In vivo efficacy and pharmacokinetics of tomopenem (CS-023), a novel carbapenem, against _Pseudomonas aeruginosa_ in a murine chronic respiratory tract infection model

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Running title: In vivo efficacy of tomopenem against *P. aeruginosa*

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Abstract

Objectives; Tomopenem (CS-023) is a novel parenteral carbapenem with broad spectrum activity against Gram-positive and -negative bacteria, as well as potent activity against drug resistant pathogens, including penicillin-resistant *Streptococcus pneumoniae*, methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. We compared the *in vivo* activity of tomopenem and that of meropenem in a chronic lower respiratory infection mouse model of *P. aeruginosa*.

Methods; Mice with chronic airway infection of *P aeruginosa* were treated with saline (as the control, twice daily), tomopenem (100 mg/kg, twice daily) or meropenem (100 mg/kg, twice daily) for seven days. After treatment, the number of viable bacteria in lungs and histopathological findings were analyzed. The pharmacokinetics of tomopenem and meropenem were also analyzed after initial treatment.

Results; The number of viable bacteria in lungs treated with saline, tomopenem or meropenem was 4.21±1.28, 2.91±0.87 and 3.01±1.00 $\log_{10}$ cfu/lung (mean ± SEM), respectively ($p<0.05$, control vs. tomopenem- or meropenem-treated groups). In the histopathological examination of lung specimens, control group revealed the features of chronic bronchial infection, however, tomopenem- and meropenem-treated groups had fewer inflammatory cells compared to control group. The pharmacokinetic parameters of % time above MIC for tomopenem and meropenem were 16% and 17% in sera, and 15% and 18% in lungs, respectively.

Conclusions; Tomopenem significantly reduced the number of viable bacteria in a murine model of chronic airway infection of *P. aeruginosa*, compared to the control. Considering the longer half-life of tomopenem in humans compared to most other carbapenems, tomopenem treatment of chronic airway infection with *P. aeruginosa* is expected to be efficacious.

Key words; chronic respiratory infections, meropenem, pharmacokinetics

Introduction

Pseudomonas aeruginosa is an important pathogen of chronic lower respiratory tract infectious diseases, such as cystic fibrosis, diffuse panbronchiolitis, chronic bronchitis and bronchiectasis. Once *P. aeruginosa* colonizes the lower respiratory tract it is difficult to treat. Chronic respiratory infection causes excessive inflammation and lung tissue damage in humans. The lung function decreases gradually and exacerbations of chronic airway infections sometimes occur. These patients require treatment with antibiotics at every acute exacerbation. Although carbapenems are active against *P. aeruginosa* and have been used to treat acute exacerbations resulting from *P. aeruginosa* infection, they are also becoming less effective against *P. aeruginosa*. In Japan, the susceptible rates of *P. aeruginosa* to imipenem has fallen from 63.8% in 1998 to 53.6% in 2003.[1] Therefore, new antibacterial agents that are effective against resistant pathogens are required.

Tomopenem (CS-023) is a novel parenteral carbapenem with broad spectrum activity against Gram-positive and -negative bacteria, and also has potent activity against drug resistant pathogens, including penicillin-resistant *Streptococcus pneumoniae* (PRSP), methicillin-resistant *Staphylococcus aureus* (MRSA) and imipenem-resistant *P. aeruginosa in vitro*.[2-4] The MIC_{90}s of tomopenem, IPM and meropenem against the clinical isolates of *P. aeruginosa* in Japan are 4, 16 and 16 mg/L, respectively.[3] Tomopenem has a longer half-life compared to other carbapenems except for ertapenem, and characteristic high stability against human renal dehydropeptidase-I (DHP-I).[5, 6] In a murine pneumonia model induced by PRSP, tomopenem showed efficacy comparable with imipenem and stronger efficacy than meropenem in the number of viable bacteria left in the lungs.[3]

In the present study, we studied the efficacy of tomopenem compared to meropenem in a chronic lower respiratory tract infection model of *P. aeruginosa*. Furthermore, we analysed the pharmacokinetics of these agents in sera and lungs.

Materials and methods

Antimicrobial agents

Tomopenem was kindly provided by Daiichi Sankyo Co., Ltd. (Tokyo, Japan). Meropenem was purchased from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan). Both agents were dissolved in saline.

Laboratory animals

Male, ddY, specific pathogen-free mice (6 weeks old, body weight, 30 to 35 g) were purchased from Shizuoka Agricultural Cooperative Association Laboratory Animals (Shizuoka, Japan). All the animals were housed in a pathogen-free environment and received sterile food and water in the Laboratory Animal Center for Biomedical Science at Nagasaki University. The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation at our institution.

