Pharmacodynamic and Pharmacokinetic Evaluation of CS-526 in Cynomolgus Monkeys

Keiichi Ito,†,a Kazuya Kinoshita, b Naotoshi Yamamura, c Atsuyuki Tomizawa, b Fumi Inaba, d
Yuka Morikawa-Inomata, b Keiichi Tabata, e and Nobuhiko Shibakawa f


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In the present study, we evaluated the effect of the novel acid pump antagonist 7-(4-fluorobenzyloxy)-2,3-dimethyl-1-[(1S,2S)-2-methylcyclopropyl][methyl]-1H-pyrrrolo[2,3-d]pyridazine (CS-526) on the intragastric acidity of cynomolgus monkeys. The study was performed in a crossover manner with five male animals. CS-526 was administered orally or intravenously at doses of 3.0, 10 and 30 mg/kg, or 0.3, 1.0 and 3.0 mg/kg, respectively. The median time period in which the intragastric pH was 4.0 or more (Time pH≥4.0) and the median pH were calculated for 24 h after the administration. The Time pH≥4.0 was elevated after CS-526 treatment. The Time pH≥4.0 was increased in a dose-dependent manner (p = 0.0292) in the oral administration, and the median pH was also increased in a dose-dependent fashion (p = 0.0491) in the intravenous administration. The plasma concentration of CS-526 and its metabolite R-130185 was increased after oral and intravenous administration of CS-526, except for one animal which did not show any detectable amount of R-130185 after intravenous administration at the lowest dose. The area under the time–concentration curve of the active component was increased in the dose proportional manner after oral and intravenous administration. The absolute bioavailability of the active component was estimated to be approximately 1%. Correlation between the pharmacodynamic parameters and the pharmacokinetic parameters was observed in oral (p = 0.0029—0.0745), but not in intravenous administration (p = 0.0588—0.2789). In conclusion, oral and intravenous administration of CS-526 showed inhibition on gastric acidity in cynomolgus monkeys using intragastric pH-metry and some pharmacokinetic and pharmacodynamic parameters were well correlated.

Key words CS-526; R-130185; cynomolgus monkey; acid pump antagonist; potassium competitive acid blocker; gastroesophageal reflux disease

Gastric H⁺,K⁺-ATPase is a proton pump located at the apical membrane of the parietal cells which transport protons into the canaliculi of parietal cells in exchange for potassium. So-called proton pump inhibitors (PPIs), with substituted benzimidazoles such as omeprazole, lansoprazole, rabeprazole, pantoprazole or esomeprazole, inactivate the H⁺,K⁺-ATPase by covalent binding to the sulfhydryl group of H⁺,K⁺-ATPase, resulting in the long-lasting inhibition of gastric acid secretion. 1) They are now widely used for the treatment of gastric acid-related diseases such as peptic ulcer and gastroesophageal reflux disease. 2, 3

Reversible acid pump antagonists (APAs), the other class of proton pump inhibitors, act by potassium competitive inhibition and reversible binding to the gastric proton pump. 4) From their competitive inhibition of potassium, they could also be called potassium competitive acid blockers. 5) The major classes of APAs are imidazopyridines 6—8) and acyl quinoline derivatives. 9—11) 7-(4-Fluorobenzyloxy)-2,3-dimethyl-1-[(1S,2S)-2-methylcyclopropyl][methyl]-1H-pyrrrolo[2,3-d]pyridazine (CS-526) is a novel acid suppressant which is different from PPIs and the aforementioned APAs in that its chemical structure includes a pyrrolopyridazine structure. 12) We have shown the potent and reversible inhibitory properties of CS-526 against porcine H⁺,K⁺-ATPase without any covalent binding formation. The potent gastric acid inhibitory effects and antiulcer efficacy of CS-526 have also been shown in rats and the efficacy of CS-526 is comparable to those of PPIs such as omeprazole, lansoprazole and rabeprazole. 12)

Well-known problems resulting from chronic usage of long-lasting acid inhibitors are induction of hypergastrinemia13—17) and rebound gastric acid hypersecretion. 18—20) We confirmed that subchronic (14-d) treatment of lansoprazole at a dose of 30 mg/kg/d showed significant elevation of the serum and antrum gastrin levels and rebound gastric acid hypersecretion after cessation of the treatment in rats. However, while CS-526 had a weak effect on serum gastrin elevation and rebound gastric acid hypersecretion, it nevertheless showed an acid suppressive effect comparable to that of lansoprazole. 21)

There are a great number of reports in which the effects of agents on gastric acid secretion are evaluated in rats and dogs. However, in terms of monkeys, there are only a few reports regarding gastric acid status 22—27) and less than 10 reports of pharmacodynamic studies. 28—34) However, we think it would be meaningful to obtain data from non-human primates because of their phylogenetic similarities with human beings.

