

Effect of omeprazole – a gastric proton pump inhibitor – on pentagastrin stimulated acid secretion in man

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SUMMARY The effect of oral omeprazole on pentagastrin stimulated gastric acid secretion was studied in 11 healthy subjects. Doses of 20–80 mg produced dose dependent inhibition of acid secretion, with total suppression at the highest dose. Omeprazole was absorbed and eliminated from plasma rapidly and the inhibitory effect was related to the area under the plasma concentration time curve. The duration of action was long and single doses of 20 and 40 mg reduced acid secretion significantly for one and three days, respectively. Omeprazole in a dose of 15 mg given once daily for five days, suppressed acid secretion continuously, the inhibitory effect stabilising after three days at a predose inhibition of about 30% and a postdose inhibition of about 80%.

Substituted benzimidazoles inhibit gastric acid secretion in several animal species, both *in vitro* and *in vivo*. *In vitro* data from isolated gastric glands support a novel mechanism of action as substituted benzimidazoles inhibit acid secretion produced by histamine, carbachol, dibutyl cyclic AMP, and high concentrations of potassium. This suggests an intracellular site of action peripheral to cyclic AMP and close to the acid formation process.¹⁻⁵ It has been postulated that the gastric proton pump at the secretory membrane of the parietal cell is an enzyme, (H⁺ K⁺)ATPase,^{6,7} and substituted benzimidazoles appear to interfere with this pump.⁸ One substituted benzimidazole, H149/94, has been shown to inhibit basal acid output *in vivo* in man as well as the gastric acid response to pentagastrin stimulation. This effect was dose dependent and long lasting, despite rapid disappearance of H149/94 from the plasma.⁹

In vitro omeprazole (H168/68) (Fig. 1), another substituted benzimidazole, is 10 times more potent than H149/94 on a molar basis. The present studies were designed to evaluate the effects of single and repeated oral doses of omeprazole on pentagastrin stimulated acid secretion in man.

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Received for publication 3 December 1982

Methods

SUBJECTS

Eleven men median age 29 years (range 22–38 years) and median weight 74 kg (range 63–88 kg) were studied. None had any history suggestive of peptic ulcer disease and all were considered healthy based on a physical examination, ECG, and a laboratory screen. During the first series of experiments the ECG, blood pressure, and pulse rate were recorded, and during all experiments the subjects were asked to report any noted effects. The study was approved by the Ethical Committee of the Medical Faculty, University of Gothenburg, Sweden, and written informed consent was obtained from all subjects.

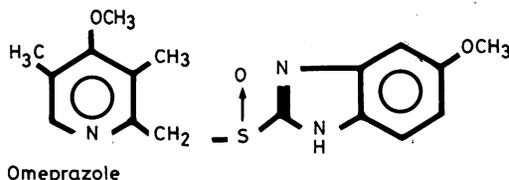


Fig. 1 Structural formula for omeprazole (H168/68) (5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl] sulphinyl]-1H-benzimidazole). Mol wt 345.4.

DRUGS

Omeprazole is degraded by acid and was therefore suspended in a 50 ml water-Methocel® solution containing 8 mmol NaHCO₃. A suspension in which omeprazole was replaced by 0.002% Bitrex® and 0.005% titanium dioxide was used as placebo. Both suspensions were given orally together with 50 ml NaHCO₃ solution (8 mmol), which was also given 10, 20, and 30 minutes after drug administration.

