Penetrability of Intravenous Biapenem Into the Peritoneal Fluid of Laparotomy Patients and the Peritoneal Pharmacodynamics Against Gram-negative Bacteria

Kazuro Ikawa, PhD[1]
Norifumi Morikawa, PhD[1]
Kayo Ikeda, PhD[1]
Mitsuru Sakashita, MD[2]
Hiroki Ohge, MD[2]
Taijiro Sueda, MD[2]

[1]*Department of Clinical Pharmacotherapy, Hiroshima University, Hiroshima, Japan*

[2]*Department of Surgery, Hiroshima University iroshima, Japan*

KEY WORDS: Carbapenem, intraabdominal infections, pharmacokinetics, pharmacodynamics

ABSTRACT

This study examined the penetrability of biapenem into the peritoneal fluid (PF) of laparotomy patients and assessed the peritoneal pharmacodynamics against common gram-negative bacteria that cause intra-abdominal infections. Biapenem (300 mg) was administered by 0.5-h infusion to 10 patients before the laparotomy. The drug concentrations in both plasma and PF were determined, analyzed pharmacokinetically, and used for a stochastic simulation with the minimum inhibitory concentration (MIC) distribution data against clinical isolates. Intravenous biapenem penetrated well into PF, with an area under the drug concentration–time curve PF/plasma ratio of 0.77 ± 0.11 (mean ± SD, n = 10). The probabilities of attaining the pharmacodynamic target (30% of the time above MIC) in PF were ≥ 90% against Escherichia coli, Klebsiella species, Enterobacter cloacae, and Proteus mirabilis with 300 mg every 8 h (0.5-h infusion). However, 600 mg every 12 h (4-h infusion) or 600 mg every 8 h (0.5-h infusion) was required to achieve a target-attainment probability of ≥ 90% against Pseudomonas aeruginosa. These results should provide better understanding of the peritoneal pharmacokinetics of biapenem, while also helping to choose the appropriate dosage for intra-abdominal infections on the basis of the pharmacodynamic assessment.

INTRODUCTION

Biapenem is a broad-spectrum carbapenem used for the treatment of intra-abdominal infections and for antibacterial prophylaxis

in abdominal surgery.1 Since biapenem acts at the infection site, the drug's penetration into an intra-abdominal site such as peritoneal fluid (PF) is a key determinant of its efficacy. However, most pharmacokinetic studies on biapenem have focused on plasma concentrations.2 The treatment of patients with an intra-abdominal infection would benefit from a more thorough understanding of the rate and extent of penetration into the abdominal cavity.

Earlier studies have revealed that the antibacterial effects of biapenem correlate with the time period during which the drug concentration is above the minimum inhibitory concentration (MIC) for the bacterium (T > MIC),[3] particularly at the infection site. Moreover, a stochastic simulation, often called a Monte Carlo simulation,[4]has allowed variability to be incorporated into individual pharmacokinetics and antibacterial activities against a bacterial population. Therefore, it is important to predict the probabilities that biapenem regimens attain the pharmacodynamic target (30% T > MIC)3 in PF against bacterial populations using a stochastic simulation, in order to rationalize and optimize the regimen for intra-abdominal infections.

The objectives of this study were thus to examine the penetrability of biapenem into PF and to assess the peritoneal pharmacodynamics against gram-negative bacteria, the most common pathogens in intra-abdominal infections.[5]

METHODS

Study protocol

The study was approved by the Ethics Committee at Hiroshima University Hospital. Ten abdominal-surgery patients for the treatment of inflammatory bowel disease were included in from March 2005 to April 2005. Biapenem (300 mg) was administered by 0.5-h infusion before the surgery. Venous blood and PF samples were obtained at the end of the infusion and 1, 2, 3, 4, 5, and 6 h thereafter. The exudate fluid in the abdominal cavity was manually collected with a syringe during surgery and was obtained post-operatively through an intra-abdominal drain. The plasma and supernatant PF samples were removed after centrifugation, and were then stabilized with an equal volume of 1 mol/L 3-morpholino-propanesulfonic acid buffer (pH 7.0) and stored at –40°C until assay.

