PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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Original Articles

Long term omeprazole therapy for reflux esophagitis: follow-up in serum gastrin levels, EC cell hyperplasia and neoplasia

Pankaj Singh, Anant Indaram, Ronald Greenberg, Vernu Visvalingam and Simmy Bank

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Abstract

AIM To evaluate the long-term safety of omeprazole in patients of gastroesophageal reflux disease resistant to treatment with H2 receptor antagonist.

METHODS We prospectively followed 33 patients on omeprazole therapy for severe erosive esophagitis for 5-8 years, with periodic gastrin levels, *H. pylori* infection, gastric biopsies for incidence of ECL cell hyperplasia, carcinoids, gastric atrophy and neoplasia. A total 185 patient follow-up years and 137 gastric biopsies were done.

RESULTS Among the 33 patients, 36% reached their peak gastrin levels in an average of 8 months to one year, then drifted Down slowly over 1-2 year period to just above their baseline level, 24% of the patients had a peak gastrin level above 400ng·L^{-1} and one patient had a peak level above 1000ng·L^{-1}. One patient had a mild ECL cell hyperplasia which was self limiting and did not show any dysplastic changes. Eighteen percent of patients were positive for *H. pylori* infection. The gastric biopsies did not show gastric atrophy, intestinal metaplasia or neoplastic changes.

CONCLUSION In a series of 33 patients followed for 5-8 years on omeprazole therapy for severe reflux esophagitis, we did not observe any evidence of significant ECL cell hyperplasia, gastric atrophy, intestinal metaplasia, dysplasia or neoplastic changes.

Division of Gastroenterology, Albert Einstein Colege of Medicine, Long Island Jewish Medical Center, New Hyde Park, New York
Dr. Pankaj Singh is a second year gastroenterology fellow in Albert Einstein College of Medicine, Long Island Jewish Hospital. He did his residency in medicine from King George Medical College, India and then from State University of New York, NY. He is currently studying the effect of alcohol on apoptosis in pancreatic cells.
Correspondence to: Dr. Pankaj Singh, Department of Gastroenterology, Long Island Jewish Medical Center, 270-05 76th Ave, New Hyde Park, NY 11040, USA
Tel. (718)-347-2393
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INTRODUCTION

Acid suppression therapy plays a pivotal role in the medical management of reflux esophagitis. The most recently developed acid suppressive agents, the proton pump inhibitors (PPIs) directly inhibit hydrogen ion exchange and inhibit acid secretion in response to all stimulatory agents[1-5]. The PPIs are benzimidazole derivatives, which are converted to active metabolites within the acidic confines of the secretary canaliculi of the gastric parietal cells. They promote oxidation of sulphydryl components of the proton pump, leading to irreversible inactivation of the enzyme[1]. Recovery of acid secretion requires synthesis of new proton pumps. There is now a definite evidence that PPIs are more effective than H-2 receptor antagonists in treating esophagitis, severe refractory reflux disease and non-healing esophageal ulcers, providing faster healing and symptomatic relief[6-9]. Esophagitis is however a chronic problem, as early relapses have been observed after cessation of H-2 blockers and omeprazole[7,8].Therefore, maintenance treatment is often required in treating the reflux esophagitis. H-2 blocker has failed, as an effective maintenance agent in preventing the relapses[9,10]. There is enough evidence to support the role of PPIs as an effective agent in maintaining healing of erosive esophagitis[8,11-16]. However, questions regarding the long-term safety of the proton pump inhibitors have been raised. The resulting hypo -/ achlorhydria and resulting hypergastrinemia have been implicated in the development of enterochromaffin cell hyperplasia and gastric carcinoids[17-20]. The epidemiological evidence of increased incidence of gastric fundal carcinoma has further raised concerns regarding, gastric atrophy and the long-term use of PPIs in acid related peptic diseases, especially in patients with *H. pylori*

infection[21].

Considering the efficacy of PPIs and possibility of their role in development of EC cell hyperplasia, it was logical to study their safety profile as long term maintenance therapeutic agents in esophagitis.

MATERIALS AND METHODS

At Gastroenterology Department, Long Island Jewish Medical Center 33 patients with severe reflux esophagitis of grade 2 and above, whose symptoms were not responding to H2 blockers and motility agents were enrolled in the study. Patients were started on omeprazole (PPI) either daily or on an alternate day regimen and were followed periodically for symptom relief, endoscopic healing, plasma gastrin level, *H. pylori* infection and gastric biopsies for occurrence of neoplasia. Esophagitis was graded endoscopically using the following scale: grade 0, normal appearing; grade 1, mucosal edema, hyperemia and/or friability; grade 2, one or more erosions/ ulcerations involving <10% of the distal five cm of the esophagus; grade 3, erosions/ulceration's involving 10% to 50% of the distal 5cm of the esophagus or an ulcer 3mm-5mm in diameter. In cases of Barrett's esophagus, the area 5cm proximal to the squamo-columnar junction was evaluated; grade 4, multiple erosions involving 50% of the distal 5cm of the esophagus or a single ulcer >5mm in diameter. Whenever clinically feasible, all endoscopies for a particular patient were performed by the same endoscopist. Complete healing of erosive reflux esophagitis was defined as the return of esophageal mucosal inflammation to grade 0 or grade 1.

