Eradication of *Helicobacter pylori* restores the inhibitory effect of cholecystokinin on postprandial gastrin release in duodenal ulcer patients

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Abstract

Helicobacter pylori infection may be associated with duodenal ulcer (DU) and accompanied by enhanced gastrin release but the mechanism of this *H. pylori* related hypergastrinaemia in DU patients is unclear. Cholecystokinin (CCK) has been implicated in the feedback control of gastrin release and gastric acid secretion in healthy subjects. This study therefore investigated if CCK participates in the impairment of postprandial gastrin release and gastric secretion in six DU patients. Tests were undertaken with and without elimination of endogenous CCK by loxiglumide, a selective CCK-A receptors antagonist, before and after eradication of *H. pylori* with triple therapy (omeprazole, amoxicillin, bismuth). In *H. pylori* positive DU patients, the postprandial decline in pH (with median pH 3.5) was accompanied by a pronounced increment in plasma gastrin but the administration of loxiglumide did not affect significantly this postprandial rise in plasma gastrin and gastric pH profile. After eradication of *H. pylori*, the plasma gastrin concentration was reduced while the median postprandial pH was significantly increased (median pH 4.3). The administration of loxiglumide resulted in significantly greater increase in postprandial plasma gastrin and greater decrease in pH (median pH 3.1) in these patients. This study shows that (a) infection with *H. pylori* is accompanied by an enhanced gastrin release and gastric acidity in DU patients, (b) the failure of loxiglumide to affect plasma gastrin or gastric acid secretion in *H. pylori* infected DU patients could be attributed, at least in part, to the failure of endogenous CCK to control gastrin release and gastric secretion by releasing somatostatin, and (c) the test with loxiglumide may be useful in the identification of patients with impaired feedback control of gastrin release and gastric secretion resulting from infection with *H. pylori*.

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Duodenal ulcer (DU) patients, as a group, tend to secrete more acid than normal subjects

both at rest and in response to secretory stimulation.¹ As, after ingestion of a meal, the important stimulant of gastric acid secretion is an increased plasma gastrin,²⁻⁴ the DU patients have been reported to have higher plasma gastrin response to a meal and to exhibit an impaired inhibition of gastrin release at lower intragastric pH.⁵ Other studies showed that endogenous cholecystokinin (CCK) may be implicated in the feedback control of gastrin release and gastric acid secretion^{6,7} because the administration of loxiglumide, a highly selective antagonist of CCK-A receptors,⁶⁻⁸ greatly enhanced the plasma gastrin and gastric acid secretion in response to ordinary feeding, protein meal or gastrin releasing peptide. Moreover, DU patients were found to exhibit the defect in the inhibitory action of endogenous CCK⁹⁻¹² on gastric release and gastric acid secretion suggesting an important role of CCK in the feedback control of gastric secretory functions.

The role of CCK as 'enterogastrone' in the control of gastric secretion by duodenal acid or fat has also been tested in dogs using highly selective CCK receptor antagonists such as L-364,718.^{13,14} These studies confirmed that CCK released by a peptone meal, especially when combined with fat¹³ or acid,¹⁴ exerts a potent inhibitory influence on gastric acid secretion and gastrin release through enhancing the release of endogenous somatostatin. Also in DU patients the defect in the inhibitory action of CCK on gastric secretion¹⁰⁻¹² has been suggested to result from the failure of CCK to activate (through the CCK-A receptors) the D cells to release somatostatin because loxiglumide in these patients did not affect significantly the plasma somatostatin concentration.¹⁰

More recently it was found that chronic infection of *H. pylori* can be found in up to 90% of DU patients and is usually accompanied by non-specific antral gastritis.¹⁵⁻¹⁷ It has been suggested that chronic *H. pylori* infection may lead to DU disease because of an inappropriate gastrin release and subsequent enhancement in gastric acid secretion. In other reports reduction in postprandial gastrin responses after eradication of *H. pylori* in DU patients have been shown.¹⁸⁻²⁰ Furthermore, studies on asymptomatic (without DU) subjects infected with *H. pylori* showed that these subjects have a significantly higher peptone meal induced plasma gastrin concentration and significantly attenuated inhibition of plasma gastrin at low

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intragastric pH compared with uninfected asymptomatic subjects.²¹ It was proposed that the impaired inhibition of gastrin release and gastric acid secretion seen previously in DU patients⁵ may be related to the infection of *H. pylori* in these patients.