Bacterial strains

P. aeruginosa S10 strain was used in this study. This strain was clinically isolated from the sputum of patients at Nagasaki University hospital and produces biofilm formation.[7] The bacteria were stored at –80°C in brain heart infusion broth (BBL Microbiology System, Cockeysville, MD) supplemented with 10% (volume/volume) glycerol and 5% (weight/volume) skim milk (Yukijirushi Co., Tokyo, Japan) until use.

Antibiotic susceptibility testing

The MICs of the agents were determined by the broth dilution method with Mueller-Hinton broth (Becton Dickinson and Company, Franklin Lakes, NJ). Microtiter plates containing 5.0×10^5 cfu/well were incubated with agents at 35°C for 24 h and the lowest concentration of the agent that prevented visible growth was considered the MIC**.**

Experimental model of chronic respiratory infection

Disposable sterile plastic cut-down intravenous catheters with a 3 Fr. (1 mm) outer diameter (Atom Co., Tokyo, Japan) were used for intubation. The tubes were 3.0 mm in length, with a few slits made at the proximal end to prevent blockage by oral secretions. To prepare the inoculum, *P. aeruginosa* was cultured on a Muller-Hinton II agar plate for 24 h, then the bacteria suspended in saline, harvested by

centrifugation (3,000 × *g*, 4°C, 10 min), resuspended in sterile saline and adjusted to 1~2×10^9 cfu/mL, as estimated by turbidimetry. The intubation tube was then immersed in the bacterial saline suspension for 3 days at 37°C. The bacterial count on these tubes 3 days after incubation just before intubation was 6.0 ± 0.3 ($\log_{10}$ cfu/mL, mean ± SD, n=9). After 3-day incubation, the bacteria were inoculated to anesthetized mice intratracheally. The method used for inducing infection has been described in detail previously.[8] Briefly, the intubation tube harbouring the bacteria was attached to the blunted tip of the needle of an intravenous catheter (Angiocath; Beckton Dickinson, Vascular Access Sandy, UT). The needle-tube was inserted through the oral cavity, and then advanced through the vocal cords. When the tip of the tube was in the trachea, the needle/catheter was pulled out and the outer sheath was pushed gently to place the precoated tube into the main bronchus.

Treatment protocol

Lower airway infection of the mice was induced with *P. aeruginosa*, as described above. Treatment commenced 7 days after inoculation. Tomopenem or meropenem was injected intraperitoneally into the mice twice a day (100 mg/kg). The same dosage of cilastatin (Wako Pure Chemical Industries, Ltd., Osaka, Japan), a DHP-I inhibitor, was also injected along with both agents. In the control group, saline was injected into the mice instead of tomopenem or meropenem. Eight mice were used for each group. After 7-day treatment (14th day after inoculation), bacteriological and histological examinations were analyzed in each group.

Bacteriological examinations

The mice were sacrificed by cervical dislocation on day 14 (12 h after the final treatment). The lungs were dissected under aseptic conditions and suspended in 1 ml of saline. The organs were homogenized with a homogenizer (AS One Co., Osaka, Japan), quantitatively inoculated onto Muller-Hinton II agar plates using serial dilutions, and incubated at 37°C for 18 h.

Histological examinations

The mice were sacrificed by cervical dislocation on day 14 (12 h after the final treatment). The lungs were fixed in 10% buffered formalin and stained with hematoxylin-eosin.

Bioanalytical procedures

Quantification of tomopenem and meropenem in lung homogenates was performed by fully validated high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). The homogenates were added to deuterium-labelled tomopenem as the internal standard for both agents. The mixture was applied to solid-phase extraction (Oasis LB 3cc cartridge, Waters Corp.) and the target agents were eluted by methanol. The extraction was dried with nitrogen gas at 40℃ and was reconstituted with purified water. The recovery of the extraction for tomopenem and meropenem was more than 86.5 % of both agents at two concentrations. The analyses were separated using an LC (Alliance 2795 Separations Module, Waters Corp.) on an ODS column (Inertsil ODS-3, 2.1 mm x 150 mm, 5 μm, GL Science) for a period of 8 min. Electrospray ionization tandem mass spectrometry (ESI-MS/MS, MicroMass Quattro II, Waters Corp.) was operated in the positive time-scheduled multi-reaction monitoring mode. The monitored positive ions of tomopenem, meropenem and the internal standard were 295, 254 and 300, respectively. The range of quantification for both agents in the lung was 0.5 μg/g as the lower limit of quantification (LLOQ) up to 200 μg/g. The intra-assay reproducibility for tomopenem using samples spiked at 0.05, 0.15, 2.5 and 15 μg/mL (final lung concentrations at 0.5, 1.5, 25 and 150 μg/g) was 96.0% to 107% as accuracy and below 3.8% as precision. The inter-assay reproducibility for tomopenem using the same samples was 98.7% to 117% at LLOQ as accuracy and below 5.5% as precision. The accuracy and precision of the intra-assay reproducibility for meropenem did not exceed 85.3% to 98.7% and 6.7%, respectively. Replicate analysis of meropenem did not exceed 90.7% to 105% as accuracy and 12.0% as precision of the inter-assay reproducibility. The stability of the agents in frozen homogenate from preparation to the end of the analysis was confirmed.

