Pharmacokinetic and Pharmacodynamic Properties of Lafutidine after Postprandial Oral Administration in Healthy Subjects: Comparison with Famotidine

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Lafutidine, a histamine H_2-receptor antagonist, inhibits gastric acid secretion during the daytime, however, the relationship between the plasma concentration and the drug response remains unclear. The aim of this study was to compare the pharmacokinetic and pharmacodynamic properties of lafutidine and famotidine following postprandial oral administration. After a lafutidine tablet (10 mg), famotidine tablet (20 mg), or water only (control) was administered, blood samples were taken and intragastric pH was measured. The plasma concentrations of lafutidine and famotidine were determined by HPLC, and the median intragastric pH values per 30 min were used as the degrees of gastric acid suppression. Data were analyzed based on a one-compartment pharmacokinetic model and a sigmoid E_{max} pharmacodynamic model. Lafutidine plasma concentrations rapidly increased after administration; famotidine required some time to increase the plasma concentrations, requiring an absorption lag time in the pharmacokinetic model. Between the plasma concentration and ΔpH (the difference in intragastric pH by the drug *vs.* control), lafutidine showed an anticlockwise hysteresis loop which indicated equilibration delay between the plasma concentration and effect site, requiring an effect site compartment in the pharmacodynamic model; famotidine showed more parallel relationship. These results indicated that the pharmacokinetic and pharmacodynamic properties of lafutidine after postprandial oral administration were different from those of famotidine at least 4.5 h after dosing.

Key words　lafutidine; famotidine; pharmacokinetics; pharmacodynamics

Lafutidine, 2-(furfurylsulfinyl)-*N*-[4-[4-(piperidinomethyl)-2-pyridyl]oxy-(*Z*)-2-butenyl] acetamide, is a newly developed histamine H_2-receptor antagonist. It is at present only approved in Japan as a tablet, and is used in the treatment of gastric ulcers, duodenal ulcers, and gastric mucosal lesions associated with acute gastritis and acute exacerbation of chronic gastritis.[1] Lafutidine possesses a potent and long-lasting gastric antisecretory effect mediated by H_2-receptor blockade in animals.[2] Lafutidine inhibits gastric acid secretion during the daytime (*i.e.*, postprandial) as well as nighttime in clinical studies.[3,4] However, its pharmacodynamics, the relationship between the plasma concentration and the drug response, such as intragastric pH, have not been reported. We believe it is clinically important to examine differences between lafutidine and famotidine to clarify the positioning of lafutidine in H_2-receptor antagonists, because famotidine is the most commonly used H_2-receptor antagonist in Japan. Thus, we compared the pharmacokinetic and pharmacodynamic properties of lafutidine and famotidine following postprandial oral administration in healthy subjects.

MATERIALS AND METHODS

Subjects　Five healthy Japanese male volunteers participated in this study. The subjects, aged 23—32 years and weighed 52—75 kg, had no history of gastrointestinal or hepatobiliary disease, and took no regular medications. Written informed consent was obtained from all subjects when they were enrolled in the study, which was approved by the Ethics Committee of Hiroshima University Hospital and conducted in compliance with the Declaration of Helsinki.

Study Schedule　This was a three-way (lafutidine, famotidine, and control) crossover study. At 11:00, a pH electrode was inserted through the nose, and its tip was positioned in the upper part of the gastric body, and from 11:30 to 17:00, the intragastric pH was measured. The pH electrode was connected to a portable digital recorder (PH-101Z; Chemical Instrument Co., Ltd., Tokyo, Japan), and the recordings were transferred to a personal computer for processing and analyzed using a software program. The median intragastric pH values per 30 min were calculated as the parameter representing the degrees of gastric acid suppression.

Between 12:00 and 12:20, a standardized meal was eaten (650 kcal; protein 25 g, lipids 20 g, carbohydrate 80 g). At 12:30, lafutidine 10 mg (Stogar tablet 10 mg; UCB Japan Co., Ltd., Tokyo, Japan), famotidine 20 mg (Gaster tablet 20 mg; Astellas Pharma Inc., Tokyo, Japan), or water only (control) was orally administered. Venous blood samples were taken before and at 1, 1.5, 2, 2.5, and 4 h after drug administration.

