

Weekend treatment with 20 and 40 mg omeprazole: effect on intragastric pH, fasting and postprandial serum gastrin, and serum pepsinogens

L C Baak, J B M J Jansen, I Biemond, C B H W Lamers

Abstract

Weekend treatment with 20 mg omeprazole reduces ulcer relapse rates but the results may improve with a higher dose regimen. We have evaluated three day weekend treatment with 20 and 40 mg doses of omeprazole in eight healthy subjects in a double blind crossover study. Twenty four hour ambulatory intragastric pH and basal and meal stimulated serum gastrin and serum pepsinogens A and C values were studied. The investigations began on the Friday before the third weekend course of omeprazole and were repeated on alternate days, except Sundays, for two weeks. When compared with values before the study, median 24 hour intragastric pH and basal and meal stimulated gastrin concentrations were significantly ($p < 0.01-0.05$), but transiently, raised with both doses of omeprazole. Basal pepsinogen A and C values were significantly ($p < 0.01$) increased on all study days, but did not return to their pre-study values before the next weekend dose, except for pepsinogen C in subjects treated with 20 mg omeprazole. A dose dependent effect was found for all parameters studied ($p < 0.05$). In conclusion, weekend treatment with 20 and 40 mg omeprazole produces pronounced and dose dependent increases in intragastric pH, basal and meal stimulated serum gastrin, and basal serum pepsinogen A and C without inducing prolonged hypoacidity or hypergastrinaemia. Weekend treatment with 40 mg omeprazole merits further study in the prevention of peptic ulcer relapse.

Omeprazole, a substituted benzimidazole, is known to be a potent antisecretory drug that acts by inhibiting the gastric proton pump (H^+/K^+ ATPase) in the parietal cell.¹ The drug is very effective in short term treatment of peptic ulcer disease, reflux oesophagitis, Zollinger-Ellison syndrome, and H_2 antagonist resistant peptic ulcer.²⁻⁷ Moreover, in most short term comparative trials, healing rates of acid related disorders were higher during 20 or 40 mg omeprazole treatment than during treatment with histamine H_2 receptor antagonists.²⁻⁴ Maintenance treatment with a low dose of omeprazole (10 mg) reduced the six month duodenal ulcer relapse rate from 83% on placebo to 29%.⁸ To achieve better prevention of peptic ulcer relapse, however, higher maintenance doses of omeprazole may be required.

Omeprazole treatment in daily doses of 20 mg or higher has been associated with hypergastrinaemia because of the drug's potent inhibition of

gastric acid secretion.⁹⁻¹⁶ In rats, long term administration of very high doses of omeprazole induced hypergastrinaemia related hyperplasia of enterochromaffin like cells and subsequent gastric carcinoid formation.¹⁷ Therefore, the long lasting hypergastrinaemia caused by omeprazole treatment is considered to be undesirable.

Because of its high potency, intermittent omeprazole treatment might obviate these undesirable side effects¹⁸⁻²⁰ while maintaining its efficacy in preventing relapse. The drug has a long lasting effect and the degree of acid inhibition is augmented after repeated once daily administration,^{11,21,22} reaching a steady state after three to five days for the oral compound.^{21,23} Recently, the first promising results of weekend treatment with omeprazole were reported in a double blind comparative trial, in which the three and six month cumulative relapse rates on weekend treatment with 20 mg omeprazole were significantly lower than with placebo (26 and 83%, respectively).⁸ In order to reduce relapse rates, however, further higher weekend doses of omeprazole may be needed.

Before undertaking clinical studies with weekend doses of omeprazole greater than 20 mg, it is important to determine, whether higher doses induce more pronounced acid inhibition without evoking continuous hypergastrinaemia. We therefore compared the effect of weekend treatment with 20 and 40 mg of omeprazole on ambulatory 24 hour intragastric acidity and fasting and postprandial serum gastrin values on all days of the week except Sunday. These comprehensive studies were performed in healthy volunteers because it has been shown that the effects of weekend treatment with 20 mg omeprazole on gastric acid and serum gastrin are comparable in healthy subjects and duodenal ulcer patients.^{18,19,20} Since it has been shown that weekend therapy with 20 mg omeprazole induces transient increases in serum pepsinogens,²⁴ we also measured serum pepsinogen A and C and their ratio. To obtain steady state conditions with the weekend doses the investigations did not begin until the third week of treatment.