MEASUREMENTS OF GASTRIC ACID SECRETION

Three different series of experiments were performed, each including six subjects who received both placebo and omeprazole. Individual experiments were separated by at least one week. After an overnight fast a double lumen nasogastric tube (Salem Sump Tube 14 CH, A Brunswick, Belgium) was positioned with its tip in the most distal part of the stomach under fluoroscopic control. A thin polyethylene catheter (Intramedic PE 160) was attached to the Salem tube and the tip of this catheter positioned in the gastric fundus. Through this, the stomach was perfused with a phenol red water solution (3 mg/l) at a rate of 225 ml/15 min to assess losses to the duodenum assuming homogeneous mixing of marker perfusate and gastric juice. Gastric contents were aspirated continuously by negative pressure, once a second, and divided into 15 minute samples. The volume and pH of each sample was recorded and the acid concentration determined by titration to pH 7 with 0.1 mol/l NaOH using an automatic titrator (Radiometer, Copenhagen). After filtration (Milliporfilter 1.2 µm) and alkalisation with 0.4 ml 2.5 mol/l NaOH the phenol red concentration in a 4 ml aliquot of each sample was determined using a Beckman B-spectrophotometer at a wave length of 560 nm. All acid concentrations given are corrected for losses to the duodenum and expressed as mmol H⁺/15 min.

SINGLE DOSE STUDIES

In all subjects the response to pentagastrin was determined in an initial experiment using an intravenous infusion of pentagastrin (Peptavlon®, ICI) with doses of 30, 91, and 298 µg/h. The dose 91 µg/h resulted in a maximal acid response in all subjects.

After collection of basal acid secretion for two 15 minute periods a submaximal intravenous pentagastrin infusion (30 µg/h) was started and continued throughout the experiment. After collection of stimulated acid secretion for one hour the drug was given and gastric perfusion and aspiration stopped. Fifty-five minutes after drug administration the stomach was emptied over five minutes, after which

perfusion and collection of gastric contents were resumed and continued for a further three hours. All subjects took part in five experiments with placebo, 40, 60, and 80 mg omeprazole in random order and 20 mg in the last experiment.

DURATION OF ACTION

An intravenous infusion of pentagastrin (91 µg/h) over a period of one hour was used to determine the maximal acid response. The response to pentagastrin was restudied during the second hour after drug administration and on the second, third, fourth, and fourteenth day. Each subject received a single dose of placebo, 20 mg and 40 mg of omeprazole according to a latin square design.

REPEATED DOSES

The experiment consisted of two study periods, each lasting five days. Subjects received 15 mg omeprazole daily during one period and placebo during the other, in random order. The maximal acid response to pentagastrin (91 µg/h) was measured before, and during the second hour after, drug/placebo administration on the first, third, and fifth day. On the second and fourth day the subjects remained in the laboratory for one hour after receiving drug/placebo but no acid measurements were performed.

LABORATORY ANALYSIS

Venous blood samples were taken from a peripheral forearm vein before and at frequent intervals after drug administration for omeprazole assay. Plasma concentrations of omeprazole were determined by high pressure liquid chromatography at Department of Analytical Chemistry at AB Hässle. A routine laboratory screen (blood: ESR, Hb, Hct, RBC, WBC, differential count, thrombocytes, ASAT, ALAT, alkaline phosphatase, bilirubin, Na⁺, K⁺, Cl⁻, Ca²⁺, creatinine, protein, bicarbonate, T₃, T₄, and TSH; urine: glucose, protein, haemoglobin, and microscopy) was performed before and after each experimental series.

CALCULATIONS AND STATISTICAL ANALYSES

The maximal acid response to the intravenous infusion of pentagastrin (91 µg/h) was calculated as the sum of the two highest consecutive 15 minute values. To eliminate placebo effects the percentage change in acid secretion was calculated for each subject using the formula:

$$\frac{\frac{b-d}{a-c}}{\frac{d}{c}} \times 100$$

where: a = acid secretion before omeprazole,*
b = acid secretion after omeprazole, c = acid
secretion before placebo,* d = acid secretion after
placebo.

