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Efficacy of primed infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: a prospective randomised controlled study

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Abstract

***Background*—In healthy subjects, continuous infusions of high dose ranitidine and omeprazole produce high intragastric pH values.**

***Aim*—To test the hypothesis that both drugs also maintain high intragastric pH values in patients with bleeding ulcers.**

***Patients and Methods*—In two parallel studies, 20 patients with bleeding duodenal ulcers and 20 patients with bleeding gastric ulcers were randomly assigned to receive either ranitidine (0·25 mg/kg/hour after a bolus of 50 mg) or omeprazole (8 mg/hour after a bolus of 80 mg) for 24 hours. Intragastric pH was continuously recorded with a glass electrode placed 5 cm below the cardia.**

***Results*—Both drugs rapidly raised the intragastric pH above 6. During the second 12 hour period, however, the percentage of time spent below a pH of 6 was 0·15% with omeprazole and 20·1% with ranitidine (p=0·0015) in patients with duodenal ulcer; in patients with gastric ulcer it was 0·1% with omeprazole and 46·1% with ranitidine (p=0·002).**

***Conclusions*—Primed infusions of omeprazole after a bolus produced consistently high intragastric pH values in patients with bleeding peptic ulcers, whereas primed infusions with ranitidine were less effective during the second half of a 24 hour treatment course. This loss of effectiveness may be due to tolerance.**

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Keywords: omeprazole, pH measurement, ranitidine, ulcer bleeding.

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Acute upper gastrointestinal haemorrhage is an important cause of morbidity and mortality,[1 2] with peptic ulcers being the most frequent source of bleeding.[1-3] The prognosis of bleeding depends on age, underlying diseases, haemodynamic status, and persistence or recurrence of bleeding.[2 4] Endoscopic therapy of peptic ulcer bleeding has been shown to be safe and effective, with reduction of further bleeding, surgery, and mortality.[5-7] On the other hand, the use of secretory inhibitors in ulcer bleeding is controversial.[8] Whereas endoscopic injection therapy gives consistently good results, many trials with secretory inhibitors were negative.[9-13] This is surprising because theoretically these drugs should work. In vitro, platelet aggregation, platelet disaggregation, coagulation, and fibrinolysis are strongly dependent on the pH of the gastric juice.[14-19] When pH falls below 6·8, platelet aggregation and blood (plasmatic) coagulation become abnormal, below pH 6·0 platelet disaggregation takes place, below pH 5·4 platelet aggregation and plasma coagulation are virtually abolished, and below pH 4·0 fibrin clots are dissolved.[15 18] In vivo, a beneficial effect of pH raising procedures on haemostasis has not been shown. Other reasons may also account for the lack of effectiveness of secretory inhibitors in patients with bleeding ulcers. The doses of H_2 receptor antagonists as well as those of omeprazole used in most clinical trials of upper gastrointestinal bleeding were too low to maintain high intragastric pH.[20-24] In patients with bleeding, the effect of drugs on acid may also be diminished by blood pooling, loss of circulating drug via bleeding, dilution by plasma expanders and blood transfusions, and by stimulation of gastric acid secretion due to blood shed into the gut. Finally, injection therapy may be so effective that an additional effect of the drugs cannot be shown.

Pharmacological studies in healthy subjects and patients with ulcers have clearly shown that primed infusions with antisecretory drugs are superior to the bolus injections that were often used in clinical trials.[8 20 25-28] In patients with duodenal ulcer disease in remission ranitidine (0·25 mg/kg/hour after a bolus of 50 mg) and omeprazole (8 mg/hour after a bolus of 80 mg) proved to be effective in maintaining gastric pH values above.[6 29] In a randomised controlled trial we tested the hypothesis that these treatment regimens may maintain high intragastric pH values in patients presenting with bleeding duodenal and gastric ulcers. We also assessed the overall effect of injection therapy plus an antisecretory drug in this series.

