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In Vitro and In Vivo Antibacterial Activities of L-084, a Novel Oral Carbapenem, against Causative Organisms of Respiratory Tract Infections

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L-084 (a prodrug of LJC 11,036 [L-036]) is a new oral carbapenem. Here we compared the in vitro and in vivo antibacterial activities of L-036 with those of imipenem, faropenem, ceditoren-pivoxil, cefdinir, amoxicillin, and levofloxacin. The MICs at which 90% of the isolates were inhibited of L-036 against methicillin-susceptible staphylococci, *Streptococcus pneumoniae* including penicillin-resistant organisms, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae* including ampicillin-resistant organisms, *Legionella pneumophila*, and *Moraxella catarrhalis* were equal to or less than 1 μg/ml. In pharmacokinetics studies of L-084 in lungs of mice, the maximum concentration in serum, half-life, and area under the concentration-time curve of this drug were 9.09 μg/g of tissue, 6.18 h, and 31.0 μg · h/ml, respectively. In murine respiratory infection models of penicillin-susceptible and -resistant *S. pneumoniae* and *H. influenzae*, the efficacies of L-084 were better than those of reference drugs. Our results indicate that the in vitro high potency and good distribution in the lungs might be the underlying mechanisms of its efficacy in the murine model of pneumonia.

Carbapenems such as imipenem, meropenem, and panipenem, which are commercially available parenteral drugs, have broad-spectrum activity against both gram-positive and gram-negative bacteria. To date, there are many types of oral antimicrobial agents such as β-lactams, fluoroquinolones, and penems with broad antibacterial activities. Recently, there has been an increase in the incidence of community-acquired respiratory tract infections caused by penicillin-resistant *Streptococcus pneumoniae*, penicillinase-producing *Haemophilus influenzae*, and β-lactamase-nonproducing ampicillin-resistant *H. influenzae* (3, 13, 18). In addition, the incidence of infections caused by fluoroquinolone-resistant organisms also seems to have increased (1, 5, 14). These conditions highlight the need for novel antimicrobial agents active against these problematic pathogens. At present, various oral carbapenems such as GV118819X, CS-834, DZ-2640, and CL191,121 remain under development (12, 15, 16, 19, 20).

L-084, pivaloyloxymethyl(4R, 5S, 6S)-6-[(R)-1-hydroxyethyl]-4-methy-7-oxo-3-{[1-(1,3-thiazolin-2-yl)azetidin-3-yl]thio}-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, is a novel oral carbapenem synthesized at the Medical Research Laboratories, Lederle (Japan), Ltd., Saitama, Japan. In the study described here, we evaluated the in vitro antibacterial properties of LJC 11,036 (L-036) and the in vivo activities of L-084 (a prodrug of L-036) by using models of murine bronchopneumonia caused by *H. influenzae* and pneumonia caused by *S. pneumoniae*. We also compared the potency of this drug with those of faropenem, imipenem, levofloxacin, cefditoren-pivoxil (a prodrug of cefditoren), cefdinir, and amoxicillin.

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MATERIALS AND METHODS

Antimicrobial agents. The following antimicrobial agents, used in this study, were obtained from the indicated sources: L-036 and L-084, Wyeth Lederle Japan, Tokyo, Japan; faropenem, Suntory, Tokyo, Japan; imipenem, Banyu Pharmaceutical Co., Tokyo, Japan; levofloxacin, Daiichi Pharmaceutical Co., Tokyo, Japan; cefditoren and cefditoren-pivoxil, Meiji Seika Co., Tokyo, Japan; cefdinir and amoxicillin, Fujisawa Pharmaceutical Co., Osaka, Japan.

Microorganisms. The clinical isolates tested in this study were obtained from hospitals in several areas of Japan during 1995 and 1997. All organisms had previously been identified by routine laboratory methods and had been stored at −80°C.