This study was designed to assess the possible role of endogenous CCK in the impaired control of gastrin release in DU patients before and after eradication of *H. pylori*.

Methods

Subjects

Studies were approved by the Research and Human Use Committee at the University Medical School, Krakow and written consent was obtained from each subject.

Studies included 10 male patients, their ages ranged from 22 to 28 years (mean age 24). All of them had active DU diagnosed by clinical history and actual gastroduodenal endoscopy. All of them had two or more episodes of symptomatic relapse within one year. None had symptoms of ulcer disease at the time of study. All drugs were withdrawn for three days before the examination.

Study protocol

Subjects were studied on three separate days before and after eradication of *H. pylori*. On one day, *H. pylori* status was tested using two endoscopic biopsy specimens obtained from the lesser curvature of the middle antrum. One specimen was assessed histologically and one by the rapid urease test for evidence of *H. pylori* infection. For histological assessment, the specimen was fixed in 10% buffer formalin, embedded in paraffin wax, and sectioned. Sections were stained with haematoxylin and eosin with Giemsa for detection of *H. pylori*. The second specimen was used for rapid urease CLO test (Delta West Pty, Bentley, Western Australia). Only *H. pylori* positive subjects were included in further studies.

Gastric secretory studies with intragastric pH monitoring

On a second day, gastric acid secretion was studied for one hour under basal conditions and then for three hours after standard liquid 500 kcal meal (500 ml Fresubin, Fresenius, Germany). This meal consisted of protein (3.8%), aminoacids (0.6%), carbohydrates (14%), fat (3.8%), minerals, vitamins, and water with osmolarity of about 300 mOsm/l and pH of about 6.0.

Throughout the examination period, the intragastric pH was monitored by means of an intraluminal system including the pH antimony electrode (Monocrystal model 9-0215, Synectics AB, Sweden) connected to the portable apparatus, which permitted the pH recording to be sampled every four seconds (Digitrapper MKII, 6200, Synectics AB, Sweden). The antimony electrode used an

external reference on the thorax with contact jelly (Hellige 217, Fritz Hellige, Germany). At the beginning and at the end of each examination, the pH electrode was accurately calibrated at 21°C with pH 7.01 and pH 1.07 (buffers 5001 and 5002, Synectics AB, Sweden) and a temperature correction for intragastric reading (37°C) was performed as described before.²² The pH electrode was passed through an anaesthetised nostril and was positioned in the gastric corpus under fluoroscopic control roughly 15 cm below the lower oesophageal sphincter. The pH recording started at about 0800 and lasted four hours and this included 60 minutes of basal period and 180 minutes after digestion of liquid meal.

Data from intragastric pH monitoring were transferred to an IBM compatible computer (80386-IBM) programmed with Gastrogram version 5.50 serial No E1024 (Gastrosoft, Irvine, TX, USA) for calculation of mean and median pH values for each three hour postprandial period. Data from all six subjects treated with placebo and loxiglumide were analysed with the use of program STATpHAC II/PHARM, version 216 D3 (Gastrosoft, Irvine, TX, USA). Gastric acidity was expressed as pH and values from each subject were transferred into 10 minute median values. The median and mean three hour intragastric pHs were pre-defined for comparison between study days using Wilcoxon's signed rank test. Box and whisker plots of median and mean intragastric pH in six patients were calculated for a three hour period after standard meal and compared in medians and means with a significance value of less than 0.05.

Each subject was tested twice before and twice after eradication of *H. pylori* using (a) standard liquid meal with oral administration of a placebo tablet 30 minutes before meal and (b) standard meal and oral administration of a loxiglumide tablet (1200 mg) given 30 minutes before meal.

Eradication of *H. pylori* was achieved with triple therapy including amoxycillin, 500 mg three times daily, for two weeks omeprazole (20 mg twice daily) for two weeks, and colloidal bismuth subcitrate, 120 mg four times daily for four weeks. Endoscopy performed four weeks after the ending of treatment showed complete ulcer healing in all examined patients but the second test for eradication of *H. pylori* including ¹³C urea breath test showed *H. pylori* eradication in only six of 10 treated patients. A second gastric secretory examination was performed five weeks after the end of treatment and was only carried out in *H. pylori* negative patients.