Methods

STUDY POPULATION

Forty patients with bleeding peptic ulcer were enrolled into two parallel running prospective randomised studies (duodenal ulcer trial: n=20

patients; gastric ulcer trial: n=20 patients). Before starting the trials, randomisation with the random number table method was carried out separately for patients with duodenal and gastric ulcers. A truncated binomial design was chosen to have 10 patients treated with ranitidine and 10 patients treated with omeprazole in each trial. Patients were allocated to the treatment groups by drawing closed envelopes.

Patients with clinical (haematemesis or melaena) and endoscopic signs of a peptic ulcer bleeding (stage I and II according to classification of Forrest *et al*[30]), older than 18 years were eligible for the studies. Exclusion criteria were treatment with antisecretory drugs and antacids during the preceding week, renal failure (creatinine ≥2·0 mg/dl), severe liver disease, previous intolerance to ranitidine or omeprazole, pregnancy and lactation, prerandomisation decision to perform surgery, status after stomach surgery except a simple closure of a perforation, clotting disorder, and lack of informed consent. The studies were conducted according to the Declaration of Helsinki. The protocols were approved by the ethics committee of the University of Essen.

PROTOCOL

Patients who were eligible for the study were randomly treated with either ranitidine (50 mg initially, then 0·25 mg/kg/hour for 24 hours) or omeprazole (80 mg initially, then 8 mg/hour for 24 hours). All drugs were given intravenously. These dosages were chosen because they have been shown to maintain intragastric pH values above 6 in patients with duodenal ulcer disease in remission.[29] The antisecretory treatment started two hours after the end of emergency endoscopy. No antibiotics were given during the intravenous treatment with antisecretory drugs.

INVESTIGATIONS

All patients were investigated clinically including a structured interview and a laboratory screen before entering the trial and at the end of the 24 hour medical treatment. An emergency endoscopy of the upper gastrointestinal tract was performed within two hours of hospital admission. In eight patients with an active bleeding peptic ulcer and in 16 patients with a visible vessel endoscopic injection therapy was carried out with adrenaline (1:10.000 with NaCl) and submucosal injection of fibrin tissue glue (Tissucol, Immuno, Heidelberg, Germany) as described elsewhere.[31] At the end of emergency gastroscopy, the gastric content was endoscopically removed as far as possible. All patients had endoscopy again after stopping the intravenous antisecretory therapy. Four antral and four body biopsies were taken and assessed for *Helicobacter pylori* by means of a rapid urease test, specific culture, and histology using Warthin and Starry stain.[32]

24 HOUR pH MEASUREMENT

A glass pH electrode with built in reference (Ingold 440-M3, Medical Instruments Corporation (MIC), Solothurn, Switzerland) was inserted transnasally and positioned fluoroscopically 5 cm below the cardia. It was calibrated before and after the pH recording with standard buffer solutions of pH 7·00 and pH 4·01 (Fresenius, Bad Homburg, Germany). Electrodes with a pH shift ≥0·2 pH units were discarded. The pH electrode was connected to a data logger (GastrograpH Mark III, MIC, Solothurn, Switzerland). At the end of each recording, the data were transferred to a personal computer, stored, and later analysed with pack-2 software (MIC, Solothurn, Switzerland).

DATA ANALYSIS AND STATISTICAL EVALUATION

The time intervals for the analysis were predefined as follows: first hour, second hour to 24th hour, second hour to 12th hour, 13th hour to 24th hour. The mean and the median gastric pH as well as the time spent above thresholds of pH 4, pH 5·4, pH 6, and pH 6·8 were calculated for each of the predefined time periods and compared by Mann-Whitney *U* test. We chose these pH cut off values because they represent important thresholds for haemostasis.[15 18]

The demographic and clinical characteristics of the study patients were compared by two sided Mann-Whitney *U* test or Fisher's exact test when appropriate. Fisher's exact test and Mantel-Haenszel statistics were used to identify differences between the two groups of patients treated with either ranitidine or omeprazole. The variables drug (ranitidine or omeprazole), age, sex, height, body weight, smoking, regular alcohol intake, history of ulcer disease, location of ulcer (duodenal ulcer or gastric ulcer), *H pylori* infection, and intake of aspirin or non-steroidal antiflammatory drugs were then introduced as explanatory variables in a multiple logistic regression analysis (forward stepwise and backward elimination selection), with the percentage of time spent with a pH of >6 during the second half of the treatment course being the dependent variable. Because the results of the pH recordings (time with a pH of >6) did not follow a normal distribution, we used a logarithmic transformation of the individual values. Significance was considered at a 5% probability level.

