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Effect of Single and Repeated Doses of Oral Omeprazole on Gastric Acid and Pepsin Secretion and Fasting Serum Gastrin and Serum Pepsinogen I Levels

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The effect of omeprazole on gastric acid and pepsin secretion and fasting serum gastrin and serum pepsinogen I levels was studied in 12 healthy volunteers. Omeprazole, 40 mg enteric-coated granules, or placebo was given once daily for nine days in a double-blind crossover study design. Twenty-four hours after a single dose of omeprazole, mean basal and mean pentagastrin-stimulated acid output decreased significantly. This effect was more pronounced after nine days of treatment. Basal pepsin output was significantly reduced only in those subjects with basal anacidity during omeprazole treatment. Stimulated pepsin output was slightly reduced after a single dose but unaltered after nine days of omeprazole. Fasting serum gastrin and serum pepsinogen I levels increased significantly during omeprazole treatment. It is concluded that omeprazole is a potent and selective inhibitor of gastric acid secretion, probably without a direct effect on pepsin secretion. However, in cases of basal anacidity during omeprazole administration, basal pepsin secretion is reduced. During omeprazole treatment, fasting serum levels of gastrin and pepsinogen I rise.

Omeprazole is a potent inhibitor of gastric acid secretion with prolonged action (1, 2). It acts by a noncompetitive inhibition of H^+, K^+-adenosine triphosphatase in the secretory membranes of the parietal cell (3). So far in man, H^+, K^+-adenosine triphosphatase has not been demonstrated outside the parietal cell, and therefore the effect of omeprazole on acid secretion may be very selective. Pepsinogen is secreted by the chief cells and converted to pepsin by gastric acid. Its secretion *in vivo* is stimulated by pentagastrin and acetylcholine. Pepsin secretion is inhibited by most drugs currently known to suppress gastric acid secretion, such as H_2-receptor antagonists (4–7) and pirenzepine (8). In previous studies in man with omeprazole, a decrease of pepsin secretion was reported (9–11). In isolated rabbit chief cells, however, omeprazole had no effect on pepsinogen secretion (12). The clinical significance of the presence of pepsinogen I in the blood is not known and its relation to the secretion of pepsinogen into the gastric lumen has not yet been established. Serum gastrin is synthesized and secreted by the gastrin-producing cells in the antrum. Longer periods of

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intragastric neutralization, as may occur during treatment with omeprazole, cause a rise in serum gastrin (13).

We studied the effects of single and repeated doses of oral omeprazole on basal and pentagastrin-stimulated gastric acid and pepsin secretion in healthy volunteers. Furthermore the effects on fasting serum gastrin and serum pepsinogen I levels were assessed.

MATERIALS AND METHODS

Twelve volunteers were studied, eight males and four females. Prestudy physical examination, laboratory screen, and electrocardiogram were clinically normal in all subjects. Their mean age was 25 years (range 20–35) and their mean weight 71 kg (range 49–94). All gave written informed consent, and the study was approved by the Ethical Committee of the Free University Hospital. Each subject was studied during two periods of 10 consecutive days with a period of two weeks in between. The study was double-blind and crossover. During each study period, omeprazole, 40 mg, or identical placebo was given orally once daily in the morning before breakfast for nine days. Omeprazole was given as enteric-coated granules in hard gelatin capsules. In each study period two gastric secretion tests were performed: the first 24 hr after the initial dose and the second 24 hr after the last dose of the study drug.

All tests were performed in the morning after an overnight fast. A double-lumen nasogastric tube was positioned in the stomach under fluoroscopic control. During the test the subjects were recumbent on their left side. The gastric content was continuously aspirated and collected on ice in 15-min aliquots. After 1 hr collection of basal gastric secretion, stimulated gastric secretion during continuous intravenous infusion of pentagastrin (1.5 μg/kg/hr) was collected for 1½ hr. Directly after each gastric secretion test, the volume, pH, and concentration of hydrogen ion were determined in each 15-min sample of gastric juice. Hydrogen ion concentration was determined by titration with 1 M NaOH to pH 7. Pepsin was determined immediately after collection of the samples using the human hemoglobin digestion method as described by Berstad (14). There was no difference in results whether the samples were analyzed at random pH or the pH of the samples was adjusted to 5.6 immediately after collection.

Fasting blood samples for determination of serum gastrin and serum pepsinogen I levels were taken before the study and at the start of each gastric secretion test. Serum gastrin was measured by radioimmunoassay (RIA) (15). Normal fasting serum gastrin levels in this assay are 6–69 pg/ml (5th to 95th percentile range). Serum pepsinogen I levels were assessed by enzyme-linked immunosorbent assay (ELISA) (16). Normal fasting serum pepsinogen I levels by this assay are 25–80 ng/ml (5th to 95th percentile range).