In vitro susceptibility tests. The MICs of various antimicrobial agents for nonfastidious organisms were determined by the broth microdilution method in 0.1-ml volumes of cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) (8). For fastidious organisms such as *Streptococcus* spp., *Enterococcus* spp., and *Moraxella catarrharis*, cation-adjusted Mueller-Hinton broth supplemented with 5% lysed horse blood was used (9). For *Legionella pneumophila*, the MICs were determined by the microdilution method using *N*-(acetamide)-2-amino-ethanesulfonic acid-buffered yeast extract broth supplemented with 0.1% α-ketoglutaric acid, 0.04% L-cysteine, and 0.025% iron(III) diphosphate and adjusted to a final pH of 6.9. For *H. influenzae*, cation-adjusted Mueller-Hinton broth was supplemented with 5% lysed horse blood plus 5 mg of yeast extract (Oxoid, Hampshire, United Kingdom) per ml and 15 μg of NAD (Sigma Chemical Co., St. Louis, Mo.). For all strains except *L. pneumophila*, incubation was carried out for 18 to 24 h at 35°C. For *L. pneumophila*, incubation was performed for 116 h. Microdilution plates were inoculated with an automatic pin inoculator (MIC-2000; Dynatech Laboratories Inc., Alexandria, Va.) so that the final inoculum was approximately 5×10^5 CFU/ml. The MIC was defined as the lowest concentration of antimicrobial agent resulting in the complete inhibition of visible bacterial growth.

In vivo activity. The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Toho University School of Medicine. Four-week-old male Slc/ICR mice (weight, 18 to 20 g; SLC Japan Inc., Shizuoka, Japan) and 4-week-old male CBA/J mice (Charles River Japan, Shizuoka, Japan) were used. CBA/J mice are susceptible to intranasal infection caused by penicillin-resistant streptococcal pneumonia (17). The bacterial suspension was prepared as previously reported (20). *S. pneumoniae* organisms were inoculated in Todd-Hewitt broth (Difco) supplemented with 30% horse serum, and the mixture was incubated at 35°C until the culture became turbid to the naked eye. When the bacteria were in the late logarithmic phase, they were harvested by centrifugation at 2,000 × *g* for 10 min at 4°C. The organisms were suspended in

TABLE 1. Comparative in vitro activities of L-036 and reference drugs against clinical isolates

