Respiratory Medicine (2006) **100**, 324–331

ELSEVIER

respiratoryMEDICINE

Pharmacokinetic study of pleural fluid penetration of carbapenem antibiotic agents in chemical pleurisy

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Received 27 October 2004; accepted 2 May 2005

KEYWORDS
Carbapenem antibiotic agent;
Penetration;
Pleurisy;
Turpentine oil;
Rabbit

Summary
Study objectives: We investigated pleural fluid penetration of carbapenem antibiotic agents [imipenem (IPM), panipenem (PAPM), meropenem (MEPM), and biapenem (BIPM)] using an experimental rabbit pleuritis model to clarify the usefulness of the carbapenem agents for the treatment of bacterial pleurisy or pyothorax.
Measurements and results: Serum and pleural fluid specimens were serially collected at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min after antibiotic administration for measurement of antibiotic levels. We investigated each agent alone as well as drug solutions containing each agent and a dehydropeptidase-I-specific inhibitor, cilastatin (CS), to remove the influence of dehydropeptidase-I-related hydrolysis. Groups of animals ($n = 3$) received each carbapenem agent with or without CS. Serum and pleural fluid antibiotic levels were measured by high-performance liquid chromatography (HPLC). Because C_{max} is not useful for evaluating the antimicrobial effects of carbapenem antibiotic agents due to their dose-dependent antimicrobial activity, we also investigated the AUC, which is correlated with the total drug levels in vivo.

Among the drug solutions containing CS, MEPM/CS had the highest pleural fluid AUC_{0-360} (1594.8 ± 510.3 μg min/ml), and the highest pleural fluid AUC_{0-360}/plasma AUC_{0-360} ratio (0.79 ± 0.04). BIPM/CS had the highest plasma AUC_{0-360} (3040.1 ± 1525.9 μg min/ml). In pleural fluid AUC_{0-360}/plasma AUC_{0-360} ratio MEPM/CS was significantly higher than those for the remaining agents. In pleural fluid

Abbreviation: IPM = imipenem; PAPM = panipenem; MEPM = meropenem; BIPM = biapenem; CS = cilastatin; DHP-I = dehydropeptidase-I; HPLC = high-performance liquid chromatography; AUC = area under the concentration–time curve; C_{max} = maximum concentration of drug in serum and pleural fluid.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2005.05.009

AUC_{0-360} and plasma AUC_{0-360} there were no significant differences among these mixed solutions.
Conclusions: MEPM had the most favorable pleural fluid penetration. Pleural fluid penetration should be examined in infection models and in clinical trials.

Introduction

Mixed infection, in which causative bacteria include gram-positive or gram-negative bacteria as well as anaerobic bacteria, occurs in many patients with bacterial pleurisy or pyothorax. In these cases, carbapenem antibiotic agents are frequently administered. To cure the infection, antimicrobial agents are commonly administered for a longer period than for other respiratory infections such as pneumonia. Administration of ineffective antibiotics for a long period causes the emergence of antibiotic-resistant bacteria. To prevent the emergence of antibiotic-resistant bacteria it is necessary to administer antibiotics that have good antimicrobial spectra and good penetration of the target organ. Some studies[1–3] have examined the penetration of carbapenem antibiotic agents into the thoracic cavity in patients with carcinomatous pleurisy and tuberculous pleurisy; no studies have compared intrathoracic penetration among these agents under the same conditions. Although some studies[4–6] using various experimental models of empyma have been done, we think that frequent collection of pleural fluid and measurements of pleural fluid using high-performance liquid chromatography (HPLC) are difficult in infection models without chemical inducers. In pleural infections, pleural fluids evolve in stages from the simple parapneumonic pleural effusions to pyothorax.[7,8] Penetration of the pleura in each stage is different. Therefore, we investigated the pharmacokinetics of the carbapenem antibiotic agents in turpentine oil-induced chemical pleurisy for the preliminary step of the exudates pleuritis.

Materials and methods

Animals

Twenty-seven Japanese white male rabbits weighing 2.5–3.5 kg were purchased from Kitayama Labes (Nagano, Japan). Animals were allowed free access to water and a standard laboratory diet. The study design was approved by the Animal Care Committee of Nagoya City University.