In the present study, to further clarify the acid suppressive effect of CS-526, we studied non-human primates (cynomolgus monkeys) utilizing intragastric pH-metry, which is widely used in clinical studies. Simultaneously, we measured

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the plasma concentration of CS-526 and its active metabolite to study the relation between the pharmacodynamic and pharmacokinetic parameters.

**MATERIALS AND METHODS**

**Chemicals** CS-526, 7-(4-fluorobenzoylxy)-2-methyl-3-hydroxymethyl-1-[(1S,2S)-2-methylcyclopropyl]methyl]-1H-pyrrolo[2,3-d]pyridazine (R-130185), 7-(4-fluorobenzoylxy)-2-methyl-3-hydroxycarbonyl-1-[(1S,2S)-2-methylcyclopropyl]methyl]-1H-pyrrolo[2,3-d]pyridazine (R-130186) and 7-(2,3,5,6-tetrahydro-4-fluorobenzox)2,3-dimethyl-1-[(1S,2S)-2-methylcyclopropyl]methyl]-1H-pyrrolo[2,3-d]pyridazine (R-127788) were synthesized in Ube Research Laboratory of Ube Industries, Ltd. (Yamaguchi, Japan) and were stored at −20 °C until use. Their chemical structures are indicated in Fig. 1. R-130185 and R-130186 are metabolites of CS-526 and R-127788 is a deuteride CS-526 derivative used as an internal standard for the LC/MS/MS system.

**Inhibitory Effect on H⁺,K⁺-ATPase Activity** The evaluation of the inhibitory effect of CS-526, R-130185 and R-130186 on H⁺,K⁺-ATPase activity was performed by the previously reported method. Briefly, the ATPase was prepared by the method of Im and Blakeman with some modifications. An enzyme sample (40 μg/ml) extracted from porcine gastric mucosa was incubated at 37 °C in 1 ml of a medium consisting of 40 mM Tris/acetic acid, pH 7.4, 2 mM MgCl₂, 2 mM ATP. The H⁺,K⁺-ATPase activity was determined in the presence of 10 mM KCl. After preincubation with the compounds for 60 min, the inorganic phosphate released from ATP for 20 min was determined by the methods of Fiske and Subbarow as an activity of ATPase.

**Animals** All the procedures regarding animal care and experiments were performed at Shin Nippon Biomedical Laboratories, Ltd. (Kagoshima, Japan) in compliance with the animal experimental guidelines established in the organization.

Five male cynomolgus monkeys (purpose-bred, B-virus negative, Guangxi Primate Center of China, Guangxi, China) weighing 2.6—3.3 kg were used. The animals were given tap water ad libitum. Each animal was housed in a stainless steel cage (according to the regulation of United States Department of Agriculture) maintained at room temperature of 23 ± 2 °C and with humidity of 50 ± 10% under a 12 h light/dark cycle (lighting period: 6:00 a.m.—6:00 p.m.). Their gastric pH in an unfed status was confirmed to be between 1 and 3 during the acclimatization period.

**Study Design** The animals were divided into 3 groups and administered CS-526 in a crossover manner at 1 week intervals, as shown in Table 1. The doses were 3.0, 10 and 30 mg/kg for the oral administration and 0.3, 1.0 and 3.0 mg/kg for the intravenous administration.

**Dosing Suspension and Solution** CS-526 was suspended in 0.5% (w/v) sodium carboxymethyl cellulose aqueous solution at concentrations of 1.5, 5.0 and 15 mg/ml for 3.0, 10 and 30 mg/kg in the oral administration, respectively. For the intravenous administration, CS-526 was dissolved in a mixed solution of N,N-dimethylacetamide, 0.1 mol/l hydrochloride and saline (composition ratio, 10:5:85) at concentrations of 0.15, 0.5 and 1.5 mg/ml for 0.3, 1.0 and 3.0 mg/kg, respectively. The suspension or solution was administered at 2 ml per kg body weight for the oral and intravenous administrations, respectively.

