Duodenal bacterial overgrowth during treatment in outpatients with omeprazole

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Abstract
The extent of duodenal bacterial overgrowth during the pronounced inhibition of acid secretion that occurs with omeprazole treatment is unknown. The bacterial content of duodenal juice of patients treated with omeprazole was therefore examined in a controlled prospective study. Duodenal juice was obtained under sterile conditions during diagnostic endoscopy. Aspirates were plated quantitatively for anaerobic and aerobic organisms. Twenty-five outpatients with peptic ulcer disease were examined after a 5-7 (0-5) weeks (mean (SEM)) treatment course with 20 mg (nine patients) or 40 mg (16 patients). The control group consisted of 15 outpatients referred for diagnostic endoscopy without prior antisecretory treatment. No patient in the control group had duodenal bacterial overgrowth. In the omeprazole group bacterial overgrowth (≥10^5 cfu/ml) was found in 14 (56%) patients (p=0.0003). The number of bacteria (log_{10}) in duodenal juice in patients treated with omeprazole was distinctly higher (median 5-7; range <2-8-7) when compared with the control group (median <2; range <2-5-0; p=0.0004). As well as orally derived bacteria, faecal type bacteria were found in seven of 14 and anaerobic bacteria in three of 14 patients. Bacterial overgrowth was similar with the two doses of omeprazole. These results indicate that duodenal bacterial overgrowth of both oral and faecal type bacteria occurs often in ambulatory patients treated with omeprazole. Further studies are needed to determine the clinical significance of these findings, particularly in high risk groups during long term treatment with omeprazole.

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Gastric acid plays an important part in the prevention of bacterial colonisation of the stomach and the small intestine. Reduction of gastric acid secretion predisposes to infection with a variety of organisms. Furthermore, it causes proliferation of a faecal type flora in the upper small intestine, which may be accompanied by various metabolic disturbances such as steatorrhea and vitamin deficiencies. Little is known about the gastric and duodenal bacterial flora during treatment with omeprazole, although omeprazole has a much higher potency to reduce gastric acid secretion compared with other inhibitors of gastric acid secretion such as H2 antagonists. In the only study so far published a small number (10) of healthy volunteers were investigated taking the drug (30 mg) for a short period (two weeks). Therefore, no conclusions can be drawn from this study regarding patients with peptic ulcer disease treated with standard doses of omeprazole during conventional treatment periods (four to eight weeks). Furthermore, bacterial colonisation of the duodenum was not investigated in this study. Thus it is not known whether small bacterial overgrowth occurs during omeprazole treatment.

We therefore examined the bacterial content of the duodenal juice of patients with peptic ulcer disease treated with omeprazole in a controlled prospective study. A novel technique for sterile aspiration of duodenal juice during endoscopy was used.

Patients and methods

Patients
The study was performed on 25 outpatients (mean age 53.4; range 25 to 83 years; 9 women). Endoscopy revealed the presence of gastric ulcers, (three), duodenal ulcers (two), pyloric ulcers (two), gastric and/or duodenal erosions (three), Barrett oesophagus (one), and reflux oesophagitis (14 patients). The patients were treated with 20 mg (nine patients for 4-7 (2-1) weeks (mean (SEM)) or 40 mg (16 patients for 6-2 (2-4) weeks) of omeprazole, the whole daily dose being taken with breakfast. All patients were investigated one day after the end of treatment. Thus the last omeprazole capsules were taken 24–28 hours before endoscopy.

Another 15 patients (mean age 46.9; range 25 to 73 years; 8 women; difference from omeprazole group NS) referred to the outpatient clinic for a routine diagnostic endoscopy with suspected peptic ulcer disease were examined as a control group. These patients had not taken H2 antagonists, omeprazole, or other antisecretory drugs within 10 days before endoscopy. In this untreated control group endoscopy showed gastric ulcer (one), duodenal ulcer (one), pyloric ulcer (one), reflux oesophagitis (one), Barrett oesophagus (one), Mallory-Weiss tear (one), gastric and/or duodenal erosions (three), and gastric polyp (one patient). Endoscopy findings were normal in five patients. Patients treated with omeprazole were asked about the presence of loose stools or diarrhoea in the last weeks before endoscopy.

Neither group of patients had received antibiotics within one month before the examination. All endoscopic examinations were performed for clinical indications and the patients were informed that material was to be aspirated for the study. The study was approved by the local ethics committee.

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SAMPLING PROCEDURE
An Olympus GIF-Q20 endoscope was used for all investigations, and a double sheathed plastic wash pipe (Mauch, Münchenein, Switzerland) was used to collect the aspirates by a previously reported technique. 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.

