Safety and Pharmacokinetics of CS-834, a New Oral Carbapenem Antibiotic, in Healthy Volunteers

KAZUO UMEMURA,1* YASUHIKO IKEDA,1 KAZUNAO KONDO,1 MITSUYOSHI NAKASHIMA,1 HIDEO NAGANUMA,2 MASAFUMI HISAOKA,2 HIROSHI NISHINO,3 AND MASAZO TAJIMA3

Department of Pharmacology, School of Medicine, Hamamatsu University, Hamamatsu 431-31,1 Sankyo Research Laboratories, Shinagawa-ku 140,2 and Sankyo Clinical Development Department, Chuo-ku 104, Japan

Received 18 February 1997/Returned for modification 15 July 1997/Accepted 19 September 1997

CS-834, (+)-[pivaloyloxymethyl (4R,5S,6S)-6-[(R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[[(R)-5-oxopyrrolidin-3-yl][thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate], is an ester-type oral carbapenem produg, and an active metabolite is R-95867, which has antibacterial activity. CS-834 was administered orally to healthy male volunteers at single doses of 50, 100, 200, and 400 mg and at a multiple dose of 150 mg three times a day for 7 days to investigate its safety and pharmacokinetic profiles. Other studies were conducted to examine the effect of food intake on the bioavailability of CS-834 and also the effect of the coadministration of probenecid on the pharmacokinetics of CS-834. In the fasting state, the concentration of R-95867 in plasma reached maximum levels from 1.1 to 1.7 h after the oral administration of CS-834, followed by a monoexponential decrease. The maximum concentrations of R-95867 in serum (C_{max}) after the administration of CS-834 at doses of 50, 100, 200, and 400 mg were 0.51, 0.97, 1.59, and 2.51 mg/ml, respectively. The half-lives (t_{1/2}) were almost constant, approximately 0.7 h. The areas under the concentration-time curves (AUCs) were proportional to the doses, ranging from 50 to 400 mg·h/ml. The cumulative recoveries in urine were approximately 30 to 35% until 24 h after drug administration. The C_{max}, AUC, t_{1/2}, and recovery in urine were not affected by food intake. Probenecid coadministration prolonged the t_{1/2} and it increased the C_{max} and AUC for R-95867 by approximately 1.5- and 2.1-fold, respectively. The multiple-dose study showed no change in the pharmacokinetics from those for the single doses and no drug accumulation in the body. A mild transient soft stool was observed in one volunteer in the study with a single dose of 400 mg. In the multiple-dose study, mild transient soft stools were observed in six volunteers, one volunteer had mild transient diarrhea, and one volunteer had elevated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels (1.4- and 2.8-fold compared with the upper limits of normal, respectively). There were no other abnormal findings for objective symptoms or laboratory findings, including blood pressure, heart rate, electrocardiogram, body temperature, hematology, blood chemistry, and urinalysis.

MATERIALS AND METHODS

Chemicals. CS-834 was supplied by Sankyo Co., Ltd., as tablets containing an equivalent amount (50, 75, or 100 mg) of the active form of CS-834, R-95867. All other chemicals used in this study were commercially available reagent-grade products unless otherwise noted.

Subjects. Healthy male Japanese volunteers submitted written informed consent to participate in the study after being fully informed of its purpose and the risks involved. The study protocol was approved by the local ethical committee. Table 1 summarizes the clinical trials and backgrounds of the volunteers in all studies. They were judged to be healthy on the basis of standard biochemical, hematological, and urinalysis screening tests, as well as physical examinations. All subjects were within 20% of their ideal body weight and had been free of other medications for 1 week or more before and during the study. Alcohol- and caffeine-containing beverages were prohibited during the study.