Experimental pleurisy

We prepared a turpentine oil-induced chemical model of pleurisy, as described by Sahn et al.[9] Rabbits were anesthetized with pentobarbital sodium salt (25 mg/kg intravenously). An 18-gauge catheter was transfixed into the left thoracic cavity using the modified Seldinger technique. Turpentine oil (0.4 ml/kg) and 0.2 ml of air were infused through the catheter, and each rabbit was rotated for approximately 1 min to induce pleurisy. Our experiment was performed 48 h after the infusion of turpentine oil.

Antibiotic agents

Carbapenem antibiotic agents, imipenem (IPM), panipenem (PAPM), meropenem (MEPM), and biapenem (BIPM), were supplied by Merck USA. Inc., Sankyo Co., Ltd., Tokyo Japan, Sumitomo Pharmaceuticals Osaka, Japan, and Meiji Seika Kaisha, Ltd., Osaka, Japan, respectively.

The dehydropeptidase-I (DHP-I) inhibitor, cilastatin (CS), was supplied by Merck USA. Inc.

Collection of blood and pleural fluid samples

After confirmation of the existence of pleural fluid by direct puncture, each carbapenem antibiotic agent (IPM, PAPM, MEPM, or BIPM, 20 mg/kg) was administered through the ear vein. Approximately 1.0 ml of blood was serially collected at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min after administration of a carbapenem antibiotic agent through the contralateral ear vein. Simultaneously, approximately 0.5 ml of pleural fluid was collected at 5, 10, 15, 30, 60, 90, 120, 180, 240, 300, and 360 min after administration of a carbapenem antibiotic agent with a heparinized syringe from the thoracic cavity into which the turpentine oil was infused. Groups of animals ($n = 3$) received each carbapenem agent.

Carbapenem antibiotic agents are hydrolyzed by DHP-I, a type of dipeptidase.[10] Therefore, we investigated each agent alone as well in drug solutions containing each agent and a CS, DHP-I-specific inhibitor,[11] to remove the influence of DHP-I-related hydrolysis [IPM/CS, PAPM/CS, MEPM/CS,

and BIPM/CS, 20/20 mg/kg, respectively]. Groups of animals ($n = 3$) received each carbapenem agent with CS.

Blood and pleural fluid were sampled just before (baseline) the administration of each antibiotic agent.

Storage of samples

Blood samples were collected, treated with heparin, and centrifuged in a refrigerated centrifuge (4 °C 3000 rpm × 10 min) to separate plasma. Plasma samples were mixed with an equivalent volume of various stabilizing agents (Table 1), and snap-frozen/stored at −80 °C. Similarly, pleural fluid was centrifuged in a refrigerated centrifuge (4 °C 3000 rpm × 10 min). The supernatant was mixed with an equivalent volume of stabilizing agents as described above, and snap-frozen/stored at −80 °C.

Measurement of drug levels

The samples were centrifuged with ultrafiltration devices (Amicon Centrifree; WR Grace & Co; Beverly, MA) with a molecular weight cutoff of 30,000 in a refrigerated centrifuge (4 °C 3000 rpm × 15 min). The filtrate was collected, and drug levels were measured by HPLC. The HPLC instrumentation (Waters, Milford, MA) consisted of a model 600E pumping system, a model 717 automatic injector, a model 2487 ultraviolet detector, and a Millennium32 Chromatography Information System capable of providing peak retention times, areas, and heights.

The conditions of HPLC used for assays of IPM were as follows: a column, STR-ODS-II, 250 mm × 4.6 mm I.D. (Shimadzu Techno-Research, Kyoto, Japan); a mobile phase: a mixture of 0.2 M borate buffer (pH 7.2)/methanol (97:3, by vol); a flow rate of 0.7 ml/min; and a wavelength of 298 nm. The injection volume was 10 μL. The lower limit of detection was 0.25 μg/ml in plasma and pleural fluid. (These methods were referred to those of Banyu Pharmaceutical Co., Ltd.)

Table 1 The stabilizations of carbapenem antibiotic agents.

