Effect of omeprazole on the secretion of intrinsic factor, gastric acid and pepsin in man

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SUMMARY The effect of an intravenous infusion of omeprazole (0.35 mg/kg) and placebo on basal and stimulated (pentagastrin 1.0 µg/kg/h) secretion of gastric acid, intrinsic factor and pepsin was studied in 10 healthy male subjects. Omeprazole caused a marked inhibition of basal and stimulated acid output. The inhibition of pepsin output was less marked, but also significant. The output of intrinsic factor, however, showed no significant change. The results indicate that acid and intrinsic factor might have different secretory mechanisms within the parietal cell.

Omeprazole (5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl)sulphonyl)-1H-benzimidazole), which is the most effective of the substituted benzimidazoles, is a potent inhibitor of acid secretion in isolated parietal cells,¹ isolated gastric glands,² as both in animals³ and in man.^{4,5} These drugs inhibit gastric acid secretion by a mechanism different from antiseoretagogues known so far, and studies have provided evidence that omeprazole inhibits the enzyme H⁺K⁺-ATP-ase,^{6,7} which is suggested to be the proton pump of the parietal cell.^{8,9}

Intrinsic factor¹⁰ as well as gastric acid is secreted by the parietal cell. Inhibitors of gastric acid secretion such as histamine H₂ receptor antagonists¹¹⁻¹³ as well as atropine¹⁴ have been shown to reduce intrinsic factor secretion. Whether or not omeprazole inhibits intrinsic factor secretion is, however, not known.

The present investigation was undertaken to measure the effect of omeprazole on acid and intrinsic factor secretion. The effect of omeprazole on pepsin secretion was also measured, since previous studies have shown different results.¹⁵⁻¹⁷

Methods

SUBJECTS

Ten healthy male volunteers (mean age 26 years, range 21-37 years) gave written informed consent to the study. The study was approved by the Ethical

Committee at Aker University Hospital, Oslo, Norway.

The gastric acid concentration was measured by titration with 0.1 M NaOH to pH 7.4 using an automatic titrator (Radiometer, Copenhagen, Denmark).

Aliquots of the gastric juice were depepsinised by adjusting the pH to 10 with 1M NaOH. After 30 minutes the pH was adjusted to 7.0 with 1 M NaOH and stored at -20°C.¹⁸

The intrinsic factor concentration was measured by the method of Gottlieb using intrinsic factor antibody from patients with pernicious anaemia.¹⁹ The concentration of intrinsic factor in the gastric juice was expressed in U/ml, where 1 unit is the amount of intrinsic factor bound to 1 ng ⁵⁷co-cyanocobalamin. The variation of duplicates in the assay was found to be 1.78%±0.22% (mean variation coefficient ±SD), and the between assay variation coefficient 11.8%. The samples from the omeprazole and the placebo experiments were analysed in the same batch.

Pepsin concentration was measured by the method of Berstad²⁰ using human haemoglobin as substrate, and samples with pH exceeding 6.0 were excluded from the statistical analysis of the pepsin data.

The samples for pepsin and gastric acid determination were kept refrigerated until analysed.

Aliquots containing 61.3 mg omeprazole dissolved in 6.13 g polyethylenglycol (MW 400) were stored at -20°C until used. Before use omeprazole was diluted in 6.7 mmol/l NaHCO₃ to a final concentration of 4 mg/ml. 6.13 g polyethylenglycol diluted in 6.7 mmol/l NaHCO₃ was used as placebo.

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PROCEDURE

The subjects fasted overnight. At 8 am a gastric tube was positioned with its tip in the distal part of the stomach under fluoroscopic control. The subjects swallowed 200 ml of water, and the contents of the stomach were immediately aspirated. Omeprazole 0.35 mg/kg or placebo was infused intravenously for five minutes in a double blind manner. One hour later an intravenous infusion of pentagastrin (Peptavlon, ICI, Pharmaceuticals Division, Cheshire, UK) at a dose of 1.0 µg/kg/h was started and continued for 90 minutes. The gastric juice was aspirated by continuous suction, and collected on ice in 15 minute portions. Outputs of intrinsic factor and acid were calculated from measurements carried out in aspirates obtained during the 60 minute basal period and the 90 minute period when pentagastrin was infused. The pepsin data were calculated from the last 60 minutes with pentagastrin.

Before and after termination of the experiments, blood and urine samples were taken for routine laboratory tests. (Blood: ESR, Hb, Hct, RBC, WBC, differential count, thrombocytes, ASAT, ALAT, alkaline phosphatase, bilirubin, Na⁺, K⁺, Cl⁻, Ca²⁺, creatinine, bicarbonate. Urine: glucose, protein, haemoglobin and microscopy). Omeprazole was well tolerated as no significant changes were observed in laboratory values. Neither were any side effects because of omeprazole seen or reported by the subjects.

The results were presented as mean values and SEM. A paired Wilcoxon's ranked sum test was used for statistical analyses, and p values <0.05 were regarded as significant.

Results

ACID SECRETION

Both basal and pentagastrin stimulated gastric acid output was significantly inhibited by omeprazole. (Figure 1 b). The inhibition of basal acid output increased subsequently during the whole basal period, indicating that the inhibition recorded was not maximal. The inhibition of stimulated acid output was 74.1%±5.2% (mean ±SEM; p<0.01), and was because of a significant inhibition of both H⁺ concentrations (mean inhibition 39.0%±9.3%; Figure 1 a), and volumes of gastric juice (mean inhibition 59.1%±4.6%).