**Intragastric pH-Metry in Cynomolgus Monkeys** The animals were given 108 g of standard diet for non-human primates (Harlan Teklad Global Diet 2055, Harlan Tekrad, Inc., Indianapolis, IN, U.S.A.) every day at around 1:00 p.m. and the remnants were collected at 3:00 p.m., except on the day of the intragastric pH measurement. On the day of the intragastric pH measurement, 48 g of the diet was given after the blood sampling at 8 h after the administration and the remnants were collected 2 h after the feeding.

The intragastric pH was measured at 0.5 h and immediately before the CS-526 administration. Thereafter, the intragastric pH was also measured at 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h after the administration. At the measuring time points, each animal was restrained for up to a maximum of 5 min in a special cage which was designed to limit its movement without any large stress. A pH-probe (diameter 1.5 mm, Multi-Use pH Catheter, 839100, Synectics Medical, Barcarena, Portugal) connected to an ambulatory pH-monitor (Digitrapper MkIII, Synectics Medical AB, Stockholm, Sweden) was introduced into the stomach via the transnasal pathway. To keep the appropriate position of the probe, we marked the position of the nasal cavity on the probe with a felt tipped pen at the first measuring period before CS-526 administration. And if the indicated pH value was above 3.0,
Results of Pharmacodynamic Analysis in Cynomolgus Monkeys The intragastric pH of cynomolgus monkeys elevated immediately after administration of CS-526 (Fig. 2). In particular, with the oral dose 2, 3 and 4 out of 5 monkeys showed an intragastric pH above 4.0 at 0.5 h after the administration at doses of 3.0, 10 and 30 mg/kg, respectively. In the intravenous administration, a somewhat slower onset was observed. Two, 0 and 2 out of 5 monkeys showed an intragastric pH above 4.0 at 0.5 h after the administration at doses of 0.3, 1.0 and 3.0 mg/kg, respectively. The mean intragastric pH was maintained above 4.0 for 8 h at oral doses of 10 and 30 mg/kg of CS-526 and two peaks of the mean intragastric pH were observed during the period. The effect after intravenous administration also showed a biphasic pattern in which the mean intragastric pH was raised above 4.0 by 4 or 5 h after the administration. It went below 4.0 once and thereafter remained above 4.0 again. These biphasic patterns of mean intragastric pH elevation were not derived artificially from asynchronous peak timing. Multiple, two or three,
peaks of intragastric pH were also observed in individual animals and the number of animals showing multiple peaks of intragastric pH increased in accordance with the increment of the dose. One, 4 and 4 out of 5 animals after oral administration at doses of 3.0, 10 and 30 mg/kg and 2, 3 and 4 out of 5 animals after intravenous administration at doses of 0.3, 1.0 and 3.0 mg/kg showed multiple peaks of intragastric pH, respectively.

The pharmacodynamic parameters, Time_{pH≥4.0} and median pH within 24 h after CS-526 administration are summarized in Table 4. Time_{pH≥4.0} increased in a dose-dependent manner in the oral administration (p=0.0292) but not in the intravenous administration (p=0.1901, Fig. 3A). On the other hand, the median pH increased in a dose-dependent manner in the intravenous administration (p=0.0491) but not in the oral administration (p=0.1283, Fig. 3B). In both parameters (Time_{pH≥4.0}, and median pH), parallel line analysis revealed that the lack of parallelism was not significant (p=0.4067 for Time_{pH≥4.0}, p=0.9973 for median pH) and the efficacy ratio (IV/PO) was 3.3 (95% CI: 0.048—14) and 4.1 (95% CI: 0.060—19), respectively.

**Pharmacokinetics Profile of CS-526 in Cynomolgus Monkeys** The plasma concentration of CS-526 (Fig. 4A) and R-130185 (Fig. 5A) increased after oral administration of CS-526 at doses of 3.0, 10 and 30 mg/kg. Three and 2 out of 5 monkeys showed two peaks of plasma CS-526 concentration at doses of 10 and 30 mg/kg, respectively. The pharmacokinetic parameters are shown in Table 5. $T_{1/2}$ of CS-526 at a dose of 10 mg/kg was prolonged (18.15 h) because of variation in the results, such as 2 out of 5 animals showed the $T_{1/2}$ over 30 h with ambiguous peak. Without these two animals, $T_{1/2}$ (mean±S.E., h) was 7.053±2.662. As the inhibitory activity against H^+K^+-ATPase of R-130185 was almost the same as that of the parent compound (Table 3), both