Organism (no. of strains)	Drug	MIC (μg/ml)[a]		
		Range	50%	90%
Staphylococcus aureus				
Methicillin-susceptible strains (43)	L-036	≤0.063	≤0.063	≤0.063
	Faropenem	≤0.063–0.25	0.125	0.25
	Imipenem	≤0.063	≤0.063	≤0.063
	Levofloxacin	0.125–1	0.25	0.5
	Cefditoren	0.5–4	1	1
	Cefdinir	0.25–4	0.5	0.5
	Amoxicillin	0.25–64	4	16
Methicillin-resistant strains (39)[b]	L-036	≤0.063–8	4	8
	Faropenem	0.125–>128	128	>128
	Imipenem	0.063–64	32	64
	Levofloxacin	0.125–>128	8	128
	Cefditoren	4–>128	64	128
	Cefdinir	0.125–>128	64	128
	Amoxicillin	8–128	64	64
Staphylococcus epidermidis				
Methicillin-susceptible strains (34)	L-036	≤0.063–1	≤0.063	0.125
	Faropenem	≤0.063–0.5	0.125	0.5
	Imipenem	≤0.063–0.125	≤0.063	0.125
	Levofloxacin	0.125–8	0.25	4
	Cefditoren	0.125–2	0.5	2
	Cefdinir	≤0.063–2	0.125	1
	Amoxicillin	0.125–8	0.5	2
Methicillin-resistant strains (30)[b]	L-036	0.5–8	2	8
	Faropenem	≤0.063–>128	2	>128
	Imipenem	0.25–64	4	64
	Levofloxacin	0.25–128	4	16
	Cefditoren	2–128	16	64
	Cefdinir	0.125–>128	16	128
	Amoxicillin	1–64	8	32
Streptococcus pneumoniae				
Penicillin-susceptible strains (66)	L-036	0.0005–0.032	0.002	0.032
	Faropenem	0.004–0.25	0.008	0.25
	Imipenem	0.002–0.25	0.008	0.125
	Levofloxacin	0.25–2	0.5	1
	Cefditoren	0.008–0.5	0.063	0.5
	Cefdinir	0.016–8	0.25	4
	Amoxicillin	0.008–0.5	0.032	0.5
Penicillin-resistant strains (32)[c]	L-036	0.032–0.5	0.063	0.125
	Faropenem	0.25–4	0.5	2
	Imipenem	0.25–2	0.25	1
	Levofloxacin	0.5–1	1	1
	Cefditoren	0.25–4	0.5	1
	Cefdinir	2–64	8	16
	Amoxicillin	1–8	2	4
Enterococcus faecalis (35)	L-036	0.25–2	0.5	2
	Faropenem	0.5–8	1	4
	Imipenem	8–>128	128	>128
	Levofloxacin	1–64	1	64
	Cefditoren	0.5–>128	32	>128
	Cefdinir	0.5–>128	4	64
	Amoxicillin	0.5–1	0.5	1
Enterococcus faecium (45)	L-036	2–>128	64	128
	Faropenem	4–>128	128	>128
	Imipenem	8–>128	128	>128
	Levofloxacin	1–128	16	64
	Cefditoren	64–>128	>128	>128
	Cefdinir	64–>128	>128	>128
	Amoxicillin	0.5–>128	64	64
Escherichia coli (42)	L-036	≤0.063	≤0.063	≤0.063
	Faropenem	0.125–2	0.5	0.5
	Imipenem	≤0.063–0.25	0.125	0.125
	Levofloxacin	≤0.063–64	≤0.063	8
	Cefditoren	≤0.063–1	0.25	0.5
	Cefdinir	≤0.063–1	0.125	0.5
	Amoxicillin	0.5–>128	4	>128
Klebsiella pneumoniae (34)	L-036	≤0.063–0.5	≤0.063	≤0.063
	Faropenem	0.25–4	0.5	0.5
	Imipenem	0.125–0.5	0.25	0.25
	Levofloxacin	≤0.063–4	≤0.063	0.25
	Cefditoren	≤0.063–64	0.25	0.5
	Cefdinir	≤0.063–128	0.125	0.25
	Amoxicillin	1–>128	64	>128
Haemophilus influenzae (38)	L-036	≤0.063–0.5	≤0.063	0.25
	Faropenem	0.125–4	0.5	1
	Imipenem	0.25–16	1	4
	Levofloxacin	≤0.063	≤0.063	≤0.063
	Cefditoren	≤0.063–0.25	≤0.063	≤0.063
	Cefdinir	0.25–4	0.5	2
	Amoxicillin	0.5–32	0.5	32
Legionella pneumophila (11)	L-036	≤0.063	≤0.063	≤0.063
	Faropenem	≤0.063	≤0.063	≤0.063
	Imipenem	≤0.063	≤0.063	≤0.063
	Levofloxacin	≤0.063	≤0.063	≤0.063
	Cefditoren	0.25–16	8	16
	Cefdinir	0.25–8	8	8
	Amoxicillin	≤0.063–1	0.5	1
Moraxella catarrhalis (34)	L-036	≤0.063	≤0.063	≤0.063
	Faropenem	≤0.063–1	0.25	0.5
	Imipenem	≤0.063–0.125	≤0.063	≤0.063
	Levofloxacin	≤0.063	≤0.063	≤0.063
	Cefditoren	≤0.063–0.5	0.25	0.5
	Cefdinir	0.125–0.5	0.25	0.5
	Amoxicillin	≤0.063–8	2	4

[a] 50% and 90%, MICs at which 50 and 90% of isolates were inhibited, respectively.
[b] Oxacillin MIC, ≥4 μg/ml.
[c] Amoxicillin MIC, ≥one μg/ml.

saline. Mice were anesthetized with ketamine-xylazine and then infected by intranasal instillation of 0.05 ml of *S. pneumoniae* TUH39 (MIC of penicillin G, 0.016 μg/ml; 9.6×10^7 CFU/ml) or *S. pneumoniae* TUM741 (MIC of penicillin G, 1.0 μg/ml; 5.1×10^5 CFU/ml). Since 4-week-old male ICR mice (body weight, about 20 g) were the most susceptible to intranasal infection caused by *H. influenzae* among test strains in preliminary experiments, mice of this strain were used in *H. influenzae* infections. An overnight culture of *H. influenzae* TMS8 was inoculated into brain heart infusion broth (Difco) supplemented with hemin and NAD, and the culture was incubated at 35°C for 3 h. The organisms in the culture were harvested by centrifugation and were suspended in RPMI 1640 medium to prepare cultures similar to the original. This bacterial suspension was added to MFL cell monolayers, and the monolayers were incubated at 35°C for 1 h with gentle shaking (10). Free-floating bacteria were removed and washed three times with saline. Then, cell-bound organisms (CBOs) were removed from the flask and suspended in RPMI 1640 medium. Three days after treatment with formalin, mice were anesthetized with ketamine-xylazine and then infected by intranasal instillation of 0.05 ml of *H. influenzae* TUM8 CBOs (4.2×10^5 CFU/ml). The inocula of *S. pneumoniae* TUH39 organisms caused 100% mortality in untreated animals at 72 to 116 h after infection. Antimicrobial drugs were administered orally once at 20 h after intranasal instillation of *S. pneumoniae* TUH39 organisms. The total number of surviving mice at each dose was recorded on day 7 after infection. The 50% effective dose (ED50) of each drug was calculated by the probit method. Oral administration of drugs commenced 2 days after infection and was continued for 3 days, with the drugs being given once a day, twice a day (at 12-h intervals), or three times a day (at 6-h intervals) for *S. pneumoniae* TUM741 and *H. influenzae* TUM8 infections. Animals were sacrificed 20 h after the last administration of the test drug (in order to minimize the influence of the administered drug), and the infected tissues were dissected and homogenized.

