

Omeprazole: A Study of Its Inhibition of Gastric pH and Oral Pharmacokinetics After Morning or Evening Dosage

PETER J. PRICHARD, NEVILLE D. YEOMANS,
GEORGE W. MIHALY, D. BRIAN JONES, PETER J. BUCKLE,
RICHARD A. SMALLWOOD, and WILLIAM J. LOUIS

Departments of Gastroenterology and Clinical Pharmacology/Therapeutics, Division of Medicine,
University of Melbourne, Austin Hospital, Heidelberg, Victoria, Australia and Astra
Pharmaceuticals, North Ryde 2113, New South Wales, Australia

Pharmacodynamic and pharmacokinetic studies of omeprazole, a new gastric antisecretory agent, were undertaken in 8 healthy subjects. The drug was administered orally as an encapsulated enteric-coated granulate (40 mg daily at 9 AM or 9 PM for 5 days), and its effect on the integrated 24-h gastric pH was determined, together with its apparent bioavailability. The pretreatment 24-h median pH was 1.9 (interquartile range 1.4-2.9). After 5 days of treatment, the median pH had risen to 5.0 (3.7-6.0) ($p < 0.01$) with morning dosage and 4.5 (3.0-5.6) ($p < 0.01$) with evening dosage. This corresponded to a >99% reduction in 24-h median hydrogen ion activity, with morning dosage having a greater effect (from 9 AM to 8 PM) ($p < 0.01$) than evening dosage. The relative bioavailability of omeprazole increased twofold from day 1 to day 5 of treatment with morning dosage ($p < 0.02$) and threefold with evening dosage ($p < 0.02$), suggesting that increased absorption of this acid-labile drug occurs with increasing inhibition of acid secretion. We conclude that this formulation of omeprazole presently being used in clinical trials is a highly potent antisecretory

agent in humans, although its optimal effect may not be observed for several days.

Omeprazole, a substituted benzimidazole, is a potent long-acting inhibitor of gastric acid secretion (2). Omeprazole has been shown to act by inhibition of H^+ , K^+ -adenosine triphosphatase, a proton pump that seems to be peculiar to the gastric parietal cell (3-7). The initial clinical studies of omeprazole appear promising in that the drug has been shown to promote duodenal ulcer healing (8,9), and to control Zollinger-Ellison syndrome symptoms when other drugs have failed (10-12). To date there is little information about the antisecretory activity of omeprazole in humans (2,13,14), and human pharmacokinetic data of this drug are restricted to those obtained using a single dose of a buffered suspension or an encapsulated uncoated granulate given with liquid buffer (2,14). As omeprazole is acid-labile, unprotected exposure to acidic gastric contents results in inactivation of >50% of an oral dose (Skanberg I, personal communication). Thus the formulation of the oral preparation will have a profound effect on the pharmacokinetics, and on the antisecretory effect of the drug.

In the present study we have examined the oral pharmacokinetics and the gastric antisecretory activity of omeprazole formulated as an encapsulated, enteric-coated granulate, which is the form currently undergoing clinical trial (8). Two particular questions have been considered: (a) whether morning or evening administration of a daily 40-mg dose gives better control of 24-h intragastric pH, and (b) whether the oral bioavailability of this formulation increases during the initial phase of treatment as acid secretion declines.

Received January 23, 1984. Accepted July 16, 1984.

Address requests for reprints to: Neville D. Yeomans, M.D., Gastroenterology Unit, Department of Medicine, Austin Hospital, Heidelberg 3084, Victoria, Australia.

This work was supported by the National Health and Medical Research Council of Australia.

A preliminary communication of part of this work has appeared as an abstract (1) and was presented at the Annual Scientific Meeting of the Gastroenterological Society of Australia, Perth, Australia, May 1983.

The authors thank Dr. John McNeil for help with computer processing.

© 1985 by the American Gastroenterological Association
0016-5085/85/\$3.30

Material and Methods

Subjects

Eight healthy male volunteers were studied. Mean age was 22 yr (range 20–26 yr), and mean weight was 74 kg (range 63–116 kg). None were smokers, and none had a history of peptic ulcer disease. Physical examination, electrocardiogram, and laboratory screen were normal before inclusion.

