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Lafutidine, a Newly Developed Antiulcer Drug, Elevates Postprandial Intragastric pH and Increases Plasma Calcitonin Gene-Related Peptide and Somatostatin Concentrations in Humans: Comparisons with Famotidine

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Lafutidine, a newly developed histamine H_2-receptor antagonist, inhibits daytime (i.e., postprandial) as well as nighttime gastric acid secretion in clinical studies. It also has gastroprotective activity that particularly affects mucosal blood flow in rats. This study focused on the efficacy of lafutidine on plasma concentrations of gastrointestinal peptides in humans. Six healthy male volunteers aged 23–32 years without *Helicobacter pylori* infection were orally administered either 10 mg lafutidine, 20 mg famotidine, or water only (control) 30 min after a standard meal (650 kcal). Plasma concentrations of lafutidine and famotidine were highest from 90 to 150 min after administration. Intragastric pH was elevated after both lafutidine and famotidine compared with the control. Plasma concentrations of calcitonin gene-related peptide (CGRP) and somatostatin were significantly increased after lafutidine at 60 and 90 min. We concluded that lafutidine increases plasma concentrations of CGRP and somatostatin in humans, which may result in inhibition of postprandial acid secretion and gastroprotective activity.

KEY WORDS: lafutidine; intragastric pH; calcitonin gene-related peptide; somatostatin; gastrin.

During the past three decades, significant therapeutic advances have been made in treatment of acid-related diseases (ARDs). The development of histamine H_2-receptor antagonists (H_2-RAs) has dramatically improved cure rates for ARDs, because H_2-RAs can strongly inhibit gastric acid secretion compared with conventional drugs such as antacids.

Further, H_2-RAs are expected to provide benefits additional to their antisecretory efficacy: ranitidine and nizatidine have antiacetylcholinesterase activity, which significantly accelerates gastric emptying (1–4). Nizatidine also increases salivary secretion and bicarbonate output (5, 6), which may improve the cure rate for gastroesophageal reflux disease. Roxatidine acetate increases mucus synthesis and secretion (7, 8), which accelerates the repair process of damaged gastric mucosa. Cimetidine and ranitidine both lack gastroprotective activity (9).

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TABLE 1. BASELINE CHARACTERISTICS OF THE SIX SUBJECTS

Subject	Age (years)	Height (cm)	Weight (kg)	Order of study phase		
				I	II	III
A	26	170	75	Control	Lafutidine, 10 mg	Famotidine, 20 mg
B	23	167	52	Control	Lafutidine, 10 mg	Famotidine, 20 mg
C	30	175	72	Famotidine, 20 mg	Control	Lafutidine, 10 mg
D	24	170	58	Famotidine, 20 mg	Control	Lafutidine, 10 mg
E	32	176	74	Lafutidine, 10 mg	Famotidine, 20 mg	Control
F	24	170	85	Lafutidine, 10 mg	Famotidine, 20 mg	Control
Median	25	170	73			
(Range)	(23–32)	(167–176)	(52–85)			

Note. This study was performed in a randomized manner,and between each study phase there was a washout period of 2–4 weeks.

Lafutidine is a newly developed antiulcer drug that was approved for clinical use in Japan in 2000. It possesses a potent and long-lasting gastric antisecretory efficacy (10) mediated by histamine H_2-receptor blockade in both rats and dogs (11). Unlike conventional H_2-RAs, lafutidine inhibits gastric acid secretion during daytime (i.e., postprandial) as well as nighttime in clinical studies in humans (12, 13); however, the mechanisms of daytime gastric acid inhibition remain unclear.

Lafutidine also has gastroprotective activity independent of its antisecretory efficacy, preventing noxious agent-induced gastric mucosal injury and accelerating the repair process following gastric mucosal damage (14–17). It also protects experimentally induced reflux esophagitis (18), indomethacin-induced intestinal ulcers (19, 20), and dextran sulfate sodium-induced colonic inflammation (21). The protective and accelerative efficacies of lafutidine are considered to work via capsaicin-sensitive afferent nerves in rats (22); however, the precise mechanisms in humans are not fully understood.

Against this background, we have simultaneously measured postprandial intragastric pH and plasma concentrations of some gastrointestinal peptides related to gastric acid secretion and gastroprotective activity after a single oral administration of lafutidine or famotidine, another conventional H_2-RA, in humans, and sought to clarify the mechanisms of gastroprotective activity and postprandial acid-suppressive efficacy of lafutidine.