Pharmacokinetic studies

These studies were undertaken to determine the pharmacokinetic profiles of tomopenem and meropenem in a chronic lower airway infectious mouse model due to *P. aeruginosa*. On the 7th day after inoculation of *P. aeruginosa*, the mice were sacrificed by cervical dislocation at 5, 15, 30, 60, 90 and 120 min after treatment with tomopenem or meropenem at the dose of 100 mg/kg in combination with cilastatin. Three or four mice were used for each group. The blood was centrifuged and then the serum was mixed with an equal volume of 3-(*N*-Morpholino) propanesulfonic acid (MOPS) buffer (pH 7.0). The

lungs were homogenized using a homogenizer after addition of 2 mL MOPS buffer (pH 7.0). The homogenate was centrifuged and then the supernatant and serum concentrations of the agents were determined by LC-MS/MS and UV-HPLC, respectively. The concentration-time profiles were analyzed using WinNonlin Professional software (Version 4.0.1; Pharsight Corp.). A 1-compartment oral model with the various dosages was fit to the observations. The best-fit model was determined by Akaike's Information Criteria. The time above MIC (%T/MIC) was calculated using SAS System Release 8.2 software (SAS Institute Inc.). The free %T/MIC (*f*%T/MIC) was also calculated, with the protein binding in the mouse serum of tomopenem and meropenem being 17.4% and 33.8%, respectively.[9, 10]

Statistical analysis

The bacterial data are expressed as the mean ± standard of the mean. Differences between the groups were examined for statistical significance by an unpaired Student's *t*-test. A p value of less than 0.05 denoted the presence of a statistically significant difference.

RESULTS

In vitro susceptibility

Against *P. aeruginosa* S10, the MICs of drugs are presented in Table 1. The MICs of tomopenem and meropenem were 1.0 and 0.5 mg/L, respectively.

Bacteriological examination

The mean colony-forming units (cfu)±SEM of *P. aeruginosa* recovered from homogenized lung tissue after treatment are shown in Figure 1. The mean number of viable bacteria in the lungs of the tomopenem, meropenem, and control mice were 2.91±0.87, 3.01±1.00 and 4.21±1.28 $\log_{10}$ cfu/lung (n=8 each), respectively. There were no sterilized mice after treatment in each group. The number of viable bacteria in the lungs of mice treated with tomopenem or meropenem was significantly less than that in lungs of the control ($p<0.05$ for each comparison). There was no statistically significant difference in the number of viable bacteria in the lungs between the tomopenem- and meropenem-treated mice ($p=0.85$).

Histopathological examination

The histopathological findings of the lung specimens from mice sacrificed 12 h after the final treatment are shown in Figure 2. In the control group, microscopic examination of the lung specimens revealed the features of chronic bronchitis. Inflammatory cells had infiltrated around the bronchi and exudates had collected in the alveolar spaces. However, both the tomopenem- and meropenem-treated groups showed fewer inflammatory cells and exudates than the control group. There were no significantly different findings between the tomopenem- and meropenem-treated groups.

Lung and serum concentrations of tomopenem and meropenem in mice

The levels of tomopenem and meropenem in the sera and lungs of infected mice are presented in Figure 3 (n=3 or 4 at each point). The calculated pharmacokinetics of the agents are presented in Table 2. The half-life ($t_{1/2}$) of tomopenem and meropenem was 0.197 h and 0.264 h in sera, and 0.343 h and 0.363 h in the lungs, respectively. The %T/MIC of tomopenem and meropenem was 16% and 17% in sera, and 15% and 18% in the lungs, respectively. The *f*%T/MIC was 16% with both agents.

DISCUSSION

In the present study, the *in vivo* activity of tomopenem, a new carbapenem, against *P. aeruginosa*, was compared with that of meropenem by evaluating its bacteriological and pharmacological effects.

