

Marked increase in gastric acid secretory capacity after omeprazole treatment

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Abstract

Background—In contrast with the histamine₂ (H₂) blockers, proton pump inhibitors have not been shown to give rebound hypersecretion of acid. Taking into consideration the hyperplasia of the enterochromaffin-like (ECL) cell provoked by hypergastrinaemia secondary to profound acid inhibition and the central role of histamine from ECL cells in the regulation of acid secretion, the lack of any rebound acid hypersecretion after treatment with proton pump inhibitors has been questioned.

Aims—To reassess the effect of treatment with omeprazole on post-treatment acid secretion.

Methods and Patients—Basal and penta-gastrin stimulated acid secretion were determined in nine patients with reflux oesophagitis before and 14 days after termination of a 90 day treatment period with the proton pump inhibitor omeprazole (40 mg daily). Basal gastrin values as well as meal stimulated gastrin release were determined before and during omeprazole treatment. Furthermore, biopsy samples from the oxyntic mucosa were taken before and at the end of the treatment period for chemical (histamine and chromogranin A (CgA)) evaluation of the ECL cell mass.

Results—A substantial increase in meal stimulated gastrin release during omeprazole treatment resulted in an increased ECL cell mass. Furthermore, CgA in serum increased during omeprazole treatment suggesting that serum CgA may be used as a test to evaluate ECL cell hyperplasia. A significant increase in basal and a marked (50%) and significant increase in pentagastrin stimulated acid secretion were found after treatment with omeprazole.

Conclusions—Increased acid secretion after a conventional treatment period with a proton pump inhibitor is probably due to ECL cell hyperplasia and may have negative consequences for acid related diseases.

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Keywords: acid secretion, acid related diseases, gastrin, histamine, proton pump inhibitors.

In humans, gastrin is the main physiological regulator of gastric acid secretion.¹ In the rat, gastrin stimulates acid secretion by releasing

histamine² from the enterochromaffin-like (ECL) cell.³⁻⁵ Also in humans⁶ and other species the stimulation of acid secretion by gastrin is probably mediated by the stimulation of histamine release from the ECL cell.⁷ Gastrin not only regulates the function but also the growth of the ECL cell,⁸ an effect probably mediated by the same receptor, as the functional and trophic effects show the same concentration dependence in rat^{2,9} and man.^{1,10,11} We have previously shown that in the isolated rat stomach maximal histamine stimulated acid secretion is higher than maximal gastrin stimulated acid secretion.¹² In vivo, the apparently similar maximal gastrin and histamine stimulated acid secretion may be due to the toxicity of histamine making it impossible to administer histamine in a dose giving maximal gastric acid secretion.¹³ Moreover, we have shown that gastrin stimulated histamine release depends on the ECL cell density or mass.¹⁴ Furthermore, longterm hypergastrinaemia secondary to profound acid inhibition has been reported to induce an increased capacity to secrete acid in the rat.¹⁵ In humans, treatment with proton pump inhibitors in conventional doses leads to marked hypergastrinaemia^{16,17} and increased density of argyrophil cells (presumably ECL cells).^{16,17} Thus one would expect that treatment with such drugs should induce a rebound acid hypersecretion also in humans. The present study was carried out to examine whether treatment with a proton pump inhibitor in a conventional dose can increase post-treatment acid secretory capacity in humans as such an effect could have a negative influence on acid related diseases. Moreover, we also wanted to explore whether chromogranin A (CgA) could be used to assess the ECL cell mass not only in patients with Zollinger-Ellison syndrome,¹⁸ but also in patients with hypergastrinaemia secondary to acid inhibition.

Methods

Patients between 20 and 70 years of age with reflux oesophagitis grade 1-3,¹⁹ were invited to participate in the study, if they had not been taking any proton pump inhibitor during the previous six months or histamine₂ (H₂) blockers during the previous two weeks. Patients with malignant disease, liver or kidney diseases, or serious heart disease as well as women of childbearing age were not included. The study was approved by the local ethical committee, and the patients were given written information and gave written consent to participate. The study was conducted in accordance with the Declaration of Helsinki.