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose (mg/kg)</th>
<th>Time_{pH≥4.0} (h)</th>
<th>Median pH</th>
</tr>
</thead>
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<tr>
<td>Oral</td>
<td>3.0</td>
<td>6.60±3.63</td>
<td>3.79±1.13</td>
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<tr>
<td></td>
<td>10</td>
<td>16.16±3.11</td>
<td>5.35±0.72</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>18.22±3.53</td>
<td>5.74±0.74</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.3</td>
<td>7.93±2.57</td>
<td>3.38±0.76</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>5.73±2.83</td>
<td>3.82±0.62</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>14.29±3.60</td>
<td>5.37±0.56</td>
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Fig. 2. Effect of CS-526 on Intragastric pH in Cynomolgus Monkeys
CS-526 was administered orally (A) at the doses of 3.0 (closed square), 10 (open circle) and 30 (closed circle) mg/kg; and intravenously (B) at the doses of 0.3 (closed square), 1.0 (open circle) and 3.0 (closed circle) mg/kg. Intragastric pH was measured at 0.5 h and immediately before the administration and 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h after the administration. Each point and bar represent the mean and S.E. of the intragastric pH obtained from 5 animals in each treatment.

Fig. 3. Dose–Response Relationships of the Pharmacodynamic Parameters (Time_{pH≥4.0} (A) and Median pH (B)) after Oral (Closed Circle) and Intravenous (Open Circle) Administration of CS-526 in Cynomolgus Monkeys
Each point and bar represent the mean±S.E. of the pharmacodynamic parameters obtained from 5 animals in each treatment. The regression lines were calculated by a parallel line analysis.
CS-526 and R-130185 were treated as the active component. $AUC_{0–24h}$ (mean±S.E., ng·h·ml$^{-1}$) of the active component was 15.85±3.779 (3.0 mg/kg), 104.0±5.099 (10 mg/kg) and 193.7±44.98 (30 mg/kg) and the dose proportionality was confirmed in this dose rage (Fig. 6).

Except for one animal which did not show any detectable amount of R-130185 after administration of the lowest dosage, CS-526 (Fig. 4B) and R-130185 (Fig. 5B) were observed after the intravenous administration of CS-526 at doses of 0.3, 1.0 and 3.0 mg/kg and the pharmacokinetic parameters are shown in Table 6. Even R-130185 was observed at doses of 0.3 and 1.0 mg/kg, the level was close to lower limit of quantification. Therefore $T_{1/2}$ of R-130185 at the dosages would be derived from some anomaly. The $AUC_{0–24h}$ ratio of R-130185 to CS-526 was remarkably small in comparison with that in the oral administration. $AUC_{0–24h}$ (mean±S.E., ng·h·ml$^{-1}$) of the active component was 116.5±6.386 (0.3 mg/kg), 417.0±30.71 (1.0 mg/kg) and 1242±83.82 (3.0 mg/kg) and the linearity was confirmed in this dose range (Fig. 6). The absolute bioavailability of the active component was estimated to be approximately 1%.

**Correlation of Pharmacodynamic and Pharmacokinetic Parameters**

The correlations between the pharmacodynamic parameters ($Time_{pH4.0}$ and median pH) and $AUC_{0–24h}$ of CS-526, R-130185 or the active component are shown in Fig. 7. In the oral administration, significant correlation was observed between $Time_{pH4.0}$ and $AUC_{0–24h}$ of CS-526, R-130185 or the active component (Figs. 7A—C). In addition, correlation between median pH and $AUC_{0–24h}$ of CS-526 was also significant (Fig. 7D).
On the other hand, in the intravenous administration, there was no significant correlation between the pharmacodynamic and pharmacokinetic parameters. To clarify the reason for these differences between oral and intravenous administration, we further analyzed the correlation between the mean intragastric pH values and the corresponding mean plasma concentrations of the active component. Diagrammatizing the mean intragastric pH against the corresponding mean plasma concentration of the active component revealed that the mean intragastric pH seemed to correlate with the mean plasma concentration of the active component in the oral administration (Fig. 8A). However, in the intravenous administration, the mean intragastric pH of the early time points (0.5 and 1 h after the administration) deviated from the predicted correlation pattern (Fig. 8B).

