Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study

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Abstract

Background—Gastric and duodenal bacterial overgrowth frequently occurs in conditions where diminished acid secretion is present. Omeprazole inhibits acid secretion more effectively than cimetidine and might therefore more frequently cause bacterial overgrowth.

Aim—This controlled prospective study compared the incidence of gastric and duodenal bacterial overgrowth in patients treated with omeprazole or cimetidine.

Methods—47 outpatients with peptic disease were randomly assigned to a four week treatment regimen with omeprazole 20 mg or cimetidine 800 mg daily. Gastric and duodenal juice were obtained during upper gastrointestinal endoscopy and plated for anaerobic and aerobic organisms.

Results—Bacterial overgrowth ($\geq 10^5$ cfu/ml) was present in 53% of the patients receiving omeprazole and in 17% receiving cimetidine ($p < 0.05$). The mean (SEM) number of gastric and duodenal bacterial counts was 6.0 (0.2) and 5.0 (0.2) respectively in the omeprazole group and 4.0 (0.2) and 4.0 (0.1) in the cimetidine group ($p < 0.001$ and < 0.01 ; respectively). Faecal type bacteria were found in 30% of the patients with bacterial overgrowth. Basal gastric pH was higher in patients treated with omeprazole compared with cimetidine (4.2 (0.5) versus 2.0 (0.2); $p < 0.001$) and in patients with bacterial overgrowth compared with those without bacterial overgrowth (5.1 (0.6) versus 2.0 (0.1); $p < 0.0001$). The nitrate, nitrite, and nitrosamine values in gastric juice did not increase after treatment with either cimetidine or omeprazole. Serum concentrations of vitamin B12, β carotene, and albumin were similar before and after treatment with both drugs.

Conclusions—These results show that the incidence of gastric and duodenal bacterial overgrowth is considerably higher in patients treated with omeprazole compared with cimetidine. This can be explained by more pronounced inhibition of gastric acid secretion. No patient developed signs of malabsorption or an increase of *N*-nitroso compounds. The clinical significance of these findings needs to be assessed in studies with long-term treatment with omeprazole, in particular in patients belonging to high risk

groups such as HIV infected and intensive care units patients.

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Keywords: bacterial overgrowth, omeprazole, cimetidine, nitrates, nitrites, *N*-nitroso compounds.

The major control factor for bacterial survival in the stomach is the acidity of gastric contents. Gastric and duodenal bacterial overgrowth frequently occurs in conditions characterised by diminished gastric acid secretion.^{1,2} At a pH above 4, salivary organisms survive and a resident gastric flora, including faecal type organisms, develops if pH rises above 5.^{3,4} During treatment with histamine H₂ receptor antagonists gastric bacterial numbers tend to rise⁵ and some studies have reported increased numbers of nitrate reducing organisms and higher concentration of nitrites.^{6,7} Little is known about gastric and duodenal bacteriology during treatment with proton pump inhibitors such as omeprazole.^{8,9} We have recently found that duodenal bacterial colonisation with oral and faecal type bacteria is present in more than half of the patients treated with omeprazole at doses of 20-40 mg daily.¹⁰ However, there is only one study comparing H₂ receptor antagonists and omeprazole.¹¹ This information is of major clinical significance as bacterial overgrowth, especially during longterm antisecretory treatment, may have important consequences, such as the development of malabsorption syndromes,¹² intestinal infections,¹³⁻¹⁶ and the formation of potentially carcinogenic compounds.¹⁷

The aim of this prospective, randomised, double blind study was therefore to evaluate the incidence of gastric and duodenal bacterial overgrowth in patients with peptic ulcer disease treated with omeprazole compared with patients treated with cimetidine and to investigate the relations between the degree of bacterial colonisation and gastric values of *N*-nitroso compounds.