TABLE 2. Therapeutic efficacy of L-084 and reference drugs in murine respiratory tract infections caused by penicillin-susceptible *S. pneumoniae* TUH39[a]

Antimicrobial agent	MIC[b] (mg/ml)	ED_{50}[c](95% confidence limits) (mg/kg)
L-084	0.0005	1.95 (1.34–3.00)
Faropenem	0.001	>20
Cefdinir	0.125	>20
Cefditoren-pivoxil	0.016	>20
Amoxicillin	0.004	>20

[a] The challenge dose was 1.5×10^6 CFU/mouse, administered by intranesal instillation.
[b] Broth microdilution method (inoculum size: 10^5 CFU/ml).
[c] ED_{50}s were calculated by the probit method based on the survival rate at 7 days after infection.

The number of viable organisms (number of CFU per lung) was determined by agar plating. Evaluation of efficacy was based on the proportional reduction of bacterial counts in the infected tissues of treated animals compared with those in infected tissues of untreated animals. The statistical significance of the observed differences was determined by the Mann-Whitney U test.

Pharmacokinetic studies with mice. One day after infection with *S. pneumoniae* TUH39, groups of three mice each orally received L-084 at a single dose of 50 mg/kg of body weight because this dosage was used for evaluation of L-084 in murine respiratory infection by *S. pneumoniae* or *H. influenzae*. Samples of heart blood as well as lung tissues were obtained 5, 15, and 30 min and 1, 2, 4, 6, and 24 h after drug administration. The lungs were briefly washed with saline in order to minimize contamination with blood. The levels of L-036 in serum and tissues were determined by a paper disk method, with *Staphylococcus aureus* Terajima as the indicator organism for L-036; the indicator organisms were incorporated into the medium (heart infusion agar; Difco).

RESULTS

In vitro antibacterial activity. Table 1 compares the in vitro activities of L-036 to those of other drugs tested against a variety of clinical isolates. L-036 exhibited high potency against methicillin-susceptible isolates of both *S. aureus* and *Staphylococcus epidermidis*, but the activities of L-036 against methicillin-resistant staphylococci were lower than those against methicillin-susceptible staphylococci. L-036 was more potent against penicillin-susceptible and -resistant *S. pneumoniae* than all compared drugs by a factor of 4 or more. For *Enterococcus faecalis*, L-36 was more potent than faropenem, levofloxacin, cefditoren, and cefdinir but was similar to imipenem and less active than amoxicillin. For both *Escherichia coli* and *Klebsiella pneumoniae*, L-036 was twice or more as active as all reference drugs. L-036 was more active against *H. influenzae* than faropenem, imipenem, cefdinir, and amoxicillin but was less active than levofloxacin and cefditoren. For *L. pneumophila* and *M. catarrhalis*, L-036 was the drug showing the most potent activity.

In vivo efficacy in mice. The in vivo activity of L-036 against penicillin-susceptible *S. pneumoniae* TUH39 was only twice that of faropenem but higher than those of other reference drugs (Table 2). Against respiratory tract infections induced by instillation of this strain, L-084 alone was very potent and effective. When infection was caused by penicillin-resistant *S. pneumoniae* TUM741, the mean number of bacteria recovered from the lungs of untreated mice was 7.36 ± 1.19 log CFU/lung (Table 3). In comparison, the number in mice treated with L-084 at a dosage of 50 mg/kg three times a day for 3 days was below the detection limits. On the other hand, treatment with 50 mg of amoxicillin/kg significantly reduced the number of recovered bacteria compared to that recovered from untreated animals and animals treated with faropenem, cefditoren-pivoxil, and cefdinir at the corresponding dose. Moreover, treatment with L-084 at a dose of 10 mg/kg resulted in a significant reduction in the number of bacteria compared with that in the lungs of untreated animals and animals treated with faropenem, cefditoren-pivoxil, cefdinir, and amoxicillin at the corresponding dose.