DISCUSSION

In vivo evaluations of the gastric acid inhibitory properties of acid suppressive agents in rats and dogs have been widely performed. Although the data from non-human primates would be useful for the prediction of clinical study results due to their phylogenetic similarities, the background knowledge of gastric acid secretion in primates is still lacking. There are only a few reports regarding the physiologic state of gastric acid secretion22—27) and less than 10 reports of acid suppressive agents in primates.

### Table 6. Pharmacokinetic Parameters of CS-526 and Its Active Metabolite R-130185 after Intravenous Administration of CS-526 (Mean±S.E.)

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>(T_{\text{max}}) (h)</th>
<th>(C_{\text{max}}) (ng/ml)</th>
<th>(T_{1/2}) (h)</th>
<th>(AUC_{0—24\text{h}}) (ng·h·ml(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>CS-526 0.8125±0.4002</td>
<td>0.6336±0.1926</td>
<td>1.788±0.3142</td>
<td>115.4±6.315</td>
</tr>
<tr>
<td></td>
<td>R-130185 1.850±1.538</td>
<td>1.958±0.4547</td>
<td>3.328±1.214</td>
<td>105.2±7.921</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>CS-526 0.7500±0.1581</td>
<td>5.354±1.347</td>
<td>2.739±0.4993</td>
<td>1219±81.38</td>
</tr>
<tr>
<td></td>
<td>R-130185 1.538</td>
<td>1.958±0.4547</td>
<td>3.328±1.214</td>
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<td>105.2±7.921</td>
</tr>
</tbody>
</table>

Fig. 6. Dose Relationship of the Plasma Concentration of the Active Component (CS-526+R-130185) after Oral (Closed Circle) and Intravenous (Open Circle) Administration of CS-526

Each point and bar represent the mean±S.E. of the area under the time–concentration curve (\(AUC_{0—24\text{h}}\)) of active component. The \(AUC_{0—24\text{h}}\) of active component was calculated by adding that of CS-526 and R-130185 in each dosing group.

Fig. 7. Correlation between Pharmacodynamic Parameters (Time pH\(4.0\) (A—C) and Median pH (D—F)) and \(AUC_{0—24\text{h}}\) of CS-526, R-130185 or Active Component

Each dot represents the individual pharmacodynamic parameters after oral (closed) or intravenous (open) administration of CS-526 against pharmacokinetic parameters.
pharmacodynamic studies. In these pharmacodynamic studies, gastric juice or infused wash solution was collected from acute gastric fistulae in anesthetized animals or nasogastric tubes in monkey chair restrained animals, respectively. With these restrictions in the experimental conditions, the duration of measurement was up to a maximum of 9h. In addition, there is difficulty in showing a definite dose–response relationship of acid suppressants in basal gastric acid secretions. Therefore, in some of the experiments of these studies, acid stimuli such as histamine or histamine H2-receptor agonist were used to obtain more quantitative data. Meanwhile, we used periodic intragastric pH-metry in conscious animals without any acid stimuli. With some modifications of the timing and the amount of diet, we could measure the intragastric pH for 24h. In clinical situations, intragastric or esophageal pH-metry is used for the evaluation of the pathophysiologic state of acid-related disease and the pharmacodynamic study of acid suppressants. Time pH<4.0 and median or mean pH are widely used as the parameters to evaluate the antisecretory efficacy of gastric acid suppressant. We also used these parameters in the present study to evaluate the gastric acid inhibitory properties of CS-526 in cynomolgus monkeys. Despite the relatively small measuring time points (11 points/24h) which might cause insignificant dose–response relationship in Time pH≥4.0 and median pH after intravenous and oral administration, respectively, these parameters showed significant dose–response relationship in the other route of administration. Though we could not confirm significant dose–response relationship under all the conditions used, we think that these parameters would generally be sufficient to evaluate the gastric acid inhibitory efficacy of CS-526.

In this crossover study, we did not check the effect of vehicle (0.5% CMC). However, the background data from other cynomolgus monkeys have been obtained at the same feeding condition and with the same method that we used in this study. In 6 animals selected by unfed gastric pH below 3 in the acclimatization period, 5 animals (83%) showed gastric pH less than 5.0 during the measurement period (from 0 to 24h after vehicle administration) with median pH (mean±S.E. for 24h of 6 animals) of 2.0±0.2 and Time pH≥4.0 (mean±S.E., h) of 0.4±0.3 (data not shown). A recent study has revealed that the gastric pH of unfed cynomolgus monkeys is generally low and that at least 60% of the animals show less than pH 5 during a 24h measurement period with the median pH between 1 and 3. There was only a small difference in the ratio of animals showing low gastric pH compared to our background data. Although the exact dose which showed a significant effect was not clarified, the inhibitory effect of CS-526 against gastric acid secretion in cynomolgus monkeys was obvious after oral or intravenous administration.

