Histamine and duodenal ulcer: effect of omeprazole on gastric histamine in patients with duodenal ulcer

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SUMMARY Gastric mucosal concentrations of histamine and of its metabolic enzyme, histamine methyltransferase activity, were measured in patients with duodenal ulcer disease and patients with an apparently normal stomach and duodenum. Patients with duodenal ulcer had significantly less ($p < 0.05$) mucosal histamine (median 204 nmol/g) than control subjects (median 252 nmol/g). There was no significant difference between the two groups in their histamine methyltransferase activity values. Omeprazole therapy did not significantly change mucosal histamine (+23%), histamine methyltransferase activity (+5%), histamine release before (+5%) or during (+7%) pentagastrin infusion. It significantly decreased acid secretion during pentagastrin stimulation (median -73%, $p < 0.001$). Omeprazole, like cimetidine, does not stop histamine release during pentagastrin stimulation.

Histamine may be involved in the pathogenesis of human peptic ulcer. Patients with duodenal ulcer have less gastric mucosal histamine and lower activity of the metabolic enzyme, histamine methyltransferase, than normal control subjects. After treatment with cimetidine,¹ or after selective gastric vagotomy,^{2,3} however, mucosal histamine and histamine methyltransferase activity rise above normal control values. The depletion of the endogenous mucosal histamine stores is associated with gastric hypersecretion, which is a prominent feature of duodenal ulcer disease.^{1,2} After vagotomy, increase in mucosal histamine parallels the reduction in peak acid output.⁴ It is not known, however, whether the mucosal changes associated with cimetidine therapy or vagotomy are direct effects, or simply because of reducing acid secretion.

Like cimetidine, omeprazole is an effective inhibitor of gastric acid secretion and increases the rate of healing of duodenal ulcer. Cimetidine blocks the H_2 receptor but omeprazole inhibits the H^+K^+ ATPase of the gastric proton pump on the parietal cell membrane.⁵

We have investigated in patients with duodenal ulcer disease the effects of omeprazole on: (a) gastric mucosal histamine and histamine methyl-

transferase activity; (b) gastric acid and histamine secretion during pentagastrin stimulation.

Methods

PATIENTS

Ten patients in whom gastroduodenoscopy revealed no visible abnormality and 14 patients with duodenal ulcer confirmed at endoscopy were included in this part of the present study. Gastric mucosal biopsies were obtained at gastroscopy and assayed for histamine and histamine methyltransferase activity. The patients had received no histamine₂ antagonists for at least a week before entering the study.

OMEPRAZOLE TRIAL

Eight out of the 14 patients with duodenal ulcer were endoscoped 24 hours before a pentagastrin stimulated gastric acid secretion test. They were given a course of omeprazole lasting for four weeks; four received 20 mg and the other four 40 mg daily as part of a prospective randomised controlled trial reported elsewhere.⁶ Antacids were consumed according to need during this period of treatment. Endoscopic biopsies and secretory assessments were then repeated. The biopsies were assayed for histamine and histamine methyltransferase activity. Gastric aspirates were assayed for acid and histamine. In addition, three other patients underwent acid secretion tests before and after a course of omeprazole; one received 20 mg and two 40 mg

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daily. Secretory assessments were carried out on these patients, but no biopsies were taken.

HISTAMINE IN GASTRIC MUCOSA

Three endoscopic biopsies, 5–10 mg each, were taken from the anterior gastric wall 45 cm from the mouth. They were stored and frozen immediately until analysis. The biopsy was homogenised in 0.5 ml ice cold 0.01 M sodium phosphate, pH 7.9, containing 0.1% (w/v) Triton X-100. The homogeniser was washed through with two portions of 0.25 ml cold buffer.

HISTAMINE ASSAY

Histamine assay was based on the fluorometric method of Troidl *et al*² and has been described in detail.⁷

Histamine methyltransferase assay

Histamine methyltransferase activity was assayed by a modification of the procedure of Taylor and Snyder.⁸ Protein was determined on 50 μ l of the homogenate supernatant by the method of Lowry *et al*.⁹ Histamine methyltransferase activity was expressed as pmol N¹-methyl histamine formed/mg protein/min incubation. The histamine methyltransferase assay appeared to be specific. The reaction was directly proportional to the amount of homogenate protein and to incubation time (Fig. 1). Aminoguanidine, an inhibitor of the oxidative deamination of histamine, did not facilitate the reaction under incubation conditions and was therefore not included in the reaction mixture. ³H-N¹-methylhistamine and ¹⁴C-N¹-methylhistamine were prepared by enzymatic formation. Recoveries through the histamine methyltransferase assay procedure were both 44% (mean values of two determinations). With each assay ³H-N¹-methylhistamine was used as internal standard and the recovery (39–47%) was used to calculate the histamine methyltransferase activity of the test sample. All assays were undertaken on material from three biopsies, and results expressed as the mean of the three.

