defined atrophic gastritis according to the internationally accepted up-dated Sydney classification as a condition with a loss of gastric glands [15]. It has been suggested that this condition does not exist without concomitant intestinal metaplasia. However, glands that are lost are not necessarily replaced with intestinal tissue. Atrophy can occur without intestinal metaplasia, a condition that, for instance, is commonly observed in patients with pernicious anemia [15]. The opposite, intestinal metaplasia without atrophy, may also occur. Metaplastic cells can sometimes be observed in the upper, foveolar layer of the gastric mucosa, without any signs of a loss of glands in the deeper glandular layer. In addition, antral specimens obtained close to the pylorus may normally contain intestinal cells as the border between gastric and intestinal tissue is not necessarily located exactly in or distal of the pylorus. In general, atrophic gastritis leads to replacement with fibrous tissue, which, therefore, is a marker for previous gland loss. Additionally, it has been argued that a

loss of gastric glands does not reflect an increased gastric cancer risk, as such an increased cancer risk is confined to patients with type III intestinal metaplasia. This statement was based on a single cohort study from Slovenia [24], in which patients in whom intestinal metaplasia had been diagnosed in the past, were re-studied after long-term follow-up. The authors suggested that the development of cancer was largely confined to patients with a previous diagnosis of type III metaplasia, which resembles colonic mucosa with sulphomucins containing columnar cells in distorted crypts. However, re-analysis of the archival paraffin-embedded gastric specimens did not reveal any metaplasia at all in a considerable proportion of patients [24]. When one takes this into account, the outcome of the study does not reveal any relation between intestinal metaplasia subtypes and gastric cancer. This outcome is in agreement with another follow-up study [25] and also explains why the large majority of patients with gastric cancer do not have any signs of type III intestinal metaplasia. In summary, our definition of atrophy is in accordance with the current international criteria and represents a condition with an increased cancer risk as it sets the stage for development of further (pre-) neoplastic changes. There is no convincing evidence that such an increased risk is confined to the small subcategory of patients with type III intestinal metaplasia.

PPIs and H. pylori: interaction dependent upon age and country of origin?

We studied the incidence of atrophic gastritis in GERD patients treated either with omeprazole or with a fundoplication and concluded that profound acid suppression in *H. pylori*-infected patients increases the rate of development of atrophic gastritis [1]. However, this was not a randomized study, but a comparison of two independent cohorts. The fundoplication patients were treated in Sweden and the omeprazole patients in the Netherlands. In addition, the mean age of the Swedes was

nine years lower (53 vs. 62 years). Could our results have been induced by these differences in age and country of origin? It is well known that atrophy is more common among elderly (i.e., the prevalence of atrophy). This has led to the assumption that the rate of new development of atrophy is also higher among elderly, i.e. the incidence of atrophy. There is, however, no literature evidence to support such conclusion. Those studies that focused on the incidence of atrophy did not find a significant relation with age [16-18]. Our study focused on the incidence of atrophy and found it more than three-fold increased in *H. pylori*-positive subjects treated with profound acid suppression. It is plausible to explain this by the effect of acid suppression on *H. pylori* and gastritis, whereas it cannot be explained by the limited age difference between our two cohorts. Could it be that Dutch individuals have a higher genetic risk for atrophic gastritis and gastric cancer? It has been suggested at an FDA meeting on this issue in November 1996 that the gastric cancer incidence is higher in the Netherlands compared to Sweden. The reverse, however, is true. The gastric cancer incidence is actually somewhat higher both for men and women in Sweden [26]. There is, therefore, no evidence that geographical differences can explain our findings. In addition, the available cohort studies on the development of atrophic gastritis consistently describe a low incidence of atrophy among subjects with a normal acid production irrespective of their age. In contrast, those studies performed during profound acid suppression consistently describe a high incidence of atrophy irrespective of the mean age.

Accelerated atrophy development refuted by other data?

As pointed out in the previous paragraphs, our findings were fully corroborated by other data. Recently, however, two new studies have been presented that were said to refute our findings and those of all

previous studies. Lundell and colleagues from Sweden presented a randomized study of GERD patients treated with either a fundoplication or omeprazole [27]. No significant differences were observed between both groups with respect to the incidence of atrophic gastritis during a follow-up of three years. However, the incidence of atrophic gastritis among the omeprazole treated patients was high (4.2 percent annually). The incidence among the fundoplication patients was lower (2.8 percent), but higher than the 1 to 2 percent observed in previous Western studies in populations with normal acid production [14, 17]. The use of omeprazole pre- and postoperatively, as well as inclusion of patients with a previous vagotomy may have been confounding factors leading to this study result.

Unpublished data presented at an FDA meeting on this issue (November 1996), described a one percent incidence of atrophic gastritis among 99 *H. pylori*-infected GERD patients treated with lansoprazole for 15 months. However, the limited size and follow-up of this study led to large confidence limit for the reported incidence. More importantly, the investigators performed a protocol by which histological specimens were stepwise scored by different pathologists in case of abnormalities. This policy is likely to have induced a selection against the diagnosis of atrophy. In another lansoprazole study, the incidence of atrophy in *H. pylori*-infected subjects was consistent with the observations during omeprazole therapy [28].

In summary, these data support the hypothesis that reduction of acid output by pharmaceutical agents (or vagotomy) induces an increase of corpus gastritis in *H. pylori*-positive patients, which leads to further reduction of acid output by accelerated development of corpus atrophy.

CONCLUSION

Proton pump inhibitors have become of pivotal importance for the treatment of GERD. Recent data have made us aware that the effect and long-term outcome of PPI treatment may depend on the *H. pylori* status of the patient. During treatment with PPIs, *H. pylori*-positive subjects have a higher intragastric pH than *H. pylori*-negative subjects. The mechanism for this phenomenon remains to be elucidated. It is likely to be related to *H. pylori*-induced corpus gastritis, which impairs parietal cell function. The available evidence, however, suggests that this phenomenon has no clinical relevance for the treatment of GERD. The 24-hr esophageal pH during PPI treatment does not depend on the *H. pylori* status, nor does the medication dose needed for maintenance therapy or the number of clinical relapses during such therapy. Therefore, a prescription of PPIs for GERD does not have to take the *H. pylori* status into account. PPIs, on the other hand, also affect *H. pylori*. During treatment with these drugs, the pattern of bacterial colonization and associated gastritis shifts proximally. The increased gastritis of the body mucosa is associated with a more rapid development of atrophic gastritis, a condition characterized by a loss of gastric glands and associated with an increased cancer risk. For these reasons, one has to consider *H. pylori* eradication in infected GERD patients in need of PPI maintenance therapy.

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