Among chronic airway infectious diseases such as chronic bronchitis, cystic fibrosis, diffuse panbronchiolitis and bronchiectasis, airway infection with *P. aeruginosa* and the accompanying inflammatory response are major clinical problems. These patients often have an acute exacerbation of *P. aeruginosa* infection and antibiotic chemotherapy is required at every exacerbation. While antibiotic chemotherapy has reduced the morbidity and early mortality of patients suffering from this infection, resistance to antibiotics has developed in *P. aeruginosa*[1]. The rates of resistance to carbapenems (>8 mg/L) of *P. aeruginosa* are slowly increasing [11-14] and treatment against *P. aeruginosa* infection is becoming more difficult.

Carbapenems have potent activity against Gram-positive and Gram-negative bacteria. In addition, tomopenem has exceptional activity against MRSA and *P. aeruginosa* compared with imipenem and meropenem *in vitro*.[3, 4]

Carbapenems are hydrolyzed at the β-lactam ring by mammalian DHP-I.[5, 15, 16] Therefore, imipenem requires the DHP-I inhibitor cilastatin when used for therapy in humans. However, 1-β-methylcarbapenems such as tomopenem, meropenem, biapenem and ertapenem show high stability in the presence of human DHP-I[15] and do not require a DHP-I inhibitor. On the other hand, DHP-I activity against tomopenem and meropenem varies greatly according to the experimental animal species and organs involved.[15, 17] To eliminate the effect of murine DHP-I as much as possible, we treated mice with cilastatin in both the tomopenem and meropenem treatment groups in this study.

In this study, tomopenem and meropenem significantly decreased the number of viable bacteria in lungs and dramatically improved histological findings compared to control. In this study, because tomopenem- or meropenem-treated groups had obviously fewer inflammatory cells in the histological findings compared with control group, we did not perform the scoring. These findings suggest tomopenem has an efficacy in treatment of chronic respiratory infection diseases of *P. aeruginosa* like meropenem.

The %T/MIC is an important pharmacodynamic parameter that influences the outcome of β-lactam antibiotics including carbapenem treatment.[18] In this study, the %T/MIC for tomopenem was similar to that for meropenem in both the sera and the lungs. There was also no difference in the serum *f*%T/MIC. This profile is consistent with our finding that there was no significant difference in the number of viable bacteria in the lungs between these two agents. Since the antibacterial target magnitude associated with efficacy has been reported to be similar among carbapenems,[19] the target value of tomopenem would be the same as that of meropenem in humans.

The half-life of a drug is another important pharmacokinetic factor because it influences the %T/MIC. Although the half-life of tomopenem in serum was a little shorter than that of meropenem in mice, it has been reported that the half-life of tomopenem is longer than that of meropenem in humans, despite of similar serum protein bindings.[6] Shibayama *et al.* reported that the lack of recognition of tomopenem by renal transporters involved in uptake across the basolateral membrane is one of the reasons for its long plasma half-life in humans compared with meropenem, since no tomopenem molecules exist as an anionic form at physiological pH.[20] The MICs of tomopenem against clinical isolates of *P. aeruginosa*

showed more activity than meropenem.[3] Considering the longer half-life of tomopenem, the %T/MIC of tomopenem is much higher than meropenem for human. Therefore, tomopenem is strongly expected to be efficacious in treating patients with lower respiratory infection of *P. aeruginosa*.

In conclusion, tomopenem significantly reduced the number of viable bacteria in a murine model of chronic airway infection of *P. aeruginosa* compared to the control. Considering the longer half-life of tomopenem in humans compared to most other carbapenems, we expect tomopenem to be effective against chronic respiratory tract infection with *P. aeruginosa*.

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FIGURE LEGENDS

Figure 1. The number of viable bacteria in the lungs after seven-day treatment with tomopenem or meropenem (100 mg/kg twice daily) and control (saline twice daily). Data express the mean ± SEM for 8 mice. Tomopenem and meropenem significantly reduced the number of viable bacteria compared to the control ($p<0.05$).

##UPLOAD IMAGE: figure 1##

Figure 2. Histopathological examination of lung specimens. The control group showed the features of chronic bronchopneumonia; inflammatory cells had infiltrated around the bronchi and exudates had collected in the alveolar spaces. However, only few inflammatory cells were observed in both the tomopenem- and meropenem-treated groups.

##UPLOAD IMAGE: figure 2##

Figure 3. The pharmacokinetics of tomopenem and meropenem in serum (a) and in the lungs (b) of infected mice. Each point represents the mean ± SD for 3 or 4 mice.