Methods

Patients

The study was performed in 47 outpatients (mean age 42; range 20 to 69; eight women) referred for routine diagnostic endoscopy. These patients had not taken antisecretory drugs or antibiotics during the month prior to the first endoscopy. Patients with diabetes or

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immunity disorders and those with low gastric acidity at the first endoscopy (intra-gastric pH > 4) were excluded. Endoscopy at inclusion showed the presence of reflux oesophagitis in 28 patients, duodenal ulcer in eight, gastric ulcer in five, and gastric or duodenal erosions, or both, in six patients.

Each patient received in a double blind, random order 20 mg omeprazole with breakfast and placebo with dinner during four weeks or 800 mg cimetidine with dinner and placebo with breakfast during four weeks. All patients were investigated one day before and one day after the treatment course. Thus, the last omeprazole capsules were taken 24 hours and the last cimetidine dose 12 hours before endoscopy.

Ten of 47 patients were excluded during the study: gastric biopsies showed an adenocarcinoma in one patient, compliance was bad in five patients, one was lost for control purposes, and treatment was stopped in three patients presenting with diarrhoea (two with omeprazole, one with cimetidine). In these three patients, diarrhoea disappeared within two days upon cessation of treatment, suggesting a side effect of the drug itself rather than an effect of bacterial overgrowth (patients did not undergo control endoscopy).

All endoscopic examinations were performed for clinical indications and written informed consent was obtained before participation. The study was approved by the medical ethical committee of the University Hospital of Lausanne.

Sampling procedure

An Olympus GIF-Q20 endoscope was used for all investigations. A double sheathed plastic wash pipe (Mauch, Münchenstein, Switzerland) was used to collect the aspirates under sterile conditions. The pipe was constructed by passing one Teflon coated plastic tube (diameter 1 mm) inside another (diameter 2.3 mm). The end of the outer tube was covered by a thin rubber plug vulcanised into its tip, so that the interior of the outer tube containing the inner tube remained sterile until the rubber plug was pierced by pushing the inner tube out of the outer tube. After assembling both tubes and vulcanisation of the rubber plug into the tip of the outer tube, the whole assembly was sterilised by autoclaving for 20 minutes at 120°C.¹⁸

All endoscopy procedures were performed after an overnight fast. No local anaesthesia was used. The patients were sedated with 2.5 to 5 mg midazolam given intravenously. Fluid samples were obtained under endoscopic visualisation in the stomach (10 ml) and about 20 cm beyond the pylorus (1 ml). Every effort was made to avoid contamination of gastric juice with saliva. Aspirates were collected in a sterile syringe and 1 ml immediately transferred to an anaerobic transport vial (Port-A-Germ, BioMérieux, France). The pH value and concentrations of nitrate, nitrite, and nitrosamine compounds were also measured in gastric samples (IARC, Lyon, France). Serum

samples were taken in all patients at first and second endoscopy for vitamin B12, beta-carotene, and albumin measurements.

Bacteriological culture

The microbiologists who cultured the duodenal and gastric aspirates had no knowledge of the clinical or endoscopic findings; nor were they informed about the treatment regimen of the patients. The contents of the transport vial were measured (volume) and quantitatively plated for both aerobic and anaerobic organisms. The samples were serially diluted with phosphate buffer containing 1% peptone. Aerobic cultures were grown by plating the samples on the following media: 5% sheep blood agar, MacConkey agar, phenyl ethyl alcohol agar, and Sabouraud glucose agar containing sheep blood supplemented with cysteine and vitamin K⁺, neomycin agar, and vancomycin/nalidixic acid agar. Media were incubated for a minimum of 72 hours with a first reading at 24 hours for aerobic growth and 48 hours for anaerobes. Bacteria were identified by standard methods to species level or, where appropriate, to genus level only. Bacterial numbers were determined by a colony count of the individual bacterial morphologies and expressed in exponential numbers per ml of clinical specimen. Cultures were considered positive for bacterial overgrowth if the total count of bacteria was $\geq 10^5$ cfu/ml in gastric or duodenal aspirates, or both.