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Endoscopy with biopsies

Nine men between 39 and 68 years of age participated. They had had symptoms of gastro-oesophageal reflux disease for 1–20 years. Upper gastrointestinal endoscopy was performed using a gastroscope GIF IT20 (Olympus, Japan) and biopsy specimens were taken from the oxyntic mucosa (5 cm oral to the angulus from the anterior and posterior wall), using biopsy forceps FB-13K E (Olympus, Japan). The examination was performed after an overnight fast and without premedication or sedation. Two biopsy specimens were frozen directly in liquid nitrogen for later chemical analysis. One of the patients had oesophagitis grade 3, three had grade 2, and five grade 1.¹⁹

Basal and pentagastrin stimulated acid secretion and meal stimulated gastrin release

A few days later and after an overnight fast, blood was taken in EDTA tubes for later determination of histamine²⁰ and in glass tubes for gastrin and CgA determination. The patients were then given a test meal consisting of 100 g beef and 150 ml water taken within 10 minutes, and multiple blood samples were drawn for gastrin determination over a 120 minute period.

Within another few days, basal and maximal acid secretion was determined by a conventional pentagastrin test using pentagastrin (Peptavlon; Zeneca, Cheshire, UK) in a dose of 6 µg/kg body weight subcutaneously as stimulant. Gastric juice was collected for eight 15 minute periods after an initial 30 minute period to empty the stomach. The H⁺ concentration in the gastric juice was determined by titration (Radiometer, Copenhagen, Denmark). Thereafter the patients were given omeprazole (Losec; Astra, Gothenburg, Sweden) 40 mg once daily for 90 days.

During the last treatment week and after an overnight fast, blood sampling and the test meal were repeated as described above. Moreover, the patients underwent a second gastroscopy with biopsy specimens taken from the same area of the stomach and handled as at inclusion. During the first 14 days after the end of the omeprazole treatment, the patients were allowed only antacids for symptomatic relief. Then, after an overnight fast, a new pentagastrin test was carried out as described above.

Blood tests

Gastrin in serum was determined by a commercial radioimmunoassay (RIA) method (Becton Dickinson, Orangeburg, NY, USA). Plasma histamine was also determined by an RIA method (Immunotech, Marseilles, France).^{5, 21} Antibody to *Helicobacter pylori* was assessed by an enzyme linked immunosorbent assay (ELISA) as previously described.²² CgA was determined in serum by a commercial ELISA method (Dako, Denmark) as previously used in our laboratory.²³ The serum/plasma samples were stored at -20°C until analysis.

Assay of histamine and CgA in the oxyntic mucosa

Biopsy samples taken from the oxyntic mucosa and stored in liquid nitrogen were weighed, dissolved in phosphate buffer at a concentration of 100 mg tissue/ml, and homogenised using a rotating knife homogeniser.¹⁵ Histamine was determined in the homogenate (after 10 minutes of boiling) by the commercial RIA method used for determination of plasma histamine, and CgA was determined by a commercial ELISA method (Dako, Denmark).²³ The blood tests as well as the biopsy specimens were examined blindly.

Statistics

Wilcoxon's paired signed rank test was used to evaluate statistically the differences induced by the treatment, and Mann-Whitney test to evaluate the differences in gastrin values between *H pylori* positive and negative patients.

Results

The oesophagitis was healed in all patients. Three of the patients were positive for *H pylori* as assessed by serology (Table I).

Plasma gastrin

Basal plasma gastrin increased in all subjects although in some only marginally. On the other hand, basal plasma gastrin increased more than eightfold in one subject and threefold in two others (Table I). Basal gastrin before treatment was significantly ($p=0.0238$) higher in the three patients with *H pylori* infection compared

TABLE I Effect of three months' treatment with omeprazole 40 mg daily on blood basal CgA, gastrin, and histamine, and meal stimulated gastrin release in patients with reflux oesophagitis