All endoscopy procedures were performed after an overnight fast. The patients were asked not to brush their teeth in the morning before endoscopy. No local anaesthesia was used. The patients were sedated with 2.5 to 5 mg midazolam (Dormicum) given intravenously.

The microbiological samples were obtained under endoscopic visualisation about 20 cm beyond the pylorus. Care was taken to use minimal air insufflation during endoscopy before obtaining the specimens to maintain the intraluminal environment as much as possible. When the collection site was chosen, the sterilised double sheathed wash pipe was passed through the suction channel. After the overture had cleared the tip of the endoscope, the inner tube was pushed forward so that its tip pierced the rubber stopper at the tip of the outer tube and emerged. About 2 ml of aspirate were collected in a sterile syringe and immediately transferred to an anaerobic transport vial (Port-A-Germ, BioMérieux, France).

BACTERIOLOGICAL CULTURE
The microbiologists who cultured the duodenal aspirates had no knowledge of the clinical or endoscopical findings; nor were they informed about the treatment regimen of the patients. The contents of the transport vial were measured (volume) and 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 gentamicin and chloramphenicol. Anaerobic cultures were grown by inoculating the following solid media: blood agar containing sheep blood supplemented with cysteine and vitamin K1, 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.

After aerobic and anaerobic incubation, cultures were considered positive for bacterial overgrowth if the total count of bacteria was \( \geq 10^7 / ml \). Cultures were considered negative for bacterial overgrowth when the total bacterial count was \(< 10^5 / ml \).

STATISTICAL EVALUATION
Values are given as medians (range). Statistical analysis of the data was by Fisher’s exact test to compare the number of patients with and without overgrowth after treatment with omeprazole and without treatment. Bacterial counts were logarithmically transformed for statistical evaluation. The bacterial counts in the duodenal juice in the two groups were compared with the non-parametric Mann-Whitney U test. Differences were considered significant with \( p \) values <0.05.

Results
Treatment with omeprazole caused bacterial overgrowth (\( \geq 10^5 \) cfu/ml) of the duodenum in 14 of 25 patients (56%). The dose of omeprazole did not influence the frequency of bacterial overgrowth. Thus a similar proportion of the patients exhibited duodenal bacterial overgrowth with 20 mg (five of nine patients) compared with 40 mg (nine of 16 patients). In the untreated control group no patient showed a significant bacterial colonisation of the duodenum (none of 15 patients). This difference from the group of patients treated with omeprazole was highly significant (\( p=0.0005 \)). The median number of bacterial counts was 5-7 (range <=2 to 8-7) in the omeprazole group compared with <2 (range <=2 to 4-8) in the controls (\( p=0.0004 \)).

Figure 1 shows the type of bacteria (\( \geq 10^4 \) cfu/ml) identified in patients treated with omeprazole who had bacterial overgrowth. Haemolytic (12 patients) and non-haemolytic (10 patients) streptococci were mostly found. Gram negative Entrobacteriaceae, such as Klebsiella species (five patients), Escherichia coli (one patient), and Pseudomonas species (two patients), enterococci (one patient), and Bacteroides species (one patient) were identified in nine patients, and anaerobes in three patients (Bacteroides species in one patient and Clostridium species in two patients). In seven of 14 patients with bacterial overgrowth faecal type bacteria (Escherichia coli, Clostridium species, Bacteroides species, enterococci, and Klebsiella species) were found, whereas only oral and pharyngeal type bacteria were identified in the other seven patients.

Two patients treated with omeprazole who had bacterial overgrowth and one patient without overgrowth reported loose stools or diarrhoea.

Discussion
Gastric acid is a major defence factor against the bacterial colonisation of the small bowel and thus contributes to the prevention of bacterial overgrowth syndromes and intestinal infection. In the past few years omeprazole – a drug with a high potency to inhibit gastric acid secretion – has been introduced into clinical practice.
Omeprazole may theoretically cause bacterial colonisation of the upper small intestine by its pronounced inhibition of gastric acid secretion. Despite this hypothetical risk, no studies have been performed to investigate the bacterial flora of the upper small intestine during treatment with omeprazole.

This study was motivated by three considerations: Firstly, omeprazole diminishes gastric acid secretion more than H2 antagonists and is thus more likely to produce duodenal bacterial overgrowth. Secondly, we have previously shown that although omeprazole raises intragastric pH above 4 for prolonged periods, the pH is less than 3 for several hours in each day. Therefore, the question of whether duodenal bacterial overgrowth occurs during omeprazole treatment cannot be decided by theoretical considerations alone. Thirdly, the methods used so far to examine duodenal bacterial overgrowth during antisecretory treatment with H2 antagonists are indirect (breath tests) and lack sensitivity and specificity, and only direct intubation of the small intestine can provide reliable data about the bacterial flora of the small intestine.