Methods

SUBJECTS

The study was carried out on eight healthy male volunteers with a mean age of 23 years (range 21-26 years). Three of them were habitual smokers. Physical examination, laboratory screen, and ECG before the study showed no abnormalities.

Department of
Gastroenterology-
Hepatology, University
Hospital Leiden, The
Netherlands
L C Baak
J B M J Jansen
I Biemond
C B H W Lamers

Correspondence to:
Professor C B H W Lamers,
Department of
Gastroenterology-Hepatology,
University Hospital Leiden,
Bldg 1, C4-P, PO Box 9600,
2300 RC Leiden,
The Netherlands.

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The study was conducted in accordance with the principles for human experimentation as defined in the Declaration of Helsinki and was approved by the local ethics committee. Each subject gave written informed consent.

STUDY DESIGN

The study was conducted as a double blind, randomised, crossover trial consisting of 14 investigations in each individual – that is, two pre-entry studies and six studies with each dose of omeprazole on all days of the week except Sunday. All subjects underwent two study periods of four weeks of weekend treatment. During these periods omeprazole, 20 mg or 40 mg, was given once daily for three consecutive mornings starting every Friday. The weekends were followed by a four day period without medication. The first period of four weeks was followed by a 'wash out' interval of two weeks before the second treatment period with the other dose of omeprazole.

Before the first treatment period each subject underwent two pre-entry investigations. Subsequently, investigations were started on the Friday or Saturday of the third weekend of treatment and repeated on alternate days, except Sundays, for two weeks. Thus, with each dose of omeprazole six investigations were performed. By the end of the study all subjects had been tested on every day of the week, except Sunday. Each investigation consisted of 24 hour intragastric pH measurement, determination of fasting serum gastrin and pepsinogen A and C values, and meal stimulated serum gastrin values.

The subjects, who had been fasting overnight since 10.00 pm, were admitted to the ward at

8.30 am. After positioning the pH electrode in the stomach, basal blood samples were drawn from an indwelling intravenous catheter in a forearm, followed by ingestion of omeprazole if indicated, and a standard test meal (Table I). Postprandial serum gastrin values were measured every 30 minutes for two hours. After the meal study had been completed, the subjects went home with the pH electrode in situ.

The subjects ingested standardised meals (Table I) at the same time on each study day. Tea and water were freely available, but fluid intake was kept constant for each subject during the various test periods. Smoking and alcohol were prohibited on study days.

At 8.00 am the next morning the subjects returned to the hospital for removal of the pH electrode.

CONTINUOUS pH MONITORING

Intragastric acidity was measured every six seconds using combined glass electrodes (model 440 m4, W Ingold AG, Urdorf, Switzerland) as published previously.²⁵ The method has been shown to provide accurate and reproducible measurements.^{26,27} These six second pH tracings were stored on solid state devices with a 15 K byte memory (Proxima Light, Mantova, Italy). After completion of each 24 hour investigation data were transferred to floppy discs using an Olivetti personal computer (m24).

Electrodes and recorders were calibrated at 20°C using commercial buffer solutions of pH 7.00 and 4.01 (Ingold AG). Temperature correction for intragastric readings (37°C) was automatically performed. The calibration procedure was checked manually before starting every investigation, and to assess electrode stability, this check was repeated afterwards. An electrode drift of ≤ 0.1 pH units was considered acceptable. Because we expected that most pH readings in our subjects would fall outside the calibration range (pH 4.01–7.00), a special calibration check was performed at lower pH values using 10 buffer solutions (pH 1.3–3.8, Ciba-Geigy).²⁸

After calibration, the electrode was passed transnasally and positioned in the body of the stomach under fluoroscopic control. The tip of the electrode was situated about 10 cm below the cardia. The distance from tip to nostrils was recorded and kept constant for all study days. Measurements started at 9.00 am and lasted for 24 hours.

