Turk J Gastroenterol 2002; 13 (3): 159-163

Does eradication of Helicobacter pylori infection reduce hypergastrinema during long term therapy with proton pump inhibitors?

Uzun süreli proton pompa inhibitörü kullanımında Helicobacter pylori eradikasyonu hipergastrinemiyi azaltır mı?

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Background/aims: *Proton pump inhibitors and Helicobacter pylori infection are the major cause of hypergastrinemia. In this study the effect of eradication therapy on blood gastrin levels in patients using long term proton pump inhibitors was evaluated.* ***Methods:*** *Twenty-seven Helicobacter pylori (positive) patients were included in the study, of whom 20 were given eradication treatment for seven days consisting of ranitidine bismuth citrate, clarithromycin and amoxicillin (eradication therapy group) and seven were given symptomatic therapy (symptomatic therapy group). Four patients who remanied Helicobacter pylori (positive) after eradication therapy were later added to the symptomatic therapy group. Lansoprazole 30 mg/day was then given to both the eradication therapy (n: 16) and the symptomatic therapy groups (n: 11) for the following three months. Fasting and non-fasting blood gastrin levels were measured initially then at one and four months after treatment.* ***Results:*** *Fasting gastrin levels were 49 % higher in the fourth month than in the first month (p<0.01) and 51 % higher than the initial level (p<0.01) in the symptomatic therapy group. There were no statistical differences between the initial, first month and fourth month non-fasting blood gastrin levels in the symptomatic therapy group (p>0.05). Fasting gastrin levels were 47 % higher in the fourth month than the first month (p<0.001) and 18 % lower than the initial level (p<0.05) in the eradication therapy group. Non-fasting gastrin levels were 4% higher in the fourth month than in the first month (p>0.05) and 34 % lower than the initial level (p< 0.05) in the eradication therapy group.* ***Conclusions:*** *It is suggested that patients receiving long term proton pump inhibitor treatment should be evaluated for Helicobacter pylori positivity and treatment of this infection would be an appropriate approach to avoid hypergastrinemia.*

Key words: Hypergastrinemia, Helicobacter pylori, Proton pump inhibitors

Amaç: *Proton pompa inhibitörleri ve Helicobacter pylori enfeksiyonu hipergastrineminin önemli sebeplerindendir. Bu çalışmada uzun süreli proton pompa inhibitörü kullanan hastalarda Helicobacter pylori eradikasyon tedavisinin açlık ve tokluk gastrin düzeyleri üzerine etkisini inceledik.* ***Yöntem:*** *Çalışmaya Helicobacter pylori pozitif 27 hasta alındı. Hastaların 20'sine ranitidin bizmut sitrat + klaritromisin + amoksisilin'den oluşan eradikasyon tedavisi, diğer 7 hastaya da semptomatik tedavi uygulandı. Bir ay sonra eradikasyon tedavi grubunda hala Helicobacter pylori (+) olan 4 hasta da semptomatik tedavi grubuna dahil edildi. Daha sonra eradikasyon tedavi grubu (n:16) ve semptomatik tedavi grubuna (n:11) gruplarına 3 ay süre ile 30 mg/gün lansaprazol verildi. Çalışmanın başangıcında, 1 inci ve 4 üncü ayların sonunda hastaların açlık ve tokluk gastrin düzeyleri ölçüldü.* ***Bulgular:*** *Semptomatik tedavi grubunda 4ncü ay açlık serum gastrin düzeyi 1nci aya göre % 49 (p<0,01), başlangıç değerine göre %51 (p<0,01) yüksek saptandı. Aynı grupta tokluk serum gastrin düzeylerinde başlangıç, 1nci ve 4 üncü ay ölçümleri arasında istatiksel olarak anlamlı farklılık saptanmadı (p>0,05). Eradikasyon tedavi grubunda ise açlık serum gastrin düzeyinde 1nci aya göre % 47 (p<0,001) artış, başlangıç değerine göre ise % 18 (p<0.05) azalma saptandı. Aynı grupta tokluk gastrin düzeylerinde 1nci aya göre % 4 (p>0,05) artış, başlangıç değerine göre de % 34 (p<0.05) azalma saptanmıştır.* ***Sonuç:*** *Hipergastrinemi riskini azaltmak için uzun süre proton pompa inhibitörleri kullanacak hastalarda Helicobacter pylori varlığının araştırılmasının ve saptanması halinde bu olgulara eradikasyon tedavisi vermenin uygun olduğu düşünüldü.*

