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DOES ERADICATION OF *HELICOBACTER PYLORI* REDUCE HYPERGASTRINAEMIA DURING LONG TERM THERAPY WITH PROTON PUMP INHIBITORS?
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DOES ERADICATION OF HELICOBACTER PYLORI REDUCE HYPERGASTRINAEMIA DURING LONG TERM THERAPY WITH PROTON PUMP INHIBITORS?

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ABSTRACT

Objectives: **To evaluate the effect of Helicobacter pylori (Hp) eradication therapy on blood gastrin levels in long-term PPI users, since proton pump inhibitors (PPIs) and *Helicobacter pylori* (Hp) are major causes of hypergastrinaemia.**
Design: **A prospective study.**
Subjects: **Twenty seven Hp (+) patients enrolled in the study. Twenty were given eradication treatment (ET group), and the rest were given symptomatic treatment (ST group). Those who remained Hp (+) after eradication therapy were also added into the ST group. Lansoprazol 30 mg/day was given to both groups for three months thereafter.**
Results: **Fasting and non-fasting blood gastrin levels (FGL and NFGL) were measured initially and one month and four months after treatment. At the end of fourth month, FGL was significantly higher than both initial and first month level ($p<0.01$) in the ST group. NFGL in this group did not change significantly ($p>0.05$) after eradication therapy. In the ET group, FGL was significantly higher in the fourth month than the first month ($p<0.001$) and than the initial level ($p<0.05$). NFGL was higher, but not statistically in the fourth month than in the first month ($p>0.05$) and significantly lower than the initial level ($p< 0.05$) in this group.**
Conclusion: **We suggest that testing for Hp positivity and treating it if detected would be an appropriate approach to avoid hypergastrinaemia, especially in candidate patients for long term PPI treatment.**

INTRODUCTION

The relationship between *Helicobacter pylori* (Hp) infection, gastric acidity and plasma gastrin levels have attracted attention of researchers in recent years. Evidence has pointed to an increase in gastrin and gastric acid secretion in Hp (+) patients (1-5). Gastrin, enhances HCI secretion from the gastric parietal cells(6-8). There are different opinions on how Hp infection contributes to gastroduodenal lesions. Goodwin *et al* have suggested that Hp disrupts local mucosal defence leading to gastroduodenal damage(9), and Levi *et al* have noted that Hp infection increases gastric acid secretion which in turn causes mucosal damage(10). In one study, however, it has been reported that Hp infection blocks normal inhibitory pathway through G cells (2).

Another factor which causes hipergastrinaemia is the use of proton pump inhibitors (PPIs). Significant increase in serum gastrin levels during treatment with PPIs have been reported (11-13). Treatment approaches that will decrease the hypergastrinaemic 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 whether Hp eradication in patients on long-term PPI treatment would affect hypergastrinaemia or not.

MATERIALS AND METHODS

Patients: Patients with endoscopically verified peptic ulcer disease and/or oesophagitis, whose gastric antrum and corpus biopsies revealed Hp positivity both in histopathologic examination and in rapid urease testing (CLO test) were included in this study. Patients with previous gastric surgery, cholecystectomy, gastric malignancy, chronic renal failure and chronic alcoholism were excluded along with patients who have been on NSAIDs, corticosteroids, bizmuth preparations, PPIs, H2 receptor blockers within four weeks prior to enrollment into the study. Twenty seven patients (14 male, 13 female) between the ages of 21 and 56 years, were enrolled in the study.

Study design: Written consent was obtained from each patient and blood samples were collected in the morning after an overnight fast for fasting serum gastrin level. Then patients

were 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°C until assayed for gastrin. Serum gastrin determinations were made using ^{125}1 radioimmunoassay LB 2104 Berthold-Multi-Well Gama Counter which has similar activity for both G17 ve G34.

All patients underwent upper gastrointestinal endoscopy (EGD) and following topical anaesthesia using 10% lidocain and sedation using 2.5-5 mg midazolam, EGD was performed using either Pentax EG 2930 or Fujinon EG 200 FP videoendoscopes. 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 in 24 hour.

Patients were classified into Hp eradication treatment group (ET group, n=20) and symptomatic treatment group (ST group, n=7). ET group was put on a treatment regime consisting of ranitidine bismuth subcitrate 400 mg, b.i.d. + clarithromycin 500 mg, b.i.d + amoxycillin 1 gr b.i.d. for 7 days. They were allowed to use antacids as needed. ST group was given only antacids for symptomatic treatment for the same period.

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

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 and 13 female, age 44.15 + 7,75) 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 first and fourth months are shown in Table.1

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

Table 1

Fasting and non-fasting serum gastrin levels in patient groups

	ST Group		ET Group	
	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)	%49.1	NS	%47	NS
(1st - 4th months)				
p	<0.01	>0.05	<0.001	>0.05
(% change)	%51	NS	%18	%341
(0 - 4th months)				
p	<0.01	>0.05	<0.05	<0.05

ST = symptomatic treatment, ET = eradication treatment, NS = non-significant

In the ET group, serum fasting and non-fasting gastrin levels decreased by 44 % and 36 % respectively, at the end of first month and the differences were statistically significant (p<0,001). After use of PPIs for three months, 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 at the beginning (p<0.05). In the same group, non-fasting gastrin levels increased non-significantly from those of the first month and decreased by 34% when compared to those at the beginning (p<0.05).

After treatment with PPIs, both fasting and non-fasting serum gastrin levels were significantly higher in patients with persistent Hp infection than in Hp eradicated patients (p<0.05).

DISCUSSION

We observed in our study that in patients who received eradication treatment, both fasting and non-fasting serum gastrin levels at the end of first month and after treatment with PPIs were lower both in the initial levels and in those of the ST group at the end of first and fourth months. Decrease in serum gastrin levels after eradication treatment is not a new observation, however, the main concern in this study is to evaluate how gastrin levels will be affected by the long term use of PPI's thereafter.

Since it is known that PPI treatment causes hypergastrinaemia, the verification of the assumption that Hp eradication can prevent hypergastrinaemia due to long term PPI treatment might be a new approach in treatment strategies.

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

Serum gastrin levels increased 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 supressed 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).

Eissele *et al* showed in Hp positive patients that with PPI treatment serum gastrin levels, antral G cell density and fundic argyrofil cell density increased significantly in three months(23).

In our study, Hp eradication was associated with a more significant decrease in non-fasting serum gastrin levels than in fasting gastrin levels. This finding supports previous findings which have noted that Hp infection causes a more important increase in non-fasting gastrin levels. On the other hand, we observed in our study 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 Hp positive and Hp negative patient groups.

In our study, Hp 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 Hp 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 Hp infection and long term PPI use cause hypergastrinaemia and that when these risks are together the impact will be more significant. We suggest that hypergastrinaemia caused by Hp infection is much more prominent than that caused by PPI use. We believe that testing for the existence of Hp 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 hypergastrinaemia, which is still believed to have important potential dangerous effects.

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