Study design. For the pilot study, the initial dose of CS-834 was set at 10 mg, which is approximately 1/60 of the no-observed-adverse-effect dose found in the

FIG. 1. Chemical structures of CS-834 and its active metabolite, R-95867.
repeated administration toxicity studies with dogs. After confidence in the toler-
ance of three subjects to CS-834 at doses of 10 and 25 mg was established, in
the pilot study, the following study was conducted. The drug was administered
early in the morning after an overnight fast. Twenty-four subjects were divided
into four groups of six subjects each to conduct the study. Each group received
a single dose of 50, 100, 200, or 400 mg of CS-834. The effect of food intake on
the pharmacokinetics of R-95867 after administration of CS-834 at a dose of 100
mg was examined in a comparative study with eight subjects. Six subjects who
were assigned to the study at the 200-mg dose participated in a further study to
investigate the effect of probenecid on the renal excretion of R-95867. They were
given two 250-mg tablets of probenecid (Probenemid; Banyu Pharmaceutical
Co., Tokyo, Japan) orally 1 h before and 6 h after the administration of CS-834.
In the multiple-dose study, nine subjects were randomly divided into two groups.
One group of six subjects received a 150-mg tablet of CS-834 three times a day
(t.i.d.) at 0900, 1500, and 2100 on days 1 through 6 and once at 0900 on day 7.
The other group of three subjects received a placebo tablet in the same manner.
In the single-dose study with the four groups, blood samples for the assay of
drug concentrations were obtained before drug administration and at 0.25, 0.5,
0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after drug administration. Urine samples
were collected before and at intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12,
and 12 to 24 h after drug administration. Total and free pivalic acid and carnitine
concentrations in plasma and urine were determined in the studies with single
doses of 200 and 400 mg. Blood samples were obtained before and 2, 4, 8, and
12 h after drug administration. Urine samples were collected before and at
intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after drug administra-
tion. Arterial blood samples were obtained before and at 1, 2, 4, 6, and 8 h after
drug administration.
In the multiple-dose study, blood samples for the assay of drug concentra-
tions were obtained just before drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6,
and 12 h after the first drug administration on day 1 and day 4 just before drug
administration and 0.5, 1, 1.5, 2, 3, 4, 6, and 24 h after the final drug adminis-
tration on day 7. On days 2, 3, 5, and 6, blood samples were obtained once just
before the first drug administration. Urine samples were collected before and at
intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 12, and 12 to 24 h after the first drug adminis-
tration on days 1, 4, and 7, and at intervals of 0 to 6, 6 to 12, and 12 to 24 h
after the first drug administration on days 2, 3, 5, and 6. To determine the
concentrations of total and free pivalic acid in plasma, blood samples were
obtained before and at 1, 2, 4, 6, and 8 h after the first drug administration on
day 1 and just before and at 1, 2, 4, 6, and 24 h after the first drug administration
on day 7. On days 2, 3, 5, and 6, blood samples were obtained once just before
the first drug administration on each day. Urine samples were also collected to
determine total and free pivalic acid concentrations before the drug administra-
tion and every 24 h after the first drug administration on days 1 through 7. To
determine the concentrations of total and free carnitine, blood samples were
obtained just before the first drug administration on days 1 through 7 and at 24,
48, 72, and 168 h after the final dosing on day 7. Urine samples were also collected
before the first drug administration and every 24 h after the first drug adminis-
tration on days 1 through 7 and at 24 of 48, 48 to 72, 72 to 96, and
168 to 192 h after the final drug administration on day 7. Plasma and urine
samples were mixed with the same volume of 1 M 3-(N-morpholino)propanesul-
fonic acid (MOPS; pH 7.0) immediately after the sampling, and they were
stored at −20°C until they were assayed.
Subjective symptoms and objective and vital signs, including blood pressure,
heart rate, and body temperature, were checked before drug administration and
periodically until 24 h after administration in the single-dose study. Routine
laboratory tests including hematology, biochemistry, and urinalysis were
performed, and 12-lead electrocardiography was performed just before and 24 h
after drug administration. In the multiple-dose study, the same items were
checked before drug administration and on days 4 and 8.