SERUM GASTRIN AND PEPSINOGEN A AND C MEASUREMENTS

Venous blood samples for serum gastrin and pepsinogen A and C determination were taken basally ($t = -5$ and 0 minutes) and postprandially at 30 minute intervals for two hours. Since meal ingestion is reported to have very little influence on serum pepsinogen A and C values,⁹ only the basal concentrations were measured. Immediately after the test the blood samples were centrifuged, coded, and stored at -20°C . All serum gastrin values were measured in one assay by a sensitive and specific radioimmunoassay as previously described.²⁹ The normal range of

TABLE I Standardised menu on study days (pH neutral)

Breakfast (test meal)	Lunch	Dinner
1 boiled egg 1 slice of white bread 15 g margarine 50 g cheese 200 ml skimmed milk (pH=5.9) (30 g protein, 20 g fat, 24 g carbohydrate)	2 slices of bread Butter 50 g cheese 1 portion jelly 200 ml skimmed milk (pH=5.7)	Iglo frozen meal: 1 meat ball, 1 portion potatoes, 1 portion cauliflower, 1 portion vanilla pudding (pH=5.8)

TABLE II Median (interquartile range) values of two hours postprandial pH, integrated incremental meal stimulated gastrin, and integrated total meal stimulated gastrin ($\mu\text{mol/l/minute}$)

Day	Median pH meal (2 hr)		Meal stimulated gastrin			
	20 mg	40 mg	Incremental		Total	
			20 mg	40 mg	20 mg	40 mg
Pre-entry	2.25 (1.7–2.8)		2.22 (1.36–12.6)		4.26 (2.34–15.3)	
Friday	2.40 (1.7–3.1)	4.35*† (2.0–6.0)	2.80 (1.59–7.27)	4.45*† (1.82–13.8)	3.69 (1.99–11.0)	5.31*† (2.21–16.2)
Saturday	3.55* (1.7–5.3)	5.50*† (1.9–6.4)	5.07* (1.68–16.5)	6.27* (1.27–14.5)	6.88* (2.40–18.4)	9.10* (1.79–19.6)
Monday	3.0* (1.7–4.5)	3.85* (2.5–4.8)	6.11* (2.46–13.4)	7.93*† (3.04–14.9)	8.79* (3.35–16.1)	10.7*† (3.94–20.2)
Tuesday	2.15 (1.7–4.6)	2.70 (2.0–3.8)	3.55 (1.82–10.5)	5.82*† (2.55–13.0)	5.68 (2.20–12.6)	7.67*† (2.83–17.2)
Wednesday	2.15 (1.4–2.4)	2.55 (1.7–3.6)	3.77 (1.64–9.23)	5.27*† (1.86–16.9)	4.95 (2.03–10.8)	6.26*† (2.41–22.0)
Thursday	2.30 (1.7–4.1)	2.70 (1.9–3.6)	3.09 (1.64–12.2)	3.68 (2.14–10.9)	4.07 (1.92–14.2)	5.03 (2.80–12.7)

* $p < 0.01$ compared with pre-entry; † $p < 0.05$, 40 mg regimen compared with 20 mg.

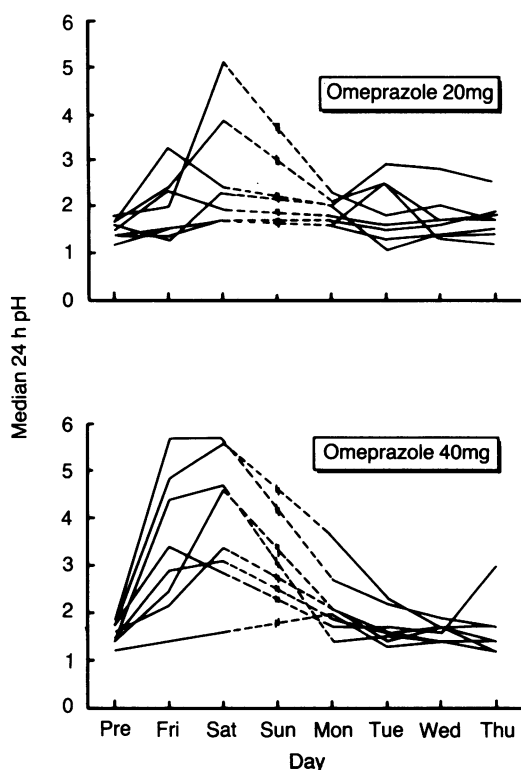


Figure 1: Individual median values of 24 hour intragastric pH monitoring during weekend treatment with 20 mg and 40 mg omeprazole. Pre=pre-entry.

serum gastrin in our laboratory is 10 to 40 pmol/l. Serum pepsinogen A and C were measured in one assay by radioimmunoassay as previously described;³⁰ Their normal ranges in our laboratory are 17–120 µg/l and up to 40 µg/l respectively.

