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Antral Helicobacter Pylori Infection, Hypergastrinemia and Peptic Ulcers: Effect of Eradicating the Organism

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Background: *A randomized prospective study on the response of fasting serum gastrin concentrations in peptic ulcer patients was performed in order to test the hypothesis that H. pylori infection in the gastric antrum increases gastrin release, and to examine whether the high fasting serum gastrin concentrations respond to treatment that eradicates H. pylori.*

Methods: *One hundred and twenty-seven patients with gastric or duodenal ulcer were included in this study. Patients were divided into three groups on the basis of antral H. pylori status and therapeutic modalities. The first group, 58 patients infected by H. pylori, was treated with metronidazole and tripotassium dicitrato bismuthate combined with ranitidine and mylanta. The second group, 40 patients also infected by H. Pylori, was treated with ranitidine and mylanta. The third group, 29 patients, free of H. pylori infection, was designed to evaluate the influence of H_2-receptor antagonist on the change of gastrin. When ulcers were completely healed, changes of gastrin concentrations and H. pylori status were re-examined.*

Results: *H. pylori was eradicated in all patients who have received antibacterial therapy in 4 weeks, and serum gastrin concentrations were significantly decreased after eradication of the organism both in gastric and in duodenal ulcer diseases. (Gastric ulcer: 129.3±47.0 pg/ml before and 63.7±21.6 pg/ml after treatement. Duodenal ulcer: 108.3±35.0 pg/ml and 66.5±21.9 pg/ml, respectively. Total: 112.7±38.2 pg/ml vs 66.0±21.6 pg/ml) ($p<0.01$). In contrast, H. pylori-positive patients who have not received antibacterial therapy were still infected at the completion of the study, and serum gastrin concentrations increased even though the difference was not significant. (Gastric ulcer: 118.4±51.2 pg/ml vs 124.0±56.5 pg/ml . Duodenal ulcer: 85.4±35.1 pg/ml vs 104.6±43.5. Total: 99.5±45.3 vs 112.9±48.7 pg/ml.) ($p>0.05$) None of the patients who were initially H. pylori-negative has been reinfected during the period of the study, and their serum gastrin concentrations were not changed. (Gastric ulcer: 69.8±38.0 pg/ml. Total: 63.2±31.1 pg/ml. Duodenal ulcer: 55.1±17.6 pg/ml vs 55.8±13.8 pg/ml. Total: 63.2±31.1 pg/ml vs 63.4±30.0 pg/ml) Four- to six-week therapy of H_2-receptor antagonist and antacid had no influence on serum gastrin concentrations.*

Conclusions: *On the basis of the above results, we confirmed that the chronic infection of H. pylori of gastric antrum in peptic ulcer patients causes increased release of serum gastrin, and eradication of the organism results in a significant fall in serum gastrin concentrations*

Key Words: *H. pylori, Gastrin, Gastric Ulcer, Duodenal Ulcer*

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INTRODUCTION

There is now convincing evidence that Helicobacter pylori (H. pylori) infection plays an important part in the pathogenesis of peptic ulcer disease. More than 95% of patients with duodenal ulcer (DU)[1] and 85% of patients with gastric ulcer (GU) have H. pylori infection of the gastric antrum, and eradication of this reduces the ulcer relapse rate[2]. The way in which the chronic H. pylori infection of the gastric antrum predisposes to peptic ulceration is umclear but stimulation of excessive gastrin release, with resulting gastric hyperacidity, may be important especially in DU formation. It has recently been shown that patients with the infection have raised serum gastrin concentrations[3] which fall when the infection has been cleared[4,5]. In addition, eradication of H. pylori infection results in a fall of 27-33% in the basal gastrin concentration and a fall of 30-58% in the integrated gastrin response to a meal[6]. Similar results have been reported by several investigators[3,6~10,18]. Because this increase in the serum gastrin concentration is associated with raised intragastric acidity after meals[4], gastrin may be the link between chronic H. pylori infection and peptic ulcer, especially DU disease[3,7]. The mechanism by which chronic infection of the antral mcosa with H. pylori results in increased gastrin release is not known, but several hypotheses have been published explaining the H. pylori-associated hypergastrinemia.

In an attempt to clarify the relationship between the chronic H. pylori infection and the serum gastrin, we have measured serum levels of the gastrin before and after the eradication of H. pylori infection.

MATERIALS AND METHODS

1. Patients

The study population was made up of 127 patients with endoscopically and histologically confirmed benign GU and DU. GU patients consisted of 30 male (range, 22-85 years, average 47. 2 years) and 27 female patients (range, 27-61 years, average 50.3 years). Sixty-six male patients, average age 39.9 years (range, 13-70 years), and 16 female patients, average age 39.3 years (range, 30-50 years) were included in DU group (Table 1).