Patient	Basal gastrin (pmol/l)		Meal stimulated gastrin release (area under curve) (pmol/min/l)		Peak meal stimulated gastrin concentration (pmol/l)		Plasma histamine (nmol/l)		Serum CgA (U/l)	
	Before	During	Before	During	Before	During	Before	During	Before	During
1	14	15	–	2 232	20	25	3.3	4.0	9.2	24.0
2	13	18	1963	7 628	20	86	2.9	5.1	9.1	9.1
3*	23	75	5060	17 095	69	176	3.6	2.6	5.4	24.0
4	12	101	2148	9 908	24	104	3.3	4.2	12.0	34.0
5	12	17	1453	4 345	13	42	2.6	3.6	11.0	16.0
6*	23	37	3660	16 893	47	172	2.6	3.0	23.0	55.0
7	12	27	1800	8 165	20	93	7.4	4.2	10.0	13.0
8*	22	64	2785	13 240	28	122	3.6	4.2	22.0	74.0
9	17	19	1678	7 783	20	91	5.9	4.6	5.4	13.0
Median	14	27	2056	8 165	20	91	3.3	4.2	10.0	24.0

**Helicobacter pylori* positive.

with the other six *H pylori* negative patients. Although plasma gastrin only increased marginally in most of the patients, the integrated two hour gastrin response to the test meal increased substantially in all subjects (Table I). The increase in meal stimulated gastrin release after omeprazole treatment depended on the meal stimulated release before treatment and increased threefold to fourfold compared with that before the treatment period (Table I). Moreover, integrated meal stimulated gastrin release before ($p=0.0357$) as well as during ($p=0.0238$) omeprazole treatment was significantly increased in patients with *H pylori* infection.

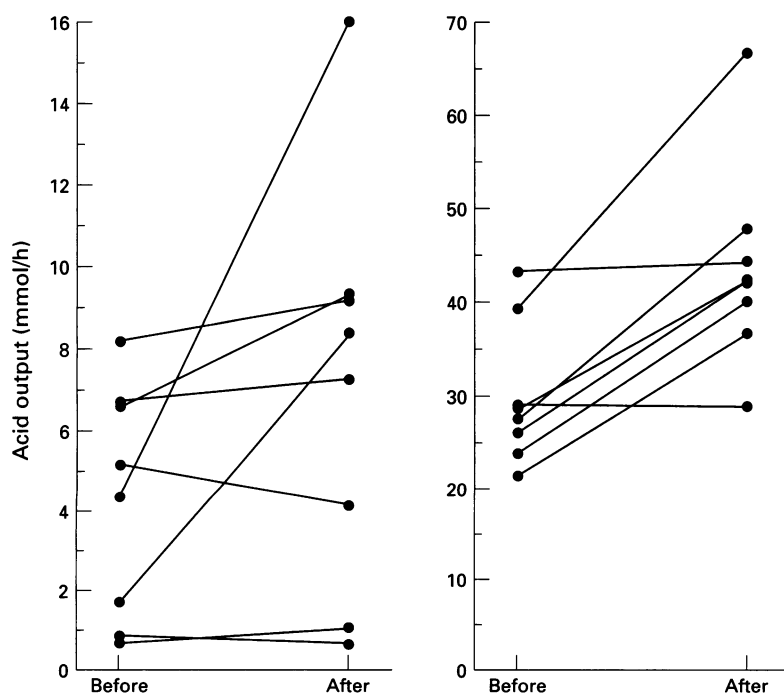
Plasma histamine and CgA in serum

Plasma histamine did not increase significantly during the omeprazole treatment period (Table I). On the other hand, serum CgA increased in eight of the patients and was unchanged in the ninth ($p=0.002$) (Table I).

Gastric acid secretion

Basal acid secretion increased significantly after omeprazole treatment ($p<0.05$). In one of the subjects, it became as high as 16 mmol/h (Figure).

Pentagastrin stimulated acid secretion increased in seven and was unchanged in one of the eight subjects studied (Figure) ($p=0.004$). In one patient (patient 3) the acid secretion could not be assessed owing to heavy duodenogastric reflux (dark brown bilirubin stained gastric juice) on both occasions. Pentagastrin stimulated acid secretion was nearly doubled in patients 5 and 6, and a substantial increase was noted in all but two patients (patients 2 and 8). Median pentagastrin stimulated acid secretion increased 50% (from 27.9 to 42.4 mmol/h).



Basal (left) and pentagastrin stimulated (right) acid secretion before and 14 days after a 90 day treatment period with omeprazole 40 mg daily.

Histamine and CgA in the oxyntic mucosa

Histamine increased significantly ($p=0.02$) in the oxyntic mucosa over the omeprazole treatment period (Table II). The increase in CgA was even more marked and highly significant ($p=0.004$) (Table II).

