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Comparison of the Pharmacodynamics of Biapenem in Bronchial Epithelial Lining Fluid in Healthy Volunteers Given Half-Hour and Three-Hour Intravenous Infusions▽

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The time above the MIC (*T*>MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) parameter that correlates with the therapeutic efficacy of beta-lactam antibiotics. A prolonged infusion can provide plasma drug concentrations that remain above the MIC for a long period. The objective of this study was to compare the PK/PD parameters in bronchial epithelial lining fluid (ELF) of biapenem given as 0.5-h and 3-h infusions by using bronchoscopic microsampling (BMS). Six healthy adult volunteers received 0.5-h and 3-h infusions of 0.3 g of biapenem with a washout interval. BMS was performed repeatedly from 0.5 to 24 h after biapenem administration in order to determine the pharmacokinetics in bronchial ELF. The subjects received intravenous biapenem with the same regimens again and then underwent bronchoalveolar lavage (BAL) at the end of infusion in order to determine the concentration of the drug in alveolar ELF. The percentages (means ± standard deviations) of *T*>MIC in bronchial ELF at MICs from 0.25 to 4 μg/ml ranged from zero to 34.6% ± 5.2% after the 0.5-h infusion and from 5.1% ± 5.6% to 52.2% ± 17.0% after the 3-h infusion. The percentage of *T*>MIC in bronchial ELF after the 3-h infusion tended to be higher than that after the 0.5-h infusion. The concentrations of the drug in alveolar ELF after 0.5-h and 3-h infusions were 3.5 ± 1.2 μg/ml and 1.3 ± 0.3 μg/ml, respectively. The present results support the use of prolonged infusions of beta-lactam antibiotics and may provide critical information for successful treatment of lower respiratory tract infections based on PK/PD parameters in bronchial ELF.

In order to maximize therapeutic antibacterial effects, antibiotics should be used based on their pharmacokinetic (PK) and pharmacodynamic (PD) parameters (2, 7). Moreover, PK/PD parameters at a potential site of infection are considered to be important because the distributions of antibiotics may differ in different tissues (23). With respect to lower respiratory tract infections, antibiotics must sufficiently penetrate target sites of infection, such as the epithelial lining fluid (ELF), which covers the epithelial lining airways and constitutes a first line of defense against inhaled pathogens (4).

Biapenem is a carbapenem antibacterial agent with a broad spectrum of activity against gram-negative, gram-positive, and anaerobic bacteria (24). The main PK/PD parameter that correlates with the therapeutic efficacy of beta-lactam antibiotics, including carbapenems, is the time above the MIC (*T*>MIC) (8, 31). Some PK/PD data suggest that continuous or prolonged infusions of beta-lactam antibiotics may maximize the *T*>MIC. A 3-h infusion of meropenem was reported to give a higher *T*>MIC in plasma than a bolus injection (14). In addition, several clinical studies have suggested that prolonged infusion of beta-lactams offers clinical and bacteriological advantages for critically ill patients, including those with pulmonary infections (15, 21, 22, 26). However, little is known about the PK/PD profile of beta-lactams in bronchial ELF and how well these drugs penetrate into bronchial regions when given intravenously by prolonged infusion.

Bronchoscopic microsampling (BMS) is a technique for sampling ELF directly and repeatedly on the surface of a bronchus by using a polyester fiber rod probe (13). Using this sampling technique, we have described the concentration-time profiles of oral antibiotics, such as levofloxacin (30), gatifloxacin (18), telithromycin (19), and clarithromycin (17), in bronchial ELF.

We conducted the present study using the BMS method to compare the PK/PD parameters in bronchial ELF of biapenem given by 3-h and 0.5-h intravenous infusions. Our aim was to clarify the impact of prolonged infusion on the pharmacokinetics and pharmacodynamics of the drug in ELF in order to optimize biapenem use in the clinical treatment of lower respiratory tract infection.

