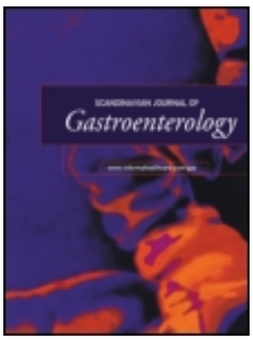

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Twenty-Four Hour Intragastric Acidity during Treatment with Oral Omeprazole

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In a series of 59 experiments on nine duodenal ulcer patients, 24-hour intragastric acidity was measured before, during and after treatment with daily oral omeprazole. Omeprazole, 10, 20, or 30 mg/day for 1 week, caused a 37%, 90%, and 97% decrease respectively of 24-hour intragastric acidity. No further decrease of acidity was observed when the dose of omeprazole was doubled to 60 mg/day, or after a second week of treatment with 30 mg/day. One week after stopping treatment with omeprazole (14 doses), there was still a significant 26% decrease of 24-hour intragastric acidity, with full recovery 7 weeks later. Fasting plasma gastrin concentration was significantly elevated during treatment with all doses of omeprazole. The optimal dose of omeprazole is 30 mg/day for a maximal decrease of 24-hour intragastric acidity in duodenal ulcer patients.

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INTRODUCTION

Measurement of 24-hour intragastric acidity was devised (1–4) to observe the effects of new antisecretory drugs under conditions which approximate to normal daily activity. This technique does not measure gastric acid secretion, but it allows a prolonged assessment of intragastric acidity during physiological stimulation, with simultaneous measurement of either drug or gastrin concentration in the plasma.

The object of this series of 24-hour intragastric acidity experiments in nine duodenal ulcer patients was to compare the effects of different doses of omeprazole, to assess duration of action of the drug, and to relate observed changes of acidity to plasma gastrin and omeprazole concentrations (5, 6).

PATIENTS AND METHODS

Patients

Nine male patients with a history of endoscopically-proved duodenal ulceration were studied during symptomatic remission. None took any other antisecretory drug for at least 2 weeks before the start of each study. Their mean age was 47.4 years (range 22–66 years) and their mean weight was 69.2 kg (range 56.8–85.0 kg). Five of the patients were cigarette smokers (mean of 14 cigarettes/day).

Intragastric acidity over 24 hours

The technique for measuring intragastric acidity has already been described (1–5). It was measured from 0900 hours to 0800 hours the next day by hourly aspirations of 5–10 ml of gastric contents through a nasogastric tube. The pH of the aspirate was measured to the nearest 0.01 pH unit using a combined glass electrode which was calibrated before, during and after each group of hourly measurements using standard buffers of pH 1.68, 4.01, and 7.00.

Identical meals, including beer or wine with lunch and dinner, were provided for each of the studies at 0915, 1115, 1315, 1615, 1915 and 2215 hours. No snacks or drinks were taken between these meals. Cigarette smoking was allowed, but the same number of cigarettes and their timing was repeated during all the studies.

Treatment

The patients were studied before, during and after treatment with omeprazole. The omeprazole was always taken orally 15 minutes before

breakfast as enteric-coated granules in a hard gelatin capsule. To encourage compliance with this once-daily regimen, the patients were each provided with a wristwatch with a 24-hour alarm for the duration of the study.

The design of the study is shown in Table I. All nine patients took part in the first five studies, but one patient was then excluded due to a possible adverse reaction to omeprazole (5); two patients were unable to join the final study for personal reasons. The studies on omeprazole treatment were performed after 1 or 2 weeks of treatment with the drug, the 7th or 14th doses being taken at 0900 hours on the morning of the respective study. On day 14 of the study, four patients had taken omeprazole, 30 mg/day for 14 doses, whereas five patients had taken omeprazole, 30 mg/day for seven doses, followed immediately by omeprazole, 60 mg/day, for the next seven doses.

