PAPERS

Omeprazole promotes proximal duodenal mucosal bicarbonate secretion in humans

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Abstract

The proton pump inhibitor, omeprazole, surprisingly resulted in higher rates of proximal duodenal mucosal bicarbonate secretion than previously reported using an H₂ receptor antagonist for gastric acid inhibition. Gastroduodenal perfusions were performed in healthy volunteers to evaluate whether this incidental finding is explained by more potent gastric acid inhibition by omeprazole or might be caused by the different mode of drug action. Basal and stimulated gastric and duodenal bicarbonate secretion rates were measured in the same subjects in control experiments (n=17) and after pretreatment with high dose omeprazole (n=17) and ranitidine (n=9), respectively, by use of a technique permitting simultaneous measurements. Concentrations of bicarbonate were measured in the respective effluents by the method of back titration. Both omeprazole and ranitidine completely inhibited gastric acid secretion (pH 6.9 *v* 6.8; *p*>0.05). Omeprazole caused higher rates of basal (mean (SEM)) (597 (48) *v* 351 (39) μ mol/h; *p*<0.02) and vagally stimulated (834 (72) *v* 474 (66) μ mol/h; *p*<0.02), but not acid stimulated (3351 (678) *v* 2550 (456) μ mol/h; *p*>0.05) duodenal bicarbonate secretion compared with control experiments. Also the combination of omeprazole and ranitidine increased (*p*=0.05) duodenal bicarbonate secretion, while ranitidine alone caused no change in either basal or stimulated secretion. In the stomach basal as well as vagally stimulated bicarbonate secretion was independent of the means of acid inhibition. These results show that the proton pump inhibitor, omeprazole, promotes proximal duodenal mucosal bicarbonate secretion apparently independent of its gastric acid inhibitory effect. The mechanism of action remains speculative.

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Keywords: bicarbonate secretion, duodenum, omeprazole, stomach, ranitidine.

Previous work has shown the existence of a pH gradient at the luminal surface of the

gastroduodenal mucosa generated by active secretion of bicarbonate into the mucus gel layer.^{1,2} As bicarbonate comprises the first line of defence against luminal acid and pepsin, recent research has focused on mucosal bicarbonate transport mechanisms both in experimental animals and in humans.³ The effect of various antiulcer drugs on gastroduodenal bicarbonate secretion has been investigated in several studies,⁴ among which a few have concentrated on the effect of the proton pump inhibitor, omeprazole. Administration of omeprazole to cats has resulted in both reduced⁵ and increased⁶ rates of gastric bicarbonate secretion, while duodenal mucosal bicarbonate secretion in cats⁷ and in rats⁸ seems unaffected. Although relevant for clinical use in the treatment of acid related disorders, the potential effect of proton pump inhibitors on human gastroduodenal mucosal bicarbonate secretion has not previously been considered.

Incidentally, we observed that omeprazole resulted in higher rates of basal and vagally stimulated proximal duodenal mucosal bicarbonate secretion than previously reported using ranitidine as an inhibitor of gastric acid. To evaluate whether this finding might be explained by more potent inhibition of gastric acid by omeprazole or by the different mode of drug action, gastric and duodenal bicarbonate secretion rates were determined by use of a technique permitting simultaneous measurements.⁸ The same healthy volunteers were studied in control experiments without acid inhibition and after administration of omeprazole and ranitidine, respectively, using supra-maximal, equipotent doses sufficiently large to obtain total inhibition of gastric acid secretion. In supplementary experiments, the combination of omeprazole and ranitidine on basal duodenal mucosal bicarbonate secretion was studied.

Methods

Healthy volunteers

Twenty one healthy volunteers (12 men and nine women, median age 32 years, range 24–50), with no history of gastrointestinal or other medical diseases, consented to the study protocol. None of the healthy volunteers had ingested aspirin, non-steroidal anti-inflammatory drugs, or alcohol during the week before

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entering the study, which was carried out according to the Helsinki II Declaration and approved by the ethics committee of Copenhagen and Frederiksberg.

Experimental design

Three series of experiments were performed. In the first series eight volunteers had simultaneous gastric and proximal duodenal perfusions twice (isotonic saline) with an interval of at least one week. The perfusions were performed in random order, that is, as one set of control perfusions (without acid suppression for determination of acid secretion in the stomach and bicarbonate secretion in the duodenum) and one set of experimental perfusions (for determination of bicarbonate secretion in the stomach and the duodenum) prior to which the subject was pretreated with a 60 mg oral dose of omeprazole (Astra A/S, Albertslund, Denmark) once daily for three days and 80 mg intravenously one hour before perfusion.

