postoperative follow up and a better understanding of the natural history of ischaemic heart disease.

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References

[1] Blackburn H. The exercise electrocardiogram in diagnosis. *Cardiology* 1977;**62**:190-205.
[2] Selwyn AP, Fox K, Eves M, *et al.* Myocardial ischaemia in patients with frequent angina pectoris. *Br Med J* 1978;ii:1594-6.
[3] Fox K, Selwyn A, Shillingford J. Praecordial electrocardiographic mapping after exercise in the diagnosis of coronary artery disease. *Am J Cardiol* 1979;**43**:541-6.
[4] Fox K, Selwyn A, Oakley D, *et al.* Relation between the praecordial projection of ST segment changes after exercise and coronary angiographic findings. *Am J Cardiol* 1979;**44**:1068-75.
[5] Selwyn A, Shillingford JP. Praecordial mapping of Q waves and RS ratio changes in acute myocardial infarction. *Cardiovasc Res* 1977;**11**: 167-71.
[6] Fox KM, Selwyn AP, Shillingford JP. Projection of electrocardiographic signs in praecordial maps after exercise in patients with ischaemic heart disease. *Br Heart J* 1979;**42**:416-21.
[7] Elamin MS, Boyle R, Kardash MM, *et al.* Accurate detection of coronary heart disease by new exercise test. *Br Heart J* 1982;**48**:311-20.
[8] Cooksey SD, Dunn M, Massie E. *Clinical vectorcardiography.* 2nd ed. Chicago: Year Book Medical Publishers, 1977:94.
[9] Gerson MC, Phillips JF, Morris SN, *et al.* Exercise induced U-wave inversion as a marker of stenosis of the left anterior descending coronary artery. *Circulation* 1979;**60**:1014-20.
[10] Horan LG, Flowers NC, Johnson JC. Significance of the diagnostic Q wave in myocardiac infarction. *Circulation* 1971;**43**:428-36.
[11] Scandinavian Committee on ECG classification. The "Minnesota code" for ECG classification. Adaptation to CR leads and modifications of the code for ECGs, recorded during and after exercise. *Acta Med Scand [suppl]* 1967;**481**:1-26.
[12] Judkins MP. Selective coronary arteriography. A direct percutaneous transfemoral technique. *Radiology* 1967;**89**:815-24.
[13] Sones FM, Shirey EK. Cine coronary arteriography. *Mod Concepts Cardiovasc Dis* 1962;**31**:735-8.
[14] Fox K, England D, Jonathan A, *et al.* Praecordial surface mapping of the exercise ECG. *Br J Hosp Med* 1982;**27**:291-9.
[15] Sketch M, Mohiudahin S, Lynch J. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary angiograms. *Am J Cardiol* 1975;**36**:169-73.
[16] Jolliffe RW. Quantitative aspects of clinical judgment. *Am J Med* 1973; **55**:431-3.
[17] Diamond GA, Forester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med* 1979;**300**: 1350-8.
[18] Second Interim Report by the European Coronary Surgery Study Group. Prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1980;ii:491-5.

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Effect of daily oral omeprazole on 24 hour intragastric acidity

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Abstract

Twenty four hour intragastric acidity was measured in nine patients with duodenal ulcer before and after one week of treatment with oral omeprazole 30 mg daily, a drug that inhibits gastric secretion by inhibition of parietal cell H^+K^+ adenosinetriphosphatase (ATPase). Omeprazole virtually eliminated intragastric acidity in all patients: the median 24 hour intragastric pH rose from 1·4 to 5·3 and the mean hourly hydrogen ion activity fell from 38·50 to 1·95 mmol(mEq)/l ($p < 0·001$). This inhibition of 24 hour intragastric acidity is more profound than that previously reported with either cimetidine 1 g daily or ranitidine 300 mg daily.