Nitrate, nitrite, and nitrosamine compounds measurement

Five ml of gastric juice destined for analysis of *N*-nitroso compounds was mixed with 60 mg sulphamic acid in glass vials with Teflon stoppers, allowed to stand for five minutes at room temperature (protected from light), and subsequently placed in a -20°C freezer. Analysis of *N*-nitroso compounds was carried out within one to two weeks after collection. Four ml of gastric juice, destined for nitrite analysis, was mixed immediately upon collection with 0.05 ml 6 N NaOH and frozen. Nitrate and nitrite were analysed according to the method described by Green *et al.*¹⁹ The concentrations of thermo and acetic acid labile TEA responsive compounds (TACs) and *N*-nitroso compounds were measured by the release of NO as previously described.²⁰

Statistical evaluation

Values are given as mean (SEM). Bacterial counts were logarithmically transformed for statistical evaluation. Statistical analysis of the data was done by Fisher's exact test to compare the number of patients with and without bacterial overgrowth after treatment with omeprazole and cimetidine. The bacterial counts in the gastric and duodenal juices; the nitrate, nitrite, and nitrosamine compounds; the intra-gastric pH and the vitamin B12, β carotene, and albumin serum concentrations

Figure 1: Type of bacteria ($\geq 10^4$ cfu/ml) in stomach and duodenum of patients with bacterial overgrowth.

in the two groups were compared by the non-parametric Mann-Whitney U test. Difference was considered significant with p values < 0.05 .

Results

Before treatment with omeprazole or cimetidine three patients (8%) had bacterial overgrowth: in one patient staphylococci were found in gastric and duodenal aspirates ($\geq 10^5$ cfu/ml); in two patients α haemolytic streptococci, non-haemolytic streptococci, staphylococci or corynebacterium species were detected in duodenal samples ($\geq 10^5$ cfu/ml) with sterile gastric aspirates. At the end of the treatment course, gastric or duodenal bacterial overgrowth, or both, was present in 10 of 19 patients receiving omeprazole (53%) and in

three of 18 patients receiving cimetidine (17%; $p < 0.05$). Seven patients had both gastric and duodenal bacterial overgrowth, three patients had gastric bacterial overgrowth only, and three patients had duodenal bacterial overgrowth only. Gastric bacterial overgrowth ($\geq 10^5$ cfu/ml) was present in eight of 19 patients receiving omeprazole (42%) and in only one of 18 patients receiving cimetidine (6%); ($p < 0.02$). Duodenal bacterial overgrowth ($\geq 10^5$ cfu/ml) was present in seven of 19 patients receiving omeprazole (37%) and in three of 18 patients receiving cimetidine (17%; $p = 0.27$). The median number of gastric and duodenal bacterial counts ($\log_{10}$) was higher in the omeprazole group (6.0 (0.2) and 5.0 (0.2) respectively) compared with the cimetidine group (4.0 (0.2) and 4.0 (0.1) respectively; $p < 0.001$ and 0.01, respectively).

Figure 1 shows the type of bacteria ($\geq 10^4$) identified in the stomach and duodenum in patients treated with omeprazole or cimetidine who had bacterial overgrowth. α Haemolytic or non-haemolytic streptococci, or both, were found in all patients. Gram negative *Enterobacteriaceae* were identified in three patients (klebsiella species in one patient, *Escherichia coli* in two patients), and pseudomonas species in one patient. Anaerobes were recovered from two patients (bacteroides species) and enterococci from one patient. In four of 13 patients with bacterial overgrowth (30%), faecal type bacteria (*Escherichia coli*, bacteroides species, enterococci, and klebsiella species) were found whereas only oral and pharyngeal type bacteria were identified in the other patients. There was no difference in the distribution of bacterial types in patients treated with omeprazole or cimetidine.

In six of seven patients with combined gastric and duodenal bacterial overgrowth, all the bacteria cultured in duodenal juice were also present in gastric juice.

Basal gastric pH was higher in patients treated with omeprazole compared with cimetidine (4.2 (0.5) versus 2.0 (0.2); $p < 0.001$) and in patients with bacterial overgrowth compared with those without bacterial overgrowth (5.1 (0.6) versus 2.0 (0.1); $p < 0.0001$). There was a close linear correlation between gastric pH and bacterial count ($r = 0.6812$; $p < 0.001$; Fig 2).