##UPLOAD IMAGE: figure 3a##

##UPLOAD IMAGE: figure 3b##

Figure 1

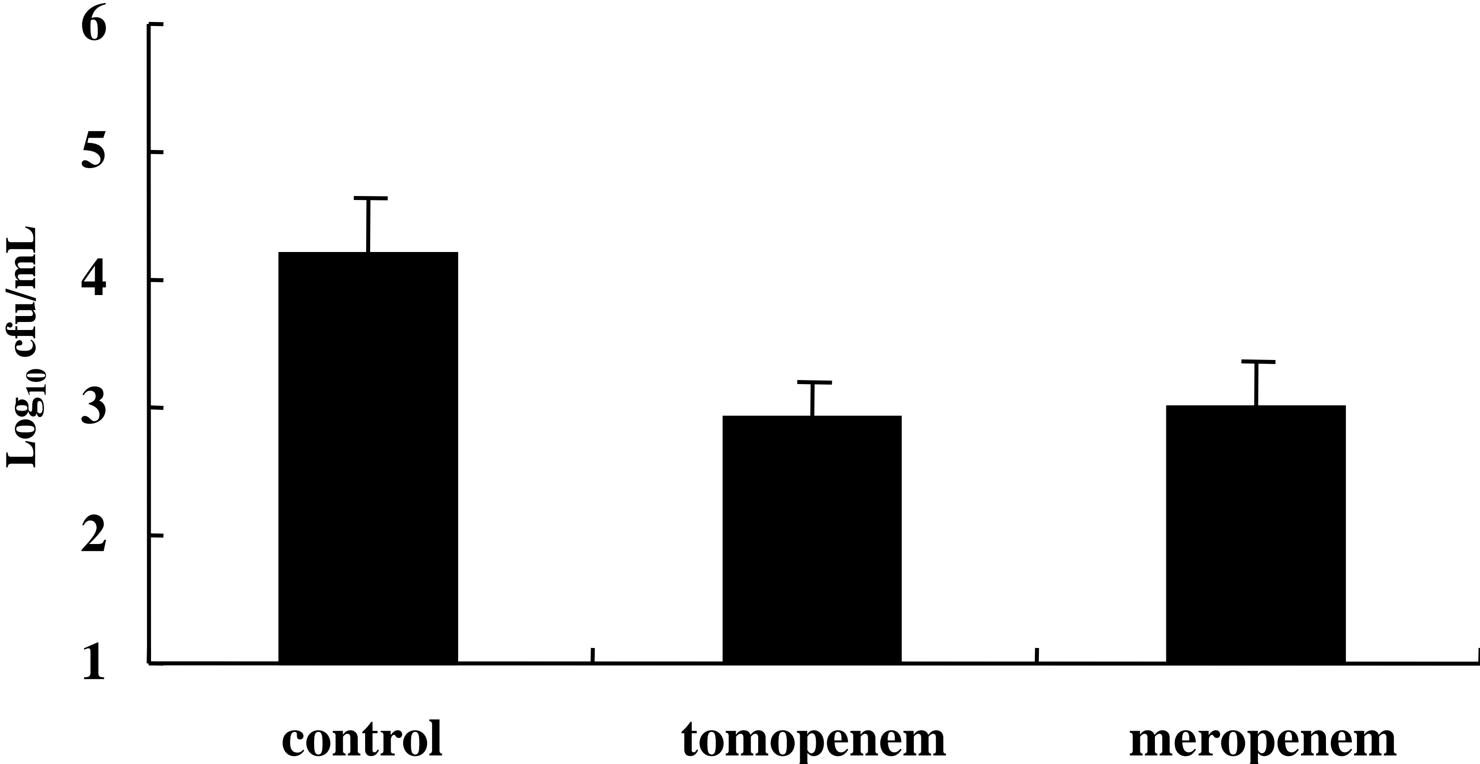