Introduction

Omeprazole is a new substituted benzimidazole (fig 1). Substituted benzimidazoles inhibit the action of the enzyme H^+K^+ adenosinetriphosphatase (ATPase), which is postulated to be the proton pump of the parietal cell.[1-7] Omeprazole inhibits both basal and pentagastrin stimulated acid secretion in normal man,[8 9] and basal secretion in patients with the Zollinger-Ellison syndrome.[10] The acid inhibitory effect of omeprazole is non-competitive and of prolonged duration.[4] The maximal antisecretory effect is observed after several days of treatment.[8]

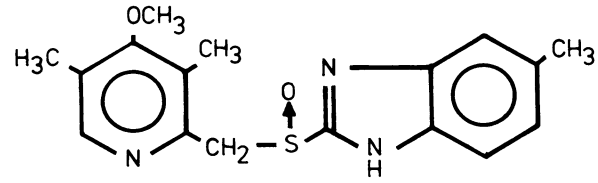

FIG 1—Chemical structure of omeprazole.

In earlier 24 hour studies with cimetidine[11 12] and ranitidine[13] we defined the effective dose of these antisecretory drugs before the start of clinical trials: both H_2 receptor antagonists decrease mean intragastric hydrogen ion activity by approximately two thirds over 24 hours in patients with duodenal ulcer. Omeprazole appears to be a more potent inhibitor of acid secretion than either cimetidine or ranitidine.[8 9] In the present study we measured the effect of a daily oral dose of omeprazole 30 mg on 24 hour intragastric acidity.

Patients and methods

Nine men with endoscopically diagnosed duodenal ulcers in remission were studied. The mean age of the patients was 47·4 (range 22-66) and their mean weight 69·2 kg (range 56·8-85·0 kg). Five were smokers, who consumed on average 14 cigarettes during each study day. No patient received any antisecretory drugs within

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two weeks before the start of the study. All patients gave written informed consent, and the study was approved by the hospital ethical committee.

Each patient was studied on two separate occasions one week apart. The experimental design was similar to that previously described, with dietary and environmental conditions identical on both study days.[14] All patients were admitted at a weekend to the day ward. Each study started at 0800, when a 10 French gauge Salem sump nasogastric tube (Argyle Medical) was passed and its tip positioned under *x* ray control to lie in the most dependent part of the stomach.

During the day the patients ate normal meals, remained ambulant within the ward, and were entertained with television, films, newspapers, and magazines. The menu (breakfast, coffee, lunch, tea, dinner, and a non-alcoholic nightcap) was identical on both study days. The pH of the meals, homogenised for laboratory analysis, was 5·05, 6·36, 5·70, 4·64, 5·16, and 6·13 respectively. Those patients who smoked kept a record of cigarette consumption throughout the first experimental day and adhered to the established pattern on the subsequent study day.

Starting at 0900 on the morning of each study day 5-10 ml samples of gastric contents were aspirated hourly for 24 hours. The pH of each sample was measured immediately to the nearest 0·01 pH unit with a glass electrode (Russell pH Ltd) and a digital pH meter (Digital 111, Corning-Eel). The electrode was calibrated with standard buffers (pH 7·00, 4·01, 1·68; Radiometer, Copenhagen) before, during, and after assessment of each batch of nine samples. The measurements of intragastric acidity were expressed in terms of either pH or hydrogen ion activity.

On the first study day the patients received no drugs. Oral omeprazole was started at 0900 after the first study day, and each patient took omeprazole 30 mg daily before breakfast for seven days. The omeprazole was in enteric coated granules within a hard gelatin capsule. The seventh day of treatment with omeprazole was the second experimental day.

Safety studies comprising a clinical examination, full blood picture, and biochemical profile were done before and after treatment with omeprazole. Statistical comparisons were made using analysis of variance after logarithmic transformation.

Results

The two studies were well tolerated by all the patients. No abnormalities in the laboratory safety studies or clinical examination were observed. The patients did not report any serious unwanted acute effects, but one developed a lichenoid eruption 11 days after stopping the drug. A biopsy specimen of the affected skin showed non-specific changes.

Omeprazole 30 mg daily for one week produced a profound decrease in intragastric acidity in all nine patients. Figure 2 shows the mean hourly intragastric hydrogen ion activity in all the patients on the two experimental days; the activity was significantly lower at every measurement when patients were taking omeprazole ($p < 0·001$). The mean (SEM) 24 hour intragastric hydrogen ion activity before treatment of 38·50 (2·03) mmol(mEq)/l fell significantly to 1·95 (0·46) mmol/l during treatment ($p < 0·001$).