Informed written consent was given by all subjects, and the study was approved by the Human Experimentation Committee of the University of Melbourne on November 24, 1982.

Drug

Omeprazole is a crystalline solid that is chemically labile and rapidly degraded in acidic media. It was therefore administered as an encapsulated, enteric-coated granulate (each capsule containing 20 mg of omeprazole). Drug and matching placebo capsules were provided by Astra Pharmaceuticals (North Ryde, Australia).

Study Design

Patients were admitted to a special hospital ward on five occasions for 24-h gastric pH or pharmacokinetic studies, or both. Meals and fluid intake were identical during each study day. Small meals and snacks were given at 8 AM, 11 AM, 4 PM, and 11 PM, and main meals were given at 12 noon and 6 PM. The patients were not confined to bed, but maintained normal daily activity within the confines of the study area.

Subjects first underwent a baseline study of gastric pH (day 0), during which placebo capsules were given at 9 AM and 9 PM. Thereafter, the subjects were randomly assigned to one of two treatment groups. The first group initially received omeprazole (40 mg) at 9 AM and placebo at 9 PM. The second received placebo at 9 AM and omeprazole at 9 PM. Each group took their medication at the specified times for 5 days (period 1), followed by a 15-day washout period when no medication was administered. The subjects were then crossed over to the alternative dosage schedule for a further 5 days of medication (period 2). Food was withheld for 1 h before and 2 h after capsule administration. On day 1 of each period, subjects underwent a pharmacokinetic study. On day 5 of each period, they were again studied in the hospital, with measurement of both pharmacokinetics and gastric pH. During the intervening days at home the subjects continued to eat meals at similar times to those during the hospital study days.

Gastric pH Studies

Each subject was intubated at 7 AM with a 10F nasogastric Salem sump tube (Argyle, St. Louis, Mo.), which was positioned, under fluoroscopic control, in the most dependent part of the stomach. Samples (2 ml) of gastric juice were aspirated hourly throughout the day from 8 AM until 9 AM on the following day. The pH of each

sample was immediately determined using a glass electrode and digital pH meter (Orion Research model 611, Orion Research Inc., Cambridge, Mass.). The pH meter was calibrated with Merck standard buffers (E. Merck, Darmstadt, West Germany) at pH 2.0 and pH 7.0, and linearity of the slope was verified at pH 4.0. The calibration was checked at regular intervals and varied by <0.1 pH units during the course of the day. Hydrogen ion activity was calculated by direct conversion of pH to millimoles per liter of free hydrogen ions.

Pharmacokinetic Studies

Each subject had an intravenous cannula inserted into a forearm vein at 7:15 AM. Five milliliters of blood was collected into a heparinized tube, before the omeprazole or placebo dose, and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, and 12 h postdose. Samples were immediately centrifuged for 5 min and the plasma was transferred to plastic tubes containing 10 μ l of 1 M Na₂CO₃. Urine samples were also collected predose, and for the period 0–12 h postdose. At the end of each collection period, urine pH and volume were determined, and a 5-ml aliquot was added to a plastic tube containing 20 μ l of 1 M Na₂CO₃. All samples of plasma and urine were stored at –20°C.

Drug Assays and Pharmacokinetic Calculations

Plasma and urine samples were assayed for omeprazole and for two of its metabolites, omeprazole sulfone and omeprazole sulfide, using a high pressure liquid chromatographic method (15). Sensitivities were 5, 30, and 50 ng/ml for omeprazole, omeprazole sulfone, and omeprazole sulfide, respectively. The corresponding coefficients of variation were 4%, 7%, and 17%.

Areas under the plasma concentration-time curve from time 0 to either the last detectable plasma level (C_t) or 12 h ($C_t=C_{12}$) (AUC_{0-t}) were determined using the linear trapezoidal rule (16). In all studies plasma levels of omeprazole were undetectable at time zero, so that there was no need to correct for residual drug in the AUC calculations after repeated dosage. The ratios of AUC_{0-t} on day 5 to that on day 1 were taken as a measure of relative bioavailability (16). Peak concentration (C_{pk}) and time to peak concentration (T_{pk}) were calculated directly from the plasma concentration data for each individual. Apparent elimination half-life ($t_{1/2\beta}$) was calculated where possible by regression of the log-linear portion of the plasma elimination phase.