MATERIALS AND METHODS

Study design and subjects. The present study was a prospective, nonblinded crossover study of the concentration profiles of biapenem in the bronchial ELF, alveolar ELF, and plasma of healthy adults. The study was conducted with six healthy, nonsmoking adult volunteers who had no clinical illness in the 2 weeks prior to the study and no history of other significant diseases. All study protocols were approved by the institutional ethics committee of the Hokkaido University School of Medicine, and written informed consent was obtained from each subject before entry into the study.

Each subject received an intravenous infusion of a single 0.3-g dose of biapenem diluted into 100 ml of normal saline via an infusion pump at a constant rate over 0.5-h and 3-h periods, with a washout interval of at least 1 week between studies. BMS and venipuncture were performed at 0.5, 1, 2, 3, 4, 6, 8,

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and 24 h after the start of biapenem infusion. Two to 3 months later, the same subjects again received single-dose intravenous infusions of biapenem over 0.5-h and 3-h periods, with a washout interval of at least 1 week, and underwent bronchoalveolar lavage (BAL) at the end of infusion.

BMS under bronchoscopy. Bronchial ELF sampling was performed with the BMS probe under bronchoscopy as described previously (17, 30). Briefly, after local anesthesia using 4% liquid lidocaine, a BC-402C BMS probe (Olympus Medical Systems, Tokyo, Japan) was inserted through the working channel of a flexible fiber optic bronchoscope into a subsegmental or subsubsegmental bronchus of the right lower lobe. The inner probe was then advanced into the distal airway, and the bronchial ELF was sampled by gently placing the probe at a targeted site on the bronchial wall for 10 s. The wet inner probe was sectioned 2 cm from the tip. For each subject, three sectioned probes from one time point were placed in a preweighed tube and weighed. A dilute solution was prepared by adding 2 ml of saline to the tube and vortexing for 1 min. The solution was transferred to a new tube and was stored at −80°C. The probe was then dried and weighed again to measure the volume of ELF recovered. In vitro experiments confirmed that the mean recovery ± standard deviation (SD) from the BMS probe absorbing 1-μg/ml biapenem solution was 93.7% ± 9.7%.

BAL under bronchoscopy. Standard BAL was performed at the end of intravenous administration of biapenem by using 150 ml of 0.9% saline divided into three 50-ml aliquots. The aspirate from the first lavage was discarded to avoid contamination with proximal airway fluid and cells, and the remaining aliquots were pooled for analysis. The lavage fluid was centrifuged immediately at 400 × *g* for 15 min, and the supernatant was immediately separated from the cells. Approximately 2 ml of the supernatant was removed to measure the urea level in the lavage sample, and the remainder of the supernatant was used to measure the concentration of biapenem. The supernatants were frozen at −80°C until the assay.

Blood samples. A blood sample for the biapenem and urea assays was collected at the same time that BMS or BAL was performed. The plasma and serum were separated immediately at 4°C and 1,000 × *g* for 15 min and were frozen until the assays for drug and urea concentrations, respectively, were performed.

Biapenem assay. Plasma biapenem concentrations were determined by high-performance liquid chromatography with UV absorbance detection. Plasma samples were transferred to an ultrafiltration device and centrifuged. Then 40 μl of the filtered solution was injected into a Waters Alliance 2690 chromatograph system using a YMC-Pack ODS-A A-303 column and a UV absorbance detector set at 300 nm. The mobile phase consisted of 98% 0.1 M acetic acid–sodium acetate (pH 5.5) and 2% acetonitrile at a flow rate of 1.0 ml/min. Calibration curves were linear in the range from 0.1 to 50 μg/ml with correlation coefficients of more than 0.99. The coefficients of variation for quality control samples at 0.1 and 50 μg of biapenem/ml were 3.2% and 0.3%, respectively. The lower limit of quantification of the present assay method was 0.1 μg/ml. The range of accuracy of the assay method was 98.1 to 103.3% at the lower limit of quantification.