Before the start of the study and at the end of each study period on day 10, routine hematologic and biochemical blood studies and urine analysis were performed (ESR, hemoglobin, hematocrit, red blood cell count, glucose, alkaline phosphatase, bilirubin, ASAT, ALAT, sodium, potassium, calcium, chloride, total protein, and creatinine). For compliance control, all subjects completed a diary card during the study stating any unusual experiences and the time of the day they took their capsule.

Calculations and Statistics. All secretion data were expressed as concentration and output per 15 min. Furthermore, the 1-hr basal output and the mean basal concentration were computed, and the output and the mean concentration during the last hour of pentagastrin stimulation were calculated (plateau output and concentration after pentagastrin). Secretion data after a single dose of omeprazole were compared with data after a single placebo dose and data after nine days of omeprazole with those after nine days of placebo. All data are presented as the mean ± SEM of observations in the 12 subjects, except where stated otherwise. Statistical evaluations were performed using Wilcoxon matched-pair signed-rank test regarding 95% confidence limits ($P < 0.05$) as significantly different.

RESULTS

Results of volume, gastric acid, and pepsin secretion per 15 min are presented in Figure 1 and the 1-hr basal and 1-hr plateau secretion after pentagastrin in Table 1.

Volume. Basal volume of gastric secretion did not change during omeprazole treatment. Pentagastrin-stimulated volume decreased significantly by about 40% both after single and repeated doses of omeprazole.

Acid Secretion. During omeprazole administration both basal and pentagastrin-stimulated gastric acid concentration were significantly reduced. Basal acid output diminished by 72% after a single dose and by 89% after repeated doses of omeprazole. Pentagastrin-stimulated acid output decreased by 55% after one and by 62% after nine days of omeprazole treatment.

Pepsin Secretion. Mean basal pepsin concentration and output were significantly diminished after repeated doses of omeprazole but not after a single dose. The observed decrease could be entirely attributed to those subjects having complete basal anacidity during omeprazole treatment. Basal anacidity was considered complete when basal acid output was 0.0 mmol/hr and the pH of all basal samples was between 6.6 and 8. This occurred in one subject after a single dose of omeprazole and in seven subjects after repeated doses. In those cases basal pepsin output was diminished by 91% ($P < 0.01$). In all other tests during omeprazole adminis-