Assays of Lafutidine and Famotidine　Plasma concentrations of lafutidine and famotidine were determined by HPLC according to the method of Itoh *et al.*[5] and Dowling *et al.*,[6] respectively.

Pharmacokinetic and Pharmacodynamic Modeling　Model analysis was performed as shown in Fig. 1 using a nonlinear least squares program MULTI.[7] We set the one-compartment model with first order absorption and elimination as a basic pharmacokinetic model, and examined whether the absorption lag time should be added to fit the drug concentration in the plasma (C_p)–time curve consider-

ing the Akaike Information Criterion (AIC) and correlation coefficient of each pharmacokinetic model. Subsequently, we tested whether the drug concentration in the effect site compartment[8] (C_e) should be assumed to fit the drug effect (ΔpH, the difference in intragastric pH by the drug *vs.* control)–time curve considering AIC and correlation coefficient of each sigmoid E_{max} model as follows:

$$\Delta pH = \frac{E_{max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

where E_{max} is the maximum effect, C is the drug concentration (C_p or C_e), EC_{50} is the drug concentration needed for 50% of E_{max}, and γ is the Hill factor, a factor describing the steepness of the sigmoid curve.

Statistical Analysis Results are expressed as means± standard error of the mean (S.E.M.). Statistical analysis was performed by the *t*-test, and $p < 0.05$ was considered significant.

RESULTS

The plasma drug concentration–time profiles are presented in Fig. 2, and the pharmacokinetic parameters are summarized in Table 1. Lafutidine concentrations in plasma rapidly increased after administration, and reached a maximum concentration (C_{max}) of 133.9±8.1 (ng/ml) at the time (T_{max}) of 1.844±0.334 (h). Famotidine required some time to increase the plasma concentrations, the absorption lag time in the pharmacokinetic model was needed to fit the simulation curve: famotidine levels, with an absorption lag time of 0.745±0.081 (h), reached a C_{max} of 71.15±4.68 (ng/ml) at T_{max} of 2.328±0.223 (h). The apparent volume of distribution

(Vd/F) and oral clearance (CL/F), where F is the bioavailability, were significantly smaller in lafutidine than in famotidine.

Plotting plasma lafutidine concentrations against ΔpH data revealed an anticlockwise hysteresis loop which indicated equilibration delay between the plasma concentration and effect site (Fig. 3A). Introduction of the effect site compartment decreased AIC by 31.77±4.12 and increased the correlation coefficient by 0.377±0.026. Thus, the effect site compartment in the pharmacodynamic model was needed to simulate the drug effect–time curve (Fig. 4A).

Famotidine showed more parallel relationship between ΔpH and the plasma concentration than lafutidine (Fig. 3B). However, addition of the effect site compartment did not improve the model fitting because it increased AIC by 8.85±5.37 and decreased the correlation coefficient by 0.016±0.032. ΔpH–time profiles were fitted to the simulation curves by the basic pharmacodynamic model in which the plasma concentration directly produced the drug effect.

The pharmacodynamic parameters are summarized in Table 1. E_{max} was significantly larger in lafutidine than in famotidine, although γ was not different between the two drugs.

Fig. 1. Schematic Diagram of Pharmacokinetic and Pharmacodynamic Modeling

Bold-line box, basic component; dotted-line box, additive component. k_a, absorption rate constant; k_{10}, elimination rate constant from the central compartment; C_p, drug concentration in the central compartment (plasma concentration); k_{1e}, inter-compartmental transfer rate constant; k_{e0}, elimination rate constant from the effect site compartment (equilibration rate constant); C_e, drug concentration in the effect site compartment, where $dC_e/dt = (k_{1e} \cdot C_p) - (k_{e0} \cdot C_e)$.