Safety Evaluation

On each hospital study day, pulse rate, blood pressure, and electrocardiogram were monitored at frequent intervals, and patients were questioned about adverse symptoms. A laboratory screen that included plasma urea and electrolytes, hepatic enzymes, thyroid function tests, hemoglobin, hematocrit, differential white cell count, platelet count, and urinary analysis was performed before the baseline day, and 7 and 28 days after the last omeprazole dose.

Statistical Analysis

Because of significant skewness (17) of the distributions of pH and hydrogen ion activity, these data have been presented not as means and standard errors but as medians with interquartile ranges. The median was a more representative measure of central location, or in other words of "average value," than either the ordinary arithmetic mean or the geometric mean (arithmetic mean of log-transformed data). Other data that were normally distributed are presented, as usual, as mean \pm SEM. Gastric pH and hydrogen ion activity were compared using distribution-independent nonparametric methods (Wilcoxon's signed-ranks test) (17). Before applying these methods, the hourly data of a subject were summarized into one value (median) for the time period being evaluated (18). Determination of significant differences in other data was made using paired Student's *t*-tests (17). A value of $p < 0.05$ was regarded as significant.

Results

Gastric Acidity Studies

The patterns of gastric pH over 24 h, before and on day 5 of treatment with omeprazole, taken either in the morning or evening, are shown in Figure 1. The gastric pH throughout the 24 h was substantially higher with both regimens of active omeprazole administration than on the control day ($p < 0.01$, Wilcoxon's signed-ranks test). The median pH's over this period were 5.0 and 4.5 for morning and evening dosage, respectively, and 1.9 for the control study.

When the pH-time profiles were divided into two 12-h periods, the median pH after morning dosage of omeprazole was 5.4 in the period from 9 AM to 8 PM and 4.5 from 9 PM to 8 AM. After evening dosage, the

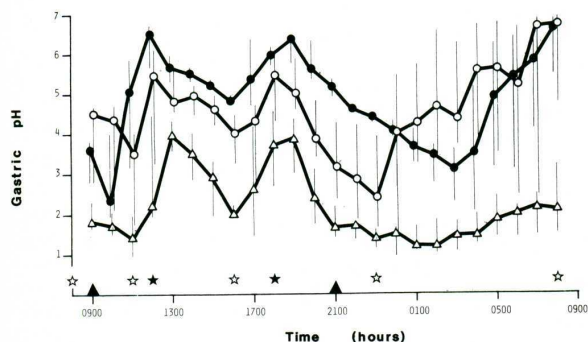


Figure 1. Gastric pH-time profiles for the baseline study (open triangles) and after 5 days of omeprazole administration in the morning (closed circles) or evening (open circles). Values are medians with interquartile ranges ($n = 8$). Closed triangles, dosage times (omeprazole or placebo); closed stars, main meals; open stars, small meals and snacks.

corresponding median pH's were both 4.3. Thus, morning dosage resulted in a higher gastric pH during the period from 9 AM to 8 PM ($p < 0.01$, Wilcoxon's signed-ranks test), but from 9 PM to 8 AM the control of gastric pH was similar with both morning and evening administration of omeprazole.

One measure of the usefulness of gastric antisecretory drugs is the proportion of the day during which the pH of gastric juice is kept above the activity range of pepsin (i.e., to $\text{pH} \geq 5.0$). During the control study, the gastric pH was ≥ 5.0 in only 3% of determinations (taken every 60 min), in contrast to 51% with morning and 34% with evening dosage administration.

When pH values were converted to hydrogen ion activities, the 24-h medians during day 5 of omeprazole treatment were 0.01 and 0.04 mmol/L for morning and evening dosage, respectively, compared with 12.6 mmol/L for the control study. For both omeprazole regimens this represents inhibition of hydrogen ion activity of $>99\%$.

The principal gastric pH and hydrogen ion activity data are summarized in Table 1. The highly significant skewness values and the large differences between variances of the individual groups [Bartlett's test, pH data: $\chi^2 = 20.6$ ($p < 0.001$); hydrogen ion activity: $\chi^2 = 744.1$ ($p < 0.001$)] indicate that the data are not normally distributed and are, therefore, not appropriately expressed as mean \pm SD. However, to allow comparison with other studies (13,19) the arithmetic mean has been included in Table 1.