Our study is therefore the first investigation to examine directly duodenal bacterial overgrowth during antisecretory treatment. Also, it is the first study to examine the bacterial flora of the small intestine in patients treated with omeprazole. By applying endoscopic intubation of the duodenum we found bacterial overgrowth in more than half of the patients treated with 20–40 mg omeprazole daily for four to eight weeks, a dose and treatment duration applied in everyday clinical routine.

Bacterial colonisation of the stomach and the upper small intestine depends on the degree of the reduction in gastric acid secretion. Patients with reduced gastric acid secretion—for example, after vagotomy and antrectomy—develop gastric and duodenal bacterial overgrowth if the gastric pH rises above 4–0. Recent studies have shown that omeprazole diminishes intragastric acidity by more than 90% in ulcer patients and healthy subjects with a median pH above 3–5–4–0 for prolonged periods. Thus the pronounced inhibition of gastric acid secretion during omeprazole treatment may explain the development of duodenal bacterial overgrowth in most of our patients. The degree of bacterial colonisation was similar with 20 or 40 mg, which may be explained by the already profound inhibition of gastric acid secretion (>90%) by the lower dose.

Conflicting results have been published about gastric bacterial overgrowth during treatment with other antisecretory drugs, in particular H2 antagonists. Several groups found an increased number of intragastric bacteria in patients receiving cimetidine or ranitidine, although other groups were unable to confirm these findings. Omeprazole has been reported to cause gastric bacterial overgrowth in healthy volunteers. Few studies have investigated the incidence of duodenal bacterial overgrowth during treatment with H2 antagonists. Two studies reported no bacterial overgrowth in the small intestine during treatment with cimetidine and ranitidine. The H2 breath tests used as the method of assessment have a low sensitivity and specificity, however. In one case report bacterial overgrowth, however, faecal type bacteria were also found including anaerobes. Thus it seems that omeprazole may also cause ascending colonisation of the upper small intestine.

What are the clinical consequences of duodenal bacterial overgrowth during omeprazole treatment, as shown in this investigation? The design of the study and the small number of patients do not allow us to draw firm conclusions about the frequency of symptoms attributable to small intestinal bacterial overgrowth. Patients were treated with omeprazole for short periods, and few reported side effects; however, the development of clinically significant manifestations of bacterial overgrowth syndromes depends on the presence of anaerobic bacteria in the upper small intestine over prolonged periods. Anaerobic colonisation can be associated with the development of vitamin B12 deficiency and malabsorption syndromes with steatorrhoea, and recently, omeprazole has been shown to decrease cobalamin absorption. The risk of bacterial overgrowth syndromes during treatment with omeprazole should therefore be evaluated in prospective controlled studies especially in risk patients with long term omeprazole treatment.

As well as the development of duodenal bacterial overgrowth syndromes, reduced gastric acid secretion during treatment with omeprazole...
may cause a rise in the number of nitrate reducing bacteria in the stomach. This has been claimed to increase the formation of potentially carcinogenic N-nitroso compounds although we could not confirm these findings in another study. \(^\text{26}\) Furthermore, reduced gastric acid secretion may be responsible for a higher incidence of intestinal infections, such as salmonellosis, \(^\text{27}\) chola, \(^\text{28}\) and parasitic infections. \(^\text{29}\) Such infections have been described in patients treated with cimetidine \(^\text{30}\) and ranitidine. \(^\text{31}\) Recently, Salmonella gastroenteritis has been reported in a patient treated with 20 mg omeprazole. \(^\text{32}\) Also, reduced gastric acid secretion during treatment with H\(_2\) antagonists has been associated with the occurrence of nosocomial infections, in particular pneumonias, in intensive care units. \(^\text{33}\) Further studies with high risk patients, such as travellers or patients in intensive care units, are needed to assess these potential risks of omeprazole treatment.

In summary, we found duodenal bacterial colonisation in more than half of the patients treated with 20–40 mg omeprazole for short periods of four to eight weeks. The bacterial flora consisted mainly of oral type bacteria, but in half of the patients faecal type bacteria including anaerobes were also present. The clinical significance of these findings needs to be assessed in controlled prospective studies, particularly during long term omeprazole treatment and in patients belonging to high risk groups.

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