Figure 3 shows all the individual measurements of pH made during the two 24 hour periods before and during treatment with omeprazole. Before treatment only 26 (12%) of the measurements were greater than 3·00 (hydrogen ion activity < 1·0 mmol/l), compared with 185 (86%) of the measurements during treatment. The median pH was 1·4 before treatment with omeprazole, rising to 5·3 during treatment.

Discussion

Oral omeprazole 30 mg daily for one week virtually eliminated intragastric acidity, although it did not produce anacidity. Indeed, it would have been impossible to show 24 hour intragastric anacidity in this study as the pH of all the meals was acid. Further studies are needed to determine whether a smaller dose of omeprazole produces a similar decrease in intragastric acidity.

Until the development of substituted benzimidazoles H_2 receptor antagonists were the most active gastric antisecretory drugs, with ranitidine being between three and five times as

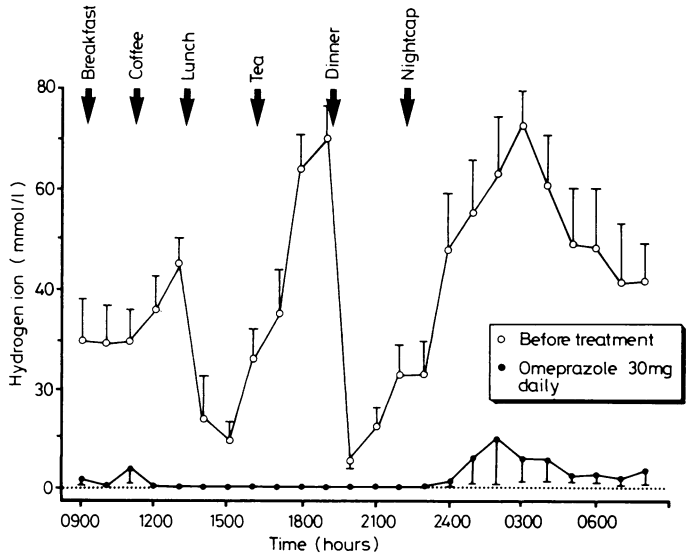

FIG 2—Mean (SEM) hourly intragastric H^+ activity before and during treatment with omeprazole 30 mg daily (n=9). Omeprazole 30 mg was taken at 0900.

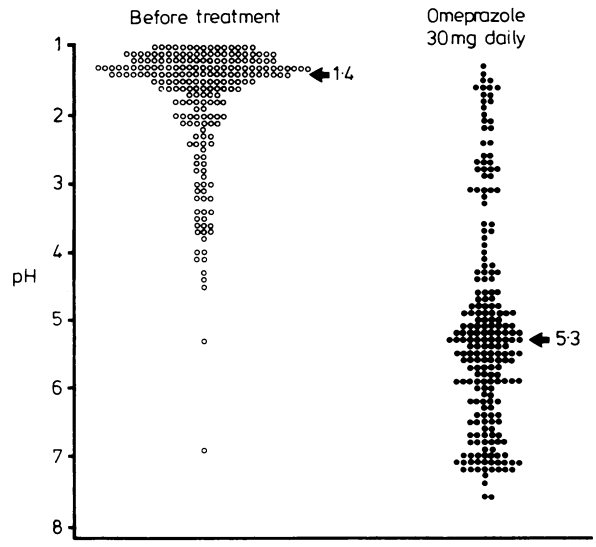

FIG 3—pH values of gastric aspirate obtained hourly from nine patients with duodenal ulcer before and during treatment with omeprazole 30 mg daily. Arrows indicate median pH.