**Assay of R-95867 in plasma and urine.** All procedures were performed in an
ice-chilled styrene foam box. To 200 μl of human plasma was added 200 μl of
ice-cold 1 M MOPS and 100 μl of isovonic acid (5 μg/ml), which was used as an
internal standard. The sample was mixed immediately and was filtered by using
an Acrodisc LC13 filter (Gelman Science Japan Ltd., Tokyo, Japan). Ten mi-
croliters of the filtrate was injected into a high-pressure liquid chromatography
(HPLC) system. The analysis was performed by the HPLC method with a
reversed-phase column, YMC-Pack ODS-A A-312 (6.0 mm [inner diameter] by
150 mm; particle size, 5 μm; YMC Co., Ltd., Kyoto, Japan). The column tem-
perature was kept at 40°C. The mobile phase consisted of 7% (vol/vol) acetoni-
trile and 93% (vol/vol) 20 mM CH₃COONH₄ (pH 5.8), and it was pumped at an
isocratic flow rate of 0.7 ml/min. The intra-assay imprecision was less than 12.4%,
and the inaccuracy varied from −2.1 to 8.3% between concentrations of 0.03 and
4 μg/ml. The assay sensitivity was 0.03 μg/ml.

To 200 μl of human urine was added 200 μl of ice-cold 1 M MOPS and 200
μl of acetaminophen (250 μg/ml), which was used as the internal standard. The
sample was mixed immediately and was filtered by using an Acrodisc LC13 filter.
Ten microliters of the filtrate was injected into an HPLC system. The analysis
was performed in a column switching mode with a strong anion-exchange col-
umn, TSK-GEL QAE-25W (4.6 mm [inner diameter] by 250 mm; Tosoh Cor-
poration, Tokyo, Japan), for sample pretreatment and a reversed-phase column,
YMC-Pack ODS-A A-312 (6.0 mm [inner diameter] by 150 mm; particle size, 5
μm; YMC Co., Ltd.), for analysis. Both columns were kept at 40°C. The mobile
phase for the pretreatment column consisted of 67 mM phosphate buffer (pH
6.4), and that for the analytical column was a mixture containing 7% (vol/vol) acetoni-
trile and 93% (vol/vol) 20 mM CH₃COONH₄ (pH 4.8). They were pumped at a
flow rate of 1.0 ml/min. The UV detector was adjusted to 300 nm. The intra-assay
imprecision was less than 2.44%, and the inaccuracy varied from 5.1 to 10% between
the concentration range of 1 and 100 μg/ml. The assay sensitivity was 0.4 μg/ml. All values below sensitivity of the assay were treated as zero.

### TABLE 1. Summary of clinical trials and backgrounds of volunteers

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Dose (mg)</th>
<th>No. of volunteers</th>
<th>Age (yr)*</th>
<th>Ht (cm)*</th>
<th>Body wt (kg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single admin. (fasting)</td>
<td>50</td>
<td>6</td>
<td>27.8 ± 7.9</td>
<td>167.5 ± 4.5</td>
<td>57.5 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>6</td>
<td>32.7 ± 11.8</td>
<td>170.2 ± 4.8</td>
<td>65.0 ± 5.3</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>6</td>
<td>32.0 ± 8.9</td>
<td>172.3 ± 7.6</td>
<td>65.2 ± 9.3</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>6</td>
<td>37.8 ± 10.1</td>
<td>171.4 ± 5.6</td>
<td>66.7 ± 4.9</td>
</tr>
<tr>
<td>Effect of food intake</td>
<td>100</td>
<td>6</td>
<td>25.1 ± 6.2</td>
<td>170.8 ± 6.1</td>
<td>60.7 ± 3.0</td>
</tr>
<tr>
<td>Effect of probenecid</td>
<td>200</td>
<td>6</td>
<td>32.0 ± 8.9</td>
<td>172.3 ± 7.6</td>
<td>65.2 ± 9.3</td>
</tr>
<tr>
<td>Multiple admin. (nonfasting)</td>
<td>150 t.i.d. for 7 days</td>
<td>6</td>
<td>27.8 ± 5.4</td>
<td>172.3 ± 5.6</td>
<td>63.6 ± 6.4</td>
</tr>
</tbody>
</table>

* Data represent means ± SDs.