While we considered that repeated administration of lafutidine and famotidine might be more appropriate for a comparative study, the acid-suppressive efficacies of H_2-RAs are known to gradually decrease during the repeated administration, indicating a kind of tolerance (23). Further, during repeated administration there are changes in basal intragastric pH and basal peptide concentrations that make it difficult to compare their postprandial changes. Therefore, in the present study, we investigated the efficacy of single administrations of these drugs.

MATERIALS AND METHODS

Subjects. Six healthy, *Helicobacter pylori* (*H. pylori*)-negative Japanese male subjects participated in this study. The subjects, aged between 23 and 32 years (median, 25 years) and weighing 52–85 kg (median, 73 kg), had no history of gastrointestinal or hepatobiliary disease, or of eradication therapy for *H. pylori*, and took no regular medications (Table 1). Full medical histories were recorded and physical examinations made of each subject.

***H. pylori* Infection.** *H. pylori* infection was determined by measuring the serum titer of IgG antibodies against *H. pylori* using an enzyme immunoassay (HM-CAP Kit; Enteric Product Inc., NY, USA) and by ^{13}C-urea breath test (UBT). Only individuals negative on both tests were considered to be free of *H. pylori* infection.

Intragastric pH Monitoring. Before each recording session, a glass electrode (CM-181; Chemical Instrument Co. Ltd.) was calibrated in buffer solutions at pH 6.86 and 4.01. The pH electrode was inserted through the nose, and its tip was positioned under fluoroscopic control in the upper part of the gastric body (10 cm below the gastroesophageal junction) and then connected to a portable digital recorder (CR-5501 or PH-101Z; Chemical Instrument Co. Ltd.). After monitoring the intragastric pH, recordings were transferred to a personal computer for processing and analyzed using a commercially available software program (Chemical Instrument Co. Ltd.). The median values of intragastric pH per 15 min were calculated as the parameter representing the degrees of gastric acid suppression.

Study Protocol. This was a prospective, randomized, three-way crossover study. At 11:00 AM the pH electrode was inserted and at 11:30 AM measurement of the intragastric pH began. Between 12:00 PM and 12:20 PM a standardized meal was eaten (total calories = 650 kcal/day; 25 g protein, 20 g lipids, 80 g carbohydrate). At 12:30 PM 10 mg lafutidine, 20 mg famotidine, or water only (control) was orally administered. Blood samples were taken at 30 min before and 0, 60, 90, 120, 150, and 240 min after drug administration (Figure 1 and Table 1).

Preparation of Plasma Extracts. Blood samples were placed in chilled tubes containing 500 kallikrein inhibitor units/ml aprotinin and 1.2 mg/ml EDTA. Immediately after collection, they were centrifuged at 3000 rpm for 5 min and stored at −20°C until assayed.

Assays of Lafutidine and Famotidine. Lafutidine concentration was determined according to the method of Itoh *et al.*

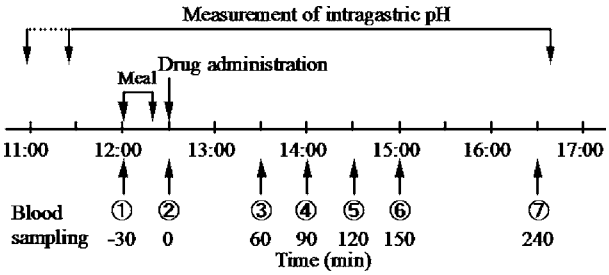

Fig 1. Study protocol.

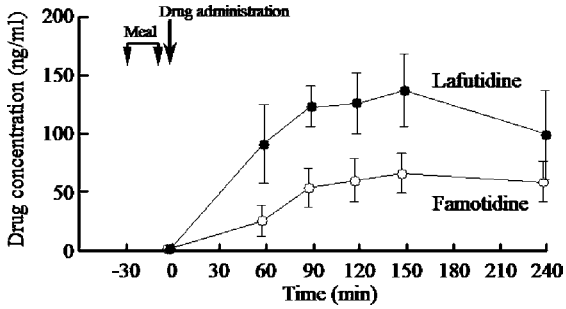

Fig 2. Profile of plasma lafutidine (●) and famotidine (○) concentrations after a single oral administration of 10 mg lafutidine and 20 mg famotidine.