Anahtar kelimeler: Hipergastrinemi, Helicobacter pylori, proton pompa inhibitörleri

INTRODUCTION

The relationship between Helicobacter pylori (H. pylori) infection, gastric acidity and plasma gastrin levels has attracted the attention of researchers in recent years and there is evidence of an increase in gastrin and gastric acid secretion due to H. pylori infection (1-5). Gastrin, which is secreted by the G cells in the gastric mucosa then secreted into both the blood circulation and stom-

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Manuscript received: 16.4.2002 **Accepted:** 6.8.2002

Table 1. Fasting and non-fasting serum gastrin levels in patient groups

	ST Group		ET Group	
Gastrin levels (ng/ml)	*Fasting*	*Non-fasting*	*Fasting*	*Non-fasting*
Beginning	54.90 ± 22,54	92.81±39.09	61.00±21.87	99.62±25.73
First month	55.81±22.00	92.50±34.76	33.93±12.59	62.93±18.04
(% Change)				
(0 – 1st months)	NS	NS	%44	%36
P	>0.05	>0.05	<0.001	<0.001
Fourth month	83.18±33.91	93.90±37.82	50.12±17.32	65.43±18.07
(% Change)				
(1st – 4th months)	%49	NS	%47	NS
P	<0.01	>0.05	<0.001	>0.05
(% Change)				
(0 – 4th months)	%51	NS	%18	%34
P	<0.01	>0.05	<0.05	<0.05

ST: Symptomatic treatment, ET: Eradication treatment, NS: non-significant

ach lumen, enhances HCl secretion from the gastric parietal cells (6-8). There are different opinions as to how H. pylori infection contributes to gastroduedonal lesions. Goodwin et al have suggested that H. pylori disrupts the local mucosal defense, which leads to gastro duodenal damage (9), while Levi et al noted that H. pylori infection increases gastric acid secretion, which in turn causes mucosal damage (10). In one study, however, it was reported that H. pylori infection blocks the normal inhibitory pathway through G cells (2).

Another cause of hypergastrinemia is the use of proton pump inhibitors (PPI), with significant increases in serum gastrin levels during treatment with PPIs having been reported (11-13). Treatment approaches which decrease the hypergastrinemic effects of the combination of these two risk factors would provide a positive contribution to the treatment of patients.

The aim of this study was to evaluate the effect of H. pylori eradication therapy on hypergastrinemia in patients receiving long term PPI therapy.