CS-834 was administered 30 min after breakfast.

Five hundred milligrams of probenecid was administered orally 1 h before and 6 h after the drug administration of CS-834.

Three volunteers received placebo.

FIG. 2. Urinary excretion of total and free pivalic acid after multiple oral administration of 150 mg of CS-834 (t.i.d.). Data represent means ± SDs for six subjects.
Plasma protein binding. The plasma protein binding of R-95867 was determined by the ultrafiltration method. Plasma samples obtained from the volunteers at two time points (1 and 4 h after dosing) in the 200-mg-dose study were applied to the ultrafiltration units (Centrifree; Grace Japan, Tokyo, Japan) and centrifuged at 1,500 \( \times g \) for 10 min to obtain protein-free filtrate. The unbound fraction (FU) in plasma was calculated as the concentration in the filtrate divided by the concentration in plasma. The plasma protein binding rate was calculated by the formula \((1 - \text{FU}) \times 100\).

Pharmacokinetic and statistical analyses. The following model-independent pharmacokinetic parameters were calculated on the basis of the concentrations of R-95867 in plasma by using noncompartmental analysis: maximum concentration in plasma (\( C_{\text{max}} \)), time to reach \( C_{\text{max}} \) (\( T_{\text{max}} \)), area under the drug concentration curve over the last sampling period (AUC\(_{0-\infty}\)) or infinite time (AUC\(_{0-\infty}\)), calculated by using the trapezoidal rule with or without the terminal-phase extrapolation; apparent plasma clearance (CL\(_{\text{p,f}}\)), defined as dose/AUC\(_{0-\infty}\); mean residence time (MRT); and elimination half-life (\( t_{1/2} \)), calculated from the terminal slope (\( b \)) in the individual semilogarithmic plots of the concentration in plasma versus time by least-squares regression analysis.

The cumulative amount of R-95867 excreted into urine over 8 h (\( X_{0-8} \)) or 24 h (\( X_{0-24} \)) was calculated in each study and was expressed as a percentage of the dose administered. In the renal excretion mechanism study, the renal clearance (CLR) was calculated from the cumulative amount of R-95867 in urine and AUC. In the multiple-dose study, \( T_{\text{max}}, C_{\text{max}}, t_{1/2}, \) AUC\(_{0-6}, X_{0-6}, \) MRT, and CL\(_{\text{p,f}}\) were obtained from concentrations in plasma and excretion in urine on days 1, 4, and 7 after the first administration on each day. Two-way analysis of variance (ANOVA) was used for the comparison of pharmacokinetic parameters. Student’s paired \( t \) test was used to analyze the effect of food intake and to compare the values of the pharmacokinetic parameters obtained daily in the multiple-dose study. A \( P \) value of <0.05 was considered significant. Data are presented as means ± standard deviations (SDs).

RESULTS
Safety and tolerance. In the study with a single dose of 400 mg, a mild transient soft stool was observed in only one of six volunteers. In the multiple-dose study (150 mg t.i.d.), mild transient soft stools were observed in all six volunteers, one had mild transient diarrhea, and one had elevated serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels (1.4- and 2.8-fold compared with the upper limits of normal, respectively). These observations coincided with CS-834 administration, but they were not considered to be serious. All stools were formed, although the volunteers said they were a little softer than usual. During this study, no volunteer reported discomfort, and there was no elevation in the level of creatine phosphokinase or lactate dehydrogenase.

FIG. 3. Concentrations of total and free carnitine in plasma after multiple oral administrations of 150 mg of CS-834 t.i.d. for 7 days. Data represent means ± SDs for six subjects.

FIG. 4. Urinary excretion of total and free carnitine after multiple oral administrations of 150 mg of CS-834 t.i.d. for 7 days. Data represent means ± SDs for 6 subjects.

FIG. 5. Concentrations of R-95867 in plasma after administration of single oral doses of 50 mg, 100 mg, 200 mg, and 400 mg of CS-834. Data represent means ± SDs for six subjects.