Biapenem Assay

The concentrations of biapenem in plasma and PF were determined by high-performance liquid chromatography as reported previously.[6] In brief, a plasma or PF sample was transferred to an ultrafiltration device. The device was centrifuged, and the filtered solution was injected onto a chromatograph with a C^{18} column and an ultraviolet absorbance detector. A mixture of sodium acetate buffer and acetonitrile was used as a mobile phase. The lower limit of quantification was 0.04 μg/mL, and the coefficients of variation were within 8% in both plasma and PF.

Pharmacokinetic Analysis

The penetrability of biapenem into PF was estimated using a non-compartmental pharmacokinetic analysis. Cmax was the observed maximum concentration of biapenem and Tmax was the time to Cmax. The area under the concentration–time curve from 0 to infinity (AUC0–∞) was calculated based on the trapezoidal rule using the MULTI program.[7]

Pharmacodynamic Analysis

The peritoneal pharmacodynamics against gram-negative bacteria was assessed using a population pharmacokinetic modeling and stochastic simulation approach[8] as follows:

(i) The drug concentrations in plasma (C1) and PF (C3) were simultaneously fit to a standard three-compartment model (Figure 1) using the NONMEM program VI (ICON Development Solutions, Ellicott, MD). The fixed-effects parameters were clearance (CL), volume of distribution of the central compartment (V1), central–peripheral clearance (Q2), volume of distribution of the peripheral compartment (V2), central–peritoneal clearance (Q3) and volume of distribution of the peritoneal compartment (V3). The inter-individual variability was modeled

Table 1. *Study patient information and non-compartmental pharmacokinetic parameters in plasma and peritoneal fluid (PF) of 300 mg biapenem after a 0.5-h infusion.*

Patient number (age and weight)	6.8Plasma C_{max} (μg/mL)	PF C_{max} (μg/mL)	PF/plasma C_{max} ratio	Plasma T_{max} (h)	PF T_{max} (h)	Plasma AUC0–∞ (μg•h/mL)	PF AUC0–∞ (μg•h/mL)	PF/plasma AUC0–∞ ratio
1 (47 yrs, 54.5 kg)	27.2	11.9	0.44	0.5	0.5	48.6	31.1	0.64
2 (23 yrs, 51.9 kg)	32.3	16.4	0.51	0.5	0.5	44.0	37.3	0.85
3 (72 yrs, 53.0 kg)	28.4	10.2	0.36	0.5	0.5	37.3	25.3	0.68
4 (48 yrs, 58.3)	35.0	12.3	0.35	0.5	0.5	45.5	33.6	0.74
5 (52 yrs, 43.0)	18.2	7.5	0.41	0.5	0.5	29.4	22.3	0.76
6 (48 yrs, 42.5 kg)	21.6	15.8	0.41	0.5	0.5	55.6	42.5	0.76
7 (36 yrs, 51.0 kg)	26.2	10.9	0.56	0.5	0.5	33.5	29.8	0.89
8 (31 yrs, 45.8 kg)	34.9	11.9	0.45	0.5	0.5	34.3	31.1	0.91
9 (40 yrs, 44.0 kg)	34.4	11.0	0.32	0.5	0.5	46.0	27.9	0.61
10 (31 yrs, 41.0 kg)	29.9	16.0	0.43	0.5	1.5	440.5	37.0	0.91
Mean	29.9	12.4	0.42	0.5	0.6	41.5	31.8	0.77
SD	6.8	2.9	0.06		0.3	8.0	6.0	0.11

C_{max}: observed maximum concentration; T_{max}: time to Cmax; AUC0–∞: area under the concentration–time curve from 0 to infinity calculated based on the trapezoidal rule.-

exponentially: $\theta i = \theta * \exp(\eta)$, where θi is the fixed effects parameter for the ith subject, θ is the mean value of the fixed effects parameter in the population, and η is a random inter-individual variable.