Table 1. Pharmacokinetic and Pharmacodynamic Parameters of Lafutidine (10 mg) and Famotidine (20 mg) after Postprandial Oral Administration

	Lafutidine	Famotidine
Pharmacokinetic model		
Absorption lag time (h)	—	0.745±0.081
k_a (1/h)	0.956±0.305	0.881±0.061
k_{10} (1/h)	0.329±0.075	0.572±0.073
Vd/F (l)	42.46±5.36	123.2±9.7
CL/F (l/h)	12.97±2.42	71.72±10.47
C_{max} (ng/ml)	133.9±8.1	71.15±4.68
T_{max} (h)	1.844±0.334	2.328±0.223
Pharmacodynamic model		
k_{1e} (1/h)	0.155±0.003	—
k_{e0} (1/h)	0.316±0.012	—
E_{max}	3.686±0.222	2.493±0.270
EC_{50} (ng/ml)	40.68±2.70 (C_e)	46.38±6.00 (C_p)
γ	2.925±0.190	3.182±0.153

Mean±S.E.M. ($n=5$). k_a, absorption rate constant; k_{10}, elimination rate constant; Vd, volume of distribution; F, fraction of absorbed dose (bioavailability); CL, total clearance; C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; k_{1e}, inter-compartmental transfer rate constant; k_{e0}, equilibration rate constant; E_{max}, maximum effect; EC_{50}, drug concentration needed for 50% of E_{max}; γ, Hill factor.
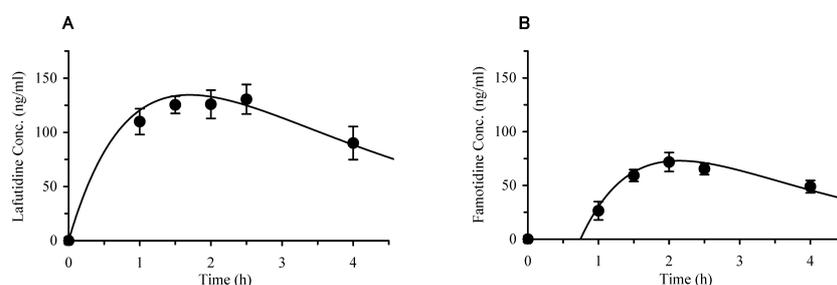
Fig. 2. The Plasma Drug Concentration–Time Plot after Postprandial Oral Administration of 10 mg Lafutidine (A) and 20 mg Famotidine (B)

Data are presented as the mean±S.E.M. of 5 subjects. The simulation curve is given by the mean pharmacokinetic parameters.
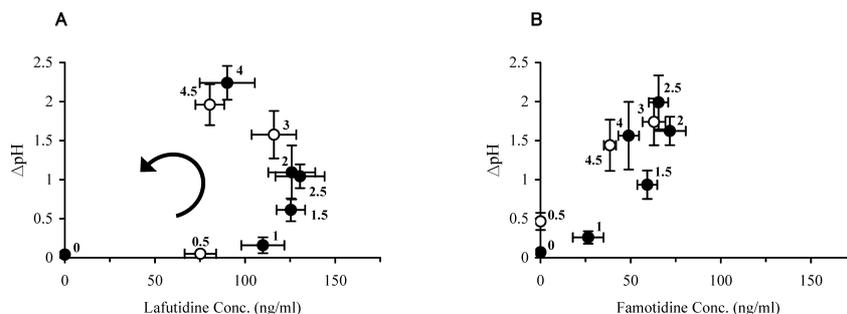
Fig. 3.   Relationship between the Plasma Drug Concentration and ΔpH after Postprandial Oral Administration of 10 mg Lafutidine (A) and 20 mg Famotidine (B)

Data are presented as the mean±S.E.M. of 5 subjects (●, plasma drug concentration measured; ○, plasma drug concentration estimated by the mean pharmacokinetic parameters). Numbers represent time (h) after drug administration. Looped arrow in panel A expresses the anticlockwise hysteresis relationship.
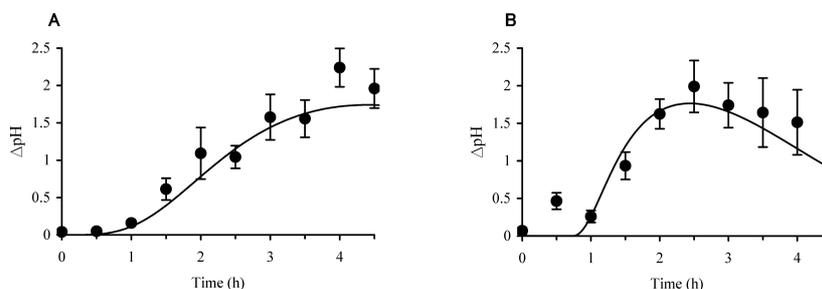
Fig. 4.   The ΔpH–Time Plot after Postprandial Oral Administration of 10 mg Lafutidine (A) and 20 mg Famotidine (B)