Results

Forty patients, 20 with duodenal and 20 with gastric ulcer bleeding entered the parallel trials. The subgroups of patients of both studies treated with either ranitidine or omeprazole were well matched for demographic and clinical characteristics (duodenal ulcer (ranitidine *v* omeprazole): median age (range): 65·5 (36–89) *v* 64·5 (39–88), proportion of men: 80% *v* 80%, proportion of smokers: 40% *v* 30%, history of ulcer disease: 60% *v* 60%, history of ulcer bleeding: 20% *v* 30%, active

bleeding ulcer or endoscopic signs of recent ulcer bleeding: 1/9 *v* 2/8; gastric ulcer (ranitidine *v* omeprazole): median age (range): 65·5 (28–88) *v* 72·0 (40–78), proportion of men 30% *v* 60%, proportion of smokers: 30% *v* 30%, history of ulcer disease: 30% *v* 30%, history of ulcer bleeding: 0% *v* 20%, active ulcer bleeding or endoscopic signs of recent ulcer bleeding: 3/7 *v* 2/8). All study patients were either infected with *H pylori* (duodenal ulcer: n=13; gastric ulcer: n=7) or had taken ulcerogenic drugs (duodenal ulcer: n=2; gastric ulcer: n=4), or both (duodenal ulcer: n=5; gastric ulcer: n=9).

None of the study patients showed clinical signs of rebleeding during the antisecretory treatment, but five patients (12·5%, 95% confidence interval (95% CI) 4 to 27%; patients treated with ranitidine: n=2; patients treated with omeprazole: n=3) had endoscopic evidence of rebleeding (blood or haematin in the stomach). One patient with a large gastric ulcer close to the left gastric artery was referred for early elective surgery, and one patient with a duodenal ulcer died of massive rebleeding on the second hospital day. Both drugs were well tolerated. Generalised side effects were not recorded. Mild thrombophlebitis at the site of drug infusion was seen in six patients treated with ranitidine and in two patients after omeprazole therapy (30% *v* 10%; p=0·24).

Both ranitidine and omeprazole rapidly raised the intragastric pH above 6 in patients with duodenal or gastric ulcers (Fig 1). The median time to reach a pH of >6 was 60 (range 10–445) minutes with ranitidine and 36 (range 7–378) minutes with omeprazole (p=0·42). High intragastric pH values were maintained throughout the entire pH recording with omeprazole, whereas the pH values decreased during the second half of the pH recording with ranitidine (Fig 1). The mean as well as the median intragastric pH values during the 2nd to 12th hour of treatment were 6·52 (95% CI 5·75 to 6·86) and 6·60 (95% CI 5·66 to 7·09) in patients with duodenal ulcer treated with ranitidine, 6·61 (95% CI 5·96 to 6·79) and 6·65 (95% CI 6·32 to 6·77) in patients with duodenal ulcer treated with omeprazole, 6·68 (95% CI 5·28 to 7·13) and 6·75 (95% CI 5·48 to 7·29) in patients with gastric ulcer treated with ranitidine, and 6·72 (95% CI 6·10 to 7·09) and 6·80 (95% CI 6·21 to 7·09) in patients with gastric ulcer treated with omeprazole (p=0·80 and p=0·97 for patients with duodenal ulcer; p=0·68 and p=0·91 for patients with gastric ulcer). During the second half of treatment, however, the mean intragastric pH was lower in patients treated with ranitidine than in patients treated with omeprazole (duodenal ulcer: 6·22 (95% CI 5·44 to 6·47) *v* 6·75 (95% CI 6·47 to 6·97), p=0·01; gastric ulcer: 5·66 (95% CI 4·92 to 6·32) *v* 6·65 (95% CI 6·07 to 7·08), p=0·03). There was a trend toward lower median intragastric pH values in patients treated with ranitidine compared with omeprazole (duodenal ulcer: 6·45 (95% CI 6·12 to 6·77) *v* 6·75 (95% CI 6·28 to 6·98), p=0·39; gastric ulcer: 5·95 (95% CI 5·12 to 6·58) *v* 6·80 (95% CI 6·06 to 7·14), p=0·08). The percentage of time spent below pH thresholds of 4, 5·4, and 6 was similar with ranitidine and omeprazole during the first half of the pH recording,