(24). Standard lafutidine was supplied by UCB Japan Co., Ltd. A 1-ml plasma sample was mixed with 0.5 ml of 1 M NaOH and then eluted twice with 3 ml of ethyl acetate. The eluate was evaporated to dryness under reduced pressure. The residue was dissolved in 1 ml of 0.1 M HCl and washed with 1 ml of ethyl acetate. A further 0.75 ml of 1M NaOH was added to the aqueous phase, and lafutidine was eluted with 3 ml ethyl acetate containing 10 ng/ml 4-amino-3-nitroanisole as an internal standard. The eluate was evaporated to dryness and reconstituted in a 200-μl mobile phase, 50 μl of the solution was injected onto a chromatograph, and high-performance liquid chromatography (HPLC) carried out using a C18 column (Symmetry C18; Waters Corp., USA) at 40°C; UV absorbance was detected at 230 nm. Acetonitrite–10 mM phosphate buffer (pH 5.9; 15:85) was used as the mobile phase with a flow rate of 1 ml/min.

Determination of famotidine concentration was performed according to the method by Dowling *et al.* (25). Standard famotidine was purchased from Wako Pure Chemical Industries, Ltd. A 1-ml plasma sample was mixed with 30 μl of 2 M NaOH and 250 μl of saturated Na_2CO_3 solution and then eluted twice with 3 ml of ethyl acetate. The eluate was evaporated to dryness under reduced pressure. The residue was reconstituted in 150 μl of mobile phase, 50 μl of the solution was injected onto a chromatograph, HPLC carried out using a C18 column (Symmetry C18; Waters Corp.) at 40°C, and UV absorbance was detected at 254 nm. Heptansulfonate (2 g/L) with acetic acid (pH 3.0)–acetonitrile–methanol (500:78:13) was used as the mobile phase at a flow rate of 1 ml/min.

The values for the areas under the plasma lafutidine and famotidine concentration-time curves from 0 to 240 min ($AUC_{0-240\,min}$) were calculated using the linear trapezoidal method.

Enzyme Immunoassays for Calcitonin Gene-Related Peptide (CGRP)-, Somatostatin-, and Gastrin-Immunoreactive Substances. Peptide concentrations in plasma were measured using a highly sensitive enzyme immunoassay for CGRP (26)-, somatostatin (27)-, and gastrin-immunoreactive substances (28), as previously described. The assay was performed by a delayed addition method. Separation of bound and free antigen was performed on an anti-rabbit IgG (55641; ICN Biomedicals, Inc., USA)-coated immunoplate (Nunc-Immuno Plate MaxiSorp Surface; Nalge Nunc International, New York, USA). Human somatostatin, CGRP, and mini gastrin I were conjugated with β-galactosidase by *N*-(ε-maleimido-caproyloxy)-succinimide according to the methods of Kitagawa *et al.* (29). The enzyme immunoassays for CGRP- somatostatin-, and gastrin-immunoreactive substances were specific and highly sensitive to detection limits of 1.0, 0.1, and 0.04 fmol/ml, respectively.

Total amounts of released CGRP, somatostatin, and gastrin (areas under the plasma CGRP, somatostatin, and gastrin concentration-time curves from 0 to 240 min) after administration of lafutidine and famotidine were calculated using the linear trapezoidal method.

Ethics. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Hiroshima University Hospital. Written informed consent was obtained from all subjects prior to entry.

Statistical Analysis. Results are expressed as means ± SD. Statistical analysis was performed using Tukey's test. Correlation between the $AUC_{0-240\,min}$ of lafutidine and famotidine and the total amount of released CGRP, somatostatin, and gastrin was quantified using the Pearson correlation coefficient. A P value of <0.05 was considered statistically significant.

RESULTS

Profiles of Plasma Lafutidine and Famotidine Concentrations After a Single Oral Administration of 10 mg Lafutidine and 20 mg Famotidine. The profiles of plasma lafutidine and famotidine concentrations against time after a single oral administration of 10 mg lafutidine and 20 mg famotidine are shown in Figure 2. The plasma concentrations of lafutidine and famotidine were highest from 90 to 150 min after drug administration.

Comparisons of Intragastric pH Profiles Without Medication and with a Single Oral Administration of 10 mg Lafutidine and 20 mg Famotidine. The intragastric pH (median pH per 15 min) profiles without medication and with a single oral administration of 10 mg lafutidine and 20 mg famotidine are shown in Figure 3. Low intragastric pH under fasting conditions was immediately neutralized by meal ingestion at 12:00 PM. In cases without medication, intragastric pH was lowered again by meal-stimulated gastric acid secretion about 90 min after eating. With lafutidine, intragastric pH gradually rose at 90 min after administration (120 min after the meal) and reached pH 4 about 210 min after administration. On the other hand, with famotidine, intragastric pH increased at 60 min after administration (90 min after the meal) and remained at approximately 3.