Periodic plasma gastrin levels were measured after an 8 hours fast prior to endoscopy. Four gastric biopsy specimens of full thickness of the mucosa (two fundal, two antrum) were obtained at the screening visit and at the end of 8-12 weeks to assess healing. At intervals of 6 to 12 months periodic upper endoscop ies were performed to monitor for carcinoids, gastric atrophy and gastric neopla sia. Bouin's fixed, paraffin-embedded, 3 microns hematoxylin and eosin-stained sections of each biopsy specimen were evaluated and graded for active and chronic inflammation. The presence of intestinal metaplasia, atrophy, dysplasia and neoplasia was evaluated. The enterochromaffin like cells of the oxyntic gastric mucosa were assessed using Grimelius stain sections and Solcia's scale of gastric endocrine growth. Two independent pathologists who were blinded to each other's assessments of the biopsy specimens reviewed gastric biopsies.

H. pylori infection was assessed by identifying the organisms and chronic inflammation in the biopsy specimens, serum *H. pylori* IgG antibodies or by CLO test. Out of the 33 patients, 22(66%) were male and 11(34%) were female (Table 1). The mean age of the patients was 76 years with a range of 34 to 86 years (Figure 1). Twenty-six (78%) patients were on omeprazole daily 10mg-20mg or 10mg-20mg twice daily. Seven (21%) patients were on alternate day 10mg-20mg omeprazole therapy for severe reflux esophagitis (Table 1).The average period of follow-up was for 6 years, with a range of 3 to 8 years, a total of 185 patient years of follow up (Figure 2). The total number of biopsies done was 137, averaging 4, with a range of 2 to 13.

Table 1 Type of treatment and sex distribution (*n*=33)

Group	Number
Alternate day omeprazole therapy	7
Daily omeprazole therapy	26
Male patients	22
Female patients	11

RESULTS

Twelve (36%) of the patients reached their peak plasma gastrin levels in one year, and then drifted to a level above their baseline levels in 1 to 2 years. Three (9%) reached their peak in 2 years, 5 (15%) in 3 years, 3 (9%) in 4 years, 5 (15%) in 5 years, 2 (6%) in 7 years, 1 (3%) in 8 years (Figure 3). Eleven (33%) of patients had plasma gastrin levels below 100pmol·L^{-1}, 24% of patients above 400pmol·L^{-1} and in one patient it was above 1000 pmol·L^{-1}. Gastric biopsies showed normal mucosa on initial biopsy in 26 and gastritis in 7. On repeat biopsy 7 changed from normal to gastritis and 4 from gastritis to normal. Nineteen were normal at all times. Of the 6 *H*p+ (*H. pylori* positive) patients, 1 was normal on all occasions, 2 showed gastritis, 2 varied from normal to gastritis and 1 from gastritis to normal. Of the 27 *H*p negative patients, 18 were normal at all times, 1 showed gastritis, 5 varied from normal to mild gastritis and 3 from gastritis to normal. No atrophy was diagnosed at any time over the 5-8 years, on any of the 137 biopsy specimens.

EC cell hyperplasia was seen in one of the biopsies. Neither fundal gastric neoplasia, nor carcinoids were seen (Table 2).

Table 2 Results of gastric biopsies in-patients on long term omeprazole therapy for reflux esophagitis

Pathology	Number
Normal throughout the treatment	19
Normal at onset, later gastritis changes	7
Initial fundal gastritis	7
Initial gastritis changed to normal	4
ECL cell hyperplasia	1
Barretts esophagus	4
H. pylori infection +ve	6
H. pylori infection -ve	27

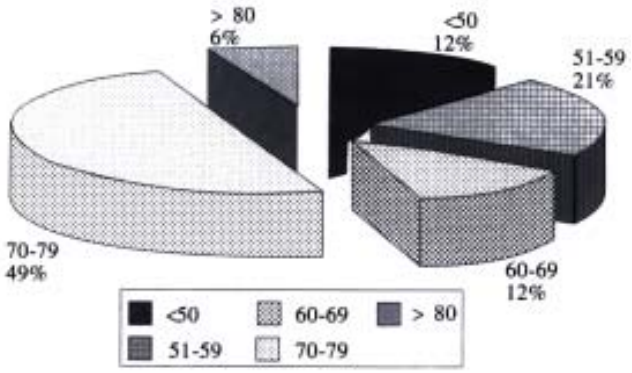

Figure 1 Age distribution of patients on long-term omeprazole treatment for reflux esophagitis.