Biapenem concentrations in the BAL fluid supernatant and a dilute solution of bronchial ELF were measured using liquid chromatography methods coupled to a tandem mass spectrometry system assay. Meropenem (Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan) was used as an internal standard at a concentration of 100 ng/ml in a buffer with 300 mmol of MOPS (3-morpholinopropanesulfonic acid)/liter (pH 5.5). The internal standard was added to samples, and the mixture was centrifuged at 20,000 × *g* for 5 min at 4°C. Then 15 μl of the supernatant was injected into the liquid chromatography–tandem mass spectrometry system.

Biapenem was chromatographically separated on an analytical column (L-column ODS; 150 mm by 2.1 mm; inner diameter, 5 μm) using a gradient of 10 mmol/liter ammonium formate–acetonitrile as the mobile phase at room temperature. The mass spectrometer was operated in positive-ion mode using the Turbo-Spray interface. Biapenem and meropenem (internal standard) were monitored as product ions at 262.5 *m/z* and 141.2 *m/z*, respectively. The coefficients of variation for quality control BAL fluid supernatant samples at 0.5 and 80 μg of biapenem/ml were 7.3% and 14.5%, respectively. The coefficients of variation for quality control bronchial ELF samples at 0.5 and 80 μg of biapenem/ml were 9.9% and 11.7%, respectively. The lower limit of quantification of the present assay method was 0.25 ng/ml. The range of accuracy of the assay method was 93.6 to 104.0% at the lower limit of quantification.

The assays in the present study measured total (free and protein-bound)-antibiotic concentrations in plasma, bronchial ELF, and alveolar ELF. Since biapenem showed only minimal serum protein binding (3.7% after a single 300-mg dose in six volunteers) (24), we did not differentiate between free and protein-bound fractions.

Quantification of the volume of ELF and the concentrations of antibiotics. Since the bronchial ELF sampled by the BMS probe was diluted with 2 ml of saline, the concentrations of antibiotic in bronchial ELF ($ABX_{br\text{-}ELF}$) were calculated as $ABX_{BMS} \times (2 + V_{br\text{-}ELF})/V_{br\text{-}ELF}$, where ABX_{BMS} is the measured concentration of the antibiotic in the saline-diluted sample and $V_{br\text{-}ELF}$ is the volume of bronchial ELF recovered by the BMS probe (13, 30).

The amount of alveolar ELF sampled by BAL was estimated using the urea dilution method (25). Concentrations of urea in serum and BAL fluid supernatants were analyzed using a commercially available assay kit (Urea Nitrogen B test; Wako Pure Chemical Industries, Osaka, Japan).

Antibiotic concentrations in alveolar ELF ($ABX_{al\text{-}ELF}$) were calculated as $ABX_{BAL} \times (Urea_{serum}/Urea_{BAL})$, where ABX_{BAL} is the measured concentration of antibiotic in BAL fluid, and $Urea_{serum}$ and $Urea_{BAL}$ are the concentrations of urea in serum and BAL fluid, respectively.

Calculation of parameters and statistical analysis. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule. The percentage of $T>$MIC was defined as the percentage of a 12-h period, the manufacturer's recommended dosing interval, when the concentrations of an antibiotic exceeded its MIC. The percentage of $T>$MIC was calculated from the individual concentration-time curves for MICs of 4, 2, 1, 0.5, and 0.25 μg/ml. The ratio of the $ABX_{al\text{-}ELF}$ to the maximum concentration of the drug (C_{max}) in plasma and the ratio of the C_{max} in bronchial ELF to the C_{max} in plasma were calculated for each individual subject as parameters to represent the penetration of tissues by the antibiotic. Paired *t* tests were used to compare drug concentrations after a 0.5-h infusion with those after a 3-h infusion. The results are presented as means ± SDs, unless otherwise stated. *P* values of <0.05 were considered statistically significant.