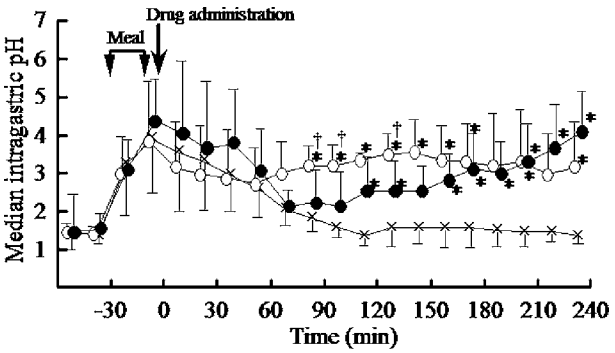

Fig 3. Comparisons of intragastric pH (median pH per 15 min) profiles without medication (×) and with a single oral administration of 10 mg lafutidine (●) and 20 mg famotidine (○). $*P < 0.05$ vs. control; $\dagger P < 0.05$ between famotidine and lafutidine.

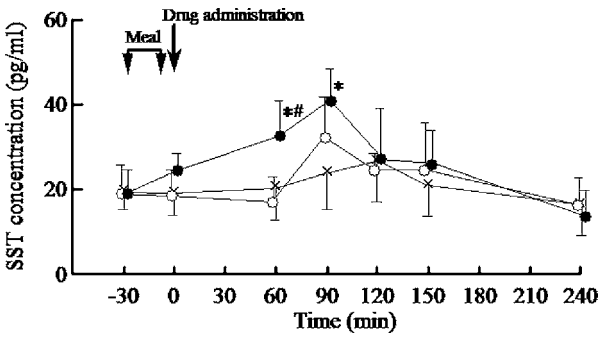

Fig 5. Comparisons of plasma somatostatin concentrations without medication (×) and with a single oral administration of 10 mg lafutidine (●) and 20 mg famotidine (○). SST, somatostatin; $*P < 0.05$ vs. control; $\#P < 0.05$ vs. famotidine.

Comparisons of Plasma CGRP, Somatostatin, and Gastrin Concentrations Without Medication and with a Single Oral Administration of 10 mg Lafutidine and 20 mg Famotidine. In all six subjects, plasma concentrations of CGRP increased and exceeded 60 pg/ml at 90 min after administration of lafutidine, compared with 40 pg/ml or less before the meal. Plasma concentrations of somatostatin also increased above 40 pg/ml at 90 min after administration of lafutidine in four of the six subjects and, consequently, doubled in five of the six subjects. Therefore, postprandial plasma concentrations of CGRP and somatostatin significantly increased at 60 to 90 min after administration of lafutidine compared with the control (Figures 4 and 5). On the other hand, plasma concentrations of CGRP did not increase above 50 pg/ml at 90 min after administration of famotidine in all six subjects, and plasma concentrations of somatostatin did not increase above 30 pg/ml in five of the six subjects. Therefore, after administration of famotidine, plasma concentrations of CGRP and somatostatin increased to some degree compared with the control; however, the degrees of increase after famotidine were far lower than those seen with lafutidine. Plasma gastrin concentration increased to some degree after the meal; however, no significant differences were observed among the three regimens (Figure 6).

Correlation Between the $AUC_{0-240\,min}$ of Lafutidine and Famotidine and the Total Amount of Released CGRP, Somatostatin, and Gastrin. The total amounts of released CGRP and somatostatin moderately correlated with the $AUC_{0-240\,min}$ of lafutidine ($r = 0.68$, $P = 0.15$, and $r = 0.62$, $P = 0.21$, respectively) (Figure 7); however, they were not correlated with the $AUC_{0-240\,min}$ of famotidine ($r = -0.09$ and $r = 0.20$, respectively). The total amount of released gastrin was not correlated with the $AUC_{0-240\,min}$ of either lafutidine ($r = -0.29$) or famotidine ($r = 0.11$).