DOSE, DOSAGE FORM, AND ADMINISTRATION

Omeprazole was administered as enteric coated granules in hard gelatin capsules each containing 20 mg or the equivalent of placebo. The daily dose was two capsules, either two times omeprazole 20 mg (40 mg) or one capsule omeprazole 20 mg and one placebo. The capsules were taken with a glass of water immediately before breakfast on three consecutive mornings, starting on Friday.

DATA PROCESSING AND STATISTICS

Pre-study values of each parameter – that is, 24 hour median pH, basal gastrin and pepsinogen A and C concentrations, and integrated meal stimulated gastrin concentrations – were determined for statistical analyses by calculating the mean of the two pre-entry results.

The 24 hour median pH and the two hour median pH during the meal were calculated for individuals and groups. Results were expressed as medians and interquartile ranges.

Basal serum gastrin and pepsinogen A and C concentrations were determined by calculating the mean of two basal values. The integrated incremental meal stimulated gastrin response was calculated after subtraction of basal values, while the integrated total meal stimulated gastrin was calculated without subtraction of basal values. Integrated values were determined by

calculating the area under the concentration-time curve using the trapezoidal rule.

Statistical analysis was performed on each data set by Friedman's non-parametric two way analysis of variance.³¹ When this indicated a probability less than 0.05 for the null hypothesis, Wilcoxon's matched pairs signed ranks test was used to sort out which values differed significantly from pre-entry values or from corresponding results in the other dosage experiment. Linear regression analysis was used on data obtained in the 20 mg and 40 mg dose regimens to determine the correlation between the integrated meal stimulated gastrin concentrations and the two hour median pH during the meal, followed by analysis of covariance (ANCOVA) on the same data sets in the two dosage studies. The slopes of the regression lines in both dosage studies were compared using the Student's *t* test (two tailed).

Results

INTRAGASTRIC pH

Results are shown in Figure 1 and Table II. Two of the 112 pH measurements had to be excluded from analysis because of technical failure (one electrode failure, one pH recorder failure). There was no significant difference between the two separate pre-entry studies of 24 hour pH (median (interquartile range), 1.45 (1.2–1.9) and 1.40 (1.2–2.0)). The median 24 hour intragastric pH was significantly raised on Friday in the 40 mg dose study and on Saturday and Monday in both dose regimens compared with pre-entry values (20 mg: 2.10 (Sat), 1.90 (Mon); 40 mg: 3.15 (Fri), 4.60 (Sat), 2.05 (Mon); pre-entry 1.55

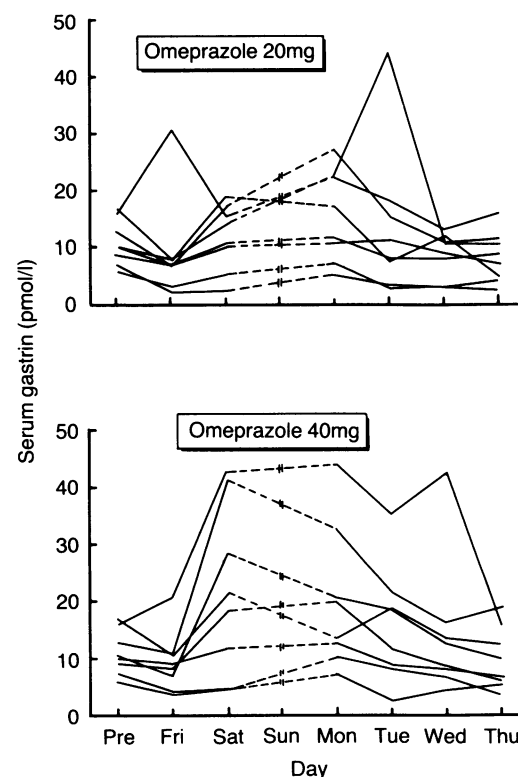


Figure 2: Individual basal serum gastrin values during weekend treatment with 20 mg and 40 mg omeprazole. Pre=pre-entry.