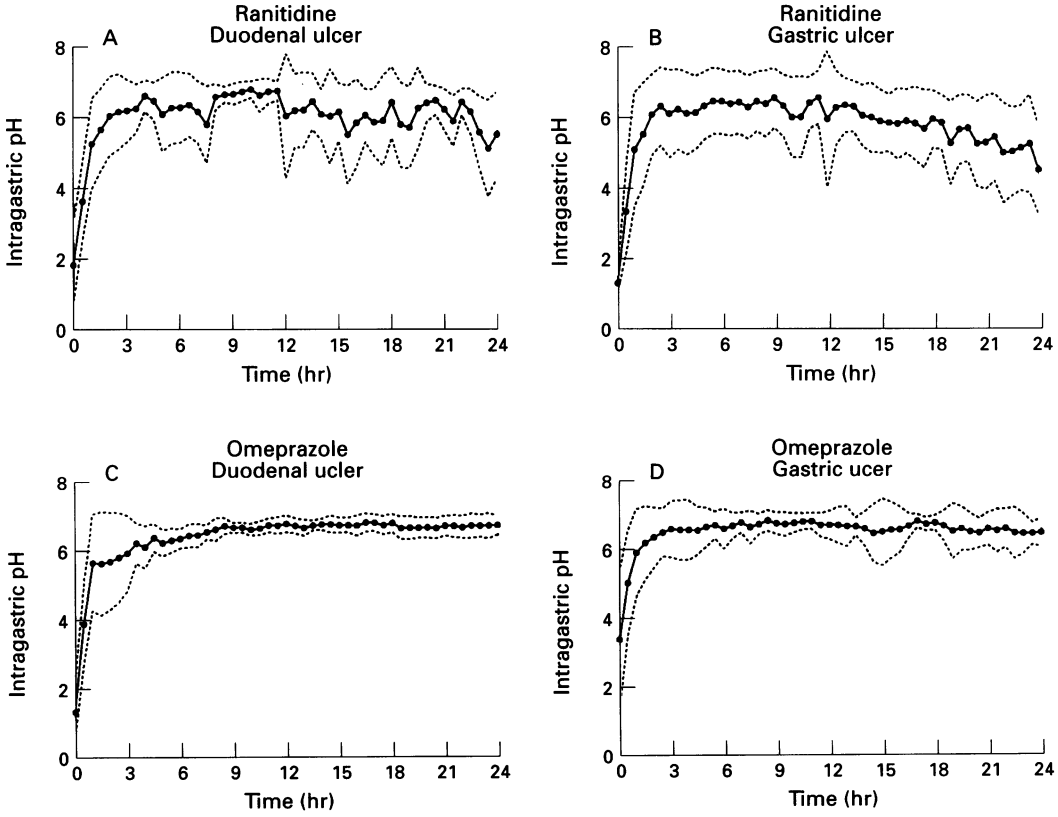

Figure 1: Mean 24 hour gastric pH and 95% CI in patients with bleeding from duodenal ulcer (n=20) or gastric ulcer (n=20) treated intravenously with ranitidine or omeprazole.

whereas ranitidine was less effective than omeprazole in maintaining the intragastric pH above these values, during the second half of the treatment (Fig 2).