Discussion

For the first time a marked gastric acid hypersecretion after treatment with a proton pump inhibitor has been found in humans. This is in agreement with a previous study in rats where gastric acid hypersecretion was recorded one week after the end of longterm treatment with omeprazole.¹⁵⁻²⁴ The acid hypersecretion in these rats persisted for at least 70 days.¹⁵⁻²⁴ Previously, tolerance to H₂ blockers has been described whereas no such tolerance has been reported after treatment with proton pump inhibitors.²⁵ Rebound acid hypersecretion has been recorded after even a relatively short treatment period of four weeks with an H₂ receptor antagonist.²⁶ The dose of omeprazole used in the present study (40 mg daily) is higher than that reported to give maximal inhibition of acid secretion in patients with duodenal ulcer by Sharma *et al.*,²⁷ but lower than the dose giving maximal inhibition of pentagastrin stimulated acid secretion in healthy volunteers.²⁸ Nevertheless, the dose used probably gave a profound inhibition of acid secretion in these patients, which is supported by the increased basal and meal stimulated gastrin release. Acid secretion as assessed by the pH in aspirated aliquots of gastric juice in healthy volunteers after a three week treatment period with either ranitidine 300 mg or omeprazole 40 mg per day has previously been studied up to 21 days after cessation of treatment without any change in nocturnal acidity.²⁹ The apparent discrepancy between that study and the present one is probably because the treatment period in the study of Prewett and coworkers was too short.²⁹ In fact, the ECL cell density as assessed by argyrophil cell density increased markedly from day 30 to day 60 of hypergastrinaemia in rats.³⁰ In agreement with previous studies,³¹ fasting gastrin and meal stimulated gastrin release were higher in patients with *H pylori* infection. One of the patients with *H pylori* infection had marked duodenogastric reflux with bile stained gastric juice. Although

TABLE II Effect of three months' treatment with omeprazole 40 mg daily on the concentration of histamine and CgA in the oxyntic mucosa

Patient	Histamine (nmol/g)		CgA (U/g)	
	Before	During	Before	During
1	96	55	0.84	0.72
2	82	91	1.45	3.80
3*	62	255	0.27	3.10
4	131	161	2.90	6.00
5	107	101	2.35	3.30
6*	91	184	0.96	4.00
7	61	120	1.30	4.30
8*	51	130	0.65	5.00
9	64	127	0.84	2.90
Median	82	127	0.96	3.80

**Helicobacter pylori* positive.

duodenogastric reflux is usually quite small, not affecting the clinical value of the gastric acid secretory test, it may vary from 0.1 to 22.3% in healthy volunteers.³² Naturally, duodenogastric reflux makes basal gastric acid secretion less reliable than stimulated values. In the present study basal gastric juice in patient 3 was not only bile stained, but also alkaline. Therefore, it was quite clear that the secretory data from this patient could not be used in the assessment of rebound acid hypersecretion in this study. Ideally, this patient should have been removed from the study at the initial phase because of the observed duodenogastric reflux. However, exclusion of this patient would have meant that only two patients with *H. pylori* infection would have had pre- and post-treatment acid secretion determined. In one of these patients (patient 8) both basal and pentagastrin stimulated acid secretion were unaffected by the treatment with omeprazole whereas it increased markedly in the other patient (patient 6) with *H. pylori* infection (pentagastrin stimulated acid secretion increased from 27.3 to 47.8 $\mu\text{mol/h}$).