(ii) Five major types of Gram-negative bacteria in intra-abdominal infections were selected5,9, and the MIC distribution data against their clinical isolates were derived from recent susceptibility surveillance reports10,11 as follows: Escherichia coli (n = 271; MIC for 50% of the clinical isolates (MIC50) = 0.063 μg/mL; MIC for 90% of the clinical isolates (MIC90) = 0.063 μg/mL), Klebsiella species (n = 251; MIC50 = 0.25 μg/mL; MIC90 = 0.5 μg/mL), Pseudomonas aeruginosa (n = 628; MIC50 = 0.5 μg/mL; MIC90 = 16 μg/mL), Enterobacter cloacae (n = 173; MIC50 = 0.125 μg/mL; MIC90 = 0.5 μg/mL) and Proteus mirabilis (n = 182; MIC50 = 2 μg/mL; MIC90 = 2 μg/mL).

(iii) Using the developed pharmacokinetic model and the MIC distribution data, the stochastic simulation was conducted for each combination of biapenem regimen (0.5-h or 4-h infusion) and bacterium. The following process was repeated from the 1st to 10000th subject using the Crystal Ball software 2000 (Decisioneering, Denver, CO): A set of fixed-effects parameters (CL, V1, Q2, V2, Q3 and V3) was randomly generated according to each mean estimate (θ) and inter-individual variance (η) of the population pharmacokinetic model. The drug concentration in PF versus time curve was created using the set of fixed-effects parameters. Subsequently, a different value of MIC (0.032, 0.063, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 or 128 μg/mL) was generated by random sampling from the bacterial population with the custom distribution. The time point at which the drug concentration coincided with the MIC was determined, and the T > MIC was calculated as the cumulative percentage for the dosing interval. The probability of attaining the pharmacodynamic target (%) was determined as the fraction that achieved at least 30% T > MIC of 10000 estimates.

RESULTS

Table 1 summarizes the study patient information and the non-compartmental pharmacokinetic parameters of biapenem. Cmax was 29.9 ± 6.8 μg/mL (n = 10) at 0.5 h in plasma and 12.4 ± 2.9 μg/mL at 0.6 ± 0.3 h in PF (i.e., mean Tmax delay of 0.1 h behind plasma), and the Cmax ratio of PF to plasma was 0.42 ± 0.06. AUC0–∞ was 41.5 ± 8.0 μg•h/mL in plasma and 31.8 ± 6.0

Table 2. *Population pharmacokinetic parameter estimates of biapenem.*

	Fixed-effects parameter, θ	Inter-individual variability, η
CL	8.12 (L/h)	0.0201
V1	6.61 (L)	0.246
Q2	1.81 (L/h)	0
V2	3.33 (L)	0
Q3	8.73 (L/h)	0.288
V3	4.96 (L)	0

μg•h/mL in PF, and the AUC0–∞ ratio of PF to plasma was 0.77 ± 0.11.

Table 2 lists the population parameter estimates for the pharmacokinetic model (Figure 1). Q2, V2 and V3 were finally evaluated as fixed values without any inter-individual variability because their η were <0.0001. Using these population pharmacokinetic parameters and the MIC distribution data, the stochastic simulation (Table 3) showed that a biapenem regimen of 300 mg every 12 h (0.5-h infusion) achieved a value of ≥90% (a clinically acceptable criterion for the target-attainment probability)[8] against E. coli, Klebsiella spp. and E. cloacae, and a regimen of 300 mg every 8 h (0.5-h infusion) achieved 93.9% against P. mirabilis. However, against P. aeruginosa, the values were lower and only regimens of 600 mg every 12 h (4-h infusion) and 600 mg every 8 h (0.5-h infusion) achieved a target-attainment probability of ≥90%.

DISCUSSION

This study examined the peritoneal pharmacokinetics of biapenem in laparotomy patients and found that intravenous biapenem penetrated into the PF rapidly (mean delay in Tmax, 0.1 h) and extensively (mean PF/plasma ratio in AUC0–∞, 0.77). This study also demonstrated that 300 mg every 8 h (0.5-h infusion) achieved a target-attainment probability of ≥90% in PF against major Gram-negative bacteria in intra-abdominal infections except P. aeruginosa.

