Effect of cimetidine on the amounts of histamine in the gastric mucosa of patients with gastric or duodenal ulcers

W K MAN, J H SAUNDERS, C INGOLDBY, AND J SPENCER

From the Department of Surgery, Royal Postgraduate Medical School Hammersmith Hospital, London

SUMMARY Measurements were made of the amounts of histamine extracted from patients with peptic ulcer disease and control subjects suffering from various gastrointestinal diseases. Patients with duodenal ulcer, gastric ulcer, or recurrent duodenal ulcer after proximal gastric vagotomy often had less gastric mucosal histamine than did normal controls. Cimetidine therapy increased the amounts of the histamine to above control levels, presumably by suppression of output. It is concluded that endogenous amounts of histamine reflect the pathogenic states in the gastric mucosa of patients with peptic ulcer diseases. Cimetidine, as does vagotomy, increases the amount of gastric mucosal histamine. These findings suggest that the increase in mucosal histamine with cimetidine is not due to activation of histamine methyl transferase, but rather to suppression of histamine output into the gastric juice.

Histamine, a chemical mediator of gastric acid secretion, may be a factor in the pathogenesis of human peptic ulcer diseases. Patients with duodenal ulcer had less gastric mucosal histamine than did normal controls, but, after selective gastric vagotomy, amounts rose to above control values. The investigators suggested that abnormalities of histamine storage may be a feature of duodenal ulcer disease.

The aim of the present study* was to measure gastric mucosal histamine in patients with peptic ulcers before and during treatment with the histamine H2 blocker cimetidine.

Methods

Patients of either sex, aged 21–83 years, attending our gastric clinic were examined endoscopically. They were grouped according to diagnosis and whether or not they were receiving cimetidine.

Three endoscopic biopsies were taken from the anterior gastric wall 45 cm from the mouth. They were frozen immediately in liquid nitrogen and stored at −20°C for up to a week before assay for histamine, using a method based on that of Troidl and co-workers.

Briefly, the biopsy specimen was weighed, homogenised in 2 ml 0-4 M perchloric acid and centrifuged at 2000 g to remove tissue debris. The supernatant was adjusted to pH 6-5 and immediately applied onto a short Dowex 50W–X8, 200–400 mesh column (0-3 × 2 cm, equilibrated with 0.1 M sodium phosphate buffer pH 6.5). The column was washed in succession with 5 ml phosphate buffer, 1 ml deionised water, and 5 ml 1·0 M hydrochloric acid. The extracted histamine was then eluted from the column by 3 ml 4 M hydrochloric acid. The fluorimetric assay of histamine was performed on a reaction mixture which consisted of 0·5 ml eluate, 0·5 ml water, 0·5 ml 5 M NaOH, and 0·1 ml o-phthalaldehyde (1% in methanol). After exactly two minutes the reaction was stopped by the addition of 1 ml M orthophosphoric acid. The fluorescence was measured in a spectrofluorometer at an excitation wavelength of 360 nm and an emission wavelength of 450 nm. Recovery of 0·543 nmol authentic histamine added to the aliquot of biopsy specimen homogenate was 96·4 ± 7·3 (SEM)% (n = 8). The variations of the histamine assays among the three biopsy samples were within 10% of the calculated mean value, which was used to represent the mucosal histamine content of that patient as recommended by Rohde et al.

Statistical comparisons were made using the Mann-Whitney U test and Wilcoxon match-pairs signed-rank test. P values <0·05 were recorded as significant.

Results

Figure 1 shows the gastric histamine values. The 25 patients in whom gastroduodenoscopy revealed no
visible abnormality in the stomach or duodenum are classified as 'normal' control subjects in Fig. 1; it is recognised, however, that endoscopic normality does not exclude other diagnoses such as duodenal ulcer in a healed phase. The median control histamine value was 204 nmol g\(^{-1}\) wet weight of the biopsy (range: 127 to 540 nmol g\(^{-1}\)).

Sixteen patients who were not on cimetidine therapy were diagnosed at endoscopy as suffering from chronic duodenal ulcer disease. Their median mucosal histamine was 160 nmol g\(^{-1}\), (range: 50 to 350), 22% lower than in controls (\(P < 0.05\)).