Pharmacokinetic Studies

The mean plasma concentration-versus-time profiles for omeprazole on days 1 and 5 after morning and evening dosage are shown in Figure 2. Pharmacokinetic parameters for omeprazole and one of its metabolites, omeprazole sulfone, are summarized in Table 2. The second metabolite, omeprazole

Table 1. Gastric pH and H^+ Activity, Medians, and Other Population Parameters for the 24-Hour Period

| | Median | Interquartile range | Arithmetic mean \pm SD | Skewness |
|--------------------------------|--------|---------------------|--------------------------|--------------------|
| pH | | | | |
| Baseline | 1.9 | 1.4–2.9 | 2.3 ± 1.2 | 1.22 ^a |
| Morning dose | 5.0 | 3.7–6.0 | 4.8 ± 1.4 | -0.41 ^b |
| Evening dose | 4.5 | 3.0–5.6 | 4.4 ± 1.7 | -0.08 |
| H^+ activity (mmol/h) | | | | |
| Baseline | 12.6 | 1.3–39.8 | 26.1 ± 32.9 | 1.47 ^a |
| Morning dose | 0.01 | 0.001–0.2 | 1.1 ± 3.3 | 4.24 ^a |
| Evening dose | 0.04 | 0.003–1.0 | 3.7 ± 10.3 | 3.86 ^a |

^a $p < 0.001$. ^b $p < 0.025$.

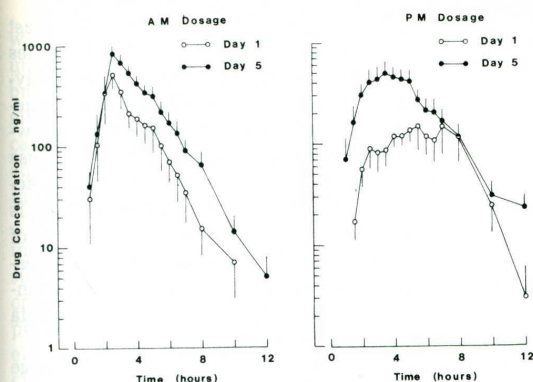


Figure 2. Plasma concentration-time curves for omeprazole (40 mg) on day 1 and day 5 of dosage, given AM or PM. Values are the mean concentration with SEM ($n = 8$).

sulfide, was infrequently detected in plasma, and was not subjected to pharmacokinetic analysis.

Between day 1 and day 5 of omeprazole dosage, given either in the morning or the evening, there was a significant increase in the area under the omeprazole plasma concentration-time curve (AUC_{0-t}) ($p < 0.02$), and also in the peak plasma concentration achieved ($p < 0.05$). This increase in AUC over 5 days, which occurred in every subject (Figure 3), represents a 1.9-fold increase in relative bioavailability with morning dosage and a 2.9-fold increase with evening dosage.

On day 1 of therapy the time to peak plasma concentration was shorter ($p < 0.02$), peak concentration was higher ($p < 0.01$), and AUC was greater ($p < 0.05$) with morning dosage. On day 5, however, the differences in these parameters between morning and evening dosage were no longer statistically significant.

Elimination half-lives ($t_{1/2\beta}$) of omeprazole could not be characterized in eight of thirty-two plasma concentration profiles because of erratic and contin-

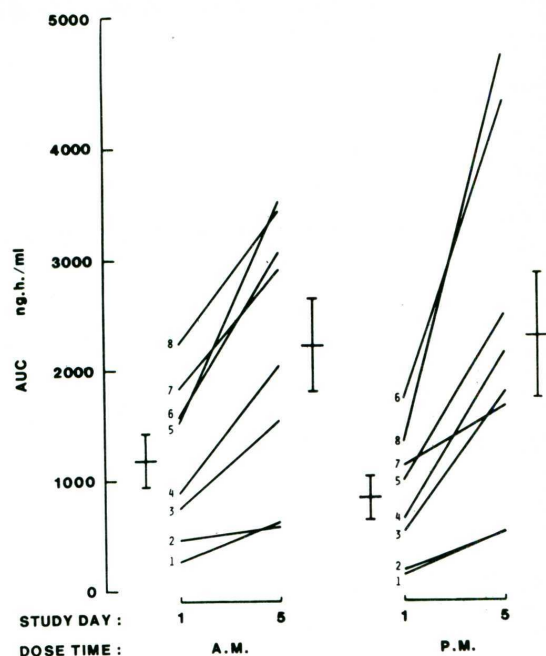


Figure 3. Area under the omeprazole plasma concentration-time curves. Subjects are numbered for comparison of AM and PM studies. Horizontal bars represent mean \pm SEM.