In the present study, the onset of action after the CS-526 administration was somewhat faster in oral administration than in intravenous administration despite the higher plasma level of CS-526 and active component after intravenous administration. We previously showed that CS-526 may act on parietal cells by two routes: one route is absorption from the small intestine and the other is direct permeation through the gastric mucosa from the gastric lumen. H+,K+-ATPase, an active site of CS-526, is localized on the apical membrane of the parietal cells. In addition, the putative APA binding site of H+,K+-ATPase, which was suspected to be a minute active site of CS-526, is the luminal side of the apical membrane. Therefore, we speculated that a compound which is rich in gastric lumen would be able to reach the active site more easily and rapidly than that from general circulation via the intercellular or intracellular routes.

The driving force of disposition of CS-526 from general circulation to the gastric mucosa would be a gradient of environmental pH. This disposition is known as the pH-partition hypothesis, which states that a basic compound tends to concentrate in a low pH environment and that an acidic compound tends to concentrate in a high pH environment. Benzimidazole derivative proton pump inhibitors are basic compounds which demonstrate a pH-dependent drug distribution based on the pH-partition hypothesis and accumulate in a lower pH environment such as the secretory canaliculi of parietal cells. As CS-526 and R-130185 are thought to be basic compounds (unpublished data), the localized distribution would be driven into the low pH gastric lumen. Once they have been secreted into the gastric lumen, the compounds might be reabsorbed afterwards. The longer half life and two peaks of plasma concentration of CS-526 in some
animals at higher doses after oral administration may reflect the reabsorption of CS-526 which was secreted into the stomach.

Interestingly, the elevation of intragastric pH after oral and intravenous administration of CS-526 showed multiple peaks, as shown in Fig. 2. This phenomenon might also be explained by the pH-partition hypothesis. The first elevation of intragastric pH after oral or intravenous administration would be induced by the compound distributed into the gastric mucosa via a direct permeation from the gastric lumen and/or from general circulation. Once intragastric pH was elevated by its pharmacodynamic activity, the compound distributed from general circulation would be reduced and the gastric anti-acidity would be attenuated. Then the intragastric pH would be lowered again and the distribution of the compound from general circulation would be potentiated. In this manner, the intragastric pH would oscillate. As CS-526 is a reversible type of compound, unlike benzimidazole derivative proton pump inhibitors, the efficacy of the gastric anti-acidity would be influenced directly by the change in the gastric mucosal content of the active component and the mucosal content would be influenced by its environmental pH.

On a pharmacokinetic basis, the inhibitory effect of CS-526 was well correlated with the AUC of CS-526, its metabolite and active component after oral administration. It is reasonable to construe that the active component would act on the parietal cells mainly from general circulation. However, the data after intravenous administration indicated a discrepancy in this idea. There were no significant relationships between the pharmacodynamic and pharmacokinetic parameters after intravenous administration. As shown in Fig. 8B, the effect of CS-526 in early-stage after the intravenous administration deviated from the expected potency. It was thought that the excess amount of CS-526 in the general circulation after intravenous administration for at least 1 h would not be effectively utilized and most of it would be excreted. Thus, the AUC of CS-526, its metabolite and active component did not correlate with the inhibitory effect of CS-526 after intravenous administration.

From this study, we can not conclude which is the main route of CS-526 after oral administration, direct permeation from gastric lumen or from general circulation after absorption. However, from the fact that absolute bioavailability of active component was about 1%, i.e. 100-time higher amount of plasma active component in intravenous administration than oral administration, the efficacy ratio between intravenous and oral administration was from 3 to 4, we think that the compound which is direct permeation from gastric lumen would participate in the effect at least partly after oral administration.

In conclusion, oral or intravenous administration of CS-526 showed a gastric acid inhibitory effect in cynomolgus monkeys, as shown by the use of periodical measurement of the intragastric pH. As well, some pharmacokinetic parameters were well correlated with the pharmacodynamic parameters.

REFERENCES