Plasma omeprazole

Blood samples were taken for estimation of the plasma omeprazole concentration at 12 predetermined intervals throughout the 24 hours of each study. Plasma omeprazole was measured by high pressure liquid chromatography (HPLC), following extraction into methylene chloride at pH 6.5–7.0 (PO Lagerstrom, personal communication).

Plasma gastrin

On each study day, venous blood was taken for measurement of plasma gastrin concentration before breakfast, and at four 30-minute intervals after the meal. A 5 ml sample of blood was added to 0.1 ml of aprotinin, 20,000 units/ml, in a lithium heparin glass tube. The plasma was separated immediately and stored at −20°C until all the samples were measured by radioimmunoassay (antibody Gas 179) in the same batch at the end of the study (7).

Safety

A clinical examination and full laboratory profile of each patient was made before and after each course of treatment with omeprazole. Written, informed consent was obtained from each patient. The study was approved by the Ethical Committee of the Royal Free Hospital.

Statistics

Statistical significance of observed differences in the acidity and gastrin data was assessed by two-way analysis of variance after logarithmic transformation.

RESULTS

Intragastric acidity during treatment

The mean hourly intragastric H^+ activity of the six patients who received each of the 7-day courses of omeprazole (10, 20 or 30 mg/day) is shown in Fig. 1. There was a dose dependent decrease of acidity. The mean 24-hour intragastric H^+ activity fell from 39.2 ± 2.3 mmol/litre (mean ± SEM) before treatment to 24.6 ± 2.2 mmol/litre, 3.9 ± 0.9 mmol/litre, and 1.1 ± 0.4 mmol/litre during treatment with omeprazole, 10, 20 and 30 mg/day, respectively. These

Table I. Study design.

Study day	Omeprazole dose/day	Weeks of treatment	Number of patients
0	None		9
7	30 mg	1	9
14	30 mg, or	2	4
	30 mg for 1 week followed by 60 mg for 1 week	2	5
21	None	1	9
70	None	8	9
77	10 mg	1	8
105	20 mg	1	6