Antibiotics	Stabilization (v/v)
IPM	1 M morpholino-ethane sulfonic acid (pH 6.0):100% ethylene glycol 1:1
PAPM	1 M morpholino-propane sulfonate (pH 7.0) (MOPS)
MEPM	None
BIPM	50% ethylene glycol: 1 M morpholino-propane sulfonate (pH 7.0) (MOPS) 1:1

The conditions of HPLC used for assays of PAPM were as follows: a column, YMC-PAC A-312 ODS, 150 mm × 6.0 mm I.D. (YMC Co., Ltd., Kyoto, Japan); a mobile phase: a mixture of acetonitrile/methanol/ammonium acetate (pH 5)/PIC B7 (1:6:92:1, by vol); a flow rate of 1.5 ml/min; and a wavelength of 290 nm. The injection volume was 20 μL. The lower limit of detection was 0.3 μg/ml in plasma and pleural fluid.[12]

The conditions of HPLC used for assays of MEPM were as follows: a column, SUMIPAX Hypersil ODS, 150 mm × 4.6 mm I.D. (Sumika Chemical Analysis Service, Osaka, Japan); a mobile phase: a mixture of PIC A (Low UV 5 mM)/methanol (77:23, by vol); a flow rate of 1.0 ml/min; and a wavelength of 300 nm. The injection volume was 50 μL. The lower limit of detection was 0.05 μg/ml in plasma and pleural fluid. (These methods were referred to those of Sumitomo Pharmaceutical Co., Ltd.)

The conditions of HPLC used for assays of BIPM were as follows: a column, TSK gel ODS 80TM, 250 mm × 4.6 mm I.D. (Tosoh, Co., Ltd., Tokyo, Japan); a mobile phase: a mixture of 0.1 M acetate buffer/acetonitrile (98.5:1.5, by vol); a flow rate of 1.2 ml/min; and a wavelength of 300 nm. The injection volume was 20 μL. The lower limit of detection was 0.1 μg/ml in plasma and pleural fluid.[13]

At every measurement, assay lines were prepared at concentrations of 50, 25, and 12.5 μg/ml, and each concentration was calculated.

Protein binding

Plasma and pleural fluid from the rabbits induced in the chemical pleurisy as described above were used.

Each carbapenem antibiotic agent (30 μl; 200 μg/ml) was added to 270 μl of rabbit plasma, agitated and incubated at 37 °C for 30 min. Drug-containing plasma samples were mixed with an equivalent volume of various stabilizing agents as described above, and centrifuged in a refrigerated centrifuge (4 °C 3000 rpm × 30 min). Filtrate drug levels (*A*) were calculated by HPLC. As a control solvent, an equivalent volume of 1/15 M phosphate-buffered isotonic saline (pH 7.4) was used instead of plasma, and filtrate drug levels (*B*) were similarly calculated.

Similarly, each carbapenem antibiotic agent (30 μl; 200 μg/ml) was added to 270 μl of rabbit pleural fluid, agitated, and incubated at 37 °C for 30 min. Drug-containing pleural fluid samples were mixed with an equivalent volume of various stabilizing agents as described above, and centrifuged in a refrigerated centrifuge (4 °C 3000 rpm × 30 min). Filtrate drug levels (*A*) were calculated by HPLC. As a control solvent, an equivalent volume of 1/15 M phosphate-buffered isotonic saline (pH 7.4) was used instead of pleural fluid, and filtrate drug levels (*B*) were similarly calculated.

The rate of protein binding in plasma and pleural fluid was calculated from the drug concentration calculated above using the following formula:

protein binding (%) $= (B - A)/B \times 100$

Measurement of each agent was triplicated.

Pharmacokinetic analysis

Areas under the concentration–time curve (AUC) over 360 min (AUC_{0-360}) for carbapenems were calculated with the trapezoidal rule. C_{max} of the plasma was calculated as follows: the concentration of 0 min (C_{max}) was calculated from the difference of the concentration of 5 min and that of 10 min. C_{max} of the pleural fluid was determined directly from the observed data.

Statistical analysis

For the significance test, the dual-placement variance analysis was performed. When there was a significant difference, Tukey's test was used. Statistical significance was defined as a P value <0.05.

Results

The plasma and pleural fluid levels of each agent are shown in Fig. 1a and b.

