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Pharmacokinetics of piperacillin-tazobactam in plasma, peritoneal fluid and peritoneum of surgery patients, and dosing considerations based on site-specific pharmacodynamic target attainment

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ABSTRACT

Piperacillin-tazobactam (PIP-TAZ) is commonly used to treat intraabdominal infections; however, its penetration into abdominal sites is unclear. A pharmacokinetic analysis of plasma, peritoneal fluid, and peritoneum drug concentrations was conducted to simulate dosing regimens needed to attain the pharmacodynamic target in abdominal sites. PIP-TAZ (4 g-0.5 g) was intravenously administered to 10 patients before abdominal surgery for inflammatory bowel disease. Blood, peritoneal fluid, and peritoneum samples were obtained at the end of infusion (0.5 h) and up to 4 h thereafter. PIP and TAZ concentrations were measured, both noncompartmental and compartmental pharmacokinetic parameters were estimated, and a simulation was conducted to evaluate site-specific pharmacodynamic target attainment. The mean peritoneal fluid:plasma ratios in the area under the drug concentration-time curve (AUC) were 0.75 for PIP and 0.79 for TAZ, and the mean peritoneal fluid:plasma ratios in the AUC were 0.49 for PIP and 0.53 for TAZ. The mean PIP:TAZ ratio was 8.1 at both peritoneal sites. The regimens that achieved a bactericidal effect with PIP (time above minimum inhibitory concentration [MIC] >50%) at both peritoneal sites were PIP-TAZ 4.5 g twice daily for an MIC of 8 mg/L, as well as 4.5 g three times daily, and 3.375 g four times daily for an MIC of 16 mg/L. These findings clarify the peritoneal pharmacokinetics of PIP-TAZ, and help consider the dosing regimens for intraabdominal infections based on site-specific pharmacodynamic target attainment.

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1. Introduction

Piperacillin-tazobactam (PIP-TAZ) is an intravenously administered combination of PIP, a penicillin antibiotic, and TAZ, a beta-lactamase inhibitor [1]. PIP-TAZ has broad-spectrum activity against Gram-positive and Gram-negative bacteria. PIP-TAZ is used to treat various infections, including pneumonia, urinary tract infections, and intraabdominal infections [2,3]. Previous pharmacokinetic studies have demonstrated that the serum concentration of PIP-TAZ increases rapidly and achieves a maximum concentration at the end of intravenous infusion [4]. However, the clinical effects of PIP-TAZ

depend on its ability to reach the site of infection. Therefore, understanding the pharmacokinetic distribution of PIP-TAZ can help clarify the pharmacodynamic effects of the drug for treating tissue-site infections such as peritonitis.

Shimizu et al [5] measured PIP-TAZ concentrations in peritoneal fluid; however, those authors did not measure plasma concentrations or characterize the peritoneal pharmacokinetics. Additionally, there have been no reports regarding PIP-TAZ concentrations in the peritoneum. Therefore, the present study was conducted to investigate the pharmacokinetics of intravenous PIP-TAZ in the plasma, peritoneal fluid, and peritoneum, and a pharmacokinetic analysis was performed to simulate dosing regimens needed to attain the pharmacodynamic target in abdominal sites.

2. Patients and methods

2.1. Study subjects

This was a prospective, open study on the peritoneal pharmacokinetics of PIP-TAZ conducted at Hiroshima University Hospital

Abbreviations: PIP-TAZ: piperacillin-tazobactam; AUC: area under the drug concentration-time curve; MIC: minimum inhibitory concentration; C_{max}: observed maximum concentration; CLSI: susceptible breakpoint MIC by Clinical and Laboratory Standards Institute; EUCAST: epidemiological cut-off MIC by European Committee on Antimicrobial Susceptibility Testing.

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from June 2014 to May 2015. The study protocol and informed consent form complied with the Declaration of Helsinki and were reviewed and approved by the ethics committee of the institution.

Patients undergoing abdominal surgery for the relief of inflammatory bowel disease were chosen as the study subjects as these patients have a sufficient amount of peritoneal exudate for sampling. The inclusion criteria were as follows: elective patients of both sexes aged over 20 years who were amenable to antibacterial prophylaxis for postoperative infections and were willing and able to provide written informed consent. Any patient who was pregnant or hypersensitive to beta-lactams was excluded.