ACID AND HISTAMINE IN GASTRIC ASPIRATE

Acid and histamine were assayed by procedures published in detail previously.⁷ Gastric acid was measured by titration to pH 7.0 using an automatic titrimeter (Copenhagen). Gastric histamine was assayed fluorometrically.

The gastric acid and histamine output were corrected for gastroduodenal loss by using an inert non-absorbable marker (phenol red) to perfuse the stomach, and duodenogastric reflux by measurement of sodium ions in the gastric aspirate.

Fig. 1 Linearity of the assay of histamine methyltransferase activity as functions of increasing homogenate volume and incubation time. (○) aminoguanidine, 1 mM, was included in the incubation mixture; (●) no aminoguanidine.

STATISTICAL ANALYSIS

Statistical comparison were made using the Mann-Whitney U test and Spearman's rank correlation test. *p* Values less than 0.05 were recorded as significant.

Results

MUCOSAL HISTAMINE AND HISTAMINE METHYLTRANSFERASE ACTIVITY BEFORE TREATMENT

Figure 2 shows the gastric histamine values in 'normal' subjects and ulcer patients. In 10 'normal' subjects the median mucosal histamine was 252 nmol/g wet weight of the biopsy, (range: 202–457 nmol/g). In 14 patients with duodenal ulcer, the median histamine was 204 nmol/g, (range: 65–298 nmol/g), 19% lower than in control subjects (*p* < 0.05).

Figure 3 shows the gastric mucosal histamine methyltransferase values. The median in control subjects was 40 pmol/mg protein/min, (range 18–64). The median in patients with duodenal ulcer was 49 pmol/mg protein/min, (range: 22–99), not significantly different from that of the control group.

No significant correlation was observed between gastric histamine and the corresponding histamine

Fig. 2 Gastric mucosal histamine concentration in normal subjects and in patients with duodenal ulcer.

Fig. 3 Gastric mucosal histamine methyltransferase activity in patients with duodenal ulcer and 'normal' subjects. (—) medians NS.

methyltransferase activity, either in the 'normal' subjects or in patients with duodenal ulcer.

OMEPRAZOLE, HISTAMINE AND PENTAGASTRIN INDUCED ACID SECRETION

All duodenal ulcers healed after omeprazole therapy.

The results of measurements of gastric mucosal histamine, histamine methyltransferase activity, and of gastric juice acid and histamine are listed in the Table. Figure 4 illustrates the measurements made after omeprazole medication; the results are expressed at a percentage of the pretreatment values.

Comparing values before and after medication in the eight patients, the median post-treatment histamine methyltransferase activity was 105% (range: 36–380), and the median gastric mucosal histamine was 123% (range: 56–160). The low dose of omeprazole was associated with an insignificant fall in histamine methyltransferase activity, but the high dose with a significant rise ($p < 0.05$).

During pentagastrin infusion, the median peak

Fig. 4 Changes in mucosal histamine, histamine methyltransferase activity, peak acid output (PAO), basal and peak histamine output (BHO, PHO) in gastric juice after omeprazole. (●) 20 mg; (▲) 40 mg daily.

Table Effect of omeprazole on histamine and pentagastrin stimulated gastric acid secretion