FIG. 6. Concentrations of R-95867 in the plasma of fasted and nonfasted subjects after administration of a single oral dose of 100 mg of CS-834. Data represent means ± SDs for eight subjects.
There were no other abnormal findings for objective signs and laboratory findings, including blood pressure, heart rate, electrocardiogram, body temperature, hematology, blood chemistry, and urinalysis.

In the studies with single doses of 200 and 400 mg and in the multiple-dose study, the concentrations of total and free pivalic acid and carnitine in plasma were proportional to the concentration of R-95867 in plasma, although the concentration of free carnitine in plasma was not affected by CS-834 administration in the single-dose study (data not shown). The urinary excretion of total carnitine was also increased by CS-834 administration, but that of free carnitine was slightly decreased (data not shown).

In the multiple-dose study, total and free pivalic acid concentrations in plasma reached steady state on day 4 (data not shown). These concentrations decreased to almost zero 24 h after the final drug administration. The urinary excretion of total pivalic acid was increased by CS-834 administration and remained almost constant during the drug administration (Fig. 2). The concentrations of total and free carnitine in plasma gradually decreased and reached the minimum level on day 5 (Fig. 3). They recovered immediately and reached the normal point. The urinary excretion of total carnitine was increased by CS-834 administration and decreased rapidly after the final drug administration (Fig. 4). Free carnitine remained at low levels during the administration period. In the control group given the placebo tablet, changes in the concentrations of total and free carnitine in plasma were almost constant during the multiple-dose study (data not shown). Changes in urinary excretion were also small in the control group.

Single-dose pharmacokinetics. Figure 5 presents the concentrations of R-95867 in plasma after the oral administration of 50, 100, 200, and 400 mg of CS-834 to fasted subjects. Table 2 presents the values of the pharmacokinetic parameters examined in the study. The Cmax of R-95867 were attained at 1.1 to 1.7 h after drug administration, although lag times of almost 15 min for drug absorption at all doses were found (Table 2). The Cmax and AUC increased almost in proportion to the dose, whereas the Cmax for the highest dose was not proportional. The t1/2 was independent of the dose, and the value was approximately 0.7 h. The cumulative urinary excretion of R-95867 ranged from 27 to 34% of the dose. The plasma protein binding of R-95867 ranged from 16 to 20% and was almost constant and independent of the R-95867 concentration. CS-834 was undetectable in plasma at any sampling point.

The pharmacokinetics of R-95867 after intake of a light meal were compared with those in the fasting state. Figure 6 presents the plasma concentration-time profiles. Food intake slightly increased the AUC but resulted in no significant changes in Cmax, Tmax, t1/2, or the urinary recovery of R-95867 (Table 3). Probencid treatment changed the pharmacokinetics of R-95867. Figure 7 presents the plasma concentration-time profiles after the administration of CS-834 alone and after coadministration with probenecid. Table 4 presents the values of the pharmacokinetic parameters examined in the study obtained after coadministration of CS-834 and probenecid. Probencid treatment increased the Cmax and AUC by approximately 1.5- and 2.1-fold, respectively, and also prolonged Tmax. The t1/2 was increased from 0.77 h with the administration of CS-834 alone to 1.05 h with cotreatment with CS-834 and probenecid.

![FIG. 7. Concentrations of R-95867 in plasma after oral administration of CS-834 alone and after coadministration with probenecid. Data represent means ± SDs for six subjects.]

### Table 2. Pharmacokinetic parameters of R-95867 following administration of a single oral dose of CS-834 to fasted healthy male volunteers