2.2. Drug administration and sample collection

Prophylactic PIP-TAZ (4 g-0.5 g) was administered intravenously by 0.5-h infusion. Venous blood (2 mL), peritoneal fluid (2 mL), and peritoneum (4 mm × 4 mm) samples were planned to be obtained at the end of infusion (0.5 h) and every hour thereafter until the completion of abdominal surgery. The plasma and supernatant peritoneal fluid samples were removed after centrifugation, and the peritoneum samples were rinsed in physiological saline. All samples were stored at -40 °C until assay.

2.3. PIP and TAZ assay

The total concentration of PIP and TAZ in plasma, peritoneal fluid, and the peritoneum was measured via high-performance liquid chromatography as previously reported, with modifications [6]. For PIP, peritoneum samples were homogenized using an overhead mixer with two volumes (w/v) of double distilled water. The homogenate was centrifuged, and the supernatant was collected for further procedures. Plasma, supernatant peritoneal fluid, and peritoneum samples (200 µL each) were added to 800 µL acetonitrile, and the resulting solution was mixed with a vortex mixer and centrifuged. The supernatants (900 µL) were then added to 4 mL dichloromethane and the resulting solution was mixed with a vortex mixer and centrifuged. Next, the supernatants (20 µL) were injected into a chromatograph with a C₁₈ column at 40 °C and an ultraviolet absorbance detector at 220 nm. The mobile phase consisted of a mixture of 230 mmol/L potassium phosphate buffer (pH 2.6) and acetonitrile (75:25) with a flow rate of 1 mL/min. The quantification ranges were 0.5–1000 mg/L for plasma and peritoneal fluid and 1.5–1500 mg/kg for peritoneum samples. For intra- and inter-day assays, the precision was 0.69–7.24% and the accuracy was 99.6–107%.

For TAZ, the same measurement methods as those described for PIP were used, except the mobile phase was 230 mmol/L potassium phosphate buffer (pH 2.6) and acetonitrile (95:5). The quantification ranges were 0.5–100 mg/L for plasma and peritoneal fluid and 1.5–150 mg/kg for peritoneum samples. For intra- and inter-day assays, the precision was 1.10–9.49% and the accuracy was 97.5–112%.

2.4. Noncompartmental pharmacokinetic analysis

For each drug, C_{max} was defined as the observed maximum concentration. The area under the drug concentration-time curve from 0 to infinity (AUC_{0-∞}) was calculated based on the trapezoidal rule using the MULTI software program (originally developed by Yamaoka et al [7] and currently maintained by the Department of Biopharmaceutics and Drug Metabolism; Kyoto University, Kyoto, Japan). In the pharmacokinetic analysis, specific gravity of the peritoneum was taken as 1 (kg = L).

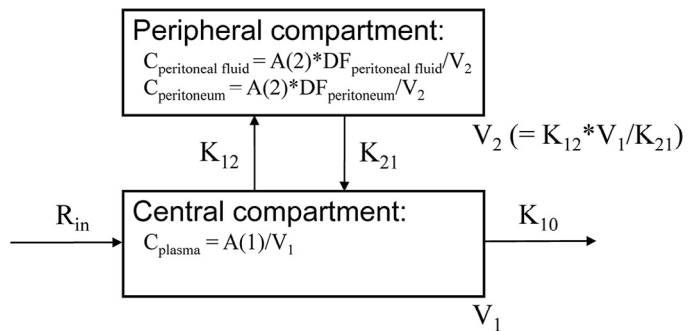


Fig. 1. Hypothetical two-compartment pharmacokinetic model for piperacillin and tazobactam. A(1) and A(2), amounts of drug in the central and peripheral (including peritoneal sites) compartments (mg); V₁ and V₂, volumes of distribution of the central and peripheral compartments (L = kg); C, concentration of drug in plasma and peritoneal fluid (mg/L) and peritoneum (mg/kg); R_{in}, intravenous infusion rate of drug (mg/h); K₁₂ and K₂₁, transfer rate constants (1/h); K₁₀, elimination rate constant (1/h); DF, distribution factors to account for drug concentration differences between plasma and peritoneal sites (fluid and tissue).