($p < 0.01$). No significant differences in intragastric pH were observed on Tuesday, Wednesday, and Thursday compared with pre-entry values. There was considerable variation in responsiveness with regard to median 24 hour pH values compared with the pH range pre-entry (Fig 1). Persistent anacidity (pH > 6.0) was never observed.

A significant dose dependent effect was shown on the days that omeprazole was administered – that is Friday and Saturday ($p < 0.05$). On Monday, the first day without medication after a three day weekend treatment, this dose dependent effect was no longer seen.

Median pH values during the two hour meal test (Table II) showed the same response pattern as the 24 hour median pH.

BASAL SERUM GASTRIN CONCENTRATIONS

Results are shown in Figure 2. The separate pre-entry studies showed no statistical difference regarding basal serum gastrin values (median (range), 8.2 (5.0–22) and 11 (3.6–29) pmol/l). Basal serum gastrin concentrations were significantly raised on Saturday morning, 24 hours after the first dose of omeprazole 40 mg, compared with pre-entry and 20 mg dose values ($p < 0.01$ and $p < 0.05$ respectively). After three consecutive treatment days, basal gastrin values were raised on Monday morning for both doses of omeprazole ($p < 0.01$) (median (range), Sat: 12 (2.7–19) and 20 (4.6–43) pmol/l; Mon: 15 (5.4–27) and 17 (7.3–44) pmol/l; 20 mg and 40 mg, respectively; pre-entry value 10 (5.9–17) pmol/l). During the trial four basal values from two volunteers fell outside the normal range out of a total of 112 measurements (43–45 pmol/l). During the four days without medication there was no significant increase in basal gastrin concentrations compared with pre-entry values.

MEAL STIMULATED GASTRIN CONCENTRATIONS

Results are shown in Table II. There was no statistical difference between the two separate pre-entry studies with regard to the integrated incremental meal stimulated gastrin responses and the integrated total meal stimulated gastrin (incremental meal stimulated gastrin response: median (range), 2.14 (1.19–10.2) and 2.46 (1.53–15.0) $\mu\text{mol/l/minute}$ integrated total meal stimulated gastrin: 4.30 (2.06–12.6) and 4.43 (2.62–18.0) $\mu\text{mol/l/minute}$). In the 20 mg study, the incremental gastrin values were significantly raised on Saturday and Monday compared with those pre-entry ($p < 0.01$). On Tuesday, Wednesday, and Thursday there were no significant differences compared with pre-entry values. On Friday, when the meal test was given immediately after omeprazole, no significant differences in two hour postprandial gastrin responses could be shown.

On Friday, however, in the 40 mg study there was significant increase in the meal stimulated gastrin response ($p < 0.01$), which lasted through Wednesday. On all these days, except on Saturday, a significant dose dependent effect could be shown ($p < 0.05$). On Thursday, the last day without medication, the meal stimulated gastrin

response was not significantly different from pre-entry values. The integrated total meal stimulated gastrin showed the same pattern as the integrated incremental meal stimulated gastrin response (Table II).

A significant correlation was found between intragastric pH values during the meal and integrated meal stimulated gastrin concentrations (expressed as incremental meal stimulated gastrin and integrated total meal stimulated gastrin) on both dose regimens (incremental meal stimulated gastrin: $r = 0.59$ ($p < 0.0001$) and $r = 0.42$ ($p < 0.002$); integrated total meal stimulated gastrin: $r = 0.64$ ($p < 0.0001$) and $r = 0.42$ ($p < 0.002$); 20 mg and 40 mg, respectively). There was no dose dependent difference between the slopes of the regression lines. Analysis of covariance showed no significant difference between the meal stimulated gastrin concentration (incremental and integrated) on the two dose regimens, when differences in pH values during the meal were taken into account.

BASAL PEPSINOGEN A AND C

Results are shown in Figure 3. There was no significant difference between the two separate pre-entry studies with regard to either serum pepsinogen (median (range), pepsinogen A, 56 (40–80) and 60 (45–79) $\mu\text{g/l}$; pepsinogen C, 18 (3–65) and 14 (0–79) $\mu\text{g/l}$). Pepsinogen A values showed a significant increase on all study days compared with pre-entry values for both regimens of omeprazole ($p < 0.01$). A significant dose dependent effect could be shown on Saturday, Monday, Tuesday, and Wednesday ($p < 0.05$). Pepsinogen A values fell outside the normal range (121–333 $\mu\text{g/l}$) on 27 occasions in four different volunteers, but this was never accompanied by gastrin concentrations outside the normal range in these subjects.