2. Methods

A blood sample was collected after an overnight fast for the measurement of serum gatrin concentration. After this, gastro-duodenal endoscopy was performed with the Fujinon EVG-FP (Japan) endoscope. H. pylori infection was confirmed in each by identification of the organism microscopically, Gram staining, culture, urease testing and by histological examination of mucosal biopsy specimens.

Serum gastrin concentrations were measured by the radioimmunoassay technique, using the GammaDab[^{125}I] Gastrin RIA kit (INCSTAR Co. UK), and each examination was duplicated.

All patients were divided into three different groups on the basis of H. pylori status and therapeutic modalities (Table 2). The first group (12 GU and 46 DU patients) was H. pylori positive and treated with metronidazole 250 mg qid., tripotassium dicitrato bismuthate (TDB) 120 mg qid., designed to eradicate H. pylori, in addition to ranitidine 300 mg at bed-time and mylanta 10 ml qid. The second group (17 GU and 23 DU patients) was H. pylori positive but treated only with ranitidine and mylanta designed to be a control group. The third group (16 GU and 13 DU patients) was free from the infection of H. pylori and ranitidine and mylanta were given. The third group was designed to evaluate the effect of H_2-receptor antagonist on the serum gastrin concentration, before and after the treatment, along with H. pylori status.

Metronidazole and TDB were given for 4 weeks and ranitidine and mylanta were given for 4 to 6

Table 1. Characteristics of Study Population

Disease	Sex	No. patients	Age(years)	
			Range	Average
Gastric ulcer	Male	39	22-85	47.2
	Female	6	27-61	50.3
Duodenal Ulcer	Male	66	13-70	39.9
	Female	16	30-50	39.3

weeks according to the size of the ulcer crater. Both healing of active ulcer crater and confirmation of eradication of H. pylori were achieved by repeating the endoscopy and mucosal biopsies.

On the day of follow-up endscopy, when ulcers were completely healed, a repeated fasting blood sample was obtained for estimation of serum gastrin levels and the H. pylori status reassessed by means of microbiologic and histologic examination of mucosal biopsies.

3. Statistiacal Evaluation of Results

Results were expressed as the Means±SD. Student's t-test was used to determine the significance of differences between means, with difference giving a p value less than 0.05 being considered significant.

RESULTS

All of the 127 patients studied, who had either GU of DU, were effectively treated with ranitidine and mylanta for 4- to 6-week without any significant side reactions, and active ulcer craters were not found in all patients on the follow-up endoscopy. The first group patients were infected by H. pylori initially, but none had antral H. pylori both in microscopic and histologic examination of biopsy specimens after 4-week treatment of metronidazole and TDB (table 2 & 3). However the second group, who were also H. pylori-positive at the beginning of the study and were given only ranitidine and mylanta, all the patients were still infected by the organism on repeated examination even though ulcers were completely healed (Table

Table 2. H. Pylori Status and Treatment Modalities in Three Different Groups

Group	Disease	No. Patients	H.pylori Status	Treatment
I	GU	12	Positive	Metronidazole TDB*, Ranitidine
	DU	46	Positive	Mylanta
II	GU	17	Positive	Ranitidine and
	DU	23	Positive	Mylanta
III	GU	16	Negative	Ranitiaine and
	DU	13	Negative	Mylanta

*TDB: Tripotassium dicitrato bismuthate

Table 3. H. Plyori Status and Serum Gastrin Concentration before and after Treatment

Group	Before Treatment		After Treatment	
	H.pylori Status	Gastrin	H.pylori Status	Gastrin
I	Positive (n=58)	112.7±38.2	Negative	66.0±21.6*
	GU (n=12)	129.3±47.0	GU	63.7±21.6*
	DU (n=46)	108.3±35.0	DU	66.5±21.9*
II	Positive (n=40)	99.5±45.3	Positive	112.9±49.7
	GU (n=17)	118.4±51.2	GU	124.0±56.65
	DU (n=23)	85.4±35.1	DU	104.6±43.5
III	Negative (n=29)	63.2±31.1**	Negative	63.4±30.0
	GU (n=16)	69.8±38.0**	GU	69.6±37.9
	DU (n=13)	55.1±17.6**	DU	55.8±13.8

Serum Gastrin Concentration: Mean±SD (pg/ml)

*$p<0.01$ compared before and after eradication of H. pylori infection.

*$p<0.05$ compared with Group I and II before treatment

No significant difference between group I and II before treatment.

2 & 3). These date suggest that H_2-receptor antagonist and antacid do not have any antibacterial action against H. pylori and the combination therapy of metronidazole and TDB for 4 weeks is highly effective for eradication of H. pylori from the mucosa. The third group, initially free from H. pylori infection, none of the patients was infected by the organism during the study (Table 2 & 3).