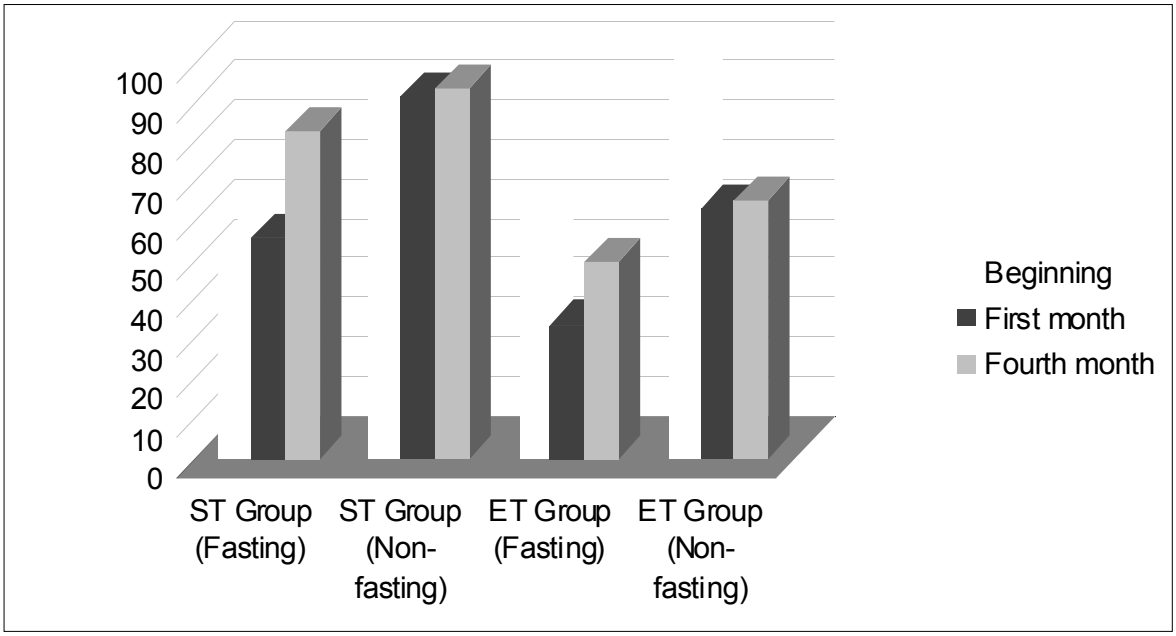
MATERIAL AND METHODS

Patients with endoscopically verified peptic ulcer disease and/or esophagitis, whose gastric antrum and corpus biopsies revealed H. pylori positivity in both histopathologic examination and rapid urease testing (CLO test) were included in this study between February 2000 and October 2000. Those with previous gastric surgery, cholecystectomy, gastric malignancy, chronic renal failure, and chronic alcoholism were excluded from the study. Patients who had taken NSAIDs, corticosteroids, bismuth preparations, PPIs or H2 receptor blockers within the four weeks prior to commencment of the study were also excluded. Twenty-seven patients (14 male, 13 female) between the ages of 21 and 56 years were included in the study.

Written consent was obtained from each patient and blood samples (10 ml venous blood) were collected in the morning after an overnight fast for fasting serum gastrin level testing. They were then given 300 ml of Biosorp Energy Plus (1.5 kcal/ml, with 16 % proteins, 35 % lipids, 49 % carbohydrates, Nutricia) and venous blood samples were obtained 45 minutes later for non-fasting gastrin levels. Serum samples from each patient were stored at – 80 ºC until assayed for gastrin. Serum gastrin determinations were made using 125I radioimmunoassay LB 2104 Berthold-Multi-Well Gama Counter that has similar activity for both G17 G34.

All patients underwent upper gastrointestinal endoscopy (UGE) and following topical anesthesia using 10% lidocaine and sedation using 2.5 mg-5 mg midazolam, UGE was performed using either Pentax EG 2930 or Fujinon EG 200 FP video endoscopes. During the procedure, two biopsy samples from the antrum and two biopsy samples from the corpus were obtained. One piece of the samples was placed into CLO test and the other piece was used for histopathologic examination. CLO test results were evaluated within 24 hours.

Patients were classified into two groups which were the H. pylori eradication treatment group



ST: Symptomatic treatment, ET: Eradication treatment

Figure 1. Fasting and non-fasting serum gastrin levels in patient groups

(ET group, n=20) and symptomatic treatment group (ST group, n=7). The ET group was prescribed a treatment regime consisting of ranitidine bismuth subcitrate 400 mg, b.i.d., clarithromycin 500 mg, b.i.d. and amoxycillin 1 gr b.i.d. for seven days. Antacids were prescribed for PRN use. The ST group was prescribed only antacids as symptomatic treatment during the same period.

One month after completion of the eradication treatment, patients in the ET group underwent endoscopic evaluation again, using the same methods and patients who remained H. pylori positive were allocated to the ST group (n=11). Gastrin levels of all patients were determined again at this stage and all patients were given lansoprazole 30 mg / day for three months. At the end of the three-month-period, fasting and non-fasting serum gastrin levels were determined again.

In statistical analysis, student's t-test, Mann-Whitney U test and Wilcoxon two-pair test were used to compare quantitative data. For the comparison of quantitative data, chi-square test was used and $p < 0.05$ was accepted as significant.

RESULTS

Twenty-seven patients (14 male, age 41.0 ± 9.63 years and 13 female, age 44.15 ±7.75 years) completed the study. There was no difference between the mean ages of the two groups ($p>0.05$). Fasting and non-fasting serum gastrin levels of both groups before treatment and at the end of the first and fourth month are shown in Table 1 and Figure 1.

In the ST group, both fasting and non-fasting gastrin levels at the end of the first month were not significantly different than those in the beginning ($p>0.05$). In this group, the fasting gastrin levels at the end of the fourth month were 49 % and 51 % higher than those at the beginning and the first month respectively, and the difference was statistically significant ($p<0.01$). There was no difference between the initial, first month's and fourth month's non-fasting gastrin levels in this group.