ued absorption of enteric-coated omeprazole during the elimination phase. When there was log-linear elimination, $t_{1/2\beta}$ was 0.7 h ($n = 8$, SEM 0.1) for morning dosage, day 1, and 1.1 h ($n = 7$, SEM 0.1) for day 5 ($p < 0.05$). For evening dosage, a similar trend was apparent (1.0 h day 1 vs. 1.5 h day 5).

Plasma concentrations of omeprazole sulfone were greater after 5 days of omeprazole administration. The corresponding increases in sulfone AUC were 2.1-fold (SEM 0.2, $p < 0.01$) and 3.9-fold (SEM 0.6, $p < 0.02$) for morning and evening dosage, respectively.

Table 2. Omeprazole and Omeprazole Sulfone Pharmacokinetic Parameters After One or Five Doses of 40 mg of Oral Omeprazole

| Pharmacokinetic parameters | Morning dosage | | Evening dosage | |
|----------------------------|----------------|------------|----------------|------------|
| | Day 1 | Day 5 | Day 1 | Day 5 |
| Omeprazole | | | | |
| AUC_{0-t} (ng · h/ml) | 1187 (246) | 2223 (425) | 842 (198) | 2303 (566) |
| C_{pk} (ng/ml) | 644 (110) | 936 (177) | 296 (65) | 705 (162) |
| T_{pk} (h) | 3.0 (0.4) | 2.9 (0.3) | 4.8 (0.6) | 3.3 (0.5) |
| Sulfone | | | | |
| AUC_{0-t} (ng · h/ml) | 1286 (321) | 2556 (576) | 871 (240) | 2338 (585) |
| C_{pk} (ng/ml) | 301 (60) | 486 (124) | 227 (59) | 353 (68) |
| T_{pk} (h) | 3.4 (0.4) | 4.6 (0.3) | 5.6 (0.6) | 4.3 (0.2) |

AUC_{0-t} , area under plasma concentration-time curve 0 to t ; C_{pk} , peak plasma concentration; T_{pk} , time to reach peak plasma concentration. Values are mean \pm SEM.

Omeprazole sulfone, but not omeprazole, was detectable in urine. On day 1, 2.7% and 6.5% of the oral dose was excreted for morning and evening dosage, respectively. Results were similar on day 5 (2.6% and 5.4%).

Safety Evaluation

Omeprazole administration produced no detectable side effects. Several subjects complained of a mild sore throat and tiredness at the end of a hospital day, but this could reasonably be attributed to the study procedures. There was no significant alteration of pulse rate, blood pressure, electrocardiogram, biochemical parameters, or urinary analysis. Hematologic indices were also normal with the exception of slight falls in the mean erythrocyte count (5.2 to $4.8 \times 10^{12}/L$), hemoglobin level (146 to 134 g/L), and hematocrit reading (0.45 to 0.41). These changes (with the exception of the hematocrit reading) were within the laboratory reference range, had reversed by the final follow-up examination, and were attributed to blood sampling during the course of the study.

Discussion

In this study, 5 days of omeprazole treatment produced a marked elevation in gastric pH that was sustained throughout an entire day. The changes in 24-h median pH correspond to reductions in hydrogen ion activity of up to 1200-fold. This reduction in hydrogen ion activity assumes greater significance when compared with the mere twofold to tenfold change that occurs with histamine H_2 -receptor antagonists (19,21). A similar effect with omeprazole given once daily in the morning was found in duodenal ulcer patients by Walt et al. (13) who obtained a median pH of 5.3, compared with our 24-h median pH of 5.0 for morning dosage.

The method used in the present study for assessing the antisecretory effects of omeprazole, the serial determination of intragastric pH over a prolonged period, has been used in a number of other clinical studies of antisecretory drugs (13,19–21). A disadvantage of this approach is that this method gives no information about the volume of secretion. The advantage, however, is that it gives information about gastric acidity under conditions of diet and activity that approximate normal living. It also allows the study of the influence of dosage time on clinically important variables such as drug effect and pharmacokinetics. The resulting information is relevant to the rational use of the drug in the clinical setting.