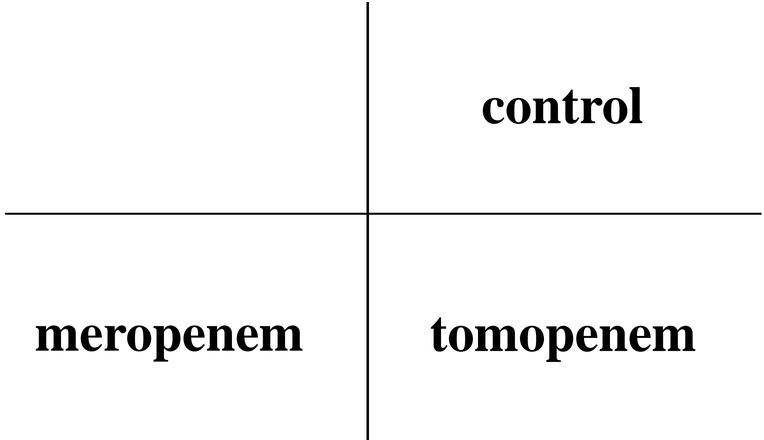
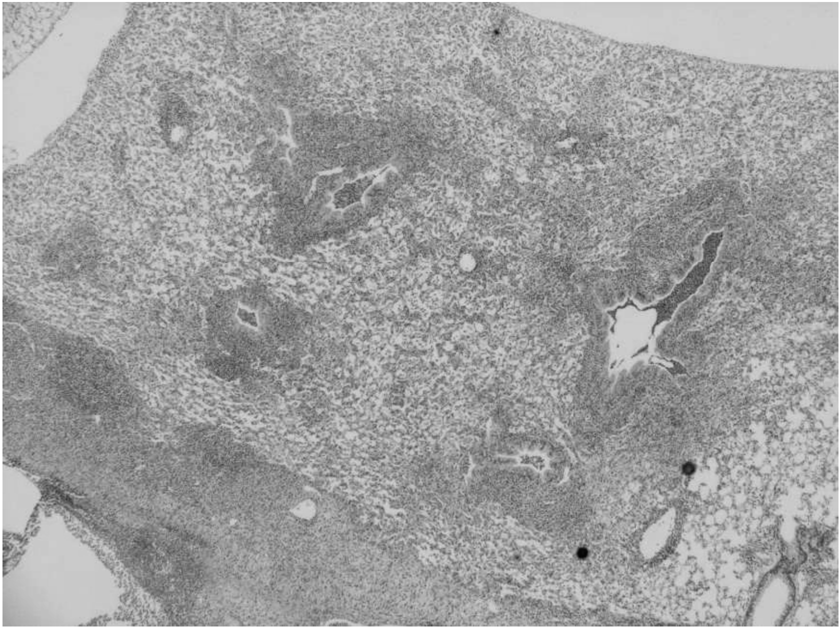
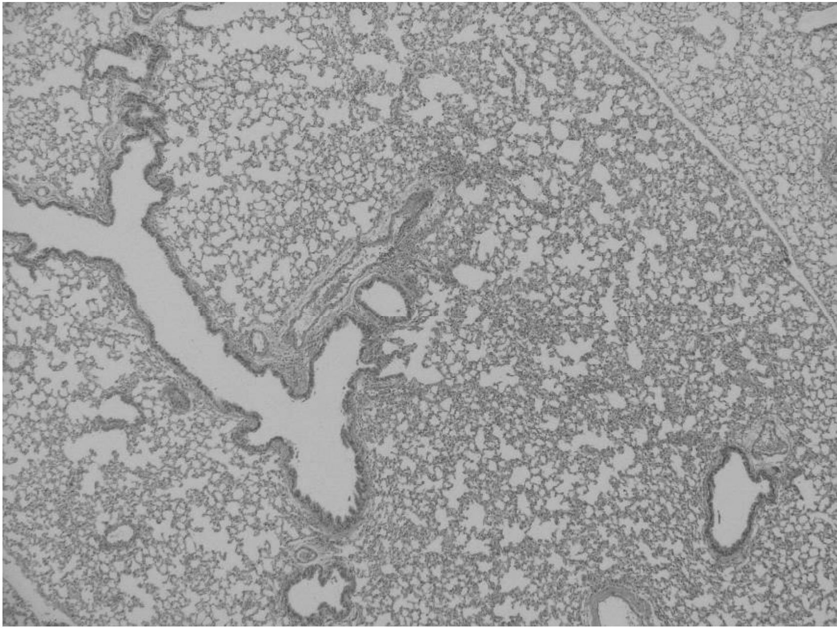