Friedman's two-way analysis of variance and
Wilcoxon's two-sided matched pair signed rank test
were used to test for drug effects on acid secretion
and a coefficient of variation (CV) for differences
within individuals was calculated. Significance was
claimed if $p \leq 0.05$. The area under the plasma
concentration-time curve (AUC) extrapolated to
infinity was calculated by trapezoidal rule with
correction for residual area after the last sample
time¹⁰ and a correlation coefficient between per cent
drug induced inhibition and AUC was calculated
after logit transformation where:

$$Y = \ln \frac{R}{R_{\max} - R}$$

(R = response as per cent inhibition and R
max = 100), and $X = \log_{10} \text{AUC}$.¹¹ The correlation
coefficient was tested using Student's *t* test.

The terminal half-life of omeprazole was
calculated by linear regression analysis using the log
concentrations measured 60–180 minutes after drug
administration. Values are given as mean \pm SEM.

Results

Omeprazole produced no side effects or changes in
the cardiovascular parameters that were recorded.
No drug related effects on the laboratory screen
were observed.

* Before first omeprazole/placebo dose when repeated doses were given.

SINGLE DOSE STUDIES

After the start of the pentagastrin infusion acid
secretion reached a plateau during the third and
fourth 15 minute periods. This level was submaximal
for pentagastrin stimulation, the median level being
65% (range 30–98%) of the maximal response.
Omeprazole produced a significant dose dependent
inhibition of acid secretion compared with placebo,
the mean percentage inhibition being 36 ± 8.5 ,
 65 ± 14.9 , 90 ± 5.3 , and $99 \pm 0.42\%$ with the 20,
40, 60, and 80 mg doses, respectively. The degree of
inhibition remained unchanged throughout the
experiment (Fig. 2) (Table 1). Omeprazole also
reduced the volume secretion but to a lesser extent
than acid secretion (21–87%) resulting in a
decreased acidity (Table 1). Plasma concentrations
of omeprazole reached a peak after about 30–40
minutes and then declined with a half-life of about
50 minutes (range 12–82 minutes) (Fig. 3). The
AUC increased with increasing doses and showed a
significant correlation with per cent inhibition of
acid secretion ($R=0.93$, $p<0.001$) (Fig. 4).

DURATION OF ACTION

During the second hour after omeprazole admini-
stration the maximal acid response was reduced by
 $51 \pm 9\%$ and $86 \pm 4\%$ respectively, with the 20 and 40
mg doses (Fig. 5, Table 2). A significant reduction of
 $26 \pm 12\%$ and $48 \pm 9\%$ respectively was still present
24 hours later. With the 20 mg dose, the acid
inhibition on the third and fourth days after drug
administration (18% and 6% respectively) was not
significantly different from placebo but the 40 mg
dose of omeprazole continued to produce significant
inhibition ($34 \pm 7\%$ and $18 \pm 4\%$ respectively).

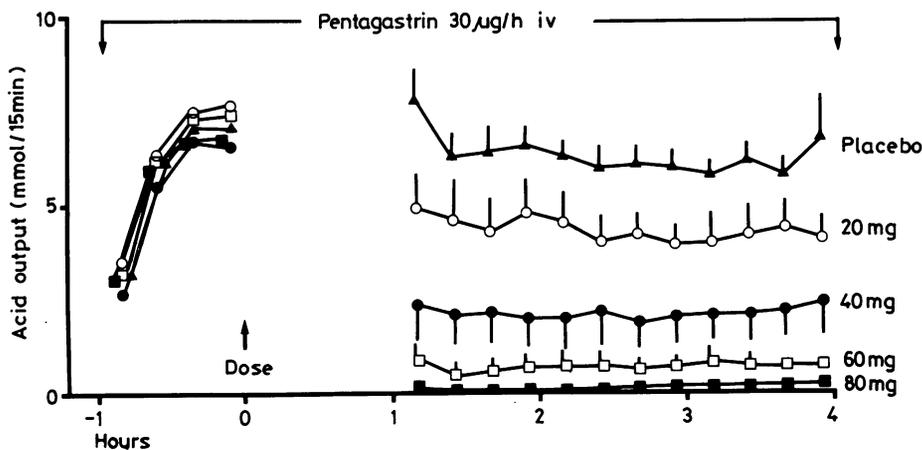


Fig. 2 Effect of oral omeprazole on pentagastrin induced acid secretion in six healthy subjects. Values are mean \pm 1 SEM.