In the second series of experiments nine other volunteers had gastric and proximal duodenal perfusion three times. The perfusions were performed in random order and included one set of control perfusions (without acid suppression) and two sets of experimental perfusions prior to which the subject was pretreated with omeprazole as described above or with a 900 mg oral dose of ranitidine (Glaxo Denmark A/S, Brøndby, Denmark) 12 and two hours before the experiment and ranitidine 50 mg/h intravenously during perfusion.

Supramaximal doses of omeprazole and ranitidine were chosen to ensure the complete suppression of gastric acid secretion required for determination of gastric bicarbonate secretion.⁹ Each perfusion in the first and second series of experiments included a 60 minute equilibration period followed by a 30 minute basal period and a 60 minute sham feeding period. In the second series of experiments the duodenal bulb was acidified (HCl 0.1 M; 20 ml; 5 min) after the sham feeding period and then the duodenum was perfused for 45 minutes with isotonic saline. Attempts to measure gastric bicarbonate secretion after acidification of the stomach failed, because it was impossible to remove all the instilled acid within 30 minutes.

In the third series of experiments another four healthy volunteers had proximal duodenal perfusion once to study the effect of the combination of omeprazole and ranitidine. Each subject was pretreated with omeprazole as described above and after a 60 minute equilibration period the duodenum was perfused during basal conditions for 60 minutes. Then a 50 mg intravenous bolus injection of ranitidine was given. After a 30 minute equilibration period the duodenum was perfused for another 60 minutes during basal conditions. Ranitidine 50 mg/h was given intravenously during this final 90 minute period.

Simultaneous gastric and duodenal perfusions

After an overnight fast a six channel tube (16

French, outside diameter 5.3 mm, Pharmacia, Uppsala, Sweden) with three balloons was introduced orally.¹⁰ A Teflon coated guide wire was used for intubation (Amplatz Extra Stiff Wire Guide, outside diameter 0.9 mm, William Cook Europe, Bjæverskov, Denmark) and the position of the tube was controlled by fluoroscopy. Proximal to a distal tungsten weight two button shaped inflatable latex balloons isolated a 3 cm long segment of the proximal duodenum. A pear shaped balloon in the distal stomach anchored the tube against the pylorus. The gastric balloon was inflated with 30 ml of air and the duodenal balloons with 5–15 ml of air. A double lumen gastric tube (16 French, AN 10 Anderson Samplers, Atlanta, GA, USA) was then placed in the distal antrum. The infusion port was located 8 cm proximal to the aspiration port. The isolated duodenal segment was perfused (Ivac 560 Pump, N C Nielsen, Glostrup, Denmark) with isotonic saline (2 ml/min; pH 7.0) using [⁵¹Cr]EDTA (10 µCi/l) as a non-absorbable marker. Similarly, the stomach was perfused with isotonic saline, containing phenol red (50 mg/l; pH 7.0), at a constant rate of 5 ml/min (LKB 2115 Multiperplex Pump, Bromma, Sweden). The effluents were collected from the stomach by intermittent suction (Pump AB, Einar Egnell, Trollhättan, Sweden) and from the duodenal segment by gravity drainage. During the perfusions saliva was continuously removed by dental suction. This has previously been shown to minimise the amount of swallowed saliva that could contribute to gastric bicarbonate content during basal conditions, but especially during modified sham feeding.¹⁰

After the 60 minute equilibration period 15 minute gastric and duodenal samples were collected, except during modified sham feeding when gastric effluents were collected at five minute intervals. Modified sham feeding was performed using chewing gum (five pieces of fruit gum for 15 minutes).¹¹ For acidification of the duodenal segment 20 ml of 100 mM HCl plus 54 mM NaCl were instilled into the segment for five minutes. In all subjects pH had returned to neutral values after 15 minutes when sampling was resumed.

Analytical procedures

Concentrations of hydrochloric acid in the gastric effluents from control experiments were determined by titration to pH=7.0 with 0.1 M NaOH (PHM82, Radiometer, Copenhagen, Denmark).

Concentrations of bicarbonate in 100 µl aliquots from gastric and duodenal effluents were determined in triplicate (Corning 965 Carbon Dioxide Analyzer, Corning Ltd, Halstead, England).¹² Before analysis the samples were gassed with CO₂ free nitrogen for five minutes to remove dissolved carbon dioxide. The Corning analyser was calibrated daily against 2.5 and 5.0 mM NaHCO₃. The coefficients of variation were 12% (n=20) and 6% (n=20), respectively.

To determine the contamination of the

TABLE I Basal gastric and duodenal pH measurements in 17 healthy volunteers during control conditions and after administration of omeprazole and ranitidine; mean (SEM)

	Stomach pH	Duodenum pH
Control	2.32 (0.11)	7.40 (0.12)
Omeprazole	6.87 (0.08)	7.27 (0.06)
Ranitidine	6.82 (0.09)	7.33 (0.11)

duodenal test segment with pancreatic juice, trypsin was measured in the duodenal effluents as previously described.¹⁰

Activities of [⁵¹Cr] and concentrations of phenol red were determined both in gastric and duodenal effluents and served as markers for recovery and contamination of the respective test segment. Activities of [⁵¹Cr] were measured by gamma spectrometry (Model 1185, Searle Nuclear Chicago Division, Chicago, IL, USA). Concentrations of phenol red were measured spectrophotometrically at 560 nm after alkalisation (pH=11) by a 4+1 dilution with a 0.5 M Na₃PO₄ solution.