RESULTS

Six volunteers (five male, one female) were enrolled in the study. Their mean age was 23.8 years (range, 23 to 24 years), and their mean body mass index was 20.1 kg/m^2 (range, 19.0 to 22.8 kg/m^2). Intravenous administration of biapenem was well tolerated, and no adverse effects were encountered. No complications were observed with the BMS and BAL procedures.

The volume of bronchial ELF recovered by the BMS probe totaled 26.4 ± 16.8 μl from three sectioned probes. Since the samples were diluted with 2 ml of saline, the dilution factor was 110 ± 73. Drug concentrations in all samples were successfully measured.

The concentration-time plots of total (free and protein-bound) biapenem in plasma and bronchial ELF for the 0.5-h and 3-h infusions are shown in Fig. 1. The PK/PD parameters for the 0.5-h and 3-h infusions of biapenem are presented in Tables 1, 2, and 3. The mean C_{max} of biapenem in plasma was significantly higher after the 0.5-h infusion than after the 3-h infusion ($P < 0.05$), and there was no significant difference between the AUCs in plasma after the 0.5-h and 3-h infusions. In contrast, the C_{max} in bronchial ELF was slightly higher after the 3-h infusion than after the 0.5-h infusion ($P = 0.12$), although this difference was not statistically significant. The AUC in bronchial ELF tended to be higher after the 3-h infusion than after the 0.5-h infusion ($P = 0.078$).

There were significant differences between the percentages of $T>$MIC in plasma after 0.5-h and 3-h infusions at all MICs between 0.25 μg/ml and 4 μg/ml ($P < 0.05$). The percentage of $T>$MIC in bronchial ELF tended to be higher after a 3-h infusion than after a 0.5-h infusion. There was a significant difference in the percentage of $T>$MIC in bronchial ELF after infusion between the 0.5- and 3-h infusions at a MIC of 0.5 μg/ml ($P = 0.021$).

Biapenem concentrations in alveolar ELF collected by BAL after 0.5-h and 3-h infusions were 3.48 ± 1.20 μg/ml and 1.33 ± 0.26 μg/ml, respectively ($P = 0.011$). The ratios of the concen-

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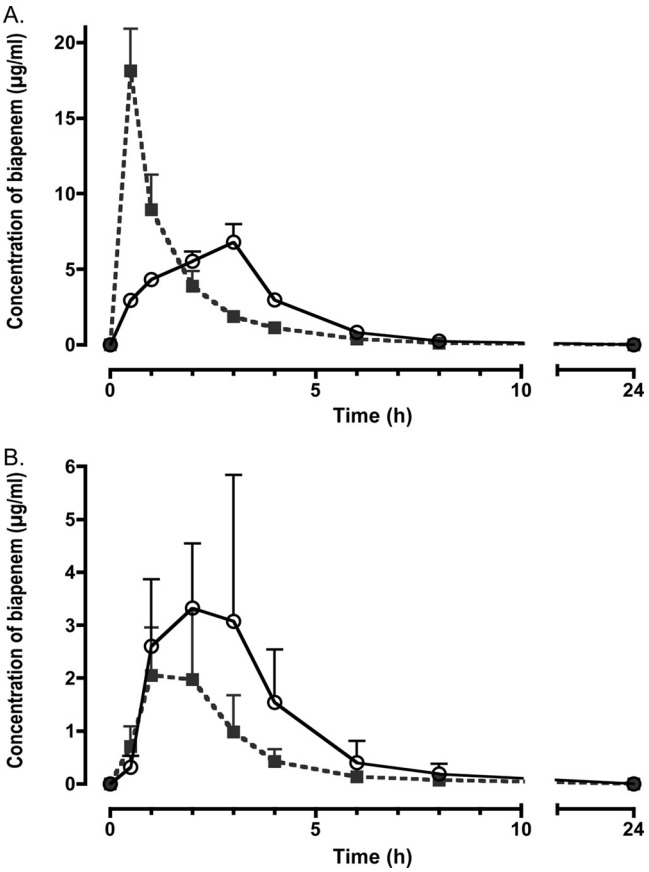