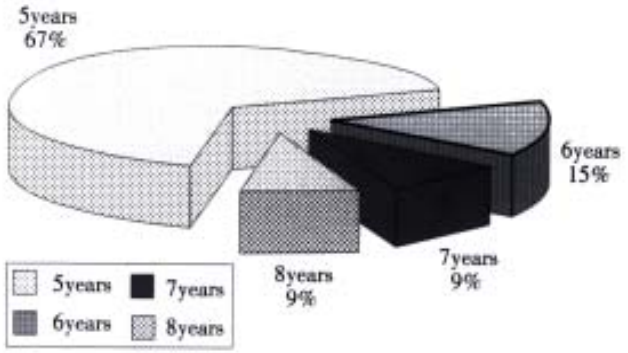

Figure 2 Distribution of follow-up years of patients on long-term omeprazole treatment for reflux esophagitis.

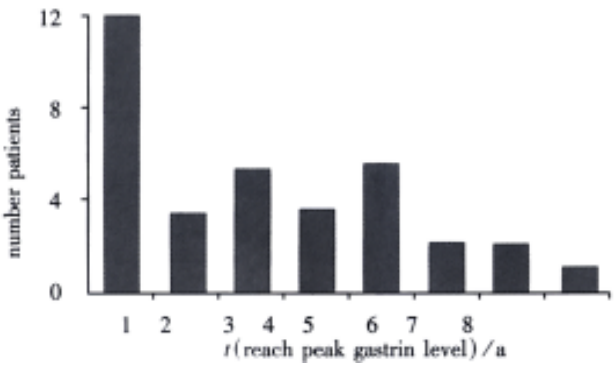

Figure 3 Time to reach maximium plasma gastrin levels in patients treated with long term omeprazole.

DISCUSSION

Esophagitis is a chronic problem with frequent early relapses[7,8]. Therefore, it is not only important to treat the reflux disease but also to prevent relapses. It is now known that PPIs are more effective than H-2 receptor antagonist in treating refractory reflux disease[1,6,12-16] providing faster healing and symptomatic and in preventing early relapses[9,10]. Concerns were raised regarding the safety of PPI as a long-term maintenance agent[17-19]. In our study, we found omeprazole to be a safe drug even when used over a long period. Hypochlorhydria, encountered with PPIs has strong association with hypergastrinemia[28]. Hypochlorhydria leads to fall in the secretion of somatostatin from antral D cells. Somatostatin is a major negative feedback mediator of gastrin release and its absence leads to persistent gastrin release[22-25]. Because PPI's are better inhibitors of gastric acid secretion than H-2 receptor antagonist is, they are associated with higher gastrin levels. Freston *et al* and other studies showed that plasma gastrin levels generally peak in the first four months of treatment with PPIs and stabilize without further increase thereafter[26,27]. In our studies, the gastrin level peaked on an average in initial 8-12 months of treatment. The early peak in other studies could have been because of development of gastric atrophy in some of their patients[26,27]. The same reason was postulated for the eventual decline in gastrin level. Although we also observed the decline in gastrin level after a period of 1-2 years, but we did not observe gastric atrophy in any of our patients. It is not yet clear why after some time the gastrin levels came down. The consequences of hypergastrinemia have aroused interest because gastrin has a trophic effect on gastrin cell, especially ECL cells[26,27]. Rat model studies, have revealed that sustained hypergastrinemia secondary to PPIs are associated with increased ECL cell hyperplasia and carcinoid tumor[26-28]. These changes regress on bringing back the gastrin level to previously normal levels. In our study, we did not observe the similar relation between gastrin and ECL cell hyperplasia and carcinoid. This is in concordance with other studies done on long term safety profile of PPIs[8,11-16,29]. However, it would be in appropriate to associate similar relations in humans, given that rats have a higher density of gastrin ECL cells and a greater gastric response to hypochlorhydria than humans[21,30]. This is further supported by the fact that, PPIs when used in other animals (e.g. dogs, guinea pigs, hamsters, mice), do not cause ECL cell carcinoids.

Borch *et al*[31] identified ECL cell carcinoids in approximately 4% of patients with pernicious anemia, thus raising the concern that this may be of relevance to use of PPIs. This seems unlikely as patients who developed carcinoid in his study had gastrin level 10-20 times normal level versus 2-4 folds during omeprazole treatment. The carcinoids were observed on an average after a period of 19 years of persistent severe hypergastrinemia[31]. The development of carcinoid has also been observed in patients with hypergastrinemia secondary to Zollinger Ellison syndrome. All of these cases had coexisting familial MEN-I α-syndrome[28]. This combined group of ZES and MEN-I α comprises 25% of all Zollinger Ellison syndromes and the fact that all the cases of carcinoid has been observed only in this subgroup suggests that familial factor also plays an important role in carcinoidogenesis[28].

It would appear from available information that severe and sustained hypergastrinemia is required to produce ECL cell hyperplasia. When coupled with other factors, such as genetic trait of MEN-1 syndrome, it may lead to carcinoid formation.

In conclusion, our results show that omeprazole is a safe drug, when used for a long-term maintenance treatment in healing reflux disease.

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