Plasma C_{max} of the test agents (Table 2)

As a single agent (Table 2), IPM achieved the highest plasma C_{max}, 84.5 ± 40.7 μg/ml, followed by BIPM, MEPM, and PAPM. There were no significant differences in the plasma C_{max} of the test agents among the single agents. Among the drug solution containing CS, MEPM/CS had the highest plasma C_{max}, 150.5 ± 60.0 μg/ml, followed by IPM/CS, PAPM/CS, and BIPM/CS. There were no significant differences in the plasma C_{max} among these mixed solutions.

Pleural fluid C_{max} of the test agents (Table 2)

In two rabbits treated with BIPM as a single agent, the pleural fluid level of BIPM reached a maximum 60 min after infusion. The pleural fluid levels of the remaining three agents reached a maximum 30 min after infusion. The highest pleural fluid C_{max} (9.4 ± 3.0 μg/ml) was obtained with PAPM, followed by BIPM, IPM, and MEPM. The pleural fluid C_{max} of PAPM and BIPM were significantly higher than that of MEPM. Among the drug solutions containing CS, the maximum level was reached in 60 min in three rabbits treated with BIPM/CS and in one rabbit treated with IPM/CS, whereas the maximum level was reached in 30 min in the remaining rabbits. MEPM/CS had the highest pleural fluid C_{max} (9.8 ± 4.0 μg/ml), followed by BIPM/CS, PAPM/CS, and IPM/CS. There were no significant differences among these mixed solutions.

Pleural fluid C_{max}/plasma C_{max} ratio (Table 2)

As a single agent, PAPM had the highest pleural fluid C_{max}/plasma C_{max} ratio (0.16 ± 0.06), followed by BIPM, IPM, and MEPM. The ratio for PAPM was significantly higher than that for MEPM. Among the drug solutions containing CS, the ratio for PAPM/CS was highest (0.12 ± 0.07), followed by BIPM/CS, MEPM/CS, and IPM/CS. The ratio for BIPM/CS was significantly higher than that for IPM/CS.

Plasma AUC_{0-360} of the test agents (Table 3)

As a single agent (Table 3), BIPM had the highest plasma AUC_{0-360} (2684.6 ± 362.8 μg min/ml), followed by PAPM, IPM, and MEPM. The plasma AUC_{0-360} of BIPM was significantly higher than with the other three agents. The plasma AUC_{0-360} of PAPM was significantly higher than that of MEPM.

Among the drug solutions containing CS, BIPM/CS had the highest plasma AUC_{0-360} (3040.1 ± 1525.9 μg min/ml), followed by PAPM/CS, IPM/CS, and MEPM/CS. There were no significant differences among these mixed solutions.

Pleural fluid AUC_{0-360} of the test agents (Table 3)

BIPM had the highest pleural fluid AUC_{0-360} (1247.3 ± 224.6 μg min/ml), followed by PAPM, MEPM, and IPM. The pleural fluid AUC_{0-360} of BIPM was significantly higher than that of MEPM and IPM. The pleural fluid AUC_{0-360} of PAPM was significantly higher than that of IPM. Among the drug solutions containing CS, MEPM/CS had the highest pleural