The nitrate, nitrite, and nitrosamine concentrations ($\mu\text{mol/l}$) measured in gastric juice were similar before and after treatment with cimetidine (496 (44) v 535 (117); 28.6 (9.1) v 44 (15.9); 0.37 (0.08) v 0.41 (0.10); 0.19 (0.08) v 0.15 (0.04), respectively, for nitrate, nitrite, TAC, and N-nitroso compounds; NS) or omeprazole (540 (93) v 801 (292); 81.4 (51.2) v 34.6 (11.3); 0.4 (0.12) v 0.54 (0.39); 0.18 (0.03) v 0.23 (0.12) respectively; NS). Similar values of these compounds were measured in patients with and without bacterial overgrowth after antisecretory treatment (771 (409) v 635 (164); 56.3 (22.9) v 33.3 (10.1); 0.20 (0.09) v 0.57 (0.28); 0.08 (0.04) v 0.23 (0.09) respectively; NS).

Vitamin B12, β carotene, and albumin serum concentrations were similar before and

Figure 2: Gastric pH and bacterial counts (cfu/ml) in patients treated with omeprazole or cimetidine. Dotted line: bacterial overgrowth defined as total bacterial count $\geq 10^5$ cfu/ml. Plain line: linear correlation between pH and bacterial counts ($p < 0.001$).

after treatment with omeprazole or cimetidine in patients with bacterial overgrowth (395 (54) *v* 389 (61); 0.55 (0.18) *v* 0.51 (0.09); 47.2 (0.6) *v* 47.7 (0.8) respectively for vitamin B12, β carotene, and albumin; NS).

Discussion

Bacterial colonisation of the stomach depends on the degree of reduction in gastric acid secretion.^{13 21} Recently, we¹⁰ and others^{9 22} have shown a high incidence of gastric and duodenal bacterial overgrowth during treatment with omeprazole. Omeprazole, which has a higher potency for gastric acid secretion inhibition than H₂ antagonists,²³ might therefore induce more often bacterial overgrowth than cimetidine. Only one study has yet been published that has compared omeprazole and H₂ antagonists in their potency to induce bacterial overgrowth.¹¹ This study showed no difference between the two forms of treatment. This question is of eminent clinical importance as reduction of gastric acid secretion has been shown to predispose to infection with a variety of organisms including salmonella, shigella, klebsiella and pseudomonas species.^{13 14} Secondly, bacterial overgrowth may cause a variety of diseases such as malabsorption syndromes,¹² nosocomial pneumonia,²⁴ infectious enteritis,^{15 16} and the formation of potentially carcinogenic *N*-nitroso compounds.¹⁷ In our study, we found gastric bacterial overgrowth in 42% of the patients treated with 20 mg omeprazole daily for four weeks but in only 6% of those receiving 800 mg cimetidine daily for a similar period. Both drugs were used in the doses that are generally accepted and recommended by the manufacturers. Some 37% of the patients receiving omeprazole also had duodenal bacterial overgrowth with a significantly higher duodenal bacterial count compared with cimetidine. Bacterial counts were highly correlated to basal gastric pH, which was higher in patients treated with omeprazole compared with cimetidine (4.2 (0.5) *v* 2.0 (0.2); *p* < 0.001).

Most of the bacteria identified in our study belong to species colonising the oral cavity and the pharynx. These results correspond to previous studies where the primary source of bacteria in subjects with achlorhydria or hypochlorhydria seems to be the oral cavity.^{2 25} Anaerobic bacteria are seldom present and the microbiological flora is dominated by streptococci, staphylococci, and haemophilus species.²⁵ In 30% we identified faecal type bacteria including anaerobes. This corresponds with our recent investigation, where we found faecal type bacteria in 50% of patients with bacterial overgrowth during omeprazole treatment.¹⁰