Pt	Dose mg/day	HMT		Mucosal histamine		Acid output, nmol/h				Histamine output, nmol/h			
		pmol/mg Pre	protein/min Post	nmol/g tissue Pre	Post	Basal		Peak		Basal		Peak	
						Pre	Post	Pre	Post	Pre	Post	Pre	Post
GD	20	75.7	53.5	143	141	1.6	0.3	55.3	35.3	2.9	4.8	8.7	12.0
McW	20	99.3	35.4	270	351	1.3	5.6	29.9	22.6	7.1	7.8	8.8	9.4
TJ	20	—	—	—	—	7.0	0.0	65.4	12.9	2.6	2.4	30.7	33.0
WR	20	38.2	15.4	105	107	1.7	0.0	67.0	21.6	1.5	3.1	25.4	21.8
AP	40	36.3	74.1	214	343	2.6	0.0	42.1	9.2	4.3	5.8	14.9	14.9
BA	40	21.9	83.2	265	374	8.6	0.0	68.5	1.2	7.9	2.8	15.2	16.8
EC	40	—	—	—	—	13.8	9.9	48.6	47.1	11.7	5.5	—	36.5
JW	40	47.9	87.3	271	152	10.0	0.0	63.4	7.5	1.4	3.6	11.9	26.8
OD	40	39.7	54.0	65	86	11.6	0.0	36.7	14.5	7.0	2.8	6.6	7.2
RS	40	—	—	—	—	3.2	0.0	30.9	2.7	5.2	2.0	11.8	5.5
SM*	20	47.1	34.5	269	305	6.1	—	40.6	—	4.1	—	7.1	—
Median		43.3	53.7	239	226	6.1	0.0	48.6	13.7	4.3	3.4	11.8	15.9

* Refused second acid test.

acid output was 27% of the value before treatment (range: 2–97), with no apparent relationship to dose of omeprazole. The median gastric histamine output assayed in the aspirate during the basal period was 105% (range: 35–257); and the median peak histamine output was 107% (range: 47–225).

During secretory tests before omeprazole, the peak histamine output (calculated from the mean of the two highest 10 minute fractions) in the aspirate during pentagastrin infusion was significantly correlated with the peak acid output ($\rho=0.71$, $p<0.02$). No such correlation was found for the corresponding data after omeprazole treatment.

Discussion

In the present study we have confirmed the finding, reported from several laboratories including ours,^{1 2 10} of significantly lower than normal gastric mucosal histamine in patients with duodenal ulcer. In contrast with the findings of others, we found no significant difference between mucosal histamine methyltransferase activity in ulcer patients and controls, neither could we demonstrate a correlation between mucosal histamine and histamine methyltransferase activity values. This may be because of the small number of patients studied.

The discrepancy between our results and those of others cannot be explained in terms of biopsy handling (prolonged ischaemia time), or by age and sex differences in the groups studied.

We have previously reported that after treatment with the histamine H₂ blocker cimetidine gastric mucosal histamine in patients with duodenal ulcer rose to above control values.¹ Similarly, selective gastric vagotomy significantly increased gastric mucosal histamine in such patients.² The rise in

gastric mucosal histamine may be because of the inhibitory effect of the treatments on gastric acid secretion, as histamine is mobilised in the secretion process.

In the present study, we measured gastric mucosal histamine and histamine methyltransferase activity before and after a course of omeprazole. The median histamine rose 23% after omeprazole. This difference was not statistically significant ($p=0.08$), perhaps because of the small numbers.

Barth *et al*³ reported that selective gastric vagotomy raised the activity of gastric mucosal histamine methyltransferase; this may have facilitated inactivation of histamine and so helped to reduce acid secretion. In the present study, the high drug dose (40 mg daily) was associated with a rise in mucosal histamine methyltransferase activity while the low dose (20 mg daily) resulted in lower histamine methyltransferase activity. There was no significant change overall, however, in the median value of histamine methyltransferase activity after omeprazole. Omeprazole in both doses used is an effective inhibitor of pentagastrin induced acid secretion, with no dose related difference in this small study. We are unable to explain the discrepancy between the high and low dose effects on histamine methyltransferase activity. The rise after 'high dose' is similar to that seen after cimetidine. If this is directly related to blocking acid secretion we would have expected a similar change after 'low dose'.

We have previously investigated the effect of pentagastrin infusion on the amount of acid and histamine assayed in the gastric aspirate in patients with duodenal ulcer and found them closely correlated.⁷ After cimetidine blockade, gastric acid fell rapidly but histamine output in gastric aspirate did not change.¹¹ We postulated that pentagastrin acts

directly, by releasing histamine in the gastric mucosa, which, in turn, releases acid from the parietal cells.

In the present study, the correlation between the peak output of acid and that of histamine in the gastric aspirate induced by pentagastrin is again shown in patients with ulcer before treatment but not after therapy. After omeprazole gastric acid fell, but histamine in the gastric aspirate did not change, either in basal or stimulated outputs. This dissociation is compatible with the hypothesis that pentagastrin stimulates acid secretion from parietal cells by releasing histamine.

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