Calculations and statistical analyses

Rates of acid and bicarbonate secretion were calculated as the mean of the two or four 15 minute values obtained during the basal periods. Similarly, the results obtained after stimulation were calculated as the mean of the three five minute values obtained in the stomach and the first 15 minute value obtained in the duodenum after start of modified sham feeding and as the mean of all values obtained in the duodenum after luminal acidification.

The results were expressed as means (SEM). The bicarbonate data were analysed using repeated measures analysis of variance (RMANOVA) for a two way model. The normality assumption for this model was tested with the Kolmogorov-Smirnov statistics. The Levene's statistic was used to test for equal variance.¹³ For most of the end points the normality assumption was violated. Thus, RMANOVA was performed on ranks. Student-Newman-Keul's multiple comparison test was used for statistical analyses. Comparison of recoveries, contamination, and pH values were performed with Student's *t* test for paired variates. All *p* values calculated were two tailed; the α value of significance was set at 0.05.

Results

Validation of methods

The mean recovery of the gastric and duodenal markers were 82 (2)% and 86 (2)%,

respectively, with no differences between control, omeprazole, and ranitidine experiments. Values of basal and stimulated gastric and duodenal fluid outputs, in addition to recoveries of phenol red, [⁵¹Cr] and trypsin, showed no significant differences (*p*>0.3) between the groups. Only a small amount of gastric contents entered the duodenum (0.3 (0.1)%, that is 0.01 ml/min). The duodenogastric reflux equalled 0.8 (0.2)%, that is 0.06 ml/min. The contents of trypsin in the duodenal effluents were 0.6 (0.2)% of the average minimum trypsin output from the pancreas¹⁴ and a total of 11 samples from five subjects containing ≥ 25 μ g/ml, 3% were excluded.

pH Measurements

Total inhibition of gastric acid secretion was achieved both after omeprazole and ranitidine administration and there was no significant difference between gastric pH values (*p*=0.8; Table I). The duodenal pH measurements showed no significant (*p*>0.7) differences between control, omeprazole and ranitidine experiments, respectively (Table I).

Gastric acid and bicarbonate secretion

In control experiments basal and vagally stimulated gastric acid secretion was 4.2 (1.1) mmol/h and 7.9 (1.7) mmol/h, respectively.

The basal rates of gastric bicarbonate secretion were 401 (56) μ mol/h and 500 (104) μ mol/h after ranitidine and omeprazole administration, respectively. The difference was not statistically significant (*p*>0.05; Table II). Modified sham feeding for 15 minutes caused a considerable rise (*p*<0.05) in bicarbonate secretion both in ranitidine, and in omeprazole experiments (Table II).

Proximal duodenal bicarbonate secretion

The basal rates of duodenal mucosal bicarbonate secretion in control and ranitidine experiments were 351 (39) μ mol/h and 363 (63) μ mol/h, respectively. In experiments with omeprazole the basal rate of proximal duodenal mucosal bicarbonate secretion was 597 (48) μ mol/h (*p*<0.02) compared with control and ranitidine experiments, respectively (Table II and Figure).

Modified sham feeding for 15 minutes caused a moderate, but significant (*p*<0.05), rise in bicarbonate secretion in all experiments. The response to modified sham feeding after omeprazole administration was significantly

TABLE II Effect of ranitidine, omeprazole, and the combination of omeprazole and ranitidine (Ome+Ran) on gastric and proximal duodenal mucosal bicarbonate secretion rates in healthy volunteers during basal conditions and after stimulation with modified sham feeding and luminal acid (0.1 M; 20 ml; 5 min); mean (SEM)

	Gastric HCO ₃ ⁻ (μ mol/h)			Duodenal HCO ₃ ⁻ (μ mol/h $\times$ 3 cm)			
	Number	Basal	Sham feeding	Number	Basal	Sham feeding	Luminal acid
Control	17	—	—	17	351 (39)	474 (66)*	2550 (456)*
Ranitidine	9	401 (56)	1316 (412)*	9	363 (63)	582 (204)*	1752 (573)*
Omeprazole	17	500 (104)	916 (196)*	17	597 (48)†	834 (72)*†	3351 (678)*
Ome+Ran	4	—	—	4	528 (78)‡	—	—

**p*<0.05 compared with basal values; †*p*<0.02 compared with control and ranitidine (Student-Newman-Keul's test); ‡*p*=0.05 compared with control (Student's *t* test).