Table 1 Pentagastrin (30 µg/h intravenously) stimulated acid (mmol/15 min) and volume (ml/15 min) output before and after (60–180 min) administration of omeprazole and area under the plasma concentration time curve (AUC) in six healthy subjects. Values are mean ± SEM

Omeprazole dose	Before administration		After administration		Omeprazole AUC µmol/h/l
	Acid	Volume	Acid	Volume	
Placebo	7.1±0.34	66.5±5.10	6.4±0.51	65.5±3.14	—
20 mg	7.6±0.78	72.0±4.05	4.3±0.67	58.5±4.11	0.94±0.19
40 mg	6.6±0.74	60.0±5.65	2.1±0.77	38.0±7.50	2.4±0.83
60 mg	7.4±0.78	67.5±4.43	0.57±0.30	20.6±5.90	3.8±0.84
80 mg	6.8±0.48	67.0±4.48	0.06±0.02	11.1±1.88	5.7±1.1

Fourteen days after the omeprazole dose the acid response to pentagastrin was identical to that with placebo. No omeprazole was detectable in plasma after 24 hours. The coefficient of variation for individual values of acid secretion within subjects during the placebo experiment was less than 10% when pentagastrin stimulation was repeated with an interval of 24 hours.

REPEATED DOSES

The first dose of omeprazole (15 mg) produced 47% inhibition of the maximal response to pentagastrin during the second hour after drug administration. On the third and fifth days before omeprazole, the acid response was reduced by 31% and 37%, respectively. The inhibition during the second hour after dosage on days three and five was 75% and 80% respectively (Fig. 6a,b. Table 3). No omeprazole was detectable in plasma before dosage on days three and five.

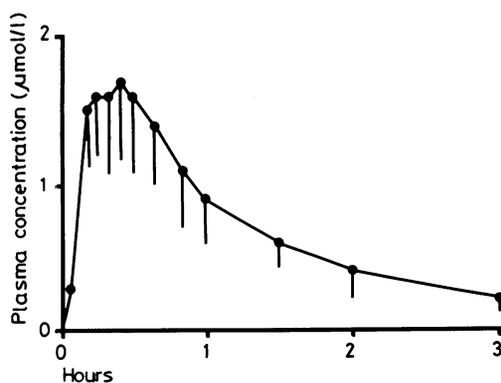


Fig. 3 Plasma concentrations of omeprazole in six healthy subjects given 40 mg orally. Values are mean ± 1 SEM.

Discussion

The histamine H₂-blocker cimetidine contain an imidazole ring and the new H₂-receptor antagonist ranitidine a furan ring which are similar from a medicinal chemical point of view.¹² Omeprazole and similar benzimidazoles also contain an imidazole ring but reduce acid secretion in a different way.⁸ Histamine H₂-antagonists block the histamine receptor on the parietal cell surface while studies with omeprazole have shown a mechanism of action with intracellular inhibition of the final step of the acid formation process.⁸ The present study shows that omeprazole is a more potent inhibitor of acid secretion in humans than is H149-94, the only substituted benzimidazole previously used in man, but with a similar inhibitory pattern.⁹

In these experiments omeprazole was given as a buffered suspension along with repeated doses of sodium bicarbonate and this could have influenced