FIG. 1. Mean concentration-time data of total (free and protein-bound) biapenem in plasma (A) and bronchial ELF (B) for six healthy adult volunteers following single intravenous infusions of 0.3 g of biapenem for 0.5 h (filled squares) and for 3 h (open circles). Error bars indicate SDs.

tration of the drug in alveolar ELF to the C_{max} in plasma after 0.5-h and 3-h infusions were 0.20 ± 0.08 and 0.20 ± 0.06, respectively. The ratios of the C_{max} in bronchial ELF to the C_{max} in plasma after 0.5-h and 3-h infusions were 0.13 ± 0.05 and 0.63 ± 0.22, respectively.

TABLE 2. PK parameters of biapenem in plasma, bronchial ELF, and alveolar ELF following single intravenous infusions of 0.3 g of biapenem for 0.5 h and 3 h

Parameter	Value (mean ± SD) with a:		*P* value
	0.5-h infusion	3-h-infusion	
Plasma			
C_{max} (μg/ml)	18.1 ± 2.8	6.8 ± 1.2	<0.01
T_{max} (h)	0.5 ± 0.0	3.0 ± 0.0	
AUC (μg · h/ml)	25.0 ± 4.5	25.4 ± 1.9	0.77
Bronchial ELF			
C_{max} (μg/ml)	2.35 ± 1.06	4.36 ± 2.07	0.12
T_{max} (h)	1.5 ± 0.6	1.8 ± 1.0	0.58
AUC (μg · h/ml)	6.4 ± 2.2	13.3 ± 6.4	0.078
Concn of drug (μg/ml) in alveolar ELF	3.48 ± 1.20	1.33 ± 0.26	0.011

DISCUSSION

Jaruratanasirikul and Sriwiriyajan demonstrated that an intravenous 3-h infusion of meropenem gave a higher $T>$MIC in plasma than an intravenous bolus infusion (14). However, little is known about the PK/PD parameters of biapenem in ELF and the impact of a prolonged infusion on the ELF PK/PD parameters. Using the BMS method, the present study evaluated the pharmacokinetics of biapenem in the bronchial ELF of healthy adult volunteers after a single intravenous infusion and demonstrated that a single 3-h infusion of biapenem tended to produce a higher $T>$MIC in bronchial ELF, as well as in plasma, than a 0.5-h infusion.

Unexpectedly, the C_{max} in bronchial ELF was slightly higher after a 3-h infusion than after a 0.5-h infusion, while the C_{max} in plasma and the concentration of the drug in alveolar ELF were significantly lower after a 3-h infusion than after a 0.5-h infusion. In addition, the bronchial-ELF-to-plasma penetration ratios for 0.5-h and 3-h infusions were 13% and 62%, respectively, while the alveolar-ELF-to-plasma penetration ratios after 0.5-h and 3-h infusions of biapenem were both 20%. Why these discrepancies exist between bronchial ELF and

TABLE 1. PK parameters of biapenem in plasma, bronchial ELF, and alveolar ELF for each individual subject following single intravenous infusions of 0.3 g of biapenem for 0.5 h and 3 h

Duration of biapenem infusion and subject	Plasma			Bronchial ELF			Concn of drug in alveolar ELF (μg/ml)
	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	C_{max} (μg/ml)	T_{max} (h)	AUC (μg · h/ml)	
0.5 h							
Subject 1	16.1	0.5	20.1	2.32	1	4.6	5.25
Subject 2	18.5	0.5	25.6	2.10	1	5.9	4.70
Subject 3	20.1	0.5	27.6	1.39	2	5.3	3.10
Subject 4	14.1	0.5	19.8	1.10	1	4.6	2.41
Subject 5	21.9	0.5	31.7	3.64	2	10.2	2.93
Subject 6	18.0	0.5	25.4	3.53	2	7.7	2.46
3 h							
Subject 1	6.2	3	24.2	4.53	3	13.5	1.24
Subject 2	8.9	3	26.3	7.97	3	19.1	1.20
Subject 3	6.3	3	24.9	5.22	2	22.7	1.33
Subject 4	5.5	3	22.7	2.84	1	8.9	1.57
Subject 5	7.3	3	28.4	3.28	1	8.3	0.97
Subject 6	6.6	3	25.7	2.32	1	7.3	1.67