As we reported previously, the PF/plasma ratios in AUC0–∞ (commonly used as the index of peritoneal penetration) were 0.74–0.90 (n = 6) for imipenem[12] and 0.70–1.07 (n = 10) for doripenem.[13] The current study indicates that biapenem (the AUC0–∞ PF/plasma ratio of 0.61–0.91, Table 1) has the same peritoneal penetrability as imipenem and doripenem. This was expected because these three carbapenems have similar physical and chemical properties (low molecular weight and low protein binding).[14]

Although earlier stochastic simulations to assess the peritoneal pharmacodynamics of β-lactams[15,16] were based only on drug concentrations in plasma, it is necessary to use drug concentrations in PF, but not in plasma, for more accurate assessment. The current simulations based on biapenem concentrations in PF showed that 300 mg every 8 h (0.5-h infusion) achieved a target-attainment probability of ≥90% against E. coli, Klebsiella spp., E. cloacae and P. mirabilis. Considering that these four bacteria account for >80%9 of the causative Gram-negative

Table 3. *Probabilities of attaining the pharmacodynamic target (30% T > MIC) in peritoneal fluid (PF) against Gram-negative clinical isolates (Escherichia coli, Klebsiella species, Pseudomonas aeruginosa, Enterobacter cloacae and Proteus mirabilis) using different biapenem regimens (0.5-h and 4-h infusions).*

Biapenem regimen	Target-attainment probability (%) in PF				
	E. coli	*Klebsiella* spp.	*P. aeruginosa*	*E. cloacae*	*P. mirabilis*
300 mg every 12 h (0.5-h infusion)	100	99.3	76.6	99.4	62.1
300 mg every 8 h (0.5-h infusion)	100	99.6	83.7	99.4	93.9
600 mg every 12 h (0.5-h infusion)	100	99.6	83.4	99.4	92.7
600 mg every 12 h (4-h infusion)	100	99.6	92.0	99.7	99.1
600 mg every 8 h (0.5-h infusion)	100	99.6	92.2	99.8	99.1

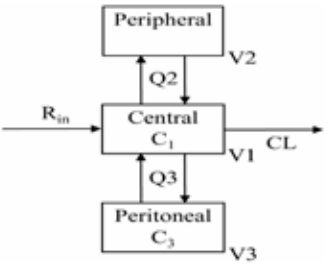

Figure 1. *Three-compartment pharmacokinetic model for biapenem. C1 and C3: the drug concentrations in the central and peritoneal compartments (μg/mL); V1, V2 and V3: volumes of distribution of the central, peripheral and peritoneal compartments (L); CL: clearance from the central compartment (L/h); Q2 and Q3: inter-compartmental clearances (L/h); Rin: drug infusion rate (mg/h).*

pathogens in intra-abdominal infections, 300 mg every 8 h (0.5-h infusion) would be, in principal, sufficient for empirical treatment of intra-abdominal infections. However, when the symptoms in a patient generate a strong suspicion of infection with resistance-developing bacteria such as P. aeruginosa (MIC90 = 16 μg/mL), a higher dosage should be recommended. In this case, 600 mg every 12 h (4-h infusion) (92.0% target-attainment probability with 1200 mg per day regimen, Table 3) can compete with 600 mg every 8 h (0.5-h infusion; 92.2% with 1800 mg per day regimen). From a pharmacoeconomic viewpoint, 600 mg every 12 h (4-h infusion) would be preferable to 600 mg every 8 h (0.5-h infusion), unless the prolongation of infusion time is unacceptable due to increasing the patient's burdens and the medical workload.

Lastly, the pharmacokinetic data of this study was obtained in abdominal-surgery patients with inflammatory bowel disease. The invasiveness of surgery might have affected the pharmacokinetics. In addition, the drug concentrations in the PF might be underestimated because inflammatory bowel disease has a greater amount of peritoneal exudate fluid than other diseases. The peritoneal pharmacoinetics of biapenem should be confirmed in another patient population.