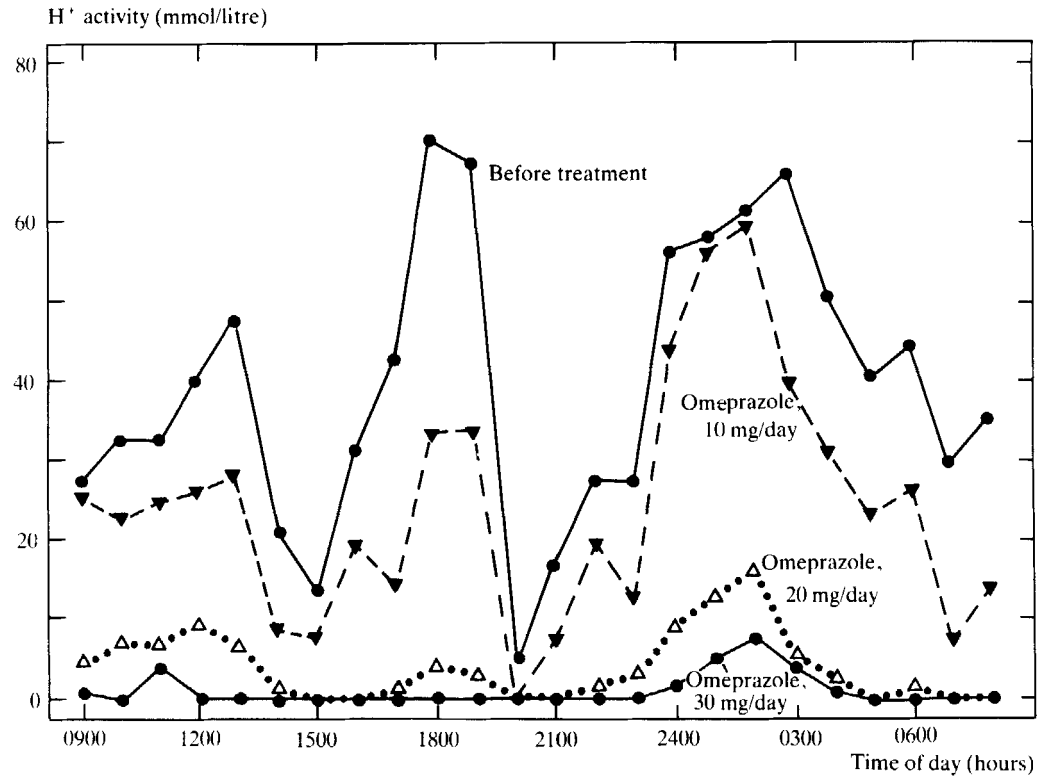

Fig. 1. Mean hourly intragastric H^+ activity in six patients before and during treatment with omeprazole, 10, 20 or 30 mg/day. The seventh dose of omeprazole was taken at 0900 hours.

represent decreases of 37%, 90% and 97% respectively and the differences between each of the regimens are significant ($p<0.01$). There was considerable variation in response to omeprazole; for example, only four of eight patients responded to the low dose of 10 mg/day.

A second week of treatment with omeprazole, either 30 mg/day (four patients) or 60 mg/day (five patients), decreased 24-hour intragastric H^+ activity by 99% and 96% respectively compared with the before treatment acidity. This decrease of acidity is not significantly different from that observed at the end of 1 week of treatment with omeprazole, 30 mg/day.

Acidity after cessation of treatment

A decrease of 24-hour intragastric acidity was observed in eight of the nine patients 1 week after the cessation of 14 days of treatment with omeprazole (Fig. 2). Mean 24-hour H^+ activity was 28.7 ± 3.4 mmol/litre (mean ± SEM) compared with 38.7 ± 3.9 mmol/litre before treatment. This 26% decrease of acidity is significant ($p<0.001$). Eight weeks after stopping omeprazole, the mean 24-hour intragastric H^+ activity was 40.3 ± 4.1 mmol/litre which is not significantly different from the intragastric acidity before treatment.

Fasting plasma gastrin

At the end of 1 week of treatment with omeprazole, 30 mg/day, there was a rise of fasting plasma gastrin concentration in all patients. The mean plasma gastrin rose significantly from 7.3 ± 1.2 pmol/litre to 17.4 ± 2.3 pmol/litre (mean ± SEM; $p<0.001$; $n=9$). During the second week of treatment with omeprazole, 30 or 60 mg/day, there was a further significant rise of fasting