Thirty-two patients with duodenal ulcer were receiving cimetidine at the time of endoscopy. The median mucosal histamine value was 240 nmol g\(^{-1}\) (range: 21 to 599), 50% higher than that of 'normal' subjects (\(P < 0.02\)). Endoscopy also revealed that two patients who had the lowest mucosal histamine content in this group were suffering from active duodenal ulcer in spite of long-term cimetidine treatment (over one year).

Eleven patients not on cimetidine had chronic gastric ulcers. The median mucosal histamine value was 142 nmol g\(^{-1}\); (range: 78 to 310), 30% lower than in controls (\(P < 0.005\)) and 11% lower than patients with duodenal ulcer but not on cimetidine (NS).

Thirty-two patients with duodenal ulcer were receiving cimetidine at the time of endoscopy. The median mucosal histamine value was 240 nmol g\(^{-1}\) (range: 21 to 599), 50% higher than that of 'normal' subjects (\(P < 0.02\)). Endoscopy also revealed that two patients who had the lowest mucosal histamine content in this group were suffering from active duodenal ulcer in spite of long-term cimetidine treatment (over one year).

Eleven patients not on cimetidine had chronic gastric ulcers. The median mucosal histamine value was 142 nmol g\(^{-1}\) (range 78 to 310), 30% lower than in the controls (\(P < 0.005\)) and 11% lower than patients with duodenal ulcer but not on cimetidine (NS).

![Fig. 1](http://gut.bmj.com/)

**Fig. 1** Gastric mucosal histamine in patients with peptic ulcer and 'normal' subjects. DU: duodenal ulcer. GU: gastric ulcer. RDU: recurrent duodenal ulcer. CIM: cimetidine therapy. (●): patients not on cimetidine. (○): patients on cimetidine therapy.

### Table: Effect of cimetidine on gastric mucosal histamine concentration

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Basal</th>
<th>During cimetidine</th>
<th>% difference</th>
<th>Period of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM</td>
<td>DU</td>
<td>154</td>
<td>312</td>
<td>+103</td>
<td>6 weeks</td>
</tr>
<tr>
<td>WB</td>
<td>DU</td>
<td>50</td>
<td>226</td>
<td>+352</td>
<td>8 weeks</td>
</tr>
<tr>
<td>SB</td>
<td>DU</td>
<td>167</td>
<td>197</td>
<td>+18</td>
<td>48 hr IV</td>
</tr>
<tr>
<td>HD</td>
<td>GU</td>
<td>99</td>
<td>227</td>
<td>+129</td>
<td>6 months</td>
</tr>
<tr>
<td>MP</td>
<td>GU</td>
<td>155</td>
<td>149</td>
<td>-4</td>
<td>6 weeks</td>
</tr>
<tr>
<td>DW</td>
<td>GU</td>
<td>135</td>
<td>141</td>
<td>+5</td>
<td>48 hr IV</td>
</tr>
<tr>
<td>DC</td>
<td>DU/PGV</td>
<td>37</td>
<td>110</td>
<td>+198</td>
<td>3 months</td>
</tr>
<tr>
<td>RC</td>
<td>Biliary bypass</td>
<td>144</td>
<td>213</td>
<td>+48</td>
<td>6 months</td>
</tr>
<tr>
<td>MJ</td>
<td>Obstructed stomach</td>
<td>212</td>
<td>277</td>
<td>+31</td>
<td>48 h IV</td>
</tr>
<tr>
<td>HH</td>
<td>Obstructed stomach</td>
<td>196</td>
<td>155</td>
<td>-21</td>
<td>48 h IV</td>
</tr>
<tr>
<td>EC</td>
<td>Obstructed duodenum</td>
<td>40</td>
<td>49</td>
<td>+22</td>
<td>48 h IV</td>
</tr>
</tbody>
</table>
Six patients with gastric ulcer were being treated with cimetidine at the time of endoscopy. Their median mucosal histamine content was 188 nmol g⁻¹ (range: 77 to 307), 32% higher than in patients with gastric ulcer, not given cimetidine, median 142 (range 78 to 310) (NS), and not significantly different from that of the ‘normal’ group.

Six patients who had undergone proximal gastric vagotomy (PGV) and were not on cimetidine, had recurrent duodenal ulcer. Their median mucosal histamine content was 16 nmol g⁻¹ (range: 44 to 405), 43% lower than in the ‘normal’ group (p<0-02) but not statistically different from that of untreated duodenal ulcer patients.