In conclusion, intravenous biapenem penetrated rapidly and extensively into the PF of laparotomy patients. A biapenem regimen of 300 mg every 8 h (0.5-h infusion) achieved a target-attainment probability of ≥90% against the major bacteria that cause intra-abdominal infections, such as E. coli, Klebsiella spp, E. cloacae and P. mirabilis. However, against resistance-developing bacteria such as P. aeruginosa, 600 mg every 12 h (4-h infusion) or 600 mg every 8 h (0.5-h infusion) was required to achieve a target-attainment probability of ≥90%. These results should provide better understanding of the peritoneal pharmacokinetics of biapenem, while also helping to choose the appropriate dosage for intra-abdominal infections on the basis of the pharmacodynamic assessment. The clinical implications of these findings in the future need to be confirmed in a larger number of patients.

REFERENCES

1. Perry CM, Ibbotson T. Biapenem. *Drugs.* 2002;62:2221–2234.
2. Mouton JW, Touzw DJ, Horrevorts AM, et al. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet.* 2000;39:185–201.
3. Takata T, Aizawa K, Shimizu A, et al. Optimization of dose and dose regimen of biapenem based on pharmacokinetic and pharmacodynamic analysis. *J Infect Chemother.* 2004;10:76–85.
4. Drusano GL, Preston SL, Hardalo C, et al. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. *Antimicrob Agents Chemother*. 2001;45:13–22.
5. Tellado JM, Wilson SE. Empiric treatment of nosocomial intra-abdominal infections: a focus on the carbapenems. *Surg Infect*. 2005;6:329–343.
6. Ikeda K, Ikawa K, Ikeda A, et al. A simple and rapid determination of biapenem in plasma by high-performance liquid chromatography. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2006;844:148–152.
7. Yamaoka K, Tanigawara Y, Nakagawa T, et al. A pharmacokinetic analysis program (multi) for microcomputer. *J Pharmacobiodyn.* 1981;4:879–885.
8. Ikawa K, Morikawa N, Hayato S, et al. Pharmacokinetic and pharmacodynamic profiling of cefepime in plasma and peritoneal fluid of abdominal surgery patients. *Int J Antimicrob Agents.* 2007;30:270–273.
9. Paterson DL, Rossi F, Baquero F, et al. In vitro susceptibilities of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: the 2003 Study for Monitoring Antimicrobial Resistance Trends

(SMART). *J Antimicrob Chemother*. 2005;55:965–973.

10. Yamaguchi K, Murakami M, Takahashi A, et al. Nationwide surveillance of parenteral antibiotics containing meropenem activities against clinically isolated strains in 2004. *Jpn J Antibiot.* 2005;58:655–689.
11. Yamaguchi K, Ishii Y, Iwata M, et al. Nationwide surveillance of parenteral antibiotics containing meropenem activities against clinically isolated strains in 2006. *Jpn J Antibiot.* 2007;60:344–377.
12. Ikawa K, Morikawa N, Sakamoto K, et al. Pharmacokinetics and pharmacodynamic assessment of imipenem in the intraperitoneal fluid of abdominal surgery patients. *Chemotherapy*. 2008;54:131–139.
13. Ikawa K, Morikawa N, Urakawa N, et al. Peritoneal penetration of doripenem after intravenous administration in abdominal-surgery patients. J *Antimicrob Chemother.* 2007;60:1395–1397.
14. Zhanel GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. *Drugs*. 2007;67:1027–1052.
15. Kotapati S, Kuti JL, Nicolau DP. Pharmacodynamic modeling of beta-lactam antibiotics for the empiric treatment of secondary peritonitis: a report from the OPTAMA program. *Surg Infect*. 2005;6:297–304.
16. Eagye KJ, Kuti JL, Dowzicky M, et al. Empiric therapy for secondary peritonitis: a pharmacodynamic analysis of cefepime, ceftazidime, ceftriaxone, imipenem, levofloxacin, piperacillin/tazobactam, and tigecycline using Monte Carlo simulation. *Clin Ther.* 2007;29:889–899.