DISCUSSION

This study showed that a single oral administration of 10 mg lafutidine or 20 mg famotidine elevated intragastric pH, and that lafutidine significantly increased plasma

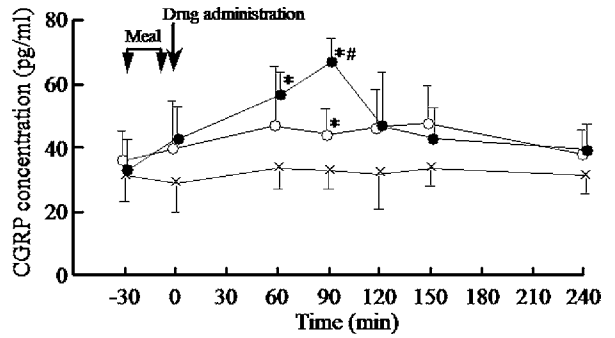

Fig 4. Comparisons of plasma calcitonin gene-related peptide (CGRP) concentrations without medication (×) and with a single oral administration of 10 mg lafutidine (●) and 20 mg famotidine (○). CGRP, calcitonin gene-related peptide; $*P < 0.05$ vs. control; $\#P < 0.05$ vs. famotidine.

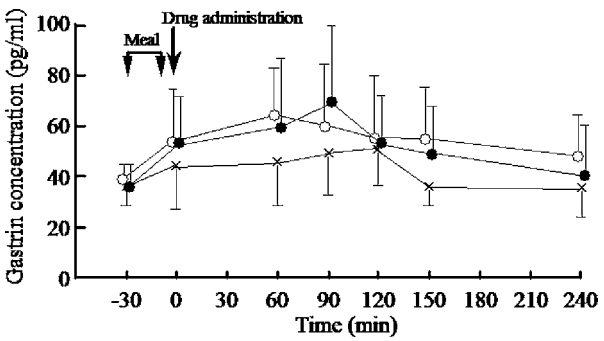

Fig 6. Comparisons of plasma gastrin concentrations without medication (×) and with a single oral administration of 10 mg lafutidine (●) and 20 mg famotidine (○).

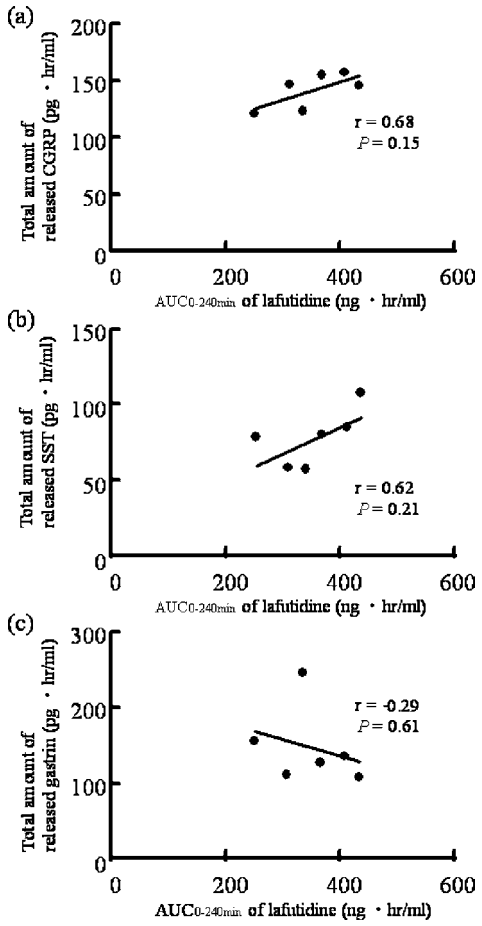

Fig 7. Correlation between the $AUC_{0-240\,min}$ of lafutidine and the total amount of released CGRP (a), somatostatin (b), and gastrin (c).

concentrations of CGRP and somatostatin. To our knowledge, this is the first report of simultaneous measurement of intragastric pH and plasma concentrations of CGRP, somatostatin, and gastrin after lafutidine or famotidine administration in humans.

Plasma concentrations of lafutidine and famotidine significantly increased at 90 min after administration and remained high for 60 min, whereas the peaks of plasma CGRP and somatostatin concentrations were observed at 90 min after drug administration. It has previously been shown that the peak of plasma concentration of lafutidine occurred 60 min after administration in a hunger state and was well correlated with the peaks of CGRP and somatostatin concentrations (24). The peaks of plasma concentrations (T_{max}) of lafutidine were significantly different between administration in a hunger or postprandial state (0.8 ± 0.1 and 2.1 ± 0.2 hr, respectively; $P < 0.001$) (30). Therefore, we considered that the differences in the results between our study and the earlier one resulted from the pharmacokinetic/pharmacodynamic characteristics of lafutidine. Another study clearly showed that lafutidine increases serum CGRP concentrations in rats after water immersion-restraint stress, whereas famotidine did not (17). These results indicate that the main factor increasing plasma CGRP and somatostatin concentrations was lafutidine itself and that plasma concentrations of lafutidine correlate with the peaks of CGRP and somatostatin concentrations.