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TABLE 3. Percentages of time above the MIC in plasma and bronchial ELF following single intravenous infusions of 0.3 g of biapenem for 0.5 h and 3 h

MIC (μg/ml)	$T>$MIC (%)[a] with a:		*P* value
	0.5-h infusion	3-h infusion	
In plasma			
4	12.6 ± 2.1	22.3 ± 2.9	<0.001
2	21.1 ± 2.6	34.3 ± 1.1	<0.001
1	31.9 ± 3.5	43.8 ± 1.1	<0.001
0.5	43.1 ± 4.3	53.7 ± 1.6	0.003
0.25	53.5 ± 8.2	64.5 ± 3.8	0.024
In bronchial ELF			
4	0.0 ± 0.0	5.1 ± 5.6	0.077
2	5.8 ± 8.0	17.4 ± 9.7	0.13
1	15.5 ± 6.3	29.1 ± 9.8	0.054
0.5	25.5 ± 4.2	41.4 ± 12.1	0.021
0.25	34.6 ± 5.2	52.2 ± 17.0	0.059

[a] Data are presented as means ± SDs.

alveolar ELF is unknown. They might be due to the difference between the blood-alveolus barrier and the blood-bronchus barrier. Another possible reason is that the concentration of the drug in alveolar ELF collected by BAL at the end of infusion may not reflect the C_{max}. We performed BAL at the end of biapenem infusion, because the peak time of drug concentration in alveolar ELF was taken as being around the peak time in plasma (16). However, Allegranzi et al. demonstrated that the time to maximum concentration of the drug (T_{max}) in alveolar ELF after a 0.5-h infusion of meropenem was 1 h after the start of infusion (1). Thus, the T_{max} in alveolar ELF after a 3-h infusion may precede the T_{max} in plasma in the same way that the T_{max} in bronchial ELF after a 3-h infusion tended to precede the T_{max} in plasma. There is no report about the T_{max} in alveolar ELF after a 3-h infusion of carbapenem. Degradation by pulmonary dehydropeptidase-I (DHP-I), which is reportedly located in Clara cells in rats (20), might also be a reason, although biapenem is more stable than other carbapenems, such as imipenem, meropenem, and panipenem, to hydrolysis by DHP-I (11).

The AUC in bronchial ELF tended to be higher after a 3-h infusion than after a 0.5-h infusion ($P = 0.078$), while the AUC in plasma after a 3-h infusion was almost the same as that after a 0.5-h infusion. The reason for the discrepancy between the bronchial ELF AUC and the plasma AUC is unknown. Conte et al. reported that the penetration of meropenem into alveolar ELF was nonlinear, in contrast to the concentrations in plasma, for unknown reasons (5). Doubling of the dose from 0.5 g to 1.0 g resulted in a 44% increase in the C_{max} and a 25% increase in the AUC from 0 to 8 h in alveolar ELF. In the present study, prolonged infusion from 0.5 to 3 h resulted in about a twofold increase. It is not known how the duration of infusion affects the penetration of biapenem into bronchial ELF, but prolonged infusion might affect the penetration more strongly than dose escalation does.