Figure 2







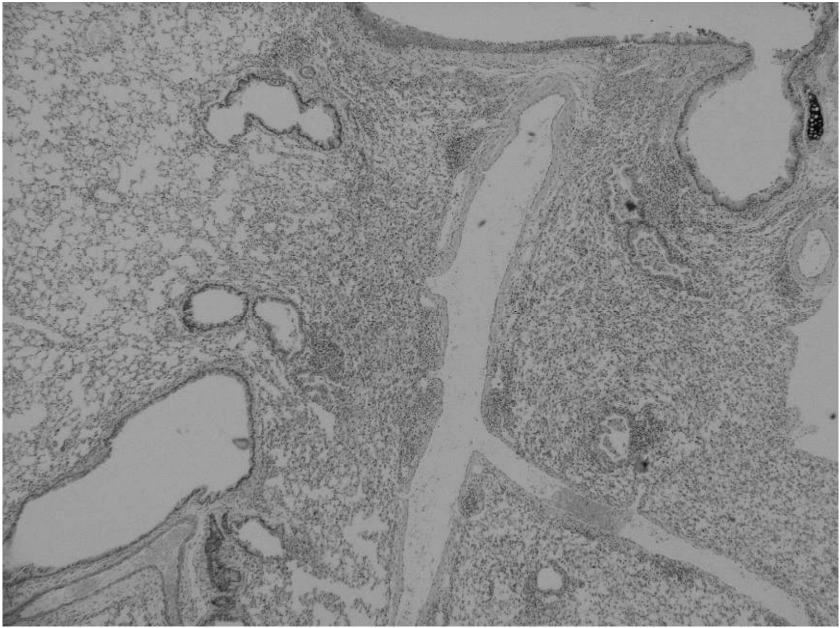


Figure 3a

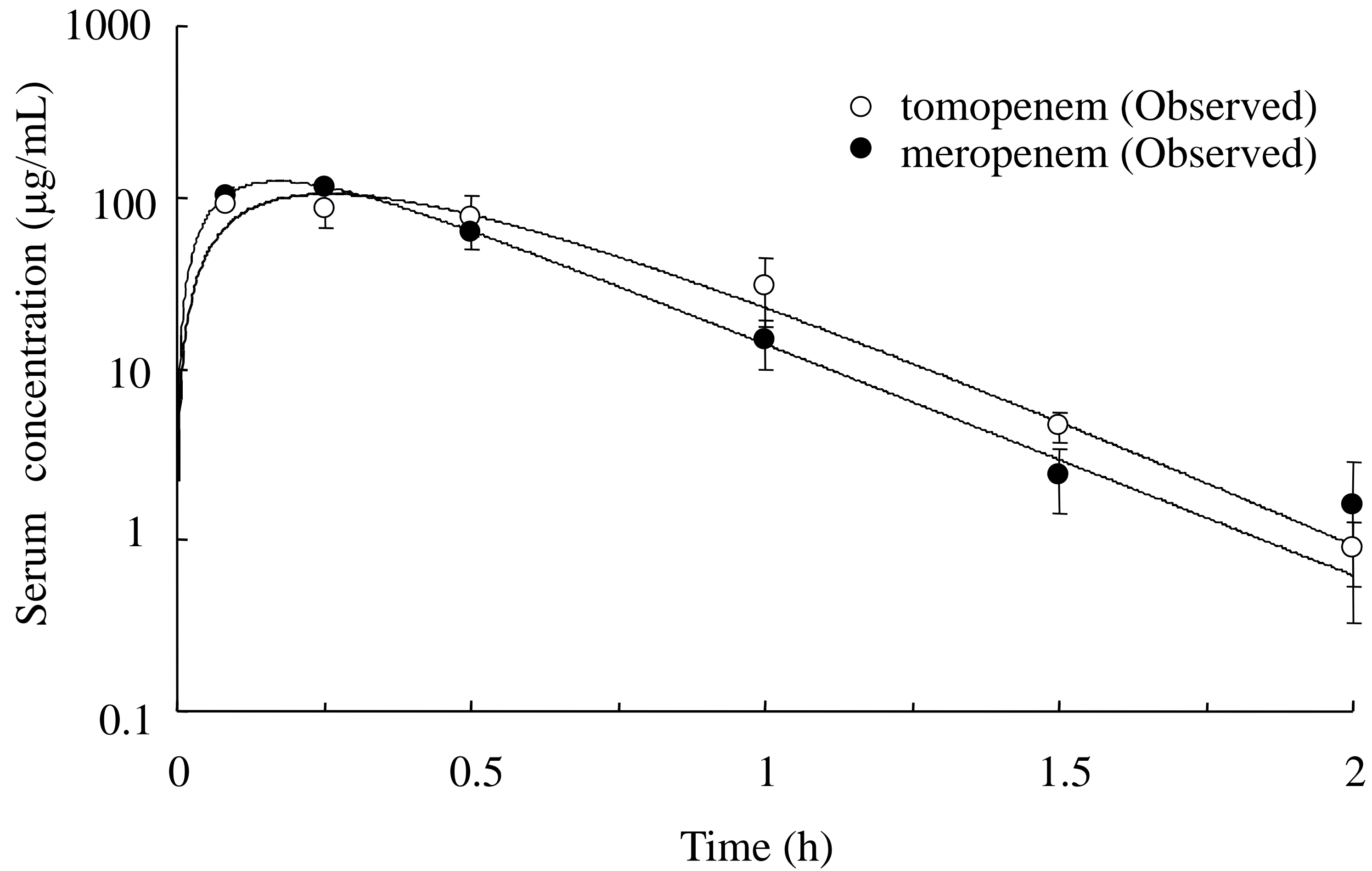


Figure 3b

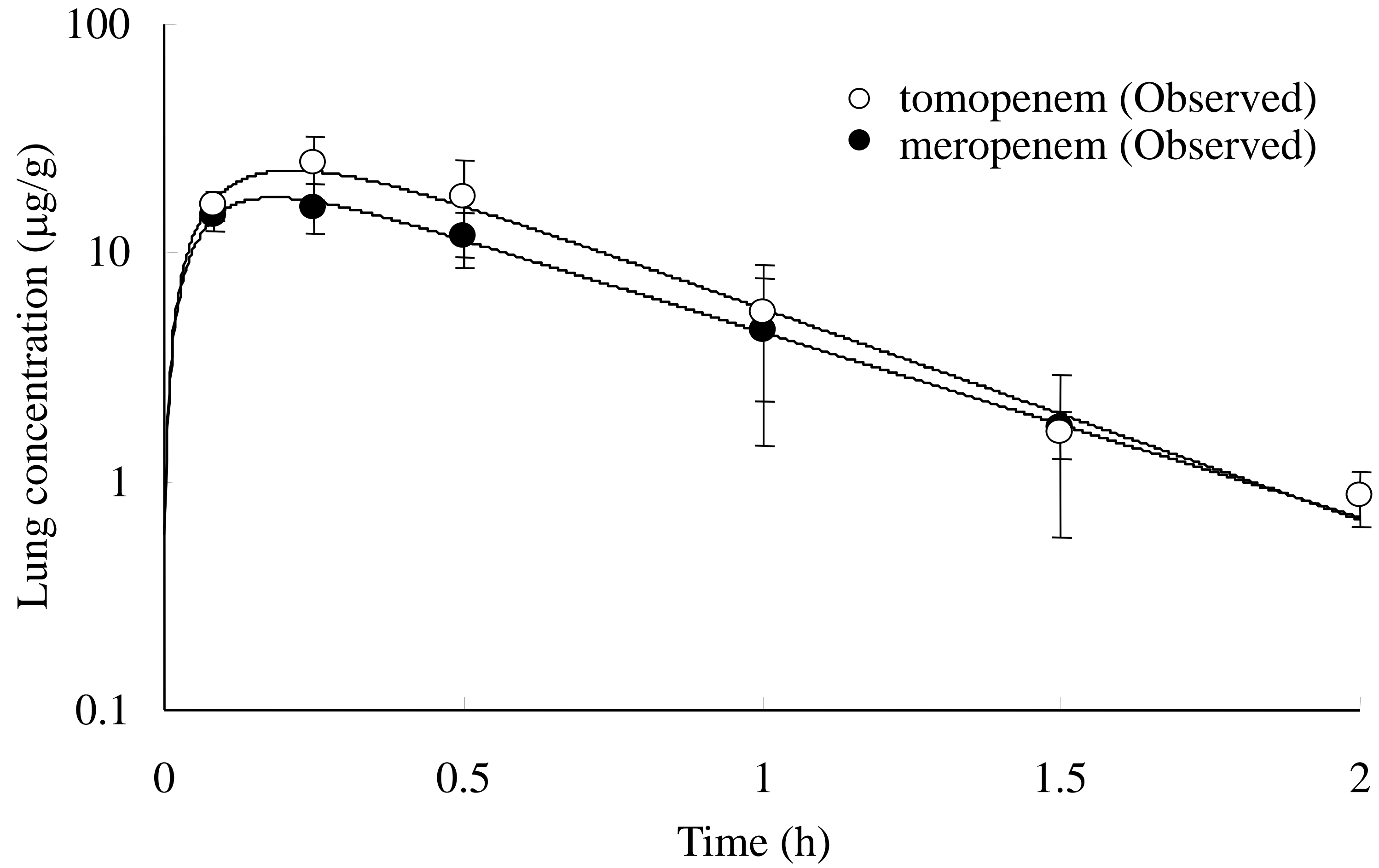


Table 1 The MICs of *Pseudomonas aeruginosa* S10 strain.

Drug	(mg/L)	Drug	(mg/L)
Piperacillin	2.0	Gentamicin	2.0
Ceftatizime	1.0	Imipenem	1.0
Cefepime	4.0	Meropenem	0.5
Ciprofloxacin	=<0.5	Tomopenem	1.0

Table 2. Selected PK parameters estimated for tomopenem and meropenem in serum and in the lung.

Site/drug	$AUC_{0\text{-}inf}$[a]	Cmax (μg/g)	$T_{1/2}$ (h)	%T/MIC[b] (%)	*f*%T/MIC[b] (%)
Serum					
Tomopenem	76.1	91.1	0.197	16	16
Meropenem	70.1	116	0.264	17	16
Lung					
Tomopenem	18	24.9	0.343	15	–
Meropenem	13.2	16.0	0.363	18	–

[a] Units for AUC are μg·h/mL for serum and μg·h/g for lung.

[b] MICs of this strain (tomopenem 1.0mg/L; meropenem 0.5mg/L) were used for calculation.