In the ET group, serum fasting and non-fasting gastrin levels decreased by 44 % and 36 % respectively at the end of the first month, and the differences were significant ($p<0.001$). After three months of PPI use, fasting gastrin levels in this

group increased by 47 % when compared to those of the first month ($p<0.001$) and decreased by 18 % when compared to those of the beginning ($p<0.05$). In the same group, non-fasting gastrin levels increased non-significantly compared to the 1st month, and decreased by 34% when compared to those of the beginning ($p<0.05$).

After a three-month-treatment period with PPIs, both fasting and non-fasting serum gastrin levels were significantly higher in patients with persistent H. pylori infection than in those in whom H. pylori had been eradicated ($p<0.05$).

DISCUSSION

In our study, it was observed that both fasting and non-fasting serum gastrin levels at the end of one month and after PPI treatment, in patients who received eradication treatment, were lower than both the initial levels and than that of the gastrin levels in the symptomatic treatment group at the end of the first and fourth month. Decrease in serum gastrin levels after H. pylori eradication treatment is not a new observation but the main concern in this study was to evaluate how gastrin levels would be effected by the long term use of PPIs thereafter. Since it is known that PPI treatment causes hypergastrinemia, verification of the assumption that H. pylori eradication can prevent hypergastrinemia due to long term PPI treatment would create a new approach in treatment strategies.

The mechanism by which H. pylori infection causes hypergastrinemia is still controversial. Olbe et al reported that the inhibitor pathways to G cells and parietal cells were blocked in patients with H. pylori infection and that this blockade returned to normal within nine months of eradication treatment (14). In addition, it has also been suggested that H. pylori infection blocks the inhibitory effect of cholecystokinin on the stomach (2) and might cause hypergastrinemia by means of other cytokines such as IL-1 and TNF-alfa (15,16). It has been observed in several studies that basal and stimulated gastrin secretions decreased significantly following H. pylori eradication treatment (17-19).

Serum gastrin levels were found to increase significantly during treatment with PPIs in several studies (11-13). Lind et al showed that the increase in plasma gastrin concentrations was related to the suppressed gastric acidity (20). In animal models, long-term use of PPIs caused an important increase in the endocrine cell and G cell population of pyloric glands (11,21,22). Recently, Zavros et al. determined the effect of H. pylori infection on gastritis, enterochromaffin-like cell density and hyperplasia, mucosal atrophy and serum gastrin in patients with gastric hypersecretion (Zollinger-Ellison syndrome) or normal gastrin before and during long-term treatment with lansoprazole. They reported that corpus enterochromaffin-like cell increases were related to serum gastrin elevation, but that neither H. pylori nor long-term treatment with lansoprazole alone or together had any effect on enterochromaffin-like cell density or hyperplasia. Corpus acute gastritis was caused by H. Pylori infection, but did not result in mucosal atrophy despite long-term proton pump inhibitor treatment, but promptly resolved with eradication of H. Pylori (23). Eissele et al showed that serum gastrin levels, antral G cell density and fundic argyrofil cell density increased significantly with PPI treatment in H. pylori positive patients within three months (24).

In our study, H. pylori eradication was related to a more significant decrease in non-fasting serum gastrin levels than in fasting gastrin levels. This finding supports previous findings which have noted that H. pylori infection causes a more important increase in non-fasting gastrin levels. On the other hand, we observed that treatment with PPIs caused a more prominent increase in fasting gastrin levels than in non-fasting gastrin levels. This observation was made in both H. pylori positive and H. pylori negative patient groups. In our study, H. pylori eradication treatment caused 18 % and 34 % reductions in fasting and non-fasting gastrin levels respectively, despite treatment with PPIs for three months. This shows that the suppressive effect of H. pylori eradication treatment is stronger than the stimulatory effect of long term PPI usage on gastrin secretion. The difference between fasting and non-fasting intragastric pH levels can account for the more prominent decrease in non-fasting gastrin levels.

Considering the previously reported findings and the results of our study, it is obvious that both H. pylori infection and long term PPI use cause hypergastrinemia and that when these risks occur together, the impact will be more significant. The present authors suggest that the hypergastrinemia caused by H. pylori infection is much more

prominent than that caused by PPI use. We believe that testing for the existence of H. pylori infection and initiating eradication treatment when infection is found in patients who are candidates for long term PPI treatment, is an appropriate management approach in order to avoid hypergastrinemia, which is still believed to have important potential dangerous effects.

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