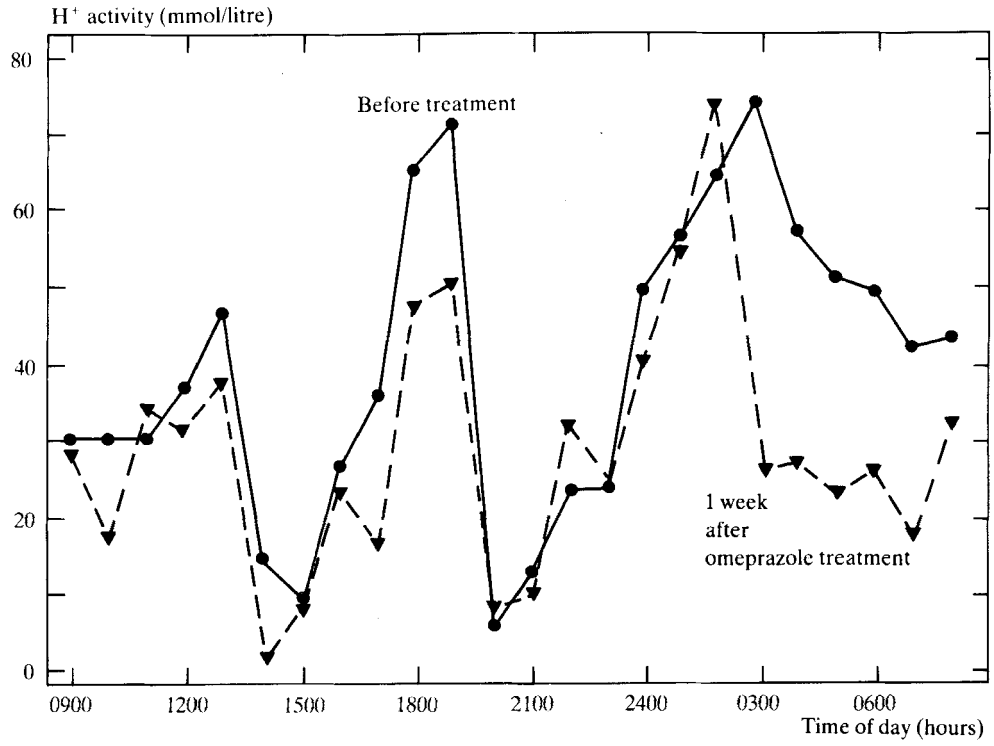

Fig. 2. Mean hourly intragastric H^+ activity in nine duodenal ulcer patients before, and 1 week after, 14 days of treatment with omeprazole, 30–60 mg/day.

plasma gastrin to 36.7 ± 7.3 pmol/litre ($p<0.01$). One week after stopping treatment with omeprazole, the fasting plasma gastrin concentration was 18.9 ± 4.4 pmol/litre, which is significantly higher than before treatment ($p<0.001$). Eight weeks after cessation of treatment, however, the concentration had fallen to 8.0 ± 3.1 pmol/litre, which is not significantly different from the value before treatment.

The postprandial plasma gastrin responses in the six patients who received omeprazole, 10, 20, or 30 mg/day are shown in Fig. 3. Compared with the values before treatment, there was a significant rise of fasting plasma gastrin concentration during each regimen (10 mg/day, $p<0.05$; 20 mg/day, $p<0.01$; 30 mg/day, $p<0.001$). These rises were reflected in elevated postprandial integrated (total) gastrin values, but there was no significant change in the postprandial integrated (incremental) gastrin response.

Plasma omeprazole

After all doses of oral omeprazole there was considerable variation in the timing and level of the peak plasma omeprazole concentration. This variation is demonstrated by the concentrations observed in eight patients after 1 week of treatment with omeprazole, 30 mg/day (Fig. 4).

The area under the plasma omeprazole concentration-time curve (AUC) was related to the dose (Fig. 5), but the relationship was non-linear. The mean AUC increased 3.8-fold (range 1.9–5.1, $n=5$) when the dose increased from 30 mg/day to 60 mg/day. In three patients taking omeprazole, 30 mg/day, the mean AUC did not change significantly between the 7th and 14th doses (3.6 to 3.3 μmol × hours/litre respectively). The AUC was also related to the percentage decrease of mean 24-hour intragastric H^+ activity (Fig. 6).

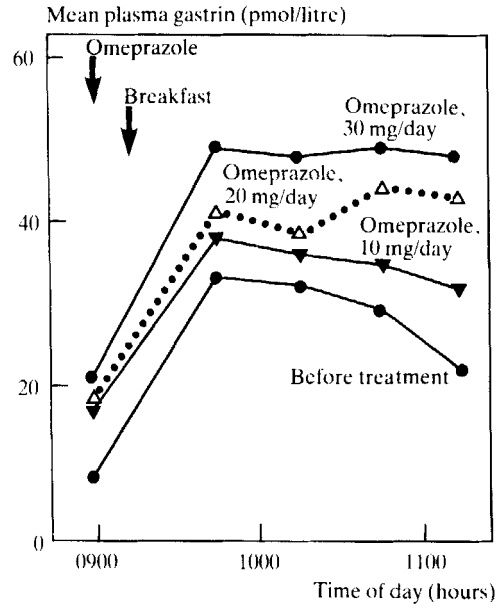

Fig. 3. Total postprandial gastrin responses in six patients before and during treatment with omeprazole, 10, 20 or 30 mg/day. The seventh dose of omeprazole taken at 0900 hours; breakfast was taken at 0915 hours.