TABLE 3. Therapeutic efficacy of L-084 and reference drugs against murine respiratory tract infection caused by penicillin-resistant *S. pneumoniae* TUM741

Drug	MIC (μg/ml)	Dose[d] (mg/kg)	Log CFU/lung (mean ± SD)
Control			7.36 ± 1.19
L-084	0.032	50	BD[a]
		10	2.53 ± 0.48[b]
Faropenem	0.25	50	6.72 ± 1.21
		10	7.90 ± 2.11
Cefditoren-pivoxil	0.25	50	6.93 ± 0.75
		10	8.42 ± 0.56
Cefdinir	2.0	50	6.74 ± 0.69
		10	7.45 ± 1.03
Amoxicillin	1.0	50	4.26 ± 0.70[c]
		10	7.21 ± 0.72

[a] BD, below the lower limit of detection.
[b] $P < 0.01$ versus control and faropenem-, cefditoren-pivoxil-, cefdinir-, and amoxicillin-treated groups at the corresponding dose.
[c] $P < 0.05$ versus control and faropenem-, cefditoren-pivoxil-, and cefdinir-treated groups at the corresponding dose.
[d] Drugs were administered orally three times a day for 3 days.

When infection was induced by instillation of penicillinase-nonproducing *H. influenzae* TUM8, the mean number of bacteria recovered from the lungs of untreated mice was 6.97 ± 1.01 or 6.91 ± 0.97 log CFU/lung (Table 4). Treatment with L-084, cefditoren-pivoxil, and amoxicillin at a dose of 20 mg/kg led to significant reductions ($P < 0.05$) in the numbers of organisms in the lungs compared with those from untreated animals and animals treated with faropenem and cefdinir at the corresponding dose. In addition, treatment with L-084 and

TABLE 4. Therapeutic efficacy of L-084 and reference drugs against murine respiratory tract infection caused by *H. influenzae* TUM8

Drug	MIC (mg/ml)	Dose[c] (mg/kg)	Log CFU/lung (mean ± SD)
Control		20	6.97 ± 1.01
		4	6.91 ± 0.97
L-084	0.016	20	2.28 ± 0.01[a]
		4	2.57 ± 0.68[b]
Faropenem	0.25	20	5.32 ± 1.75
		4	5.25 ± 1.12
Cefditoren-pivoxil	0.002	20	2.28 ± 0.01[a]
		4	3.40 ± 0.43[b]
Cefdinir	0.25	20	4.72 ± 0.50
		4	6.09 ± 0.76
Amoxicillin	0.25	20	3.72 ± 1.27[a]
		4	5.95 ± 0.63

[a] $P < 0.05$ versus control and faropenem- and cefdinir-treated groups at the corresponding dose.
[b] $P < 0.01$ versus control and faropenem-, cefdinir-, and amoxicillin-treated groups at the corresponding dose.
[c] Drugs were administered orally twice a day for 3 days.

cefditoren-pivoxil at a dose of 4 mg/kg resulted in significant reductions ($P < 0.01$) in the numbers of organisms compared to those from untreated animals and animals treated with faropenem, cefdinir, and amoxicillin at the corresponding dose.

Effect of frequency of drug administration on the efficacy of L-084. In mice infected with pneumonia caused by penicillin-resistant *S. pneumoniae* TUM741, the number of organisms in the lungs of those treated with L-084 three times a day (6-h intervals), with each dose being 5 mg/kg (total daily dose, 15 mg/kg), was 2.40 ± 1.26 log CFU/lung. The numbers in mice treated with the same daily dose but administered twice a day (12-h intervals, each 7.5 mg/kg) or once a day (15 mg/kg) were 2.13 ± 1.06 and 3.06 ± 0.74 log CFU/lung, respectively. There was no significant difference in the efficacy of the drug between these three regimens.

Pharmacokinetics in pneumonic mice. When the concentrations of L-036 in the plasma and lungs of mice infected with *S. pneumoniae* TUH39 were calculated, the maximum concentrations of L-036 in the lungs and serum (C_{max}) were 9.03 μg/g of tissue and 51.24 μg/ml, respectively. The areas under the concentration-time curve (AUC) for L-084 in the lungs and serum were 31.0 and 142.2 μg × h/ml, respectively. The half-lives ($t_{1/2}$) of L-084 in the lungs and serum were 6.18 and 3.88 h, respectively.