2.5. Compartmental pharmacokinetic analysis

The preliminary analysis for each drug indicated that a three- or four-compartment model to describe the three drug concentrations (plasma, peritoneal fluid, and peritoneum) was too complicated; rather, a simpler model could be used because of the parallel drug elimination slopes for the peritoneal fluid and peritoneum. Therefore, the concentration-time data were fitted to a hypothetical two-compartment model with distribution factors [8] to account for concentration differences between the plasma and peritoneal sites (Fig. 1). The differential equations for changes in the amount of drug in the central compartment (A[1], mg) and peripheral compartment (including peritoneal fluid and peritoneum) (A[2], mg) regarding time (t) are as follows:

$$dA(1)/dt = R_{in} - (K_{12} + K_{10}) * A(1) + K_{21} * A(2)$$

$$dA(2)/dt = K_{12} * A(1) - K_{21} * A(2)$$

where R_{in} is the intravenous infusion rate of drug (mg/h), K₁₂ and K₂₁ are the transfer rate constants (1/h) connecting the central and peripheral compartments, and K₁₀ is the elimination rate constant (1/h) from the central compartment.

In this model, the distribution volumes are V₁ for the central compartment (L) and V₂ for the peripheral compartment (L) (V₂ = K₁₂*V₁/K₂₁). Assuming distribution factors to account for drug concentration differences between the plasma and peritoneal fluid (DF_{peritoneal fluid}) and between the plasma and peritoneum (DF_{peritoneum}), the equations for the drug concentration in plasma (C_{plasma}, mg/L), peritoneal fluid (C_{peritoneal fluid}, mg/L), and peritoneum (C_{peritoneum}, mg/L) are expressed as follows:

$$C_{plasma} = A(1)/V_1$$

$$C_{peritoneal\ fluid} = A(2) * DF_{peritoneal\ fluid} / V_2 \\ = A(2) * DF_{peritoneal\ fluid} * K_{21} / [K_{12} * V_1]$$

$$C_{peritoneum} = A(2) * DF_{peritoneum} / V_2 = A(2) * DF_{peritoneum} * K_{21} / [K_{12} * V_1]$$

These six pharmacokinetic model parameters (K₁₂, K₂₁, K₁₀, V₁, DF_{peritoneal fluid}, and DF_{peritoneum}) were estimated for each patient using the MULTI software program [7].

2.6. Site-specific pharmacodynamic target attainment analysis

For each PIP-TAZ regimen (4 g-0.5 g or 3 g-0.375 g; twice, three times, or four times daily; 0.5-h infusion), the duration for which the drug concentration was above the minimum inhibitory concentration ($T > MIC$) for PIP in the peritoneal fluid and peritoneum was predicted. Using the same method as in the earlier simulation [6,9,10], the drug concentration was not adjusted for protein binding, but treated as the free fraction; the protein-binding values of PIP at these peritoneal sites are currently unknown. Using mean estimates for the six pharmacokinetic model parameters for PIP, the time point at which the simulated drug concentration in the peritoneal fluid and peritoneum coincided with an MIC (0.031–128 mg/L) was determined, and the $T > MIC$ was calculated as the cumulative percentage of a 24-h period.

Based on the findings from the analysis of pharmacodynamic target attainment, the site-specific pharmacodynamic breakpoint MIC was defined as the highest MIC at which $T > MIC$ in both the peritoneal fluid and peritoneum was greater than the bactericidal target of 50% for PIP.

3. Results

3.1. Study subjects

Eight male and two female patients were included in this study. The patients had inflammatory bowel disease (nine patients had Crohn's disease and one had ulcerative colitis) and underwent abdominal surgery (five underwent proctocolectomy, three underwent colectomy, and two underwent small bowel resection). Patient demographics were as follows: age, 40.3 ± 13.8 years (mean \pm standard deviation [SD]); weight, 56.8 ± 11.4 kg; body mass index, 21.3 ± 5.1 kg/m²; creatinine clearance estimated by the Cockcroft-Gault formula, 87.4 ± 30.6 mL/min; total bilirubin, 0.7 ± 0.4 mg/dL; aspartate aminotransferase, 30.9 ± 12.6 IU/L; and alanine aminotransferase, 46.3 ± 45.5 IU/L.

3.2. Sample collection and PIP and TAZ assay

A total of 47 plasma samples, 26 peritoneal fluid samples, and 27 peritoneum samples were collected. PIP concentrations ranged from 12.6–534.0 mg/L for plasma, 14.6–297.8 mg/L for peritoneal fluid, and 14.4–220.2 mg/kg for the peritoneum; TAZ concentrations ranged from 1.5–59.2 mg/L, 2.0–33.4 mg/L, and 1.8–27.2 mg/kg, respectively. All measurements were above each limit of quantification.