Patients infected by H. pylori had significantly higher fasting serum gastrin concentrations than those negative for the organism. Serum gastrin concentrations of GU patients in the first group were 129.3±47.0 pg/ml (range 82.4−225.7 pg/ml) and those in the second group were 118.4±51.2 pg/ml (range 62.2−185.8 pg/ml). H. pylori-negative GU patients had significantly lower level of serum gastrin (range 45.6−168.7 pg/ml, 69.8±38.0 pg/ml) than H. pylori-positive GU patients. ($p<0.05$) (Table 3). Similar results have also been found in patients with DU: 108.3±35.0 pg/ml (range 49.4−197.2 pg/ml) in the first group and 85.4±35.1 pg/ml (range 34.5−167.4 pg/ml) in the second group, but the gastrin level of H. pylori-negative DU patients, the third group, was 55.1±17.6 pg/ml (range 40.6−98.7 pg/ml) ($p<0.05$). (Table 3).

In the 12 GU patients with successful eradication of H. pylori, there was a significant fall in the fasting serum gastrin concentration from 129.3±47.0 pg/ml to 63/7±21.6 pg/ml after treatment ($p<0.05$) (Table 3, Fig. 1). In the 46 DU patients, the result was similar as in the GU: 108.3±35.0 pg/ml to 66.5±21.9 pg/ml after eradication ($p<0.05$) (Table 3, Fig. 1). . In comparing results before and after eradication of the organism in the first group patients, serum gastrin concentrations fell significantly from 112.7±38.2 to 66.0±21.6 pg/ml ($p<0.01$) (Table 3, Fig. 1). Incontrast, fasting serum

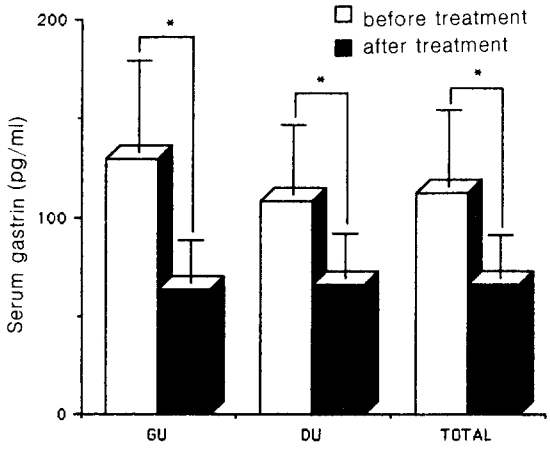

Fig. 1. Changes in serum gastrin concentrations before and after treatment in group I. Group I patients are HP (+) patients treated with metronidazole, TDB, ranitidine and mylante. The columns represent the mean value & error bars the range. The asterik indicates less than pre-treatment at $p<0.01$.

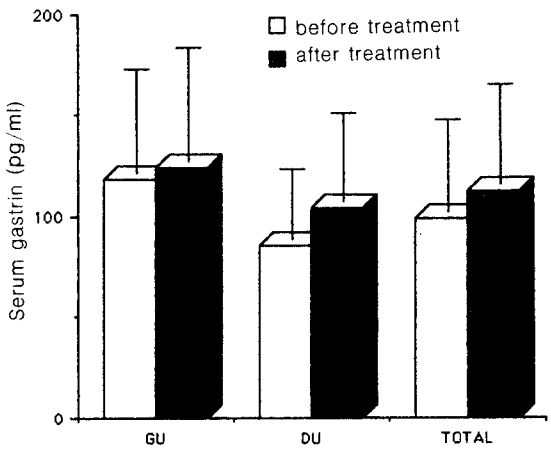

Fig. 2. Changes in serum gastrin concentrations before & after treatment in group II patients. Group II patients are HP (+) patients treated with ranitidine and mylanta.

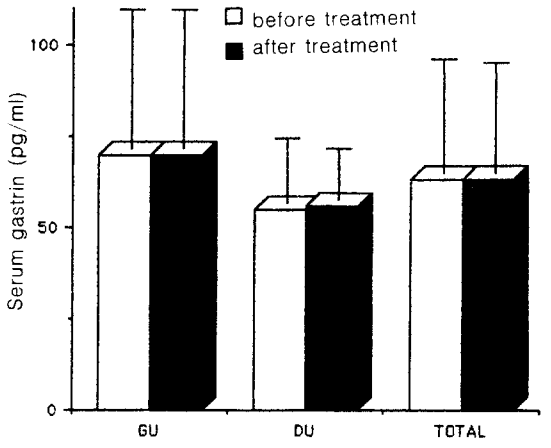

Fig. 3. Changes in serum gastrin concentrations before & after treatment in group III patients. Group III patients are HP (−) patients treated with ranitidine and mylante.

gastrin concentrations of the second group patients, in whom the H. pylori was not eradicated, were increased even though the difference was not statistically significant (pre-treatment value: 99.5± 45.3 pg/ml and post-treatment value: 112.9±49.7 pg/ml)(Table 3, Fig. 2). In the third group, there was no change in the fasting serum gastrin concentration, with pre-treatment value being 63.2± 31.1 pg/ml and post-treatment value being 63.4± 30.0 pg/ml (Table 3, Fig. 3).