Thus, the present study suggests that the rate and manner of penetration of the drug into bronchial ELF after a single intravenous administration of biapenem might differ from those into alveolar ELF. Unlike BAL, which is an established technique for measuring antibiotic concentrations in the ELFs of the bronchiolar and alveolar regions (4, 16), BMS is a new technique for sampling ELF directly from the surface of the bronchial wall by using a fiber rod probe inserted through a bronchoscope, and it enables repeated measurements of drug concentrations in bronchial ELF, avoiding some potential errors associated with BAL with respect to the urea dilution method and the contamination by cells and cell lysis that may occur in the sampling of ELF by BAL (16). The BMS technique has been used for measuring concentrations of biochemical substances such as KL-6, albumin, and tumor markers in bronchial ELF (12, 29). We have used this technique for the measurement of drug delivery to bronchial ELF and provided some validation data (18, 19). We have further described the difference between bronchial ELF and alveolar ELF (17–19, 30), which could not be addressed without this technique. Thus, measurement of drug concentration in bronchial ELF using BMS may provide additional information for the optimization of doses and dose regimens of antibiotics in the treatment of lower respiratory tract infection based on PK/PD analysis.

Our study had several limitations. First, the sample size was small. Second, the participants were healthy volunteers. In the presence of inflammation, the blood-bronchus and alveolus-capillary barriers may be damaged, and the partitioning of antimicrobial agents in tissue compartments may be altered because of increases in membrane permeability (3). Third, because of the nature of microsampling of ELF, the data may vary not only because of biological factors but also for technical reasons. The rate of recovery from the BMS probe may vary according to drug concentration and may affect the results, although the recovery rate was as high as 93.7% at 1 μg of biapenem/ml. Previous reports have demonstrated that the recovery rate was more than 90% for serum biochemical constituents from 2 to 20 μl of human serum (12, 13) and for several antibiotics (17–19, 30). Despite such limitations, we believe that the data presented in this study are valuable for optimizing the usage of antibiotics for the treatment of lower respiratory tract infections based on PK/PD analysis.

The present study was not designed to measure the effect of protein binding on the biapenem concentration or on pharmacodynamics. Our assay measured total (free and protein-bound)-antibiotic concentrations in plasma, bronchial ELF, and alveolar ELF. Biapenem was reported to have a minimal serum protein binding rate of less than 4% after a single 300-mg dose in six volunteers (24). In addition, concentrations of protein and albumin in ELF were reported to be much lower (4.6 and 0.68 mg/ml by tracheal aspiration and 3.3 and 0.89 mg/ml by nonbronchoscopic BAL, respectively, in infants with normal lungs) than levels in serum (9). At these low levels of protein and albumin in ELF, the protein binding of antibiotics is expected to be negligible, especially for antibiotics with low levels of protein binding (16).

The MICs of biapenem at which 90% of isolates are inhibited, for pathogens isolated from respiratory specimens in Japan between 1999 and 2000, were reported as follows: 0.25 μg/ml against methicillin (meticillin)-susceptible *Staphylococcus aureus*, 32 μg/ml against methicillin-resistant *Staphylococcus aureus*, 0.06 μg/ml against penicillin-susceptible *Streptococcus pneumoniae*, 0.25 μg/ml against penicillin-resistant *Streptococcus pneumoniae*, 8 μg/ml against *Pseudomonas*

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aeruginosa, 0.12 μg/ml against *Moraxella catarrhalis*, and 4 μg/ml against *Haemophilus influenzae* (28). A PK/PD analysis using a murine thigh infection model reported that the percentage of $T>$MIC predictive of clinical efficacy of biapenem was ≥17% (27). Another study using a mouse model reported that bacteriostatic effects of carbapenems were observed when the percentage of $T>$MIC in serum was >20% and that the percentage of $T>$MIC required for bactericidal activity was 40% (6, 10). Thus, the present study showed that a single intravenous dose of 0.3 g of biapenem, especially by a 3-h infusion, achieved an adequate concentration in bronchial ELF, as well as in plasma, against these bacteria except for methicillin-resistant *S. aureus* and *P. aeruginosa*.

In conclusion, intravenous administration of biapenem by a 3-h infusion produces better penetration into bronchial ELF than that by a 0.5-h infusion. The present results support the use of a prolonged infusion of a beta-lactam antibiotic, and they may provide valuable information for the successful treatment of lower respiratory tract infections in terms of PK/PD parameters in bronchial ELF. However, further investigation is required to clarify the clinical significance of the present findings.

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