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
<th>AUC0-24 (μg · h/ml)</th>
<th>X0-24 (%)</th>
<th>MRT (h)</th>
<th>CL/F (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.51 ± 0.17</td>
<td>1.08 ± 0.20</td>
<td>0.76 ± 0.21</td>
<td>0.94 ± 0.29</td>
<td>30.0 ± 7.8</td>
<td>1.72 ± 0.10</td>
<td>1.015 ± 0.53</td>
</tr>
<tr>
<td>100</td>
<td>0.97 ± 0.21</td>
<td>1.25 ± 0.27</td>
<td>0.73 ± 0.21</td>
<td>1.91 ± 0.21</td>
<td>32.5 ± 5.6</td>
<td>1.62 ± 0.21</td>
<td>0.883 ± 0.108</td>
</tr>
<tr>
<td>200</td>
<td>1.59 ± 0.55</td>
<td>1.38 ± 0.83</td>
<td>0.77 ± 0.12</td>
<td>3.30 ± 0.81</td>
<td>27.2 ± 5.6</td>
<td>1.98 ± 0.51</td>
<td>1.063 ± 0.268</td>
</tr>
<tr>
<td>400</td>
<td>2.51 ± 0.42</td>
<td>1.67 ± 0.26</td>
<td>0.66 ± 0.04</td>
<td>6.61 ± 0.77</td>
<td>33.5 ± 4.8</td>
<td>2.20 ± 0.24</td>
<td>1.021 ± 0.126</td>
</tr>
</tbody>
</table>

ANOVA<sup>b</sup> —<sup>c</sup> NS<sup>d</sup> NS NS NS NS

<sup>a</sup> Data represent means ± SDs for six subjects.
<sup>b</sup> One-way ANOVA.
<sup>c</sup> —, statistical comparison was not tried.
<sup>d</sup> NS, significant difference was not observed.

### Table 3. Influence of food intake on pharmacokinetics of R-95867 following administration of a single oral dose of CS-834 (100 mg) to healthy male volunteers

<table>
<thead>
<tr>
<th>State</th>
<th>Cmax (μg/ml)</th>
<th>Tmax (h)</th>
<th>t1/2 (h)</th>
<th>AUC0-24 (μg · h/ml)</th>
<th>X0-24 (%)</th>
<th>t test&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted</td>
<td>0.82 ± 0.23</td>
<td>1.56 ± 0.78</td>
<td>0.72 ± 0.17</td>
<td>1.65 ± 0.23</td>
<td>34.1 ± 7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Nonfasted</td>
<td>0.95 ± 0.23</td>
<td>1.50 ± 0.38</td>
<td>0.77 ± 0.19</td>
<td>2.00 ± 0.27</td>
<td>32.0 ± 7.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data represent means ± SDs for six subjects.
<sup>b</sup> Paired t test.
<sup>c</sup> NS, significant difference was not observed.
<sup>d</sup> Significant difference was observed with a risk probability of less than 5%.
Probenecid treatment did not affect the cumulative urinary excretion of R-95867 until 24 h after administration.

**Multiple-dose pharmacokinetics.** Figures 8 and 9 present the plasma concentration-time profiles for the multiple-dose study. Table 5 presents the values of the pharmacokinetic parameters obtained on days 1, 4, and 7. The values of the pharmacokinetic parameters obtained from concentrations in plasma were almost the same among those days; this was not the case for MRT, however. The MRT slightly decreased after repeated administrations of CS-834. The $C_{\text{max}}$s of R-95867 after the first drug administrations on days 1, 4, and 7 were 1.53 ± 0.52, 1.26 ± 0.27, and 1.35 ± 0.17 mg/ml, respectively, which were achieved at approximately 1.5 h after drug administration. The mean urinary excretion rates of R-95867 after each administration were almost constant. These values were almost the same as those obtained in the single-dose studies.

**DISCUSSION**

Throughout the entire investigation, no major abnormality attributable to CS-834 was observed. There were no abnormal objective or vital signs. There were no significant changes in the values of routine laboratory tests, which were thoroughly monitored. These indicate that CS-834 was well tolerated by healthy subjects.