3.3. Noncompartmental pharmacokinetic analysis

The noncompartmental pharmacokinetic parameters are summarized in Table 1. The mean peritoneal fluid:plasma ratios were 0.52–0.75 for PIP, which are roughly the same as those for TAZ (0.50–0.79). The mean peritoneum:plasma ratios were 0.32–0.49 for PIP and 0.34–0.53 for TAZ, which are less than the peritoneal fluid:plasma ratios measured for PIP and TAZ. The mean PIP:TAZ ratios were 8.7–9.3 for plasma, 8.1–8.4 for peritoneal fluid, and 8.1–9.1 for the peritoneum. Similarly, regression equations for the observed concentrations showed that the PIP:TAZ ratios were 8.53 for peritoneal fluid (Fig. 2a) and 8.61 for the peritoneum (Fig. 2b). These values were roughly the same as the combination ratio (8:1) of PIP and TAZ.

3.4. Compartmental pharmacokinetic analysis

The pharmacokinetic parameters in the hypothetical two-compartment model (Fig. 1) are summarized in Table 2. The

Table 1

Noncompartmental pharmacokinetic parameters of piperacillin and tazobactam after 0.5-h intravenous infusion of 4 g-0.5 g.

Sample type and parameter	Value (mean \pm SD, n = 10)		
	Piperacillin (4 g)	Tazobactam (0.5 g)	Piperacillin:tazobactam ratio
Plasma			
C_{max} (mg/L)	394.3 \pm 104.5	42.4 \pm 11.8	9.3 \pm 0.4
$AUC_{0-\infty}$ (mg \cdot h/L)	636.0 \pm 120.9	72.7 \pm 13.4	8.7 \pm 0.3
Peritoneal fluid			
C_{max} (mg/L)	192.7 \pm 48.5	23.6 \pm 5.7	8.4 \pm 0.7
$AUC_{0-\infty}$ (mg \cdot h/L)	498.1 \pm 161.4	61.4 \pm 19.1	8.1 \pm 0.6
Peritoneum			
C_{max} (mg/kg)	131.3 \pm 64.6	14.9 \pm 8.0	9.1 \pm 1.1
$AUC_{0-\infty}$ (mg \cdot h/kg)	327.6 \pm 84.0	41.2 \pm 12.4	8.1 \pm 0.8
Peritoneal fluid:plasma ratio			
C_{max}	0.52 \pm 0.19	0.50 \pm 0.12	
$AUC_{0-\infty}$	0.75 \pm 0.21	0.79 \pm 0.19	
Peritoneum:plasma ratio			
C_{max}	0.32 \pm 0.14	0.34 \pm 0.15	
$AUC_{0-\infty}$	0.49 \pm 0.12	0.53 \pm 0.14	

C_{max} , observed maximum concentration.

$AUC_{0-\infty}$, area under the drug concentration-time curve from 0 to infinity calculated based on the trapezoidal rule.

SD, standard deviation.