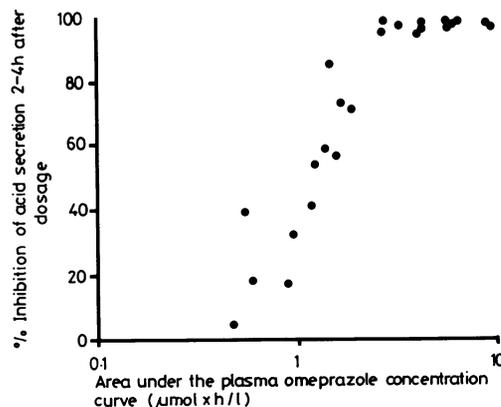
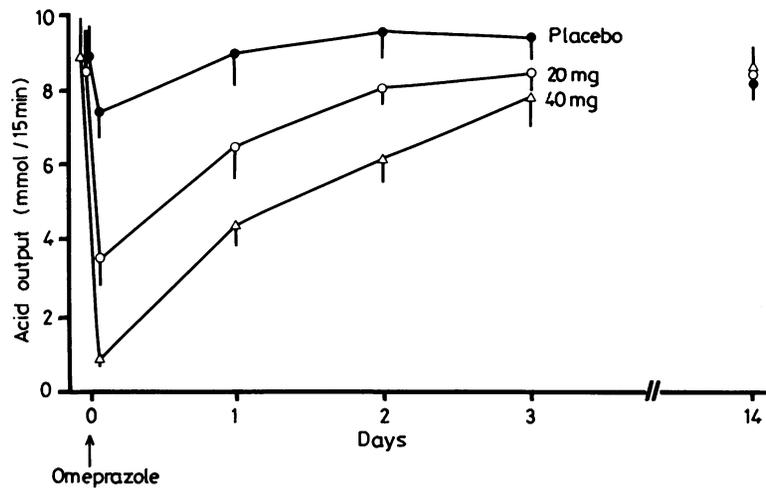


Fig. 4. Relationship between % inhibition of pentagastrin (30 µg/h intravenously) induced acid secretion during the second to fourth hour after drug administration and the area under the plasma omeprazole concentration-time curve. Correlation coefficient = 0.93, $p < 0.001$, $n = 24$.

Fig. 5 Duration of action of two different single oral doses of omeprazole in six healthy subjects estimated by repeated measurements of maximal response to one hour infusion of 91 µg pentagastrin. Values are mean ± 1 SEM.



subsequent acid secretion. In the present experiments the stomach was emptied of gastric contents one hour after both drug and placebo administration and, furthermore, the shape of the placebo curve did not change significantly during the second hour (Fig. 2). This implies that the sodium bicarbonate did not affect acid secretion. An enteric-coated granule formulation, which can be given without sodium bicarbonate, has been developed for future clinical evaluation.

Increasing doses of omeprazole (20–80 mg) produced dose dependent inhibition of submaximal pentagastrin induced acid secretion and total suppression with the highest dose. A single dose of 20 mg omeprazole reduced the maximal acid response to pentagastrin significantly even after 24 hours and with 40 mg of omeprazole there was a slight but significant inhibition of acid secretion three days after dosage. The inhibitory effect was reversible, however, in all subjects which accords with results from animal studies in which the duration of inhibition never exceeded three to four

days even with extremely high doses of omeprazole.¹³ A maximal pentagastrin dose was used in these experiments to obtain reproducible responses. The coefficient of variation was less than 10% when the test was repeated after 24 hours. When the test was repeated after one hour, however, a reduced response was observed.

Repeated low doses of omeprazole given once daily reduced the maximal acid response to pentagastrin significantly compared with placebo. The predose inhibition – that is, 24 hours after the last dose – as well as the postdose inhibition did not differ significantly between the third and fifth day. This suggests that the inhibitory effect had stabilised after about three days. With this low dose of omeprazole the degree of inhibition varied during a 24 hour period from 30–40% before dosing and 75–80% two hours after a dose. A somewhat greater degree of inhibition might be necessary clinically which could be achieved with a slight increase of daily dose.