Our use of a nonparametric method (Wilcoxon's signed-ranks test) for statistical significance testing, and of the median with interquartile range for pre-

sentation of gastric pH and acidity data, is in contrast to other studies (13,19–22). These previous studies used parametric tests of significance (such as analysis of variance), and often presented data as arithmetic means and standard errors. Because of the skewness and non-Gaussian distribution of these parameters, the arithmetic mean \pm SEM poorly describes the data, and the use of parametric tests is hazardous (17). For example, the arithmetic mean of pH and hydrogen ion activity respectively underestimates and overestimates the point of central tendency as given by the median. In some of our data this discrepancy was marked.

Gastric pH was measured after 5 days of dosage because the effect of omeprazole on gastric acid secretion reaches a plateau over this period (23). This may largely reflect the long half-time of inhibition of acid secretion of 24 h (2), which is thought to be due to the persistence of omeprazole or metabolite within the parietal cell (4,14,24). However, the delay in reaching a maximal effect on acid secretion is likely to be due in part to the increasing bioavailability of omeprazole over this time (Figure 3).

One purpose of this study was to determine whether morning or evening dosage gave better control of 24-h intragastric pH. Whereas a 40-mg dose of omeprazole in the evening substantially elevated intragastric pH throughout the day and night, the elevation was greater overall after morning dosage, due to better control of acidity during the period from 9 AM to 8 PM. A possible explanation is that, after morning dosage, intracellular concentrations of omeprazole were higher during the day, when there were more stimuli to acid secretion (e.g., meals); whereas after evening dosage, these concentrations were maximal when stimuli to acid secretion were few. This finding would suggest that morning dosage should be the regimen of choice for future ulcer-healing studies.

Two previous reports have provided some pharmacokinetic information about omeprazole in humans (2,14). In these a single dose of drug, either as a micronized suspension or as uncoated granules, was given with bicarbonate followed by repeated administration of bicarbonate. The purpose of this method of dosing was to minimize intraluminal degradation as omeprazole is acid-labile. The time to peak plasma concentration was reported to be 30–40 min, and the plasma half-life averaged 50 min. In our study we have used an encapsulated enteric-coated granulate to minimize acid degradation. We found the plasma half-life after a single dose of the enteric-coated granulate to be similar to that previously reported (44 min for morning dosage), but as expected the time to peak plasma concentration was delayed to several hours when the enteric-coated granulate was used. The AUC for single dosage of this granulate

was similar to that obtained with equivalent doses of uncoated drug administered with bicarbonate (2,14), but considerably greater than after uncoated drug given without buffer (Skanberg I, personal communication). In addition, it was apparent in our study that absorption was faster when a single dose was given in the morning than in the evening.

In every subject, bioavailability of omeprazole increased during repeated dosage, coincident with substantial reduction in gastric acidity. This increased bioavailability, together with greater peak plasma concentrations, could theoretically be due to either increased absorption or decreased plasma clearance. In the absence of intravenous kinetic data, decreased clearance cannot be excluded, but given the acid lability of the drug it is highly likely that increased absorption is primarily responsible for the increased bioavailability.

What significance can be put on plasma pharmacokinetic data for a drug that has sustained effects on its target organ long after it is cleared from plasma? Although there is no direct temporal relationship between the plasma concentration of omeprazole and its antisecretory effect, the AUC for this drug correlates well with the magnitude of acid inhibition (2,14). Thus the substantial increase in AUC, i.e., in bioavailability, observed in the present study is likely to be reflected in increased acid inhibition, and alterations in drug dosage should take this delayed effect into account. Moreover, the increase in AUC with repeated dosage over several days may prove to have important toxicologic implications.

This drug has several interesting facets. It has a prolonged effect on acid secretion that persists long after the drug has disappeared from plasma—presumably because it accumulates in the parietal cell. This sustained action allows substantial control of gastric acidity with only once-daily dosage. To date omeprazole has been free of side effects—which would be in keeping with it targeting to an enzyme specifically found so far only in parietal cells. It appears to also have the unusual property of improving its own bioavailability with repeated dosage. It therefore seems likely that omeprazole, or related compounds, will be useful in a variety of conditions in which gastric acidity plays a pathogenetic role.