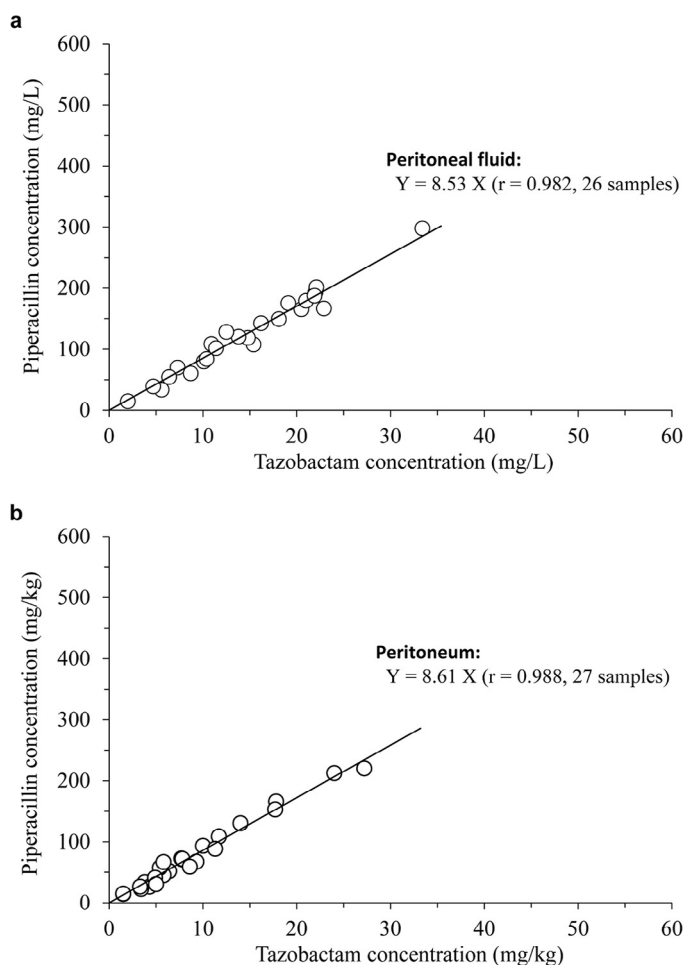


Fig. 2. Relationship between the observed concentrations of piperacillin and tazobactam in the peritoneal fluid (a) and peritoneum (b) after 0.5-h intravenous infusion of 4 g-0.5 g. The lines represent regression equations.

Table 2
Pharmacokinetic parameters for piperacillin and tazobactam in the hypothetical two-compartment model (Fig. 1)

Parameter	Estimate (mean \pm SD, n = 10)	
	Piperacillin	Tazobactam
K_{12} (1/h)	2.85 \pm 0.45	3.76 \pm 1.21
K_{21} (1/h)	3.13 \pm 0.99	3.46 \pm 1.41
K_{10} (1/h)	1.23 \pm 0.14	1.25 \pm 0.20
V_1 (L)	5.48 \pm 1.03	5.92 \pm 0.98
$DF_{\text{peritoneal fluid}}$	0.220 \pm 0.151	0.179 \pm 0.136
$DF_{\text{peritoneum}}$	0.286 \pm 0.264	0.271 \pm 0.254

K_{12} and K_{21} , transfer rate constants connecting central and peripheral compartments. K_{10} , elimination rate constant from central compartment. V_1 , distribution volume of central compartment. $DF_{\text{peritoneal fluid}}$ and $DF_{\text{peritoneum}}$, distribution factors to account for concentration differences between plasma and peritoneal sites (fluid and tissue). SD, standard deviation.

simulation curves drawn using mean parameter estimates ($K_{12} = 2.85$ 1/h, $K_{21} = 3.13$ 1/h, $K_{10} = 1.23$ 1/h, $V_1 = 5.48$ L, $DF_{\text{peritoneal fluid}} = 0.220$, and $DF_{\text{peritoneum}} = 0.286$ for PIP; $K_{12} = 3.76$ 1/h, $K_{21} = 3.46$ 1/h, $K_{10} = 1.25$ 1/h, $V_1 = 5.92$ L, $DF_{\text{peritoneal fluid}} = 0.179$, and $DF_{\text{peritoneum}} = 0.271$ for TAZ) were well-fit to all mean measurements in plasma, peritoneal fluid, and peritoneum for PIP (Fig. 3a) and TAZ (Fig. 3b). The regression