Basal pepsinogen C values showed a significant increase on all study days in the 40 mg study, and on Monday after a weekend dosing with 20 mg omeprazole ($p < 0.01$). A significant dose dependent effect could be shown on Monday and Tuesday ($p < 0.05$), but not on the other days. Pepsinogen C values fell outside the normal range on 19 occasions in two volunteers (41–201 $\mu\text{g/l}$) and paralleled these subjects' prostaglandin A values, which were also outside the normal range. The ratio of pepsinogen A to C did not show any significant change on any study day compared with pre-entry values.

SAFETY MONITORING

No adverse symptoms were reported by the subjects and no significant changes in laboratory values were observed at the end of the study.

Discussion

This study showed that intermittent weekend treatment with 20 mg and 40 mg omeprazole increased intragastric pH, basal and meal stimulated serum gastrin concentrations, and pepsinogen A and C values in a dose dependent fashion. The effects on gastric acid and serum gastrin were abolished before beginning the next

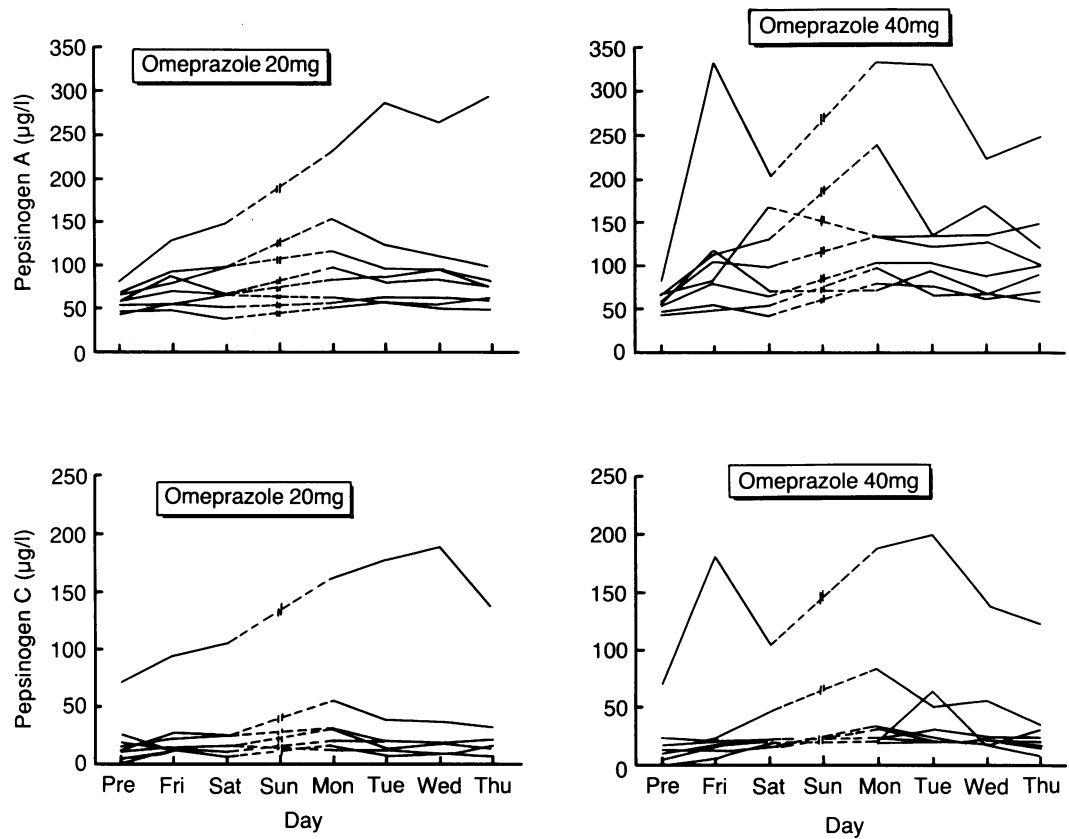


Figure 3: Individual basal pepsinogen A and C values during weekend treatment with 20 mg and 40 mg omeprazole. Pre=pre-entry.

weekend dose. Serum pepsinogen A values after both dosage regimens, and pepsinogen C after the 40 mg dose of omeprazole, were still significantly raised, however, on the Thursday before the subsequent weekend course.