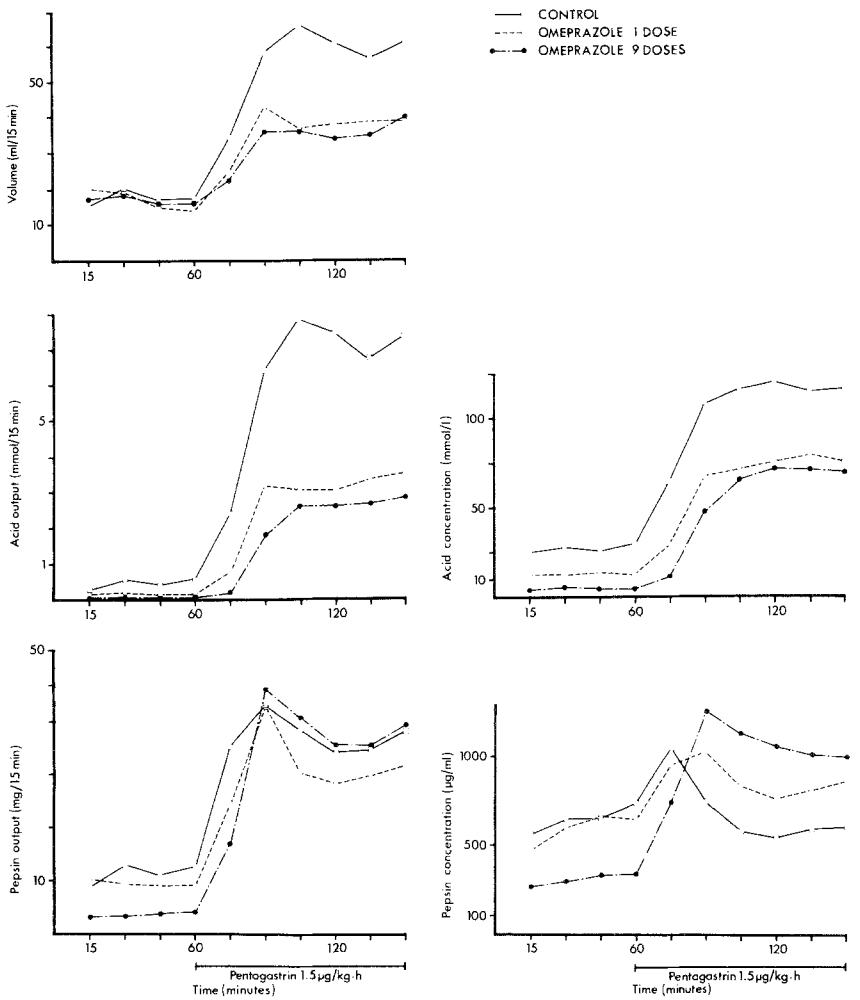

Fig 1. The effect of one and nine days of treatment with omeprazole on mean volume secretion and acid and pepsin output (left) and concentration (right) per 15 min basal and during stimulation with pentagastrin in 12 healthy volunteers. The mean of the two experiments during placebo is represented as control curve.

TABLE 1. GASTRIC SECRETION DATA IN 12 HEALTHY SUBJECTS IN PLACEBO EXPERIMENTS AND DURING TREATMENT WITH OMEPRAZOLE

	PLACEBO[1]		*OMEPRAZOLE single dose*		*OMEPRAZOLE 9 days*	
	basal	*pentagastrin stimulated*[2]	*basal*	*pentagastrin stimulated*	*basal*	*pentagastrin stimulated*
Volume (ml)	69 ± 8	246 ± 22	67 ± 7	152 ± 21**	67 ± 8	146 ± 14^{++}
H^+ concentration (mmol/L)	25 ± 5	118 ± 3	12 ± 5*	75 ± 9**	5 ± 3^{++}	70 ± 6^{++}
H^+output (mmol/ hr)	1.9 ± 0.3	29.4 ± 3.1	0.7 ± 0.2	12.9 ± 2.6**	0.3 ± $0.1^{++\circ}$	10.7 ± 1.7^{++}
Pepsin conc. (µg/ml)	663 ± 57	587 ± 22	618 ± 103	826 ± 63*	321 ± 94^{+}	1058 ± $63^{++\circ\circ}$
Pepsin output (mg/hr)	45.3 ± 5.6	147 ± 15	38.3 ± 9.0	122 ± 16	15.0 ± $4.6^{++\circ}$	153 ± 16

1 mean of the two experiments during placebo.
2 last hour during pentagastrin stimulation.
*$p < 0.05$, **$p < 0.01$: compared to results after single dose of placebo.
°$p < 0.05$, °°$p < 0.01$: compared to results after single dose of omeprazole.
$^{+}p < 0.05$, $^{++}p < 0.01$: compared to results after 9 days placebo administration.

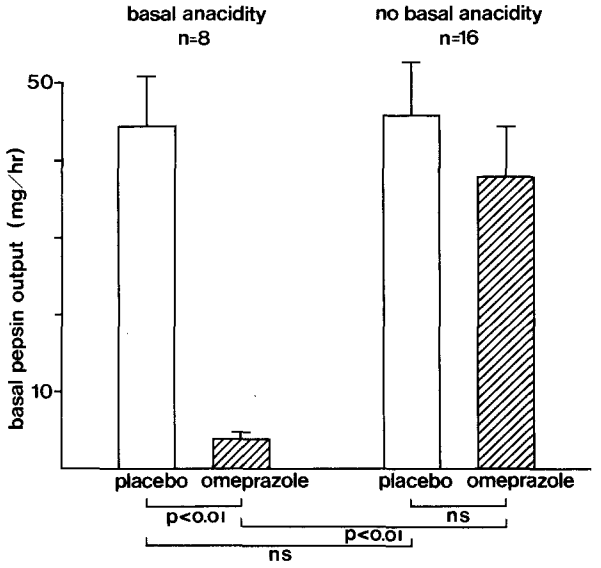

Fig 2. Basal pepsin output (mg/hr; mean ± SEM) during placebo and omeprazole in subjects with concomitant basal anacidity during omeprazole administration (left) and no basal anacidity during omeprazole (right).

tration, when no basal anacidity was found, basal pepsin output was only 17% (NS) lower than control (Figure 2). In no case was anacidity observed during pentagastrin stimulation. Mean stimulated pepsin output was slightly reduced after a single dose of omeprazole but was not different from control after nine days. Mean stimulated pepsin concentration was significantly increased in both tests during omeprazole administration.