Radioimmunoassays

Venous blood samples were obtained from a peripheral vein under basal conditions (twice) at 30 minute intervals before and after a standard meal (six times) before and after eradication of *H. pylori* in subjects receiving placebo or loxiglumide tablets. Plasma gastrin was determined using gastrin antiserum 4562 (kindly donated by Professor J E Rehfeld of

Figure 1: Median intragastric pH in DU patients before (A) and after (B) eradication of *H. pylori* before and after a standard meal in tests with administration of placebo or loxiglumide. Six tests on six patients. Box-whisker plots of three hour postprandial pH measurement period in tests with placebo (PL) or loxiglumide (LOX) treatment.

Copenhagen, Denmark) and used in a final dilution of 1:140 000. The antibody used recognises G17 and G34 equally. The sensitivity of the gastrin measurement in the present assay was 2.5 pmol/ml serum equivalent to human G-17 as described previously.²³

Plasma CCK concentrations were determined by a radioimmunoassay using antiserum NY 11 (kindly provided by Professor N Yanaihara, Skizuoka, Japan), which recognises the sulphated residue of CCK-8 but has only negligible cross reactivity with sulphated G-17 (<5%) and does not cross react with unrelated gastrointestinal peptides. Plasma samples were extracted with ethanol/acetic acid mixture, dried in a vacuum, and restituted with assay diluent just before the assay. Synthetic sulphated human CCK-8 (gift of Professor N Yanaihara) was used as a standard and ¹²⁵I-labelled with Bolton and Hunter reagent (Amersham, UK) as a tracer.¹¹ The detection limit of the assay was 0.5 pmol/ml plasma CCK-8 standard. Intra-assay and interassay coefficients of variation were 8% and 12%, respectively.

Plasma somatostatin was measured using a commercially available radioimmunoassay kit purchased from Milab, Malmö Immun-Labs Ab, Malmö, Sweden as described.¹¹ The antiserum used recognises only cyclic forms of somatostatin-14 and somatostatin-28 equally and did not cross react with any known gastrointestinal peptide. Plasma somatostatin was extracted with ethanol/acetic acid mixture, dried in a vacuum, and restituted as in the case of CCK. The detection limit was 0.5 pmol/ml. Interassay and intra-assay variations were 8% and 12%, respectively.

Statistics

The results of plasma hormones are expressed

as means (SEM). Statistical significance was determined by both the Wilcoxon signed rank test and the paired *t* test. Significance was accepted with a *p* value of less than 0.05.

Results

Of 10 *H. pylori* positive patients initially included in the study, only six had negative histological, rapid urease (CLO test), and ¹³C urea breath tests four weeks after the end of triple therapy. The results presented in this report concern only the six subjects who showed negative *H. pylori* status and who completed the intragastric pH monitoring tests with placebo and loxiglumide before and after eradication of *H. pylori*.

Figure 1 shows the pH profile recorded during one hour of basal state and during three hours after ingestion of standard liquid meal. The pH value in *H. pylori* positive patients during the basal period was about 1.1 and was not significantly different between placebo and loxiglumide treated subjects. With the ingestion of a meal, the median pH immediately rose to about 6 and then slowly declined within about 90 minutes to the pre-meal value, the median pH for three hours of the postprandial period being about 3.5. In subjects treated with loxiglumide, the median pH also rose to pH 6.0 and then declined to the pre-meal value within about 60 minutes, the median pH for the examined period (three hours) being about 3.1. The difference in the median postprandial pH between placebo and loxiglumide treated *H. pylori* positive DU patients was not statistically significant.

The pH profile in DU patients with negative *H. pylori* status, showed similar basal pH value (pH 1.3) and similar pH peak (about pH 6) after ingestion of standard meal. The return of intragastric pH after a meal to the pre-meal value occurred after about 120 minutes in placebo treated subjects and after about 60 minutes in loxiglumide treated subjects. The median pH for the examined period (three hours) was significantly lower in tests with loxiglumide (pH 3.1) than in tests with placebo (pH 4.2).