The clinical significance of bacterial overgrowth in patients with hypochlorhydria remains uncertain. Although the decrease in gastric acid secretion may be responsible for the increased likelihood of developing bacterial overgrowth and malabsorption in elderly patients, these patients have a low level of upper intestinal anaerobic bacteria²⁶ and most

studies found little or no effect of this so called 'simple colonisation'.^{25 27} In patients treated with cimetidine or ranitidine, gut infection such as salmonellosis, cholera, and parasitic infections have been reported,^{16 28 29} but conflicting results have been published about gastric and duodenal bacterial overgrowth during treatment with H₂ receptor antagonists. Some studies showed gastric bacterial proliferation in patients receiving cimetidine^{5 30-34} or ranitidine,^{35 36} but other groups were unable to confirm these findings.³⁷⁻⁴¹ Incidence of duodenal bacterial overgrowth during treatment with H₂ antagonists seems to be much lower compared with gastric overgrowth, but there are only a few investigations^{37 38} and the H₂ breath test used as the method of assessment in these studies has a low sensitivity and specificity for duodenal bacterial overgrowth.^{9 42} Data are far more limited with omeprazole but salmonella gastroenteritis has also been reported in a patient treated with 20 mg omeprazole.¹⁵ Data are also lacking in patients in high risk groups but recently the occurrence of nosocomial infections in intensive care units has been found to be increased by antisecretory treatment with H₂ antagonists.^{24 35} In HIV infected patients, hypochlorhydria, disturbance of gastric emptying, and impaired local immunity have been reported,⁴³⁻⁴⁷ and gastric or duodenal bacterial overgrowth was present in 30% of them.⁴⁸

Anaerobic colonisation can be associated with malabsorption syndromes leading to steatorrhea and vitamin B12 deficiency.^{12 49 50} Omeprazole has been shown to decrease cobalamin absorption⁵⁰ and the consequences of longterm treatment with omeprazole are not known. In this study we found no modification of vitamin B12, β carotene, and albumin blood concentrations in patients with bacterial overgrowth. Our results correspond with those of a recently published study, where no evidence of fat or carbohydrate malabsorption was found in elderly patients with bacterial overgrowth caused by atrophic gastritis or omeprazole treatment.⁹ We only treated our patients for four weeks, however, which is probably too short for the development of a pronounced vitamin B12 deficiency. Further studies with longterm omeprazole treatment are necessary to clarify this issue.

Reduced gastric acid secretion may cause colonisation of nitrate reducing bacteria in the stomach. This has been claimed to increase the formation of potentially carcinogenic *N*-nitroso compounds.¹⁷ Whether these changes have any clinical significance, and particularly in relation to the development of gastric cancer, has been extensively investigated and debated but remains controversial.⁵¹⁻⁵⁵ In some studies higher *N*-nitroso compounds concentrations were found in subjects treated with H₂ antagonists^{6 56} and omeprazole⁸ while others,^{36 41} including our group⁵⁷ could not confirm these earlier reports. In this study we did not find any significant modification of the gastric nitrate, nitrite, and *N*-nitroso compounds concentrations during treatment with either cimetidine or omeprazole. One explanation for these controversial results is that the

production of bacterially catalysed *N*-nitroso compounds in the stomach is dependent on the species and strains present^{58, 59} and on the duration of the antisecretory treatment. Indeed, we found only a few nitrate reducing bacteria such as *Escherichia coli*, pseudomonas, and klebsiella species in the stomach of patients treated with either drug.

To summarise, we found that the incidence of gastric and duodenal bacterial overgrowth was considerably higher in patients treated with 20 mg omeprazole compared with 800 mg cimetidine daily for four weeks, doses usually used and recommended in clinical practice for the treatment of peptic diseases. This result may be explained by the more potent inhibition of gastric acid secretion by omeprazole. The bacterial flora consisted mainly of oral type bacteria. Despite the presence of faecal type bacteria in 30% of the patients, no patient developed a malabsorption syndrome or an increase of *N*-nitroso compounds. The clinical significance of these findings needs to be assessed in studies with longterm treatment with omeprazole, in particular in patients in high risk groups.

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