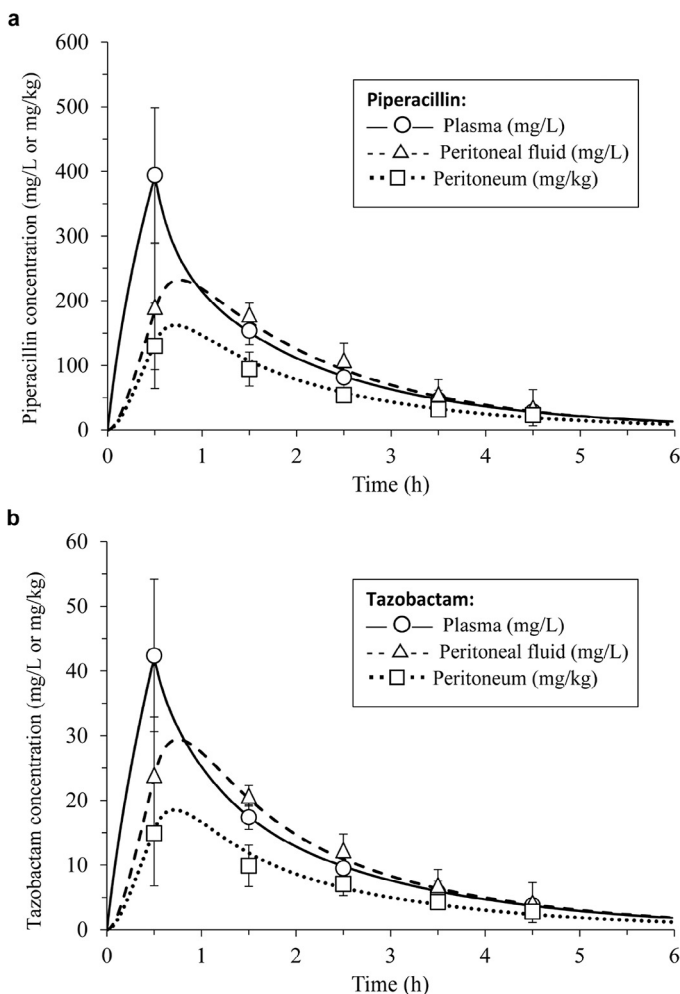


Fig. 3. Observed concentrations (mean \pm SD, n = 10) and simulation curves for piperacillin (a) and tazobactam (b) in plasma, peritoneal fluid and peritoneum after 0.5-h intravenous infusion of 4 g-0.5 g. The simulation curves were drawn using the mean pharmacokinetic model parameters for each drug (Table 2).

equations between the predicted concentration (Y) and the individual predicted concentration were $Y = 1.01 X - 2.06$ ($r = 0.992$, 100 samples) for PIP and $Y = 1.05 X - 0.276$ ($r = 0.989$, 100 samples) for TAZ. The normalized mean prediction error (as a bias index) and the normalized mean absolute prediction error (as an accuracy index) values were 0.0291 and 0.0930 for PIP and 0.0338 and 0.103 for TAZ, respectively.

3.5. Site-specific pharmacodynamic target attainment analysis

Using mean estimates for the six pharmacokinetic model parameters for PIP, drug concentrations were predicted for different dosing regimens to determine whether pharmacodynamic target attainment could be achieved in peritoneal fluid (Fig. 4a) and the peritoneum (Fig. 4b). Based on the findings from previous studies, we assumed that PIP exerts a bactericidal effect when $T > MIC$ is greater than 50%. The regimens that achieved the target at both peritoneal sites were PIP-TAZ 4.5 g twice daily (total 9 g/day) for an MIC of 8 mg/L and 4.5 g three times daily and 3.375 g four times daily (both total 13.5 g/day) for an MIC of 16 mg/L, as summarized in Table 3. PIP-TAZ 4.5 g four times daily was needed for an MIC of 32 mg/L; however, for an MIC of 64 mg/L, 4.5 g four times daily achieved a value $> 50\%$ in the peritoneal fluid, but not in the peritoneum.