It has been hypothesized that capsaicin-sensitive sensory nerves play an important role as a defensive factor against mucosal damage through local regulation of gastric mucosal blood flow in rats (31, 32). CGRP is particularly abundant in capsaicin-sensitive neurons around the blood vessels of the mucosa, muscularis mucosae, and submucosa in the rat stomach (33). Intravenous and intragastric administration of lafutidine elevated gastric mucosal blood flow in rats (34, 35). Lafutidine, however, is unlikely to bind to the vanilloid receptor subtype 1, which binds capsaicin (36), its efficacy being thought to be due to the activation of capsaicin-sensitive afferent neurons (14, 22). In the present study in humans, administration of lafutidine significantly increased postprandial plasma CGRP concentration, whereas famotidine did not. These results indicate that lafutidine accelerates CGRP release, possibly exerting gastric mucosal protection by increasing blood flow in the gastric mucosa in humans as well. Considering the moderate correlation between the $AUC_{0-240\,min}$ of lafutidine and the total amount of CGRP release, as the dosage of lafutidine increases, CGRP release will also increase, resulting in an increase in gastroprotective activity. The efficacy of lafutidine on gastric mucosal blood flow in damaged mucosa, particularly in nonsteroidal anti-inflammatory drug (NSAID)-associated mucosal damage, could be expected.

It was not possible to fully understand the mechanism of the increase in plasma concentrations of CGRP at the timing of the administration of lafutidine and famotidine compared with those before the meal (Figures 4 and 5). This study was performed in a randomized manner (Table 1), and between each study phase there was a washout period of 2–4 weeks. One possible reason can be found in the facts that in two subjects, plasma concentration of CGRP was relatively increased at the time of lafutidine (from 39 to 58 pg/ml in subject 3) and famotidine (from 40 to 69 pg/ml in subject 1) administration compared with those before the meal; therefore, mean values of plasma CGRP and somatostatin concentrations tended to be higher at the time of drug administration. We considered that unpredictable factors, e.g., the contents of breakfasts that subjects ate before the study, could have influenced these concentrations.

It is known that capsaicin-sensitive afferent nerves in gastric mucosa also respond to luminal acidification and

represent a negative feedback system in gastric acid secretory control (37). Accumulation of acid in the gastric lumen releases CGRP to facilitate the release of somatostatin from antral D cells (37–39). Somatostatin inhibits gastric acid secretion, directly acting on somatostatin receptors on parietal cells and indirectly decreasing gastrin release from antral G cells (40). Increased plasma somatostatin concentration might possibly inhibit meal-stimulated increase in plasma gastrin concentration and therefore inhibit meal-stimulated gastric acid secretion. Considering this, we expected that the administration of lafutidine would elevate intragastric pH even in the early postprandial state via these CGRP-, somatostatin-, and gastrin-related mechanisms (37–39). In the present study, administration of lafutidine did significantly increase plasma CGRP and somatostatin concentrations. However, in line with the previous study by Itoh *et al.* (23), increases in plasma gastrin concentration and elevation of early postprandial intragastric pH were not significant; therefore, a single administration of lafutidine was confirmed not to affect intragastric pH in the early postprandial state, particularly for approximately 2 hr after a meal. Plasma gastrin concentration did not increase after a meal even in the control; however, we could not compare the inhibitory efficacies of lafutidine and famotidine on meal-stimulated gastrin release. Further investigations should be carried out in patients with *H. pylori*-positive antrum-predominant gastritis, whose meal-stimulated gastrin release is exaggerated because of the deficiency in the negative feedback in gastrin link (41). Alternatively, special meals that stimulate the release of gastrin could be served and the results studied. In addition, the efficacy of repeated administration of lafutidine on plasma concentrations of these peptides and early postprandial intragastric pH need to be evaluated in a follow-up study.

In conclusion, a single administration of lafutidine elevated late postprandial intragastric pH and plasma CGRP and somatostatin concentrations in humans. Increases in plasma CGRP and somatostatin concentrations may result in increased gastric mucosal blood flow and inhibition of postprandial gastric acid secretion, respectively. The present study indicates that lafutidine has therapeutic potential in NSAID-associated gastric mucosal injury in humans; however, further investigation is required, particularly with respect to the efficacy of repeated administration of lafutidine.

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