Nine patients with recurrent duodenal ulcer after proximal gastric vagotomy were receiving cimetidine at the time of endoscopy. Their median mucosal histamine content was 183 nmol g⁻¹ (range: 94 to 314), 58% higher than that of clinically comparable patients who were not receiving cimetidine, median 116 (range: 37-405) p=0-21 (NS).

In 11 patients, suffering from various upper gastrointestinal tract disorders, gastric mucosal histamine was assayed before and after receiving cimetidine therapy, as specified in the Table. Nine patients showed a mean rise of 80% in histamine content during treatment with cimetidine (Fig. 2) (p<0-01).

In four out of five patients infused intravenously with cimetidine for 48 hours, mucosal histamine increased, though to an extent significantly less than in patients receiving cimetidine orally for more than six weeks (p<0-01).

Discussion

We have confirmed the finding by Troidl et al.² of a significant decrease in gastric mucosal histamine in patients with duodenal ulcer. The median histamine values for ‘normal’ patients and those with duodenal ulcer agree well with those reported by previous workers.² ⁵

Histamine in human gastric mucosa is predominantly localised in mast cells,⁵ and its amount in gastric juice is related to acid output stimulated by pentagastrin. As duodenal ulcer disease is associated with a gastric hypersecretion, increased histamine loss through secretion into the gastric lumen may deplete endogenous mucosal histamine stores.

In contrast with the finding of Troidl et al. (1976),¹ we found significantly less gastric mucosal histamine in patients with gastric ulcer. The significance of this reduction is not yet apparent. Histamine may play a pathophysiological role in the production of gastric lesions in several experimental animal models. Partial depletion of the tissue histamine lessened restraint-induced stress ulcer in the rat stomach.⁷ However, severe gastric lesions induced by intraperitoneal instillation of adrenaline in rabbits were associated with a fall in mucosal histamine.⁸

Troidl et al. (1978) reported that selective gastric vagotomy raised the amount of gastric mucosal histamine in patients with duodenal ulcer to above control values.² Three of their patients had recurrent duodenal ulcer after surgery and the mucosal histamine content was as low as that of duodenal ulcer patients with operation. In the present study we also found that patients who developed recurrent duodenal ulcer had significantly less gastric mucosal histamine than did ‘normal’ subjects, the amounts being as low as those of duodenal ulcer patients without surgical treatment.

Cimetidine, like vagotomy, significantly increased gastric mucosal histamine in patients with peptic ulcers. This phenomenon may be explained by inhibition of gastric secretion, and less histamine may be lost into the gastric juice, so that the endogenous histamine stores may increase. Thus, patients on cimetidine have a higher-than-normal content of gastric mucosal histamine. This tendency in gastric ulcer patients and those with recurrent duodenal ulcer was not statistically significant, possibly because of the small numbers.

Barth et al. (1977) have produced evidence that
both vagotomy and the administration of an H2-blocker increased the mucosal concentration of histamine methyl-transferase.\(^9\) It has been suggested that this increases histamine inactivation, so reducing acid secretion. However, such inactivation and removal of free histamine would be expected to reduce mucosal histamine stores. Our data, however, indicate that cimetidine increases mucosal histamine, as does vagotomy,\(^5\) by a mechanism which is not understood.

In conclusion, patients with peptic ulcer disease have depleted gastric mucosal histamine. Cimetidine, like vagotomy, significantly increases the amount of gastric mucosal histamine. Additional studies are required to examine the possible role of mucosal histamine in the aetiology of peptic ulcer diseases in man by monitoring changes in storage site, mast cells, and parietal cells during stimulation of secretion by different agonists.

We thank Staff Nurse L Francis-Reme, Miss M Golden, Mr J Barr, and Mr Kang Li for their skilled technical assistance and Mrs Iris Fisher for typing the manuscript.

References

Effect of cimetidine on the amounts of histamine in the gastric mucosa of patients with gastric or duodenal ulcers.

W K Man, J H Saunders, C Ingoldby and J Spencer

*Gut* 1981 22: 923-926
doi: 10.1136/gut.22.11.923

Updated information and services can be found at:
http://gut.bmj.com/content/22/11/923

These include:

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections

- Gastrointestinal hormones (848)
- Ulcer (484)
- Drugs: gastrointestinal system (207)
- Stomach and duodenum (1689)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/