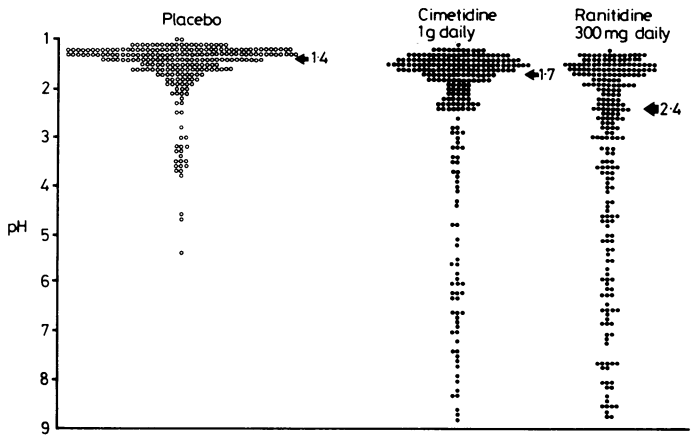

FIG 4—pH values of gastric aspirate obtained hourly from 10 patients with duodenal ulcer receiving placebo, cimetidine 1 g daily, or ranitidine 300 mg daily recalculated from original data.[13] Arrows indicate median pH.

potent as cimetidine on a weight for weight basis.[13 15] We studied cimetidine and ranitidine in an earlier series of 24 hour experiments,[13] in which patients were treated with H_2 antagonists for only 24 hours before study. As there is no evidence that H_2 blockade is cumulative during prolonged treatment these earlier findings may be compared with the present data. Figure 4 shows the individual pH values in 10 patients with duodenal ulcer treated by mouth with placebo, ranitidine 300 mg daily, or cimetidine 1 g daily. The distribution of pH values in the placebo group in that study (fig 4) was virtually identical with that in the present patients before treatment (fig 3). The mean 24 hour intragastric hydrogen ion activity in the original placebo group was 41·8 mmol/l, compared with 38·5 mmol/l in the present study; the median pH in both studies was 1·4. As the pattern of intragastric acidity in the two groups of untreated duodenal patients was similar it is valid to compare the effectiveness of the different types of antisecretory drugs used in the two studies.

Cimetidine 1 g/day and ranitidine 300 mg/day significantly decreased mean 24 hour intragastric hydrogen ion activity by 48% and 69% respectively, whereas omeprazole 30 mg/day caused a 95% decrease. Treatment with cimetidine caused the median 24 hour intragastric pH to rise from 1·4 to 1·7 (a twofold decrease in acidity), whereas during treatment with ranitidine the median pH rose to 2·4 (a 10-fold decrease). After one week of treatment with omeprazole 30 mg daily the median 24 hour intragastric pH had risen to 5·3 (an 8000-fold decrease in acidity). During treatment with omeprazole, cimetidine, or ranitidine intragastric pH was greater than 3·0 in 86%, 12%, and 24% samples, respectively. Whichever way the data are analysed,[16] omeprazole suppressed intragastric acidity much more effectively than either of the H_2 receptor antagonists at the optimum doses tested.

During treatment with omeprazole 30 mg daily intragastric acidity was completely eliminated during the later afternoon and early evening, a period during which acidity is poorly controlled by H_2 blockers.[11-14] Even though omeprazole was given as a single dose in the morning, intragastric acidity during the following night was negligible.

The beneficial effects of H_2 antagonists are thought to depend on inhibition of gastric acid secretion. Because of its more profound antisecretory activity omeprazole may possibly produce superior clinical results. Better patient compliance might also be expected with once daily dosage. About 70-80% of duodenal ulcers heal during one month of treatment with either cimetidine or ranitidine[17-19]; improved clinical results may be possible with omeprazole.

Treatment with omeprazole for one week was free from any unwanted acute effects. Animal studies suggest that H^+K^+ adenosinetriphosphatase is found only in the gastric parietal cells,[20] but further investigation is needed in man. A sustained decrease in intragastric acidity might be expected to permit bacterial contamination of the stomach,[21] but this is unlikely to be harmful if full dose treatment with omeprazole is prescribed for only a short time, until ulcer healing occurs.

The results of the present study, under conditions that approximate to everyday life, show that once daily omeprazole is a potent inhibitor of intragastric acidity. Clinical trials are indicated in those conditions in which control of gastric acid secretion is thought to be beneficial.