In the single-dose study, the AUC was proportional to the dose, suggesting linear pharmacokinetics in terms of the extent of bioavailability. However, the prolonged $T_{\text{max}}$ and the leveled off $C_{\text{max}}$ in the study with the highest dose (400 mg) indicated a dose-dependent decrease in the rate of bioavailability. This phenomenon might be explained by either the low solubility of drug (less than 1 mg/ml) in gastric fluid or an energy-requiring, carrier-mediated transport mechanism. The latter, however, must be less possible for CS-834, because the saturable absorption usually accompanied a significant decrease in the extent of bioavailability, showing a nonlinear increase in AUC as a function of dose as well as $C_{\text{max}}$. A similar finding was also observed for an ester-type antibiotic prodrug, bacampicillin (6). The mean $t_{1/2}$ of R-95867 ranged between 0.66 and 0.77 h, and it was almost constant regardless of the dose administered. In the multiple-dose study, the pharmacokinetic parameters were virtually identical to those expected from the single-dose study. No significant difference in the values of $C_{\text{max}}$, AUC, and $t_{1/2}$ among days 1, 4, and 7 was observed. The MRT decreased slightly after the repeated administrations; however, no change in the extent of bioavailability was observed from these results. It is therefore suggested that there is no change in the safety of CS-834 as a result of repeated administration. The urinary recovery of R-95867 on each day was almost constant during the multiple-dose study. These results indicate that there is no significant change in pharmacokinetic parameters and no accumulation of the drug in the body when CS-834 is administered repeatedly. In the study with a single dose of 100 mg, of bioavailability. However, the prolonged $T_{\text{max}}$ and the leveled off $C_{\text{max}}$ in the study with the highest dose (400 mg) indicated a dose-dependent decrease in the rate of bioavailability. This phenomenon might be explained by either the low solubility of drug (less than 1 mg/ml) in gastric fluid or an energy-requiring, carrier-mediated transport mechanism. The latter, however, must be less possible for CS-834, because the saturable absorption usually accompanied a significant decrease in the extent of bioavailability, showing a nonlinear increase in AUC as a function of dose as well as $C_{\text{max}}$. A similar finding was also observed for an ester-type antibiotic prodrug, bacampicillin (6). The mean $t_{1/2}$ of R-95867 ranged between 0.66 and 0.77 h, and it was almost constant regardless of the dose administered. In the multiple-dose study, the pharmacokinetic parameters were virtually identical to those expected from the single-dose study. No significant difference in the values of $C_{\text{max}}$, AUC, and $t_{1/2}$ among days 1, 4, and 7 was observed. The MRT decreased slightly after the repeated administrations; however, no change in the extent of bioavailability was observed from these results. It is therefore suggested that there is no change in the safety of CS-834 as a result of repeated administration. The urinary recovery of R-95867 on each day was almost constant during the multiple-dose study. These results indicate that there is no significant change in pharmacokinetic parameters and no accumulation of the drug in the body when CS-834 is administered repeatedly. In the study with a single dose of 100 mg,
CS-834 was not detected in plasma. CS-834, an ester-type prodrug of R-95867, is supposed to be hydrolyzed rapidly by esterases to produce R-95867 during absorption through the intestinal wall.

It was reported that some β-lactam antibiotics with the pivalic moiety reduced the carminine level in skeletal muscle and increased total and free plasma carnitine concentrations (5). The changes in carnitine levels in plasma and urine in this study were almost comparable to those of other antibiotics with the pivalic moiety, which have already been used clinically (2), and no muscle pain or weakness was observed in any of the subjects.

The mean CL\text{R} of R-95867 observed in the single-dose study, 280 to 360 ml/min, was much greater than the normal creatinine clearance level (70 to 130 ml/min). Probenecid, a specific inhibitor of tubular secretion for organic anions, reduced the CL\text{R} of R-95867 by approximately 1.5- and 2.1-fold, respectively. This suggests that renal tubular secretion, as well as glomerular filtration, participated in the urinary excretion of R-95867.

In conclusion, CS-834 was well tolerated when given as a single oral dose of up to 400 mg and as multiple-doses of 150 mg t.i.d. for 7 days. It was absorbed orally and converted rapidly to the active metabolite, R-95867, during absorption through the intestinal wall. R-95867 was primarily eliminated in urine. CS-834 is expected to be an effective therapeutic agent in the treatment of various infectious diseases.