Data are presented as the mean±S.E.M. of 5 subjects. The simulation curve is given by the mean pharmacokinetic and pharmacodynamic parameters.

DISCUSSION

This study demonstrated that lafutidine was rapidly absorbed in the absence of a lag time after postprandial oral administration; however, the intragastric pH-elevating effect was delayed until the plasma concentration decreased (anticlockwise hysteresis relationship). These pharmacokinetic and pharmacodynamic properties of lafutidine were opposite to those of famotidine.

There have been studies on the pharmacokinetics of lafutidine or famotidine. Haruki et $al.$[9] reported that CL/F, C_{max}, and T_{max} were 11.8 ± 1.3 (l/h), 167 ± 17 (ng/ml), and 2.1 ± 0.2 (h), respectively, after postprandial administration of a lafutidine tablet (10 mg) in healthy volunteers. Inotsume et $al.$[10] found that Vd/F, CL/F, C_{max}, and T_{max} were 172 ± 24.6 (l), 46.1 ± 1.9 (l/h), 70.1 ± 3.7 (ng/ml), and 2.3 ± 0.2 (h), respectively, after administration of a famotidine tablet (20 mg) during a fasting state in healthy volunteers. Lin et $al.$[11] noted no influences of food on the pharmacokinetics of famotidine. The present study was the first to directly compare pharmacokinetics between lafutidine and famotidine by the crossover method in the same experiment, and confirmed differences in pharmacokinetics between the two drugs (and dosage forms).

Concerning the plasma concentration–effect relationship, there have been no reports on famotidine tablets, but famotidine for injection has been reported to fit the sigmoid E_{max} model. Echizen et $al.$[12] found that E_{max} (pH), EC_{50}, and γ were 7.2 ± 0.1, 26.5 ± 4.2 (ng/ml), and 11.9 ± 2.4, respectively, after a 5-min infusion of 0.1 mg/kg famotidine during fasting in healthy volunteers. In the present study, since tablets were used, a lag time occurred until an increase in the plasma concentration, but the plasma concentration–effect relationship fitted the sigmoid E_{max} model, as was observed in previous studies. However, lafutidine showed a delay in the development of effects compared with the increase in the plasma concentration and maintenance of the effect even after a decrease in the plasma concentration (Fig. 3A). This plasma concentration–effect relationship fitted the model after introducing the effect site compartment, although the model could not clarify the mechanism of this delay. In the approved protocol, the plasma concentration and pH more than 5 h after administration were not measured. However, at least 4.5 h after dosing, simulation showed the maintenance of the pH-increasing effect of lafutidine (Fig. 4A) compared with famotidine (Fig. 4B) even when its plasma concentration decreased. This pharmacokinetic and pharmacodynamic finding explains the marked postprandial pH-increasing effect of lafutidine as previously reported, and suggests that lafutidine can be more suitable candidate for the treatment of disorders in which postprandial gastric acid should be suppressed, $e.g.$, gastroesophageal reflux disease (GERD). Since the E_{max} of lafutidine is higher than that of famotidine (Table 1), it is possible that an increase in the dose ($e.g.$, from 10 to 20 mg within the range of the approved dose) raises the plasma concentration of lafutidine, and results in a more marked postprandial pH-increasing effect than that of famotidine.

To our knowledge, this is the first report describing the plasma concentration–effect relationship of lafutidine after its postprandial oral administration. However, this study had several limitations: the number of subjects was small, sampling time was insufficient, and we did not perform repeat administrations. Further study is needed to confirm our findings.

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