Effect of H₂-Receptor Antagonists Cimetidine and Famotidine on Interdigestive Gastric Motor Activity and Lower Esophageal Sphincter Pressure in Progressive Systemic Sclerosis

Tsutomu Horikoshi, Tsutomu Matsuzaki and Toshikazu Sekiguchi

The effect of the H₂-receptor antagonists cimetidine and famotidine on interdigestive gastric motor activity and lower esophageal sphincter pressure was assessed in 41 patients with uncomplicated progressive systemic sclerosis. There was no significant change in gastric phasic motor activity after the intravenous administration of cimetidine (n=6), famotidine (n=13), and physiological saline (n=15), or the intragastric infusion of 7% sodium bicarbonate (n=7). The lower esophageal sphincter pressure was increased significantly by both cimetidine and famotidine, but only famotidine caused a significant pressure rise in patients without an increase of gastric motility. Cimetidine and physiological saline produced a similar pattern of change in the esophageal sphincter pressure, as did famotidine and sodium bicarbonate. These findings suggest that the inhibition of acetylcholinesterase activity and gastric acid secretion may be involved in the respective mechanisms of action of cimetidine and famotidine.

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Key words: interdigestive state, intragastric alkalinization, phasic motor activity

Introduction

Impairment of upper gastrointestinal motility (1, 2), including a reduction of the lower esophageal sphincter (LES) pressure, causes reflux esophagitis in about 60% of patients with progressive systemic sclerosis (PSS) (3,4). We have previously reported that the histamine H₂-receptor antagonist famotidine increases the LES pressure in PSS patients without affecting interdigestive gastric motor activity (5). In animal experiments, histamine H₂-receptor antagonists have been found to inhibit gastrointestinal acetylcholinesterase (AChE) activity, suggesting that they may have a cholinergic effect and stimulate gastrointestinal motility (6, 7). However, various effects have been reported in humans, and H₂-receptor antagonists have been variously shown to increase (8–10), decrease (11), or have no effect (12–15) on the LES pressure. These discrepancies may be attributable to differences in the drugs, doses, and methods of administration used in the various studies. Another important factor may be that these studies disregarded the close relationship between gastric motor activity and LES pressure, although it is known that the LES pressure gradually rises as motor activity in the stomach proceeds from phase I to phase III (16). The purpose of the present study was to compare the effect of two H₂-receptor antagonists, cimetidine and famotidine, on the upper gastrointestinal tract in PSS patients with consideration given to gastric motor activity. In addition, to determine the influence of intragastric alkalinization, we also assessed the changes in upper gastrointestinal motility caused by the intragastric infusion of sodium bicarbonate.

Subjects and Methods

The subjects were 41 patients (3 men and 38 women) with PSS without any complications. Diagnosis of PSS was performed on the basis of clinical and histologic features. The subjects were randomly divided into 4 groups given cimetidine, famotidine, physiological saline, and sodium bicarbonate, respectively (Table 1). Informed consent was obtained from all of the subjects. Measurement of gastrointestinal motility was performed by the infused catheter method using a Dent sleeve sensor (17), and the amplitude of esophageal peristalsis, the LES pressure, and the gastric phasic motor activity were measured in the interdigestive state. Eight polyvinyl tubes (internal diameter: 0.8 mm) were formed into a bundle with an external diameter of 4.8 mm (excluding the sleeve), and the sleeve sensor was connected to one of these tubes. Side holes for
Table 1. Clinical Characteristics of the Four Groups

<table>
<thead>
<tr>
<th></th>
<th>Cimetidine group</th>
<th>Famotidine group</th>
<th>Saline group</th>
<th>NaHCO3 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>6</td>
<td>13</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr; mean±SE)</td>
<td>48.7±7.6</td>
<td>45.8±2.6</td>
<td>51.3±2.8</td>
<td>50.7±2.7</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>12</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Amplitude</td>
<td>60.5±20.5</td>
<td>35.4±10.8</td>
<td>54.4±11.9</td>
<td>70.4±27.5</td>
</tr>
</tbody>
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Amplitude: peristaltic pressure of lower esophagus (mmHg).