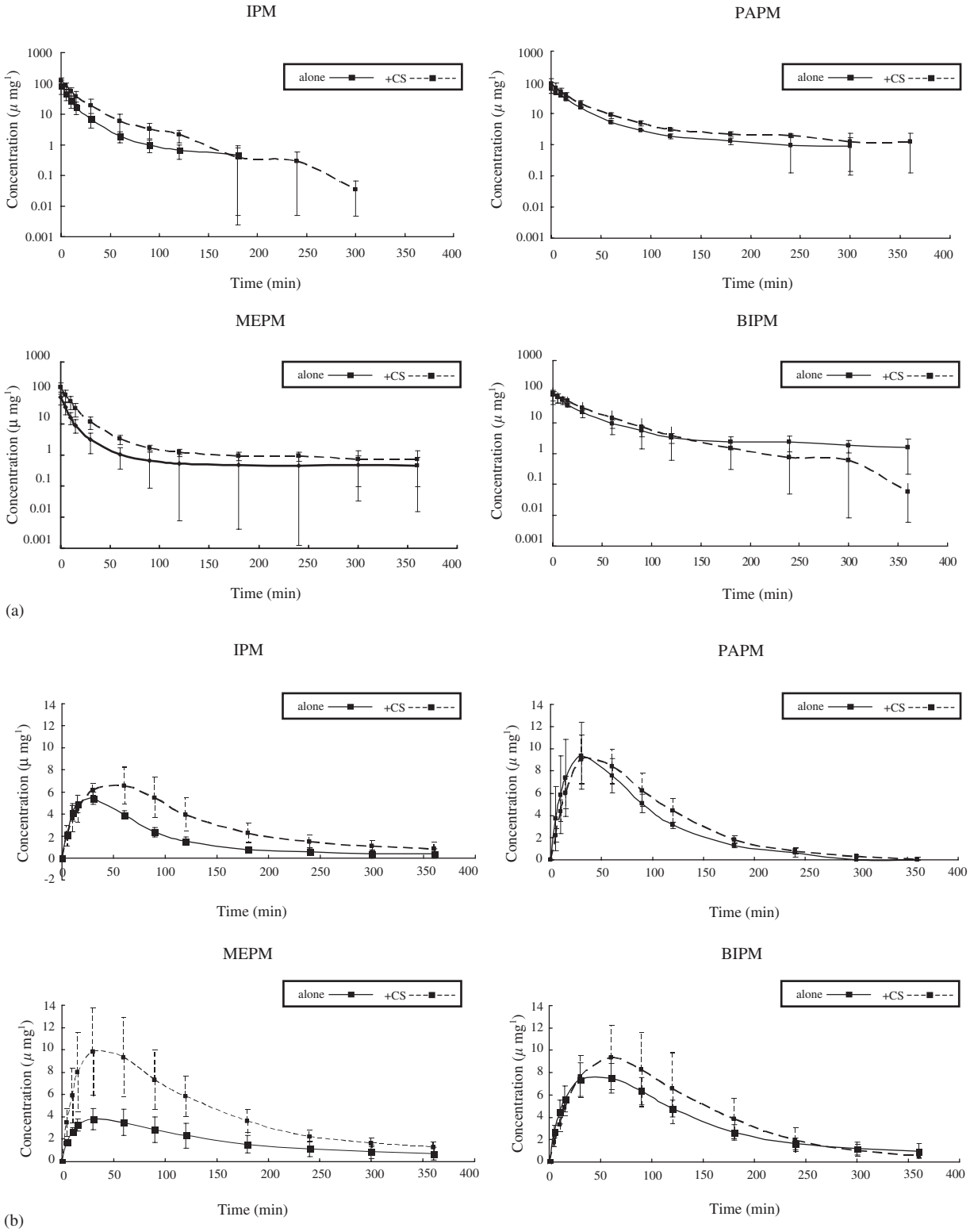

Figure 1 (a) Levels of carbapenem antibiotic agents in the plasma after administration of carbapenems. The plasma level of IPM was below the detection limit more than 180, 300 min after administration of IPM and IPM/CS. The plasma level of PAPM was below the detection limit more than 300 min after administration of PAPM. Other drug levels could be measured. Each group: $n = 3$. (b) Levels of carbapenem antibiotic agents in the pleural fluid after administration of carbapenems. The pleural fluid level of PAPM was below the detection limit more than 300 min after administration. Other drug levels could be measured. Each group: $n = 3$.

Table 2 Pharmacokinetic profile of carbapenem antibiotic agents C_{max} in the plasma and in the pleural fluid (each group: $n = 3$).

	Plasma C_{max} (μg/ml)		Pleural fluid C_{max} (μg/ml)		Pleural fluid C_{max}/Plasma C_{max}	
	Alone	+CS	Alone	+CS	Alone	+CS
IPM	84.5±40.7	119.2±28.8	5.4±0.5	7.0±1.4	0.08±0.05	0.06±0.02
PAPM	60.2±14.6	87.8±44.3	9.4±3.0[a]	9.0±2.2	0.16±0.06[b]	0.12±0.07
MEPM	72.4±31.7	150.5±60.0	3.8±0.9	9.8±4.0	0.06±0.02	0.07±0.01
BIPM	79.2±30.0	87.1±48.8	7.6±1.4[c]	9.3±2.9	0.11±0.06	0.12±0.03[d]

[a]Significantly different from MEPM ($P = 0.04$, Tukey).
[b]Significantly different from MEPM ($P = 0.004$, Tukey).
[c]Significantly different from MEPM ($P = 0.02$, Tukey).
[d]Significantly different from IPM ($P = 0.04$, Tukey).