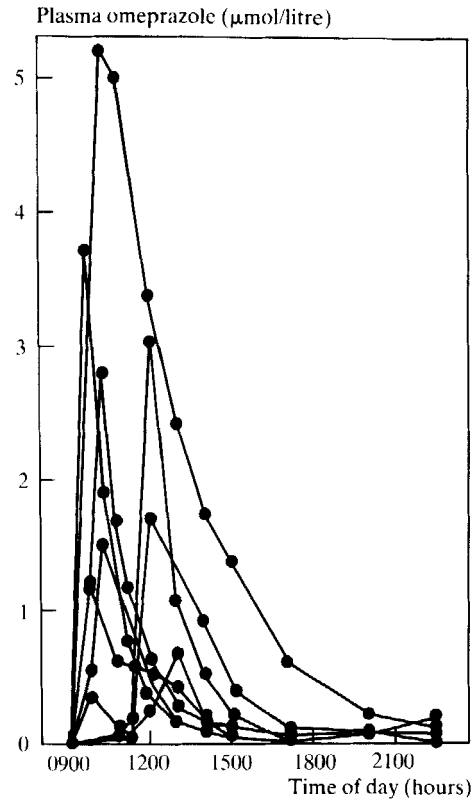

Fig. 4. Plasma omeprazole concentrations in eight patients after the seventh dose of omeprazole, 30 mg, at 0900 hours.

Safety studies

Omeprazole was well tolerated. No significant abnormalities were noted in the biochemistry or haematology profiles. One patient developed a lichen planus-like eruption 11 days after receiving omeprazole treatment for 2 weeks (30 and 60 mg/day, each for 1 week). The eruption cleared without treatment (5).

DISCUSSION

Decrease of intragastric acidity

The results of this study demonstrate that, for a maximal decrease of 24-hour intragastric acidity, the optimal dose of omeprazole is 30 mg/day. Increasing the dose of oral omeprazole from 10 to 30 mg/day caused a progressive decrease of 24-hour intragastric acidity. After 7 days of treatment, omeprazole, 30 mg/day, caused a 97% decrease of 24-hour intragastric acidity, with virtual anacidity from midday to midnight (Fig. 1). Median 24-hour pH rose from 1.4 before treatment to 5.3 during treatment (5). No further significant decrease of acidity was observed when the same dose was continued for an additional 7 days, nor when the dose of omeprazole was doubled to 60 mg/day. By comparison, cimetidine, 1 g/day, and ranitidine, 300 mg/day, significantly decreased the mean 24-hour intragastric H^+ activity by only 48% and 69%, respectively (4, 5).

Omeprazole, 20 mg/day, caused a 90% decrease of mean 24-hour intragastric acidity. Not only was more acid present in the stomach during the morning and the night than with the 30 mg/day dose, but there was also a return of acid in the early evening. A dose of 20 mg/day, however, caused a more profound and consistent decrease of acidity throughout the 24 hours (Fig. 1) than that observed with either cimetidine or ranitidine in conventional dose regimens (4). Omeprazole, 20 mg/day, caused the median