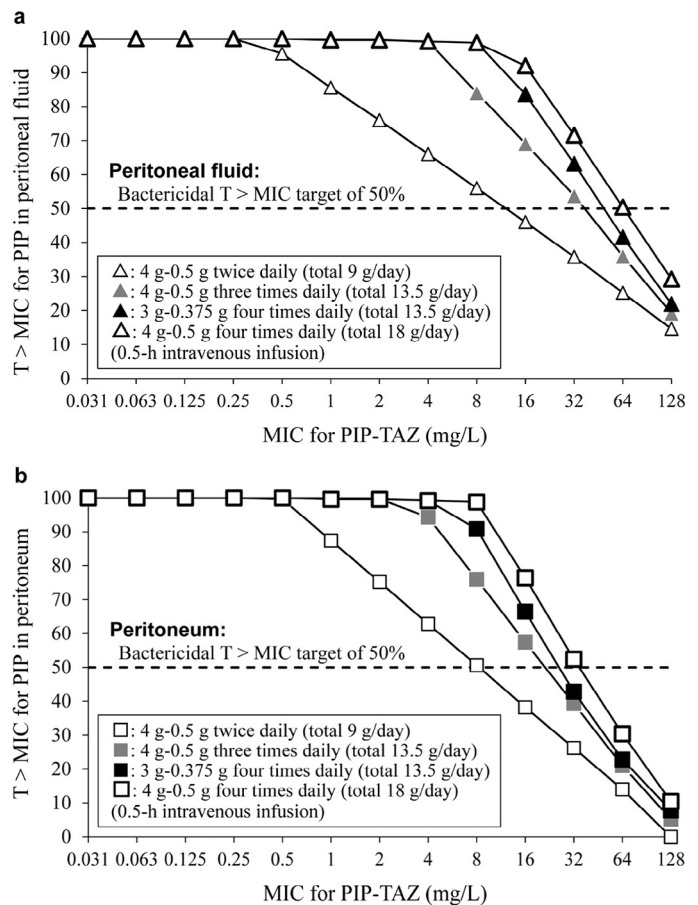


Fig. 4. Site-specific time that drug concentration was above the minimum inhibitory concentration ($T > MIC$) for piperacillin in the peritoneal fluid (a) and peritoneum (b), at an MIC of 0.031–128 mg/L, using four piperacillin (PIP)-tazobactam (TAZ) regimens. The $T > MIC$ values were predicted using the mean pharmacokinetic model parameters for PIP (Table 2). The dashed lines represent the bactericidal target (50% $T > MIC$) for PIP.

Table 3

Minimum inhibitory concentration (MIC) values against *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Pseudomonas aeruginosa*, and the piperacillin (PIP)-tazobactam (TAZ) regimens needed for site-specific pharmacodynamic breakpoints.

Bacterium	CLSI	EUCAST	Site-specific pharmacodynamic breakpoint (Needed PIP-TAZ regimen)
<i>E. coli</i> , <i>K. pneumoniae</i> <i>E. cloacae</i>	16 mg/L	8 mg/L	8 mg/L (4 g-0.5 g twice daily [total 9 g/day]) 16 mg/L (4 g-0.5 g three times daily [total 13.5 g/day]) or 3 g-0.375 g four times daily [total 13.5 g/day])
<i>P. aeruginosa</i>	16 mg/L	16 mg/L	16 mg/L (4 g-0.5 g three times daily [total 13.5 g/day]) or 3 g-0.375 g four times daily [total 13.5 g/day])

CLSI, susceptible breakpoint MIC by Clinical and Laboratory Standards Institute (2012). EUCAST, epidemiological cut-off MIC by European Committee on Antimicrobial Susceptibility Testing (2016).

Site-specific pharmacodynamic breakpoint, the highest MIC at which $T > MIC$ in both peritoneal fluid and peritoneum is greater than bactericidal target of 50% for PIP (Fig. 4).

4. Discussion

This study was conducted to investigate the peritoneal pharmacokinetics of PIP-TAZ in abdominal patients and revealed that the mean ratios for peritoneal fluid:plasma are 0.75–0.79 and for peritoneum:plasma are 0.49–0.53; the mean PIP:TAZ ratio is 8.1 in both the peritoneal fluid and peritoneum. Based on site-specific pharmacodynamic target attainment, this study also shows that the PIP-TAZ 4.5 g twice daily for an MIC of 8 mg/L and PIP-TAZ 4.5 g three times daily and 3.375 g four times daily for an MIC of 16 mg/L regimens achieved the desired bactericidal effect of PIP.

Shimizu et al [5] measured the concentration of PIP-TAZ (2 g-0.5 g twice daily regimen) in the peritoneal fluid of five patients at 24, 48, and 72 h; however, those authors did not measure plasma concentrations or characterize peritoneal pharmacokinetics. Wittmann et al [11] and Hary et al [12] reported the penetration of PIP alone into the peritoneal fluid, but not that of PIP-TAZ. There have been no previous reports regarding PIP-TAZ concentrations in the peritoneum. To our knowledge, this is the first report of PIP-TAZ penetration into the peritoneal fluid and peritoneum.

In general, healthy subjects are recruited to study drug tissue penetration; however, peritoneal cavity conditions of peritonitis patients are assumed to differ markedly from those of healthy subjects. The present study was conducted to investigate the tissue concentration of antibiotics during bowel resection for patients with inflammatory bowel disease. As these patients had an inflamed condition, they were considered to be suitable as an inflamed peritoneal cavity model. Although exact comparisons were difficult because the pharmacokinetic model analyses differed, the mean parameter values in 10 inflammatory bowel disease patients (Table 2) for V_1 (5.48 L for PIP and 5.92 L for TAZ) and K_{10} (1.23 1/h for PIP and 1.25 1/h for TAZ) were similar to the mean values in 47 prostatic hypertrophy patients [6] for V_1 [L] (8.44 L for PIP and 6.76 L for TAZ) and K_{10} (1.08 1/h for PIP and 1.30 1/h for TAZ), respectively. In addition, K_{10} values in the current study were almost within the range of those in five pancreaticoduodenectomy patients (0.578–0.866 1/h for PIP and 0.365–1.73 1/h for TAZ) [4]. These pharmacokinetic results indicate the suitability and generality of inflammatory bowel disease patients as study subjects.