Basal plasma gastrin, CCK, and somatostatin in placebo treated *H. pylori* positive DU patients averaged 27 (3), 0.8 (0.2), and 3.8 (0.3) pmol/l. Ingestion of a standard liquid meal by those patients treated with placebo resulted in a significant increment (above basal) of plasma concentrations of gastrin (Fig 2), plasma CCK (Fig 3), and somatostatin (Fig 4) by about 88%, 150%, and 68%, respectively. In tests with loxiglumide basal plasma hormone concentrations were not significantly affected compared with placebo but the postprandial increments of plasma gastrin and somatostatin were similar to those seen in those patients after treatment with placebo. The increment of meal induced plasma CCK was almost twofold higher in tests with loxiglumide than with placebo.

After eradication of *H. pylori* in DU patients, the basal concentrations of plasma gastrin were significantly reduced, while plasma CCK and

Figure 2: Plasma gastrin under basal conditions and after a standard meal in DU patients before (A) and after (B) eradication of *H. pylori* in tests with placebo or loxiglumide. Mean of six tests on six patients. *Shows significant increase above the basal value; †shows significant change compared with the value obtained with placebo.

somatostatin values were similar to those in patients before the *H. pylori* eradication. The postprandial increment in plasma gastrin in placebo treated patients was similar to that seen in subjects before the eradication but in tests with loxiglumide, the increment in the postprandial plasma gastrin was about twice as high as in tests with placebo (Fig 2). The postprandial increment in plasma CCK concentrations in *H. pylori* negative DU patients treated with placebo were significantly lower than those in tests with loxiglumide. Thus, the administration of loxiglumide resulted in a significant rise in plasma CCK over that seen in placebo treated subjects both before and after the eradication of *H. pylori* (Fig 3).

Plasma somatostatin concentrations showed only a small increase over basal when a standard meal was given to placebo treated patients both with *H. pylori* positive and *H. pylori* negative status. On the other hand, in *H. pylori* negative DU patients, the increment in plasma somatostatin in tests with loxiglumide was significantly smaller than that in tests with placebo (Fig 4).

Discussion

This study confirms that eradication of *H. pylori* in DU patients reduces plasma gastrin release^{20 24 25} and attenuates the postprandial gastric acid response in these patients.^{20 25-28} The most important finding of this study is that the blockade of CCK-A receptors with loxiglumide in DU patients infected with *H. pylori* did not influence significantly the postprandial gastrin concentrations or gastric acid secretion but after eradication of *H. pylori* in the same patients, loxiglumide resulted in a pronounced increment in plasma gastrin concentrations similar to that seen previously in healthy subjects.^{6 7} These results could be interpreted that the *H. pylori* infection in DU is responsible for the increased basal plasma gastrin concentrations and increased gastric

acid secretion and that these effects of *H. pylori* infection could be caused, at least in part, by the abolition of the gastric inhibitory effects of endogenous CCK.

Previous studies on healthy subjects showed that CCK exerts a potent inhibitory influence on gastrin release and gastric acid secretion in response to ordinary feeding or administration of gastrin releasing peptide.^{6 7} It has been proposed that CCK exerts a tonic inhibitory influence of gastric secretory functions and participates in the negative feedback control of gastrin release and gastric secretion.¹⁰ This suggestion was supported by the finding that the removal of the biological effects (by loxiglumide) of CCK either given exogenously or released endogenously by peptone meal or infusion of gastrin releasing peptide resulted in a pronounced increase in plasma gastrin and gastric acid secretion.

Our further studies with DU patients showed that blockade of CCK-A receptors with loxiglumide failed to influence the enhanced basal or postprandial plasma gastrin and gastric acid secretion in these patients suggesting an impaired inhibition of gastric functions by endogenous CCK possibly caused by the failure of this CCK to stimulate somatostatin release from the D cells.¹⁰⁻¹² The implication of somatostatin in the 'enterogastrone-like' action of CCK originates from the studies on dogs^{10 13 14} in which an addition to a peptone meal of fat or acid (which are known releasers of CCK) significantly inhibited gastrin release and gastric acid secretion. These inhibitory effects were completely eliminated by the blockade of CCK-A receptors with L-364,718, a specific antagonist of these receptors. As CCK is known to stimulate the release of somatostatin from isolated canine fundic D cells in vitro²⁹ and the administration of L-367,718 in vivo also reduced the postprandial release of somatostatin^{13 14} it was proposed that the major factor

Figure 3: Plasma CCK concentrations under basal conditions and after a standard meal in DU patients before (A) and after (B) eradication of *H. pylori* in tests with placebo or loxiglumide. Mean of six tests on six patients. *Shows significant increase above the basal value; †shows significant change compared with the value obtained with placebo.