The effect of omeprazole persists for at least one week.²⁷ Therefore, it is mandatory to wait for longer than this to be able to detect rebound acid hypersecretion. In the present study we determined acid secretion two weeks after the end of treatment with the proton pump inhibitor and detected an increased pentagastrin stimulated as well as basal acid secretion. In vivo 24 hour gastric acidity reflects basal as well as food stimulated acid secretion. Since gastrin is the dominating secretagogue for meal stimulated acid secretion,¹ the described increase in pentagastrin stimulated acid secretion would be expected to lead to an augmented food stimulated acid secretion. Furthermore, as longterm inhibition of acid secretion also leads to an increase in antral G cells and decrease in somatostatin (D) cells,³⁰ food stimulated acid secretion after long-term treatment with potent inhibitors of acid secretion could lead to an even more marked acid hypersecretion than detected by pentagastrin stimulated acid secretion. It is possible that GRP stimulated acid secretion³³ could be an even more sensitive test for post-treatment acid hypersecretion. The clinical impact of this post-treatment acid hypersecretion remains to be shown. However, gastric acid plays a pathogenetic part in both peptic ulcer disease and reflux oesophagitis. Therefore, it is conceivable that the demonstrated acid hypersecretion may have a negative effect and contribute to the recurrence of both these diseases. The hypergastrinaemia secondary to the inhibition of acid secretion by omeprazole probably induced the post-treatment gastric acid hypersecretion. Basal gastrin increased in all subjects during treatment. The increase in basal gastrin was, however, slight or moderate with a value above 100 pmol/l in only one patient. However, even moderate hypergastrinaemia has a significant trophic effect on the ECL cell.⁹

Furthermore, as shown in this study, basal gastrin values during treatment with proton

pump inhibitors underestimate the postprandial hypergastrinaemia, which was greatly increased in all subjects during omeprazole treatment. Thus, the 24 hour gastrin stimulation is considerably raised in patients treated with proton pump inhibitors. Taking into consideration that the maximal trophic effect of gastrin on the ECL cell is reached at a lower concentration than previously thought in humans,¹⁰ as in the rat,⁹ it is probable that near maximal stimulation of ECL cell growth was obtained during a greater part of the day in some of the patients, for instance patients 3 and 6, who both had postprandial gastrin values just above 170 pmol/l (Table I).

It is now established that the ECL cell plays a central part in the regulation of gastric acid secretion.⁷ Furthermore, it is probable that gastrin induced histamine release is the limiting factor for gastric acid secretion after gastrin stimulation as well as meal stimulated acid secretion.³⁴ We found an increased histamine concentration in the oxyntic mucosa after omeprazole treatment, which probably reflects an increase in the ECL cell mass, especially as it was accompanied by a similar increase in CgA. An increased ECL cell density in the oxyntic mucosa in humans is well known after omeprazole treatment.¹⁶ Lamberts *et al* reported a doubling of the density of argyrophil cells in the oxyntic mucosa in patients with peptic ulcer treated with omeprazole for one to two years at the dose of 40 mg daily.¹⁶ Taking into consideration that the ECL cell, the only argyrophilic cell in the oxyntic mucosa where gastrin has a positive trophic effect,³⁵ normally represents only 35% of these cells,³⁶ a doubling of the density of the argyrophilic cells probably indicates an even more marked increase in the ECL cell density than just a doubling. Furthermore, gastrin has a negative trophic effect on the D cell in the oxyntic mucosa.³⁷ Accordingly, the described increase in argyrophilic cell density represents a massive increase in the ECL cell mass and function in the oxyntic mucosa. On the other hand, proton pump inhibitor treatment seems not to induce an increase in parietal cell density.¹⁵

Longterm hypergastrinaemia in humans is accompanied by gastric acid hypersecretion.³⁸ This gastric acid hypersecretion may be controlled by treatment with proton pump inhibitors in normal doses,³⁹ whereas H_2 blockers have to be used in greatly increased doses,⁴⁰ suggesting an increase in the histamine concentration in the oxyntic mucosa.³⁴ Altogether, the findings of this study and previous studies^{16 34-40} suggest that increased histamine due to ECL cell hyperplasia is the most important mechanism for increased acid secretory capacity after prolonged hypergastrinaemia. Furthermore, this study shows that CgA in blood may be used to assess the neuroendocrine cell mass in the stomach whereas plasma histamine cannot be used to estimate the ECL cell mass (Table I). Contamination of histamine released from granulocytes at the blood sampling and preparation of plasma²⁰ is probably the main reason for the lack of correlation between plasma histamine

on one hand and serum CgA or ECL cell mass on the other.

In conclusion, this study shows for the first time that treatment with a proton pump inhibitor in a conventional dose even in humans induces post-treatment gastric acid hypersecretion, which may have negative influences on the diseases for which they were prescribed. Furthermore, this increase in acid secretion is probably due to an increased ECL cell mass secondary to hypergastrinaemia during the treatment period.

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