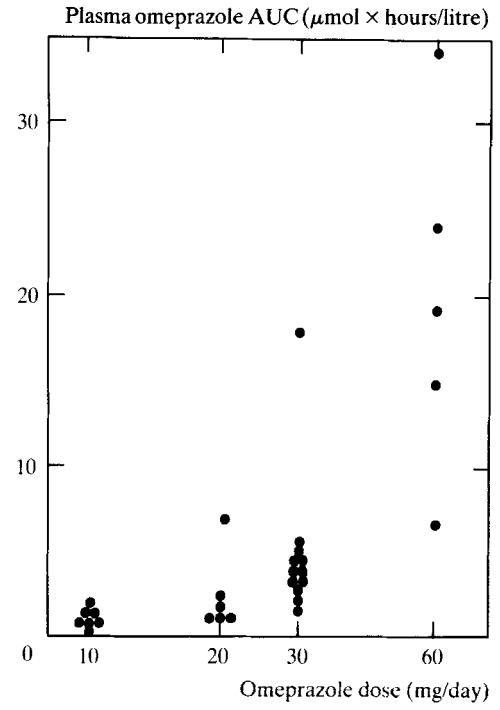

Fig. 5. Oral dose of omeprazole compared with the area under plasma omeprazole concentration-time curve (AUC).

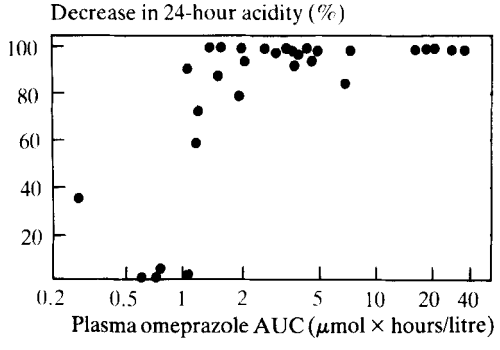

Fig. 6. Area under plasma omeprazole concentration-time curve (AUC) compared with percentage decrease of mean 24-hour intragastric acidity.

24-hour intragastric pH to rise from 1.4 to 5.0, whereas ranitidine, 300 mg/day, or cimetidine, 1 g/day, caused the median pH to rise from 1.4 to 1.7 and 2.4, respectively (5).

Although omeprazole, 10 mg/day, caused a statistically significant 37% decrease of mean 24-hour intragastric acidity, only four out of eight patients contributed to this decrease. The remaining patients showed no decrease in acidity with this low dose of omeprazole. This variation in response indicates that 10 mg/day may not be a suitable dose for the maintenance therapy of peptic ulceration.

Plasma gastrin concentration

The consistent rises of fasting plasma gastrin observed during and after treatment with omeprazole probably reflect the prolonged decrease of intragastric acidity caused by the drug. There was, however, a significant further rise of fasting plasma gastrin between the 7th and 14th doses of omeprazole, when there was no further decrease of intragastric acidity. Significant elevations of serum gastrin have been observed in duodenal ulcer patients during alkalinization of the stomach using exogenous sodium bicarbonate solution (8), but this change in gastrin was only observed when the intragastric environment was held at pH 7 for 5 hours.

Elevations of fasting plasma gastrin concentration have also been observed during treatment with either cimetidine or ranitidine (9–15).

The postprandial plasma gastrin concentration may be elevated during cimetidine or ranitidine treatment, when intragastric acidity is not neutralized by intragastric titration with alkali (16–18). Postprandial hypergastrinaemia during H_2-receptor blockade develops 1–2 hours after the meal (14, 15), whereas there is a consistent elevation of postprandial plasma gastrin during omeprazole treatment (Fig. 3), due to the elevation of fasting plasma gastrin concentration. Probably, during full dose omeprazole treatment, there is a significant elevation of plasma gastrin throughout the day and night.

Sustained decrease of acidity

Omeprazole, taken as a capsule 15 minutes before breakfast, causes a sustained decrease of intragastric acidity which persists after clearance of the drug from the plasma (Figs. 1 and 4). This continuation of antisecretory activity by omeprazole has been observed before (19), but its long duration is confirmed by the finding of a

significant decrease of mean 24-hour intragastric acidity 7 days after the last of 14 doses of omeprazole. The persistant decrease of intragastric acidity was seen throughout the 24-hour study, but was most marked during the basal secretion of the later part of the night (Fig. 2). The patients also had a persistent elevation of fasting plasma gastrin 7 days after stopping omeprazole, presumably due to the continuing decrease of intragastric acidity.