DISCUSSION

Epidemiological evidence of a relation between colonization of the gastric antrum with H. pylori and DU disease consists of the high prevalence of H. pylori colonization in most of DU patients[11], the longer remissions of the disease obtained with treatments that suppress or eradicate H. pylori infection than with those that do not[12], and the finding that, after eradication of H. pylori, ulcers rarely recur before reinfection with the organism[2,13,14].

Patients with DU disease have higher gastric acid secretion, both basal and pentagastrin-stimulted, and also tend to have higher peak postprandial gastrin response than normal subjects. It has been shown that a low intragastric pH inhibits antral gastrin release less effectively in patients with DU disease than in normal subjects[15].

Before evaluating effects of H. pylori infection on the change of serum gastrin concentration, we examined any possible influences of 4- to 6-week treatment of H_2-receptor antagonist (ranitidine) and antacids (mylanta) on serum gastrin levels. There was no change in fasting serum gastrin concentrations between the pre-treatment and the post-treatment period (63.2±31.1 pg/ml vs 63.4± 30.0 pg/ml0. These observations suggest that short-term treatment with either H_2-receptor antagonists or antacids does not have an influence on serum gastrin concentrations.

Our study has shown that H. pylori-positive DU disease has significantly higher fasting serum gastrin concentrations (108.3±35.0 and 85.4±35.1 pg/ml) than those (55.1±17.6 pg/ml) of H. pylori-negative patients. Similar results habe been reported by several investigaters[3,5~10]. In patients with GU, serum gastrin concentrations were also significantly higher in H. pylori-positive subjects (129.3± 47.0 pg/ml in the first group and 99.5±45.3 pg/ml in the second group) than H. pylori-negative patients (69.8±38.0 pg/ml). This is the first report regarding the relation between antral H. pylori infections and serum gastrin levels in patients with GU infected by H. pylori.

This study also showed that eradication of H. pylori infection was accompanied by a significant fall in the serum gastrin concentrations in both GU and DU patients. In contrast, serum gastrin concentrations have increased in patients showing continuously positive for H. pylori and has not changed in those negative for H. pylori infection in both the beginning and the end of study. Our results are similar to those of previous reports[3,5,6,7,9,10].

The mechanism of the hypergastrinemia in DU patients with H. pylori infection is unclear. It has been proposed that the increased serum gastrin concentrations are caused by the organisms ammonia production raising antral surface pH[7]. This would prevent the physiologic suppression of gastrin release by intragastric acid, resulting in inappropriate release of the hormone.

However, Chittajallu RS, et al.[6,9] and Nujumi AME, et al.[10] have demonstrated that median basal gastrin concentration remained unchanged despite either the threefold increase in ammonia production by intragastric infusion of urea, or the complete suppression of bacterial urease activity with acetohydroxamic acid. On the basis of these observations, they have concluded that H. pylori-associated hypergastrinemia is not related to the organisms urease activity and ammonia production.

A second possible mechanism, by which H. pylori infection of the gastric antrum may be stimulating excessive gastrin release, is the effects of antral gastritis. Eradication of the infection results in resolution of the antral gastritis and it is possible that it is the inflammatory cell infiltrate in the region of the G cells that is responsible for hypergastrinemia. Wyatt JI, et al.[16] have demonstrated that hypergastrinemia correlates better with antral gastritis than with H. pylori status.

A third explanation for hypergastrinemia is that it is a compensatory response to inhibition of parietal cell function by H. pylori. Cave DR, et al.[17] have found that the organism has been shown to inhibit parietal cells in vitro and Graham DY, et al.[8] have demonstrated that acute H. pylori infection may result in profound hypochlorhydria in humans. Some inhibition of parietal cell function may persist during chronic infection of H. pylori, producing

a compensatory increase in gastrin release.

Recently, it has been reported that the gastrin-releasing-peptide (GRP), one of non-luminal stimlants of gastrin, might be responsible for hypergastrinemia in patients with DU infected by H. pylori[19].

On the basis of our observations, we have confirmed that chronic antral H. pylori infection causes increased release of serum gastrin, and eradication of the organism results in significant lowering of serum gastrin concentrations in patients with DU. Similar results were also found in patients with GU.

We are further investigating the possible causes that might be responsible for the H. pylori-induced hypergastrinemaia by evaluating changes of antral histologies and by measuring the antral G- and D-cell populations before and after eradication of the organism in peptic ulcer patients.

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