INTRINSIC FACTOR SECRETION

Both basal and stimulated concentration of intrinsic factor was higher after omeprazole infusion than after placebo, whereas the output of intrinsic factor did not significantly change (Figure 2 a, b; Table).

Fig. 1 Effect of iv omeprazole 0.35 mg/kg on basal and pentagastrin stimulated acid concentration (a), and acid output (b). Arrows indicate when omeprazole or placebo were infused. The results are shown as mean ± SEM. (○ - - - omeprazole, ● — placebo).

PEPSIN SECRETION

In the basal period omeprazole caused a marked rise in pH in gastric juice that exceeded 6 in several samples. As pepsin is irreversibly degraded at pH above 6,²¹ the pepsin data from the basal period were considered unreliable and was excluded from the statistical analyses. During pentagastrin stimulation mean pepsin output decreased from 125.3 mg±7.9 mg (placebo) to 79.6 mg±6.3 mg after omeprazole (p<0.01) whereas the mean pepsin concentration increased from 413 mg/l±34 mg/l (placebo) to 817 mg/l±189 mg/l after omeprazole (p<0.01; Figure 3 a, b).

Discussion

The potent inhibitory effect of omeprazole on acid secretion was confirmed in the present study when stimulating the secretion with a submaximal dose of pentagastrin (1.0 µg/kg/h; Fig 1 a, b). The output of intrinsic factor was unchanged after omeprazole (Table, Fig 2 b). The concentration of intrinsic factor in the gastric juice increased, probably

Table Basal and pentagastrin (Pg) stimulated intrinsic factor concentration and intrinsic factor output after an intravenous infusion of omeprazole and placebo (Mean±SEM) (ns = not significant)

	Intrinsic factor concentration (U/ml)		Cumulative intrinsic factor output	
	Basal	Pg	Basal (U/60 min)	Pg (U/90 min)
Omeprazole	41.0±4.1	82.4±18.5	2479±540	13719±3172
Placebo	28.1±0.5	42.6±13.5	3239±836	16424±2051
P	<0.01	<0.01	ns	ns

because of reduced volume secretion. Hence, the results show that omeprazole, at a dose causing marked inhibition of acid secretion, has no effect on basal and pentagastrin stimulated intrinsic factor secretion. The effect of maximal doses of omeprazole on intrinsic factor secretion is, however, not known.

As the parietal cell is the site of both acid and intrinsic factor production,¹⁰ the different effect of omeprazole on intrinsic factor and acid secretion is of interest. It is known that omeprazole interacts with the enzyme H⁺K⁺-ATP-ase, which is located

in the secretory membrane of the parietal cell,^{6,7} and appears as such to be a peripheral step in the secretory mechanism of hydrochloric acid. The different effect of omeprazole on acid and intrinsic factor secretion therefore support the hypothesis that acid and intrinsic factor have separate secretory mechanisms in the parietal cell.

Intrinsic factor is essential for normal absorption of vitamin B₁₂. One might therefore expect that omeprazole treatment should be without effect on absorption of vitamin B₁₂. Nevertheless it has been proposed that achlorhydria or hypochlorhydria

Fig. 2 Effect of iv omeprazole on basal and pentagastrin stimulated intrinsic factor concentration (a) and intrinsic factor output (b). (Symbols as in Fig. 1.)

Fig. 3 Effect of iv omeprazole on basal and pentagastrin stimulated pepsin concentration (a) and output (b). n = number of samples in each period with pH <6.0. (Symbols as in Fig. 1.)

might reduce the absorption of food-bound vitamin B₁₂, even in presence of sufficient amounts of intrinsic factor to ensure normal absorption of unbound vitamin B₁₂.²² It has been shown that treatment with the histamine H₂-receptor antagonists cimetidine and ranitidine reduced the absorption of radioactive cyanocobalamin bound to chicken serum,^{13, 23} but has no effect on the absorption of unbound radioactive cyanocobalamin.²³ Whether or not omeprazole inhibits the absorption of vitamin B₁₂ still remains to be investigated.

The results also show a moderate inhibition of pentagastrin stimulated pepsin output (Fig 3 a,b). The inhibition of pepsin output ($38.2\% \pm 7.0\%$) was less marked than the inhibition of acid output ($74.1\% \pm 5.2\%$; $p < 0.01$). During the pentagastrin stimulation the pepsin concentration markedly increased, probably as an effect of reduced volume secretion. The present results are in agreement with those reported in man by Wilson *et al.*¹⁷

The mechanism by which omeprazole inhibits pepsin secretion is unknown. Fryklund *et al.*¹⁶ found that omeprazole did not inhibit pepsinogen released in isolated zymogen cells from rabbit mucosa, whereas the formation of acid in isolated parietal cells was strongly inhibited. The inhibition of pepsin secretion can therefore not be explained by direct omeprazole interaction with the pepsin producing cells. It might be speculated whether the inhibition of pepsin secretion could be an effect secondary to the inhibition of acid secretion, a theory supported by findings that topical application of hydrochloric acid stimulates the secretion of pepsin *in vitro*²⁴ as well as in healthy man.²⁵

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