Serum Gastrin and Serum Pepsinogen I. Mean fasting serum gastrin levels were 36 ± 3 pg/ml before the study, 36 ± 3 pg/ml after one day, and 32 ± 3 pg/ml after nine days in the placebo period. They rose after one dose of omeprazole to 49 ± 6 pg/ml ($P < 0.01$) and showed a further increase to 59 ± 6 pg/ml after nine days of omeprazole administration ($P < 0.002$ compared to placebo; $P < 0.05$ compared to after one dose of omeprazole).

Mean fasting serum pepsinogen I levels were 51 ± 4 ng/ml before the study and 48 ± 6 ng/ml and 48 ± 5 ng/ml during the placebo period. After one-day administration of omeprazole, serum pepsinogen I levels increased to 105 ± 20 ng/ml ($P < 0.02$) and after nine days to 106 ± 12 ng/ml ($P < 0.0005$ compared to placebo; NS compared to after one day of omeprazole).

During the study, no side effects were reported by the volunteers, and no clinical significant changes were seen in the laboratory screens.

DISCUSSION

This study shows that single and repeated doses of 40 mg omeprazole inhibited pentagastrin-stimulated acid output by about 60% when measured 24 hr after drug administration. Both volume and H^+ concentration of secretion were diminished. This high potency of omeprazole in reducing gastric acid secretion is in keeping with earlier reports (1, 2, 9, 17). Omeprazole is therefore a much more potent inhibitor of gastric acid secretion with action of much longer duration than the currently known H_2-receptor antagonists (5–7).

Pentagastrin-stimulated pepsin output after a single dose of omeprazole was only slightly reduced, and stimulated pepsin output after nine days of omeprazole and basal pepsin output after a single dose of omeprazole were unaltered. Omeprazole has therefore probably no direct effect on pepsin secretion *in vivo*. Basal concentration and output of pepsin were remarkably reduced only in subjects with basal anacidity during omeprazole treatment. In the assay, all pepsinogen is converted into pepsin, and the intragastric pH was not in a range that pepsin could have been degraded. Therefore the observed inhibition of pepsinogen secretion was probably due to the absence of gastric acid.

The unchanged basal pepsin concentration and output in the other subjects without anacidity demonstrated that only small amounts of acid secretion are required for a normal pepsinogen secretion, as basal acid secretion in these subjects was often very low. Hydrochloric acid is a stimulus for pepsinogen secretion (18, 19), probably via local cholinergic stimulation in the gastric mucosa, as postulated by Johnson (20). To our knowledge, however, the observation that in the absence of gastric acid hardly any pepsinogen is secreted has not previously been reported in man. It seems unlikely that a diminished flow in the gastric gland or pyloric loss is responsible for this phenomenon because, at the same time, no decrease in volume of gastric secretion was observed (Figure 1).

Several previous studies with omeprazole in man reported a decrease of pepsin secretion (9–11). In one of these studies, a 100% inhibition of acid secretion in a subgroup of patients was parallelled by a 100% inhibition of pepsin output (10). In the other reports no separate mention has been made of findings during anacidity. In pepsinogen-rich cell fractions from rabbit gastric mucosa, omeprazole had no effect on pepsinogen secretion (12).

Fasting serum gastrin levels increased during omeprazole administration. As early as 24 hr after a single 40-mg dose of omeprazole, a significant increase was observed and a further significant increment occurred if treatment was continued for nine days. In an earlier study of healthy volunteers given 30 mg of omeprazole daily, we also demonstrated that meal-stimulated serum gastrin levels rose during omeprazole treatment and that fasting and meal-stimulated serum gastrin levels normalized within one week after stopping omeprazole administration (21). In that study, however, no increase in fasting serum gastrin levels was observed 24 hr after a single dose. Omeprazole in a dose of 40 mg produced a more rapid effect on fasting serum gastrin levels than 30 mg. Probably the increase in serum gastrin is due to changes in gastric acidity. This is supported by earlier reports that serum gastrin levels rose after intragastric alkalinization (13) and that subjects with a high basal pH (22) and low pentagastrin-stimulated gastric acid secretion (23) had higher fasting serum gastrin levels.

Fasting serum pepsinogen I levels rose significantly both after single and repeated doses of omeprazole. But here again 40 mg of omeprazole had a more rapid effect than 30 mg, when comparing the present findings with the results of our previous study (21). In that study serum pepsinogen I levels did not significantly increase 24 hr after a single dose. The clinical significance of the rise in serum pepsinogen is, however, not clear as it is unknown how and why pepsinogens are released to the blood.

In conclusion, omeprazole is a potent inhibitor of gastric acid secretion, probably without a direct effect on the secretion of pepsin. However, basal pepsin secretion is greatly reduced in cases of basal anacidity during omeprazole. During treatment with omeprazole, a rise in fasting serum gastrin and serum pepsinogen I levels is observed.

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