Results

Gastric phasic motor activity

An increase in gastric motor activity was observed in 3/6 patients (50%) in the cimetidine group, 5/13 patients (38.5%) in the famotidine group, 6/15 patients (40%) in the physiological saline group, and 2/7 patients (28.6%) in the sodium bicarbonate group (Fig. 1). Although there was a greater than 20% difference between the cimetidine and bicarbonate groups, no significant difference between the cimetidine and famotidine groups, or any of the other groups was found by the chi-square test.
**Motility Effect of H₂-Receptor Antagonists**

**LES pressure**

The mean (±SE) LES pressure in the cimetidine group increased significantly from 8.7±3.8 mmHg before administration to 12.2±4.8 mmHg at 10 minutes after administration, and the values at 20, 25, and 30 minutes afterwards were also significantly higher than before cimetidine administration (p<0.05, paired t-test). In the famotidine group, there was a significant increase from 15.6±3.9 mmHg before the drug administration to 18.2±4.5 mmHg at 15 minutes after drug administration, and a significant increase was also observed at 20, 25, and 30 minutes after drug administration (p<0.05, paired t-test). In contrast, the LES pressure showed no significant change after drug administration in the physiological saline and sodium bicarbonate groups (Fig. 2). In addition, there was no significant difference between the mean LES pressures of the individual groups in any 5-minutes interval from before drug administration to 30 minutes after administration.

However, when the mean LES pressures were compared with allowance for the changes in gastric phasic motor activity, no significant differences were found between any of the groups. In addition, there was no significant increase of LES pressure related to changes in gastric phasic motor activity in any of the groups. The famotidine and sodium bicarbonate groups resembled each other with respect to the changes of LES pressure associated with the different phases of gastric phasic motor activity, as did the cimetidine and physiological saline groups (Fig. 3).

There were 3 patients in the cimetidine group, 8 in the famotidine group, 9 in the physiological saline group, and 5 in the sodium bicarbonate group who did not show any changes in gastric phasic motor activity after administration of the various agents. We examined the LES pressure in these patients at 5-minute intervals from 5 minutes before until 30 minutes after drug administration. In the famotidine group, there was a significant increase from 16.5±6.2 mmHg before infusion to 21.9±8.0 mmHg at 30 minutes afterwards (p<0.05, two-tailed Wilcoxon test). In the sodium bicarbonate group, there was also a significant increase from 13.7±5.8 mmHg before administration to 21.7±7.7 mmHg at 25 minutes after administration (p<0.05, two-tailed Wilcoxon test). However, no significant changes in LES pressure were observed in the cimetidine or physiological saline groups.

**Discussion**

Previous studies regarding the effects of H₂-receptor antagonists on upper gastrointestinal motility (especially LES pressure) have yielded conflicting results, possibly because no allowance was made for the fact that gastric motility and LES pressure are intimately related, i.e., that LES pressure increases as gastric phasic motor activity proceeds from phase I to III (16). Smout et al conducted a double-blind study in which gastric phasic motor activity was taken into consideration, and reported that the human interdigestive LES pressure is significantly reduced by intravenous administration of cimetidine or ranitidine in comparison with placebo, while the increase of...
LES pressure associated with gastric phasic motor activity is unaffected (19).

In the present study, the intravenous administration of cimetidine, famotidine, and physiological saline as well as the intragastric infusion of sodium bicarbonate had no significant effect on gastric phasic motor activity. When increases of LES pressure accompanying the changes in gastric phasic motor activity were not excluded, the present data showed a significant increase in LES pressure following the infusion of both cimetidine and famotidine, but no significant increase in response to either intravenous physiological saline or intragastric sodium bicarbonate. However, when we assessed the LES pressure responses in relation to the changes of gastric phasic motor activity, the significant rise in LES pressure that normally accompanies phasic motor activity was not found. Thus, our patients with PSS appeared to have such severe impairment of LES function that a rise in LES pressure did not occur with an increase of gastric motor activity. Despite this, there was a significant increase of LES pressure in response to intravenous famotidine and intragastric sodium bicarbonate among the patients with no change of gastric phasic motor activity after drug administration. It has been reported that esophageal motility (especially lower esophageal motility) is generally impaired earlier than gastric motility in PSS (2), while enhanced gastric phasic motor activity and an increased LES pressure are linked to the inhibition of gastric acid secretion in normal individuals (20). Here, since the rapid effect of intravenous famotidine on LES pressure resembled that produced by sodium bicarbonate as a result of intragastric alkalinization (Fig. 3), famotidine may have increased LES pressure without stimulating gastric motility by raising the intragastric pH. An intravenous dose of 200 mg of cimetidine is reported to have a rapid inhibitory effect on gastric acid secretion equal to or greater than that of 20 mg of intravenous famotidine (21). However, we found that cimetidine produced the same LES response as physiological saline and did not cause a significant rise of LES pressure in the patients with constant gastric phasic motor activity. These results suggest that cimetidine, unlike famotidine, caused LES pressure to increase by stimulating gastric motility. Finally, the finding that sodium bicarbonate significantly increased LES pressure in patients showing no increase of gastric motility suggests that an increase of gastric pH is more likely to influence the LES than