As judged from multiple logistic regression analysis, the only independent variable related to the pH response (percentage of time spent with a pH >6 during the second half of treatment) was the type of antisecretory drug given (ranitidine *v* omeprazole; p<0·0001). The patients' age (p=0·17), sex (p=0·70), height (p=0·91), body weight (p=0·64), smoking (p=0·99), drinking habits (p=0·75), history of ulcer disease (p=0·27), location of the bleeding ulcer (duodenum *v* stomach, p=0·72), current *H pylori* status (p=0·56), and previous intake of aspirin or non-steroidal anti-inflammatory drugs (p=0·78) were not related to the pH response.

Discussion

This study has shown that omeprazole (8 mg/hour after a bolus of 80 mg) maintains intragastric pH values >6 in patients with duodenal and gastric ulcer bleeding. Ranitidine (0·25 mg/kg/h after a bolus of 50 mg) was similarly effective during the first 12 hours of treatment but less effective during the second half of the 24 hour treatment course. The studies were conducted in a parallel group design. Confounding variables may, therefore, have had an impact on the pH response. The results of the multiple logistic regression analysis, however, clearly indicated that this was not the case, the type of antisecretory drug being the only determinant of the pH response. Our results are in accordance with preliminary data reported by Barnert *et al*,[33] who treated patients with a bleeding peptic ulcer. They also accord with a recent pharmacological study.[29] Although not specifically stated by the authors, others have also found a decreasing effect of ranitidine on the intragastric pH within 24 hours of continuous infusions at constant rate.[8 34]

The apparent loss of the efficacy of ranitidine during continuous infusion might be explained by changes of gastric acid secretion or by tolerance to the drug. Acid secretion follows a circadian rhythm, with a maximum occurring during early evening.[35] If all treatments had been started during the day, this could account for the loss of effectiveness during the second 12 hour period.[36] As this is not the case, circadian variations of gastric acid secretion cannot explain the decrease of the efficacy of ranitidine. In addition, the unchanged effectiveness of omeprazole does not support this hypothesis.

Tolerance is known to occur in response to repetitive dosing of H_2 receptor antagonists.[37] It has never been found with proton pump inhibitors. By contrast with omeprazole, continuous infusion of the H_2 receptor antagonist famotidine has been shown to increase the concentration of proton pump protein. As the level of gene expression remains unchanged, H_2 receptor antagonists may decrease enzyme turnover.[38] In addition, alternate pathways of stimulation of acid secretion may also contribute to the tolerance