The mechanism of this prolonged inhibition of acid secretion is unclear, particularly as omeprazole induced inhibition of acid secretion is rapidly reversible in isolated guinea-pig parietal cells (20). The long duration of activity could prove to be of major therapeutic benefit, as control of intragastric acidity would be sustained despite minor lapses of compliance by the patient. Eight weeks after the last dose of omeprazole, intragastric acidity had returned to the pretreatment level, demonstrating recovery of normal gastric function.

Potential disadvantages of little intragastric acid

The hypergastrinaemia observed in this study could possibly promote parietal cell hyperplasia (21–23), with the risk of associated rebound hyperacidity following withdrawal of omeprazole treatment. A controlled study of post-treatment acid secretion has shown that this does not occur in healthy volunteers after 2 weeks of treatment with omeprazole, 40 mg/day (24).

Decreased intragastric acidity during treatment with omeprazole, 30 mg/day, does allow short-lived intragastric bacterial proliferation (25), but this is unlikely to be of importance if full doses of the drug are used only for the acute treatment of peptic ulceration.

Plasma omeprazole concentrations

The pattern of plasma omeprazole concentrations was extremely variable following the oral administration of this preparation of the drug. As omeprazole is unstable in an acid environment, the drug was protected in this study by an enteric coating. The enteric-coated granules appear to leave the stomach with either breakfast or morning coffee, causing peak concentrations in the plasma at 1000 hours or 1200 hours (Fig. 4). When omeprazole is taken in 50 ml of a water–Methocel® suspension, containing 8 mmol of sodium bicarbonate, there is rapid absorption with a peak plasma concentration of the drug at 30–40 minutes (19).

The area under the plasma omeprazole concentration-time curve is related to the oral dose of omeprazole, and also to the percentage decrease of 24-hour intragastric acidity (Figs. 5 and 6). Statistical analyses of these relationships are difficult because of insufficient middle-of-the-range values with which to plot a full dose-response curve. The relationship between dose of omeprazole and AUC was non-linear, as shown by nearly 4-fold increases in AUC when the dose doubled from 30 to 60 mg/day. This suggests that an excretory or metabolic pathway becomes saturated at this dose. Therefore it is important that there was no accumulation of the drug when patients took 30 mg/day for 2 weeks.

Other studies of intragastric acidity with omeprazole

Changes in 24-hour intragastric acidity on omeprazole treatment observed in other studies are summarized in Table II.

Mean hourly nocturnal intragastric acidity (2100 hours to 0700 hours) in ten healthy English volunteers, after the 14th daily dose of omeprazole, 30 mg, was decreased by 75% when compared with the before treatment acidity (25); the comparable decrease in the present study was 92% in duodenal ulcer patients.

Hence, it appears that duodenal ulcer patients are more susceptible to the antisecretory effect of omeprazole than healthy volunteers. In addition, the return of normal acid secretion appears to be faster in healthy volunteers (24, 25, 29) than in the duodenal ulcer patients of the present study.

CONCLUSION

This study demonstrates that omeprazole, 30 mg/day, is the optimal dose for a maximal decrease of 24-hour intragastric acidity in duodenal ulcer patients.

Table II. Studies on 24-hour intragastric acidity during omeprazole treatment.

	Number of patients	Mean decrease in H^+ activity (%)	Median pH	Omeprazole dose regimen
Healthy volunteers				
Germany*	8	72		30 mg/day for 9 days
	8	82		60 mg/day for 9 days
Australia†	8		1.9→5.0	40 mg/day for 7 days
Duodenal ulcer patients				
Sweden‡	12	99		40 mg/day for 7 days (± 80 mg loading dose)
Present study	9	97	1.4→5.3	30 mg/day for 7 days
	6	90	1.4→5.0	20 mg/day for 7 days

* From reference 26
† From reference 27
‡ From reference 28

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