References

- Prichard PJ, Yeomans ND, Mihaly GW, Jones DB, Smallwood RA, Louis WJ. The effect of omeprazole on $(H^+ + K^+)$ ATPase inhibitor, on 24 h gastric pH profile in man. *Aust NZ J Med* 1983;13:432–3.
- 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.
- Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking $(H^+ + K^+)$ ATPase. *Nature* 1981;290:159–61.
- Fellenius E, Elander B, Wallmark B, Helander H, Berglindh T. Inhibition of acid secretion in isolated glands by substituted benzimidazoles. *Am J Physiol* 1982;243:G505–10.
- Wallmark B, Jaresten B-M, Larsson H, Ryberg B, Brandstrom A, Fellenius E. Differentiation among inhibitory actions of omeprazole, cimetidine, and SCN^- on gastric acid secretion. *Am J Physiol* 1983;245:G64–71.
- Saccomani G, Helander HF, Crago S, Chang HH, Dailey DW, Sachs G. Characterization of gastric mucosal membranes. X. Immunological studies of gastric $(H^+ + K^+)$ ATPase. *J Cell Biol* 1979;83:271–83.
- Forste JF, Lee HC. Gastric adenosine triphosphatases: a review of their possible role in HCl secretion. *Gastroenterology* 1977;73:921–6.
- Gustavsson S, Adami H, Lööf L, Nyberg A, Nyrén O. Rapid healing of duodenal ulcers with omeprazole: double-blind dose-comparative trial. *Lancet* 1983;ii:124–5.
- Walan A, Bergsäter-Aspöy J, Farup P, et al. Four week study of the rate of duodenal ulcer healing with omeprazole (abstr). *Gut* 1983;24:A972.
- Blanchi A, Delchier J-C, Soule J-C, Payen D, Bader J-P. Control of acute Zollinger-Ellison syndrome with intravenous omeprazole. *Lancet* 1982;ii:1223–4.
- Öberg K, Lindström K. Reduction of gastric hypersecretion in Zollinger-Ellison syndrome with omeprazole. *Lancet* 1983;i:66–7.
- Lamers CBHW, Lind T, Moberg S, Jansen JBMJ, Olbe L. Omeprazole in Zollinger-Ellison syndrome. *New Engl J Med* 1984;310:758–61.
- Walt RP, Gomes M de FA, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J* 1983;287:12–4.
- Londong W, Londong V, Cederberg C, Steffen H. Dose-response study of omeprazole on meal-stimulated gastric acid secretion and gastrin release. *Gastroenterology* 1983;85:1373–8.
- Mihaly GW, Prichard PJ, Smallwood RA, Yeomans ND, Louis WJ. Simultaneous high pressure liquid chromatographic analysis of omeprazole and its sulphone and sulphide metabolites in human plasma and urine. *J Chromatogr* 1983;278:311–9.
- Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York: Marcel Dekker, 1982.
- Sokal RR, Rohlf FJ. *Biometry*. 2nd ed. San Francisco: W.H. Freeman, 1981.
- Elashoff JD. Down with multiple t-tests. *Gastroenterology* 1981;80:615–20.
- Walt RP, Male P-J, Rawlings J, Hunt RH, 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.
- Pounder RE, Williams JG, Milton-Thompson GJ, Misiewicz JJ. Effect of cimetidine on 24-hour intragastric acidity in normal subjects. *Gut* 1976;17:133–8.
- Peterson WL, Barnett C, Feldman M, Richardson CT. Reduction of twenty-four-hour gastric acidity with combination drug therapy in patients with duodenal ulcer. *Gastroenterology* 1979;77:1015–20.
- Lucas M. pH or hydrogen-ion concentration in statistic. *Lancet* 1977;ii:826.
- Müller P, Dammann H-G, Seitz H, Simon B. Effect of repeated once-daily, oral omeprazole on gastric secretion. *Lancet* 1983;i:66.
- Larsson H, Carlsson E, Junggren V, et al. Inhibition of gastric acid secretion by omeprazole in the dog and rat. *Gastroenterology* 1983;85:900–7.