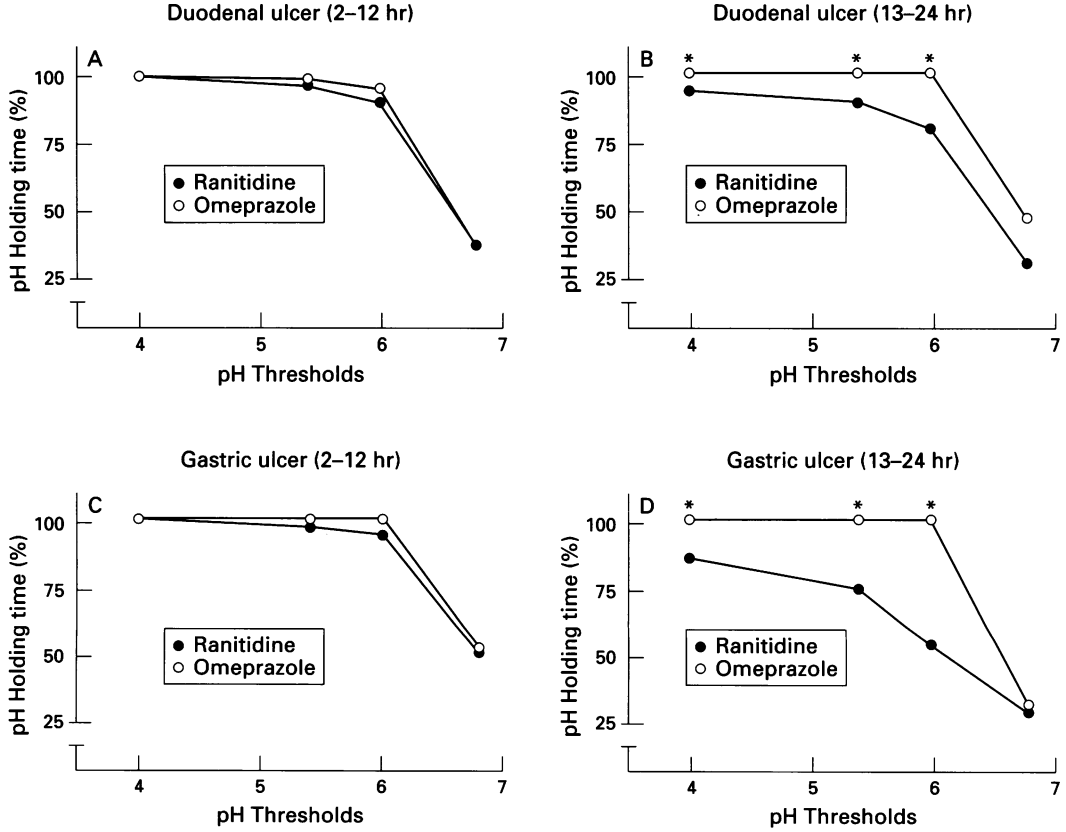

*Figure 2: pH holding time: median percentage of time spent above pH thresholds of 4, 5·4, 6, and 6·8 during the 2nd to 12th hour and the 13th to 24th hour with ranitidine or omeprazole in patients with bleeding from either duodenal or gastric ulcer (*p<0·003).*

found with H_2 receptor antagonists in humans.[38 39] By contrast with ranitidine, the pH response to omeprazole in this study showed little interindividual variation. In previous studies, both oral omeprazole and treatment in the form of repeated bolus injections were associated with large interindividual variations of the pH response.[24 40–44] These variations may be due to individual variations of acid pump turnover; continuous infusion of omeprazole is, on the basis of in vitro studies, better suited to bind all pumps than other forms of administration.[45] In addition, the degree of acid inhibition produced by omeprazole is closely related to the area under the curve, but not to the plasma concentration at any given point in time.[45] It is, therefore, conceivable that omeprazole delivered at a constant rate will be more effective than repeated boluses for the control of intragastric pH, and this study corroborates this expectation.

The acid response to omeprazole at a dose of 20 mg given orally depends on the presence or absence of *H pylori*.[43] Omeprazole produces much higher intragastric pH values before than after cure of the infection, both in healthy subjects and in patients with duodenal ulcer.[43 46] This may be due to neutralising substances such as ammonia generated by *H pylori*. Although this study was not designed to test the effect of *H pylori* on pH, the multiple logistic regression analysis suggests that high doses of inhibitors of acid secretion are similarly effective in infected and non-infected patients with peptic ulcer. It is conceivable that in infected patients lower doses of omeprazole may be sufficient to sustain a high intragastric pH. This should be tested in future studies.

The fall in pH during continuous treatment with ranitidine over 24 hours is less pronounced with an increasing dose of the drug.[36] Also, in patients with bleeding duodenal ulcers pH adjusted infusion of famotidine was clearly superior to famotidine delivered at a constant rate.[47] Thus it would be interesting to study the effect of a second bolus of ranitidine given after 12 hours. Alternatively, a higher dose of ranitidine may be given during the second half of a 24 hour course of treatment. However, in previous studies increasing doses of ranitidine were progressively less able to maintain a gastric pH >4.[48] By contrast, with omeprazole increasingly lower doses were required to obtain the same effect.[48 49]

The question whether consistently high intragastric pH values would improve the outcome of bleeding peptic ulcers remains unanswered. In our series, rebleeding was not related to the control of pH. In two large, randomised, double blind, placebo controlled multicentre trials an omeprazole regimen similar to the one used in our study had a beneficial effect but the results are preliminary,[50 51] and in two small scale randomised studies omeprazole infusions were as effective as endoscopic injection therapy,[52 53] but these studies may be criticised and are difficult to interpret.

In conclusion, primed infusions of high dose omeprazole should be preferred over ranitidine if consistently high intragastric pH values are desired for more than 12 hours.

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