Our results, indicating that pH values had returned to pre-entry values before the next weekend medication, were in line with previous studies using weekend therapy with 20 mg omeprazole.^{19,21} The present study, however, adds new important findings. Firstly, a higher weekend dose of 40 mg was compared with the 20 mg omeprazole dose and, secondly, studies were performed on all days of the week except Sunday, using continuous 24 hour intragastric pH monitoring, and provide more detailed information on the duration of action of the weekend treatment regimens. It was found that omeprazole increased 24 hour intragastric pH in a dose dependent fashion, the 40 mg dose showing a more rapid and pronounced increase than the 20 mg dose. Within 48 hours of ending medication, however, neither dose regimen was accompanied by substantial increases in intragastric pH values.

In addition, our study showed that basal serum gastrin concentrations were raised dose dependently during and 24 hours after weekend administration of omeprazole (40 mg on Saturday; 20 mg and 40 mg on Monday, respectively). Increases in fasting serum gastrin values were mild, however, and did not exceed the upper limit of normal, except for four measurements in two different subjects. There was a rapid return of basal gastrin values to pre-entry values – that is within 48 hours of stopping medication – in both

dose regimens, which paralleled the rapid return of pH values.

Furthermore, our data showed a dose dependent increase in meal stimulated gastrin concentrations during and after weekend treatment. In both dose regimens, a significant correlation was shown between intragastric pH values and gastrin concentrations during the meal. After correction was made for differences in pH values there was no longer a dose dependent effect of omeprazole on the meal stimulated gastrin concentration. This suggested that both the higher postprandial gastrin values in the 40 mg study period and the delayed return to pre-entry values during the week compared with the 20 mg study period depended largely upon differences in pH values.

Basal serum pepsinogen A and C values were raised in a dose dependent fashion after weekend administration of omeprazole, as has been described for the 20 mg omeprazole dose.²⁴ Contrary to findings with intragastric pH and basal and meal stimulated gastrin concentrations, pepsinogens did not return to pre-entry values during the week, except for pepsinogen C in the 20 mg dose regimen. The mechanism of increased pepsinogen values during omeprazole administration has not been fully explained. As renal clearance of pepsinogens is not inhibited by omeprazole,³² it has been hypothesised that omeprazole directly or indirectly increases intracellular pepsinogen concentrations, followed by increased back diffusion from the gastric mucosa into the circulation.³³ The reason for the prolonged increases in serum pepsinogens, compared with gastric acidity and serum gastrin

concentrations is not clear but the finding may indicate that back diffusion of pepsinogens into serum is a rather extended process or that the disappearance of pepsinogens from plasma takes longer than that of gastrin (which is known to have a very short half life in plasma),³⁴ or both. The clinical importance of the rise in serum pepsinogens, however, is at present unknown.

In our study healthy subjects were investigated. Most studies of weekend treatment with 20 mg omeprazole have shown that the responses of healthy people are comparable with those of duodenal ulcer patients.¹⁸⁻²⁰ Other studies, however, suggest that duodenal ulcer patients may show higher degrees of acid inhibition after administration of omeprazole.³⁵ This difference may not necessarily be disease related, however,³⁵ as most patients were twice as old as the healthy volunteers. Nevertheless, we cannot conclude with certainty that our results do represent the effects of intermittent doses of omeprazole in duodenal ulcer patients.

In conclusion, intermittent weekend treatment with omeprazole produced substantial but transient increases in intragastric pH and basal and meal stimulated gastrin concentrations. The 40 mg dosage showed a more rapid and pronounced increase compared with the 20 mg regimen. Neither dose regimen caused sustained hypoacidity or hypergastrinaemia, but serum pepsinogen A and C values did not return to pre-entry concentrations. Therefore, both the 20 mg and 40 mg dose regimens are worthy of evaluation as weekend treatment to prevent relapse of peptic ulcer.

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