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References

[1] Olbe L, Haglund U, Leth R, *et al.* Effects of substituted benzimidazole (H149/94) on gastric acid secretion in humans. *Gastroenterology* 1982; **83**:193-8.

[2] Sachs G, Chang HH, Rabon E, Schackman R, Lewin M, Saccomani G. A non-electrogenic H^+ pump in plasma membranes of hog stomach. *J Biol Chem* 1976;**251**:7690-8.

[3] Saccomani G, Helander HF, Crago S, Chang HH, Dailey DW, Sachs G. Characterisation of gastric mucosal membranes. *J Cell Biology* 1979; **83**:271-83.

[4] Fellenius E, Berglindh T, Sachs G, *et al.* Substituted benzimidazoles inhibit acid secretion by blocking (H^+K^+) ATPase. *Nature* 1981; **290**:150-61.

[5] Fellenius E, Berglindh T, Brandstrom A, *et al.* The inhibitory action of substituted benzimidazoles on isolated oxyntic glands and H^+, K^+ ATPase. In: Schultz I, Sachs G, Forte JG, Ullrich KJ, eds. *Hydrogen in transport in epithelia.* Amsterdam: Elsevier/North Holland Press, 1980:193-202.

[6] Fellenius E, Elander B, Wallmark B, Helander HF, Berglindh T. Inhibition of acid secretion in isolated gastric glands by substituted benzimidazoles. *Am J Phys* 1982;**243**:G505-10.

[7] Wallmark B, Sach G, Mardh S, Fellenius E. Inhibition of gastric H^+K^+ ATPase by the substituted benzimidazole picoprazole. *Biochem Biophys Acta* (in press).

[8] Howden CW, Forrest J, Reid J. The effects of omeprazole on gastric secretion in man. *Clin Sci* 1982;**64**:74p.

[9] Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut* 1983;**24**:270-6.

[10] Blanchi A, Delchier J, Soule J, Payen D, Bader J. Control of acute Zollinger-Ellison syndrome with intravenous omeprazole. *Lancet* 1982;ii:1223-4.

[11] Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. 24 hour control of intragastric acidity by cimetidine in duodenal ulcer patients. *Lancet* 1975;ii:1069-72.

[12] Pounder RE, Vincent SH, Hunt RH, Milton-Thompson GJ, Misiewicz JJ. 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer during oral administration of cimetidine and atropine. *Gut* 1977;**18**:85-90.

[13] Walt RP, Male PJ, Rawlings J, Hunt R, Milton-Thompson GJ, Misiewicz JJ. Comparison of the effects of ranitidine, cimetidine and placebo on the 24 hour intragastric acidity and nocturnal acid secretion in patients with duodenal ulcer. *Gut* 1981;**22**:49-54.

[14] Pounder RE, Williams J, Milton-Thompson GJ, Misiewicz JJ. Effect of cimetidine on 24 hour intragastric acidity in normal subjects. *Gut* 1976;**17**:133-8.

[15] Domschke S, Domschke W. New histamine H_2-receptor antagonists. *Hepatogastroenterology* 1980;**3**:163-8.

[16] Lucas M. pH or hydrogen-ion concentration in statistics? *Lancet* 1977; ii:826.

[17] Pounder RE. Model of medical treatment for peptic ulcer. *Lancet* 1981; i:29-30.

[18] Anonymous. Cimetidine and ranitidine [Editorial]. *Lancet* 1982;i:601-2.

[19] Peterson W, Barnett C, Feldman M, Richardson C. Reduction of twenty four hour gastric acidity with combination drug therapy in patients with duodenal ulcer. *Gastroenterology* 1979;**77**:1015-20.

[20] Forte JG, Lee HC. Gastric adenosine triphosphatases: a review of their possible role in HCl secretion. *Gastroenterology* 1977;**73**:921-6.

[21] Stockbrugger RW, Cotton PB, Eugenides N, Bartholomew BA, Hill MJ, Walters CL. Intragastric nitrites, nitrosamines and bacterial overgrowth during cimetidine treatment. *Gut* 1982;**23**:1048-54.

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