The primary antimicrobial activity of PIP-TAZ depends on PIP; therefore, the $AUC_{0-\infty}$ of PIP should reflect the antimicrobial effect and site-specific penetration of PIP-TAZ. In earlier reports, the penetration ratios of PIP were 2.9–15.9% in pancreatic juice [4], 169.8–218.3% in the renal cortex, 229.5–364.7% in the renal medulla [13], 12.7–67.9% in pulmonary tissue [14], and 15% ± 17% in bone tissue [15]. Regarding the PIP:TAZ ratio, 8:1 is regarded as optimal

[16]. Bertazzoni Minelli et al [4] demonstrated that the ratio in pancreatic juice differs based on sampling time (30, 60, and 90 min), ranging from 4.0 to 10.4. In our study, mean PIP ratios in $AUC_{0-\infty}$ were 75% for peritoneal fluid:plasma and 49% for peritoneum:plasma (Table 1), and PIP:TAZ ratios at both peritoneal sites maintained a combination ratio of 8:1 (Fig. 2). These results provide a pharmacokinetic rationale for the use of PIP:TAZ in the treatment of intraabdominal infections.

As mentioned in the guidelines of the Surgical Infection Society and the Infectious Disease Society of America, the most common Gram-negative bacteria causing intraabdominal infections are *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* [17]. Table 3 lists the reported PIP-TAZ MIC values for these organisms as per the Clinical and Laboratory Standards Institute (CLSI) in 2012 [18] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) in 2015 [19]. Using mean pharmacokinetic model parameter estimates, the present study predicted the concentration of PIP-TAZ for different dosing regimens to determine whether pharmacodynamic target attainment could be achieved in the peritoneal fluid and peritoneum. The results (Table 3) show that PIP-TAZ at 4.5 g twice daily (total 9 g/day) and at 4.5 g three times daily or 3-0.375 g four times daily (both total 13.5 g/day) results in a bactericidal effect against *E. coli*, *Klebsiella* species, *P. aeruginosa*, and *E. cloacae* at both peritoneal sites.

This study has four major limitations. (1) The number of study patients was small ($n = 10$). (2) Surgery of inflamed bowel was hypothesized to be comparable to peritonitis; however, these conditions are not exactly equal. Mori et al [20] reported that the penetration of carbapenem, an antimicrobial panipenem, into human alveolar tissue is dependent on the vasopermeability associated with inflammation and that the concentration of panipenem was higher at sites of inflammation. The same may be true for PIP-TAZ penetration into the peritoneal fluid or peritoneum in the presence of inflammation. Conversely, the PIP-TAZ concentration may be low under conditions of impaired blood flow, such as sepsis or septic shock. (3) Critically ill patients with infection often have renal dysfunction, which causes low clearance and maintains the drug concentrations in plasma and peritoneal sites (that is, $T > MIC$ will be longer), because PIP-TAZ is primarily eliminated renally [1]. The patients in the present study all had normal renal function, with a creatinine clearance of 87.4 mL/min. (4) The pharmacodynamic results are based on the simulated bactericidal effect and not the therapeutic efficacy or clinical outcome. Our results provide useful information; however, these findings do not confirm the optimum dosing regimens for treating patients with intraabdominal infections. Considering these four limitations of the present study, clinical studies should be conducted in a larger number and variety of patients with intraabdominal infections to confirm our pharmacokinetic results and to clarify their therapeutic significance by investigating the relationship between peritoneal penetration and pharmacodynamic exposure of PIP-TAZ and therapeutic efficacy.

In conclusion, our results help clarify the pharmacokinetics of PIP-TAZ in the plasma, peritoneal fluid, and peritoneum of surgery patients, while providing guidance regarding dosing regimens for intraabdominal infections based on pharmacodynamic target attainment. Further studies in a larger number of infected patients are needed to confirm our findings and clarify their therapeutic implications.

Declarations

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Competing interests: None declared.

Ethical approval: The Ethics Committee of Hiroshima University Hospital, Japan.

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