Omeprazole was rapidly absorbed and dis-

Table 2 Maximal acid response (mmol/15 min) to pentagastrin (91 µg intravenously) before and at different intervals after single dose of omeprazole and area under plasma concentration time curve (AUC) in six healthy subjects. Values are given as mean ± SEM

Omeprazole dose	Before administration			After administration			AUC µmol/h/l
	–60–0 min	60–120 min	23–24 h	47–48 h	71–72 h	14 days	
Placebo	8.8±0.78	7.4±0.76	9.0±0.89	9.6±0.66	9.5±0.63	8.4±1.1	—
20 mg	9.1±0.66	3.6±0.66	6.4±0.65	7.9±0.42	8.7±0.46	8.6±0.43	1.1±0.33
40 mg	8.9±1.1	0.90±0.23	4.3±0.58	6.3±0.58	7.9±0.87	8.9±0.69	3.0±0.64

Table 3 Maximal acid response (mmol/15 min) to pentagastrin (91 µg intravenously) during repeated administration, measured before and after 1st, 3rd, and 5th dose and area under plasma concentration time curve in six healthy subjects. Values are given as mean ± SEM

	Before administration			After administration		
	Days 1	3	5	Days 1	3	5
Placebo	9.3±0.60	8.9±0.74	8.5±0.58	8.3±0.53	7.6±0.73	7.3±0.66
15 mg	9.3±0.74	5.9±0.76	5.1±0.71	4.3±0.74	1.8±0.78	1.4±0.61
AUC	—	—	—	0.95±0.19	1.1±0.31	1.3±0.35

appeared rapidly from plasma. After three hours plasma concentrations were very low (Fig. 3) while the maximum inhibitory effect was reached during the first hour and remained unchanged throughout the remainder of the experiment (Fig. 2). It is possible that substituted benzimidazoles accumulate intracellularly in the parietal cells as they are weak bases.¹⁴ Such a process could contribute to the long duration of action despite the short half-life in plasma. The area under the plasma concentration curve (AUC) was taken to reflect the amount of drug that had been absorbed and there was a good correlation between AUC and the inhibitory effect

(Fig. 4). An inhibition of volume secretion was also observed but this was less pronounced than the inhibition of acid secretion. As gastric volume secretion is only partly due to parietal cell secretion the smaller reduction could be explained on the basis that omeprazole only affects parietal cell secretion.

Substituted benzimidazoles have previously been shown to have a selective action on parietal cell function. In man, single daily doses of omeprazole produce pronounced and long lasting inhibition of gastric acid secretion which could be of clinical benefit in the treatment of peptic ulcer disease.

This study was sponsored by grants from the Swedish Medical Research Council (project no. 17X-760).

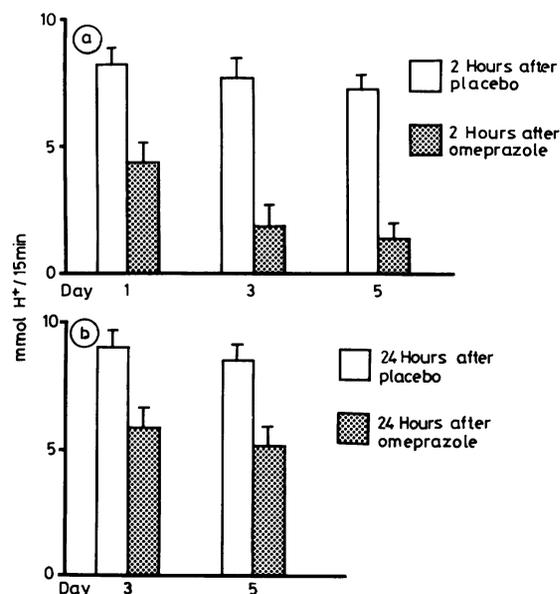


Fig. 6 Effect of repeated once daily oral administration of 15 mg omeprazole on maximal response to pentagastrin in six healthy subjects. Measurements were taken during the 2nd hour (postdosage, 6a) and 24th hour (predosage, 6b) after omeprazole administration. Values are mean ± SEM.

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