Table 3 Pharmacokinetic profile of carbapenem antibiotic agents AUC in the plasma and in the pleural fluid (each group: $n = 3$).

	Plasma $AUC_{0–360}$ (μg min/ml)		Pleural fluid $AUC_{0–360}$ (μg min/ml)		Pleural fluid $AUC_{0–360}$/Plasma $AUC_{0–360}$	
	Alone	+CS	Alone	+CS	Alone	+CS
IPM	1055.3±420.3	2193.9±881.4	573.2±81.8	1062.7±206.8[a]	0.58±0.17	0.51±0.11
PAPM	1762.6±244.2[b]	2596.8±479.3	970.4±220.1[c]	1108.3±235.1	0.55±0.13	0.43±0.03
MEPM	776.3±354.6	2033.0±747.7	669.2±278.8	1594.9±510.3	0.89±0.13[d]	0.79±0.04[e]
BIPM	2684.6±362.8[f]	3040.1±1525.9	1247.3±224.6[g]	1495.7±594.0	0.48±0.13	0.51±0.08

[a]Significantly different from IPM (alone) ($P = 0.018$, Tukey).
[b]Significantly different from MEPM ($P = 0.02$, Tukey).
[c]Significantly different from IPM ($P = 0.042$, Tukey).
[d]Significantly different from BIPM ($P = 0.002$, Tukey) and significantly different from PAPM ($P = 0.03$, Tukey).
[e]Significantly different from PAPM ($P = 0.0002$, Tukey) and significantly different from BIPM ($P = 0.005$, Tukey) and significantly different from IPM ($P = 0.01$, Tukey).
[f]Significantly different from MEPM ($P = 0.002$, Tukey) and significantly different from IPM ($P = 0.007$, Tukey) and significantly different from PAPM ($P = 0.02$, Tukey).
[g]Significantly different from IPM ($P = 0.008$, Tukey) and significantly different from MEPM ($P = 0.048$, Tukey).

fluid $AUC_{0–360}$ (1594.8±510.3 μg min/ml), followed by BIPM/CS, PAPM/CS, and IPM/CS. There were no significant differences among these mixed solutions.

Pleural fluid $AUC_{0–360}$/plasma $AUC_{0–360}$ ratio (Table 3)

As a single agent, MEPM had the highest pleural fluid $AUC_{0–360}$/plasma $AUC_{0–360}$ ratio (0.89 ± 0.13), followed by IPM, PAPM, and BIPM. The ratio for MEPM was significantly higher than that for PAPM and BIPM. Among the drug solutions containing CS, the ratio for MEPM/CS was highest (0.79 ± 0.04), followed by IPM/CS, BIPM/CS, and PAPM/CS. The ratio for MEPM/CS was significantly higher than those for the remaining three agents.

Influence of CS (Tables 2 and 3)

We compared the test agents alone with the drug solutions containing CS. CS influenced the AUC of IPM in pleural fluid via inhibition of DHP-I-related hydrolysis.

Protein binding (Table 4)

The highest rates of protein binding in plasma and pleural fluid were obtained with MEPM (21.7±4.2%, 26.1±2.1%, respectively), followed by IPM, PAPM, and BIPM. BIPM produced a value significantly lower

Table 4 Protein binding of carbapenem antibiotic agents in the plasma and pleural fluid (each group: $n = 3$).

	Plasma (%)	Pleural fluid (%)
IPM	19.6 ± 1.5^{a}	25.0 ± 2.8^{b}
PAPM	14.8 ± 1.3^{c}	18.3 ± 3.2^{d}
MEPM	21.7 ± 4.2^{e}	26.1 ± 2.1^{f}
BIPM	2.3 ± 1.3	5.7 ± 3.8

[a]Significantly different from BIPM ($P = 0.0001$, Tukey) and significantly different from PAPM ($P = 0.01$, Tukey).
[b]Significantly different from BIPM ($P = 0.002$, Tukey).
[c]Significantly different from BIPM ($P = 0.0003$, Tukey).
[d]Significantly different from BIPM ($P = 0.01$, Tukey).
[e]Significantly different from BIPM ($P = 0.001$, Tukey).
[f]Significantly different from BIPM ($P = 0.001$, Tukey) and significantly different from PAPM ($P = 0.02$, Tukey).

than those of the remaining three agents. PAPM produced a value significantly lower than IPM. There was significantly lower pleural fluid protein binding with BIPM than with the remaining three agents. A significantly lower value was seen with PAPM than with MEPM.