Figure 4: Plasma somatostatin concentrations under basal conditions and after a standard meal in DU patients before (A) and after (B) eradication of *H. pylori* in tests with placebo or loxiglumide. Mean of six tests on six patients. *Shows significant increase above the basal value; †shows significant change compared with the value obtained with placebo.

in the mechanism of gastric acid inhibition by CCK in dogs is probably somatostatin acting predominantly by a paracrine pathway on the G cells and oxyntic cells.

The somatostatin hypothesis in the control of gastric secretion in humans, particularly in DU patients, is attractive because the deficiency of somatostatin in DU patients has been suggested previously.^{30,31} The reports^{26,27} that gastric D cells are suppressed in *H. pylori* positive duodenal ulcer disease offered an explanation for the deficient inhibitory pathway and support the somatostatin link in this disease. Our results show that after a standard meal in DU patients with or without *H. pylori* infection, there was a small but significant increment in plasma somatostatin, which may not be able by itself to inhibit gastrin release or gastric acid secretion but it may reflect the important changes in paracrine release of somatostatin by CCK just around the G cells or oxyntic cells. This could explain the apparent discrepancy between the pronounced increment in the postprandial plasma gastrin by loxiglumide in *H. pylori* negative DU patients and the comparatively small decrease in the concentrations of circulating plasma somatostatin. DU patients infected with *H. pylori* may exhibit the defective inhibitory action of endogenous CCK on paracrine release of somatostatin resulting in augmented basal plasma gastrin release and gastric acid secretion in response to a meal in these patients. After eradication of *H. pylori*, loxiglumide could suppress the release of somatostatin possibly by antagonising CCK-A receptors localised to these cells. The antagonism of CCK-A receptors and the fall in somatostatin output will remove the G cells from the paracrine inhibitory influence of somatostatin with subsequent excessive postprandial release of gastrin and greatly increased gastric acidity. This is in keeping with our data that after the eradication of

H. pylori, a significant decrease in basal plasma gastrin and gastric acid responses to the meal was seen but the blockade of CCK-A receptors with loxiglumide resulted in a greatly increased postprandial gastrin release and enhanced gastric acid secretion, similar to those seen in healthy subjects.^{6,7} As no significant differences in plasma CCK and somatostatin values were seen before and after eradication of *H. pylori*, it is probable that in addition to the proposed CCK-somatostatin-gastrin link there are other factors, such as cytokines (for example, interleukin 1) that may impair the normal physiological feedback loop for gastrin regulation in chronic inflammation resulting from infection by *H. pylori*. Indeed, animals studies³² showed that interleukin 1 given intravenously increased plasma gastrin concentration while inhibiting gastric acid secretion and these effects were mediated by the prostaglandin pathway. Further studies are needed to elucidate the relative contribution of various factors in the control of gastrin release and gastric secretion in the *H. pylori* infected patients.

It is of interest that loxiglumide resulted in a considerable increase in postprandial plasma CCK concentration both in *H. pylori* positive and *H. pylori* negative DU patients. This actually confirms previous findings⁶ regarding higher postprandial concentrations of circulating CCK in loxiglumide treated patients compared with placebo treated subjects. Higher plasma CCK concentrations in tests with loxiglumide were reported previously in healthy subjects^{6,11,12} and, according to this study, this is also true for DU patients after eradication of *H. pylori*.

Our results show that the infection of *H. pylori* not only enhanced gastrin release but also increased postprandial gastric acid secretion as reported by some investigators^{15,24,25} but this is a controversial issue because other reports showed that *H. pylori* infection is accompanied by hypergastrinaemia but not by hyperchlorhydria^{28,33,34} or increased integrated 24 hour intragastric acidity.³⁵

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