Fig. 3. Effect of the 4 agents on LES pressure (with allowance for gastric phasic motor activity). When changes of LES pressure (mean±SE) in response to the 4 agents were compared with allowance for gastric phasic motor activity, no significant differences were found between the groups. There were no changes of LES pressure in response to changes in gastric phasic motor activity (phase III of cimetidine and 7% NaHCO₃ group: n=1). The pattern of change in the LES pressure with the various phases of gastric motor activity was similar for famotidine and 7% NaHCO₃, as well as for cimetidine and saline.
Motility Effect of H₂-Receptor Antagonists

Regarding the mechanism underlying the rise of LES pressure and the increase of gastrointestinal motility in response to H₂-receptor antagonists, Hansen and Bertle (22, 23) have reported that both cimetidine and ranitidine show an inhibitory effect on AChE. In addition, Aono et al (24) studied isolated guinea pig ileum and stomach preparations, and found that the rank order of the AChE inhibitory effect of H₂-receptor antagonists was ranitidine > oxatidine > cimetidine > famotidine. They also suggested that the actions of these drugs are expressed via a cholinergic mechanism. However, Jensen and Gugler (25) found no AChE inhibitory activity after routine doses of ranitidine and cimetidine in humans. Thus, the issue remains unresolved.

Hayashi et al (26) found that gastric acid hypersecretion inhibits motilin-induced gastric antral motility in dogs, while the motility returns to normal when acid hypersecretion is inhibited by cimetidine. In addition, Kusano et al (27) reported that abnormalities of the gastric antral interdigestive migrating complex in patients with duodenal ulcer were reversed by famotidine. Thus, the rise of intragastric pH due to inhibition of gastric acid secretion in the present study was probably also related to the increase in gastric motor activity and the rise in LES pressure. However, when the stomach was alkalinized by intragastric infusion of 7% sodium bicarbonate, an increase of gastric motor activity was found in only 2/7 subjects. In addition, since it has been reported that upper gastrointestinal motility is not increased by omeprazole, a proton-pump inhibitor which more potently inhibits gastric acid secretion than H₂-receptor antagonists (28, 29), the rise in intragastric pH does not appear to be the only cause of the increase in gastrointestinal motility.

As a result of experiments in dogs, Okajima (30) found that histamine tonically reduces postprandial gastroduodenal motility and that H₂-receptor antagonists increase gastrointestinal motility by antagonizing this inhibition. Another mechanism was suggested by Mitznegg et al (31), who reported that the blood level of motilin, which is involved in phase III interdigestive motility (32), peaks sharply in response to acidification of the duodenum in healthy individuals. Moreover, Rees et al (33) have reported that the interdigestive plasma motilin concentration is significantly higher in PSS patients with considerable impairment of gastrointestinal motility than in healthy individuals. Thus, since the basal plasma motilin level appears to be elevated in PSS patients and gastric acid clearance is poor because gastric motility is low, it is presumably difficult for a plasma motilin peak to be produced. Accordingly, there appears to be various factors which oppose an increase of upper gastrointestinal motility associated with phase III motor activity in PSS patients. Kusano et al (27) found no significant change in plasma motilin levels after famotidine administration in duodenal ulcer patients. Consequently, motilin may have no role in the increase of upper gastrointestinal motility in response to H₂-receptor antagonists. In addition, the study of Smout et al (19) and our own data (5) suggest that gastrin is not involved in the mechanism by which H₂-receptor antagonists increase gastrointestinal motility.

This study was not a crossover trial, but there were no significant differences of LES pressure between the different groups of PSS patients before drug administration, and all of the groups appeared to have similar impairment of gastrointestinal motility (Table 1). Since we did not test different doses of each H₂-receptor antagonist, whether any of the effects noted were dose-dependent remains unknown. However, since the administration of cimetidine was followed by an increase of gastric phasic motor activity in the highest percentages of patients, if the dose had been increased, greater AChE inhibition and a more marked effect on gastric phasic motor activity may have been observed.

In conclusion, cimetidine and famotidine increased the interdigestive LES pressure in PSS patients, with this action appearing to be principally mediated by their inhibitory effect on AChE activity and gastric acid secretion, respectively.

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References