Discussion

Generally, when agents are dissolved in blood they are present as free components or are bound to plasma protein. Release-type components are diffused passively through the extravascular tissue to exhibit their pharmacologic actions. In this study, we measured release-type components alone by HPLC using an ultrafiltration membrane.

Carbapenem antibiotic agents are hydrolyzed by DHP-I; however, the amount of hydrolysis differs among species.[14,15] MEPM was easily hydrolyzed by DHP-I from rabbits,[16] but was stable in human. In clinical practice, CS is contained in carbapenem antibiotic agents to achieve drug stabilization against human DHP-I. In this study, CS-containing solutions of the four agents had a higher plasma C_{max} and plasma AUC than those of the agents alone, although the differences were not significant. PAPM and MEPM, compared with IPM and BIPM, were rather easily hydrolyzed by DHP-1 from rabbits, as demonstrated by the large change in the plasma AUC. This might have been because CS prevented the influence of rabbit DHP-I-related hydrolysis on carbapenem antibiotic agents. Therefore, in this experiment, CS-containing solutions of the four agents might be appropriate for more accurate clinical evaluation.

Time above MIC is useful for evaluating the antimicrobial effect because of the time-dependent antimicrobial activity of these agents. But we could not calculate time above MIC, because this study did not use the infection models. Therefore, we investigated the C_{max} and AUC which are correlated with the total drug levels in vivo. Briefly, the ratio pleural fluid AUC/plasma AUC correlates with the penetration of a drug in the pleural space; therefore, it might be a useful index of pleural fluid penetration.

Molecular weight, presence or absence of liposolubility,[17] and protein binding[18,19] are important for the penetration of antimicrobial agents. Drugs with a lower molecular weight have better penetration. With respect to the presence or absence of fat solubility, many agents consist of slightly acidic organic acids or weak bases, and are present as non-ionic and ionic substances in a water environment. Non-ionic substances are fat soluble; they rapidly pass through the cell membrane, and are diffused. In comparison to non-ionic substances, however, ionic substances have poor diffusion due to electrical impedance related to the charge on the cell membrane. There were no marked differences in the molecular weights of IPM, PAPM, MEPM, and BIPM (i.e., 317, 339, 437, and 380, respectively). Furthermore, all carbapenem antibiotic agents consist of weak bases, and are present in blood as ionic substances, which might have resulted in the absence of marked differences. Concerning protein binding, the binding rate is low in rabbit peripheral lymph[18] or subcutaneous Visking Chamber[19] penetration, and penetration is better when the proportion of release-type components is higher.

Both MEPM alone and MEPM/CS had a high rate of pleural fluid penetration as demonstrated by the AUC measurements. As a single agent, PAPM produced the highest pleural fluid C_{max} and BIPM had the highest pleural fluid AUC. Among the drug solutions containing CS, however, MEPM produced both the highest pleural fluid C_{max} and the pleural fluid AUC. This might have been because the addition of CS eliminated the influence of DHP-I-related hydrolysis, maintaining the blood MEPM level and improving pleural fluid penetration in comparison to MEPM alone, as MEPM is unstable against rabbit DHP-I.[15] Both MEPM alone and MEPM/CS had a high rate of pleural fluid penetration. Cephem agents with a low protein-binding rate have good lymph and subcutaneous chamber penetration. In the present experiment, however, MEPM, with the highest protein binding rate, had the most favorable pleural fluid penetration, suggesting that the rate of protein binding is not

useful for evaluating pleural fluid penetration of carbapenem antibiotic agents.

Conclusion

In the present study, MEPM had the most favorable pleural fluid penetration, although it is necessary to study the pleural fluid penetration in various infection models and clinical trials. AUC may play the role of a useful maker for evaluating the bactericidal effect of β lactam antibiotics.

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