DISCUSSION

Hikita et al. (6) reported that L-036 was more potent than imipenem, faropenem, and cefdinir against the main organisms of respiratory and urinary tract infections such as those due to *S. pneumoniae*, *Streptococcus pyogenes*, *H. influenzae*, *K. pneumoniae*, *M. catarrhalis*, and *E. coli*. The present results were similar to those from the above study and indicated that L-036 concentration was maintained at ≥1 μg/g in the lungs for at least 6 h after oral administration of 50 mg/kg. In addition, the MICs of L-036 at which 90% of the isolates of methicillin-susceptible staphylococci, *S. pneumoniae* including penicillin-resistant organisms, *E. coli*, *K. pneumoniae*, *H. influenzae*, *L. pneumophila*, and *M. catarrhalis* were inhibited were <1 μg/ml. *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are commonly isolated respiratory tract infections, with ever-increasing levels of antimicrobial resistance among isolates (4). It is well known that β-lactams have not been useful in treating *Legionella* infections because of poor penetration into host cells. Thus in vitro activity of L-036 dose not ensure in vivo activity of L-084 agaisnt *Legionella* infection. Collectively, these data indicate that this novel oral carbapenem has a potentially significant role in the treatment of community-acquired respiratory infections except for *Legionella* infection.

In general, oral fluoroquinolones and oral expanded-spectrum cephems have been used clinically for the treatment of community-acquired infections. The results indicate that fluoroquinolene-resistant organisms tend to increase with increased use of these agents. In addition, other reports have described extended-spectrum β-lactamaso-producing *Enterobacteriaceae* isolated from specimens (2, 7). These data indicate that novel antimicrobial agents showing highly potent activity against drug-resistant organisms are needed for patients infected with those organisms.

As stated above, new oral carbapenems have been developed recently. The ED_{50}s of CS-834 and sanfetrinem-cilexetil, when administered orally in mice infected with *S. pneumoniae* TUH39 twice a day for 3 days or twice a day for 2 days, were 1.78 and 0.18 mg/kg, respectively (15, 20). The former value was similar to, and the latter was 1/10 of, the ED_{50} of L-084 when this drug was orally administered once. The in vitro activity of L-084 against this strain was 32 times more potent than that of CS-834 and 8 times more potent than that of sanfetrinem-cilexetil. Oral administration of each of these drugs at a dose of 10 mg/kg to mice infected with *S. pneumoniae* TUM741 three times or twice a day for 3 days produced a differential effect. The number of bacteria recovered from the lungs of mice treated with L-084 was significantly lower than the control, but those from the lungs of mice treated with sanfetrinem-cilexetil and CS-834 were not different from the control. The in vitro activity of L-084 was 8 and 16 times more potent than those of sanfetrinem-cilexetil and CS-834, respectively. When L-084 or CS-834 was administered orally to mice infected with *H. influenzae* TUM8 at a dose of 20 mg/kg twice a day for 3 days, the percent reduction in the number of viable bacteria in lungs of mice treated with L-084 was a little higher than that in lungs of mice treated with CS-834, and the in vitro activity of L-084 was 8 times more potent than that of CS-834. These results indicate that, in murine respiratory infection models with *S. pneumoniae* and *H. influenzae*, the efficacy of L-084 is better than those of other drugs because the in vitro activity of L-084 against infecting organisms is more potent than those of other drugs.

Previous studies have shown that C_{max}, $t_{1/2}$, and AUC of sanfetrinem-cilexetil in lung tissues were 1.94 μg/ml, 0.41 h, and 1.52 μg × h/ml, respectively (15). On the other hand, C_{max} and AUC of CS-834 in lung tissues were 0.9 μg/ml and 0.7 μg × h/ml, respectively (20). Our results showed that the C_{max} of L-084 was 5 to 10 times higher than those of the above two drugs, that $t_{1/2}$ of L-084 was 15 times longer than that of sanfetrinem, and that the AUC of L-084 was 20 to 44 times larger than those of the above two drugs. The better pharmacokinetic parameters of L-084 in lungs of mice infected with *S. pneumoniae* also favor this agent for respiratory infection models.

In conclusion, we have demonstrated in the present study that L-084 is a promising novel oral carbapenem for the treatment of respiratory tract bacterial infections. Our findings for animals need to be confirmed in clinical trials before any conclusions regarding the efficacy of L-084 in human pulmonary infectons can be made.

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