The effects of omeprazole (□—□) and ranitidine (○—○) on basal and stimulated (modified sham feeding=MSF; acid load=HCl) proximal duodenal mucosal bicarbonate secretion in healthy volunteers compared with no treatment (Δ—Δ); mean (SEM). * $p < 0.02$ compared with control and ranitidine (Student-Newman-Keul's multiple comparison test).

($p < 0.02$) higher than that seen in control and ranitidine experiments, respectively (Table II).

Luminal acidification of the duodenal bulb caused a considerable rise in bicarbonate secretion in all experiments. No significant differences in response were seen between control, omeprazole, and ranitidine experiments (Table II).

The basal rates of proximal duodenal bicarbonate secretion in the third series of experiments were 513 (93) $\mu\text{mol/h}$ after omeprazole alone and 528 (78) $\mu\text{mol/h}$ after the combination of omeprazole and ranitidine ($p > 0.05$; Table II).

Discussion

The results of this study show that the proton pump inhibitor, omeprazole, promotes proximal duodenal mucosal bicarbonate secretion, but not gastric bicarbonate secretion, in healthy volunteers, apparently independent of its acid inhibitory effect. While basal and sham feeding stimulated transport rates of bicarbonate in the duodenum were significantly higher in omeprazole experiments than in control and ranitidine experiments, it cannot be excluded that a type II error occurred when testing the results obtained during luminal acidification caused by a large variation between subjects.

The basal rates of gastric bicarbonate secretion seen in ranitidine and omeprazole experiments were in the same order of magnitude as those previously reported by others.⁹⁻¹⁵ Similarly, the rates of basal and stimulated proximal duodenal mucosal bicarbonate secretion seen in control and ranitidine experiments were similar to those obtained by others using the same six channel tube with three occluding balloons.¹²⁻¹⁶

The overall results of this study are, however, difficult to reconcile with much of the existing body of data relating to the action of omeprazole, considering that the compound is a highly specific, irreversible inhibitor of

H^+, K^+ adenosine triphosphatase (ATPase), which blocks acid secretion in response to all modes of stimulation.¹⁷ H^+, K^+ ATPase inhibition has been reported to modulate ion transport in the small intestine of some amphibia,¹⁸ but this does not seem to occur in mammals.^{7,8} The mechanism responsible for the unexpected finding remains, therefore, obscure and theoretical considerations are speculative.

Nevertheless, omeprazole, compared with ranitidine, could inhibit acid secretion from heterotopic parietal cells in the duodenum^{19,20} with abnormal or lacking H_2 receptors and thus seem to stimulate bicarbonate secretion. This is compatible with the finding that the combination of omeprazole and ranitidine resulted in the same rates of proximal duodenal mucosal bicarbonate secretion as omeprazole alone.

Omeprazole might also act to increase bicarbonate secretion indirectly by influencing the distribution of bicarbonate in the tissue, the mucosal blood flow, motility, or local nerves, while a role of *Helicobacter pylori* is unlikely in this paired design study. The possibility that omeprazole modulates neural reflexes would explain the discrepancy between results obtained in anaesthetised animals⁵⁻⁸ and conscious humans.

The possibility that duodenal bicarbonate secretion is inhibited by ranitidine, rather than promoted by omeprazole, should also be considered. If that was the case, histamine H_2 receptor antagonists might be expected to decrease bicarbonate secretion both in the stomach and in the duodenum. Acid inhibition by supramaximal doses of ranitidine did not modulate gastric bicarbonate secretion, however, either in this study or in previous studies of healthy volunteers²¹ and duodenal mucosal bicarbonate secretion has been shown to be unaffected by ranitidine in animals.^{7,8} The apparent lack of effect of ranitidine could also be taken to imply that leakage of gastric acid occurred in control experiments despite the presence of occluding balloons. The rate of neutralised bicarbonate, however, as calculated from the appearance of the gastric marker in the duodenal effluents, did not exceed 20 $\mu\text{mol/h}$.

In conclusion, our results show that omeprazole promotes proximal duodenal mucosal bicarbonate secretion, but do not support the notion that histamine H_2 receptor blockade inhibits mucosal bicarbonate secretion. While the normal basal output of bicarbonate from the duodenum equals approximately 1000 $\mu\text{mol/h}$ (duodenum about 9 cm; see Table II), or 25% of basal gastric acid secretion, the omeprazole induced duodenal bicarbonate output amounts to approximately 1800 $\mu\text{mol/h}$, or 40% of basal gastric acid secretion, which could be neutralised by this alkali. Thus, the observed increase in duodenal neutralising capacity caused by omeprazole is likely to add to the well documented superiority of omeprazole (compared with histamine H_2 receptor antagonists) in duodenal ulcer healing.

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