



Ceftolozane–Tazobactam Pharmacokinetics in the Abdominal Tissue of Patients Undergoing Lower Gastrointestinal Surgery: Dosing Considerations Based on Site-Specific Pharmacodynamic Target Attainment

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ABSTRACT

Introduction: Recently, complicated intra-abdominal infections (cIAI) have been caused not only by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*, but also by extended-spectrum β -lactamase-producing Enterobacterales members. Ceftolozane–tazobactam (CTLZ–TAZ) is considered to exhibit therapeutic effects against cIAI. Studies on the concentrations of antibiotics in abdominal tissues directly affected by cIAI are limited. Therefore, in this study, we investigated the pharmacokinetics of CTLZ–TAZ in abdominal tissue and simulated the administration regimen required to achieve the pharmacodynamic target for cIAI-causing bacteria.

Methods: Patients scheduled for elective lower gastrointestinal surgery were intravenously administered preoperative CTLZ–TAZ (1 g CTLZ and 0.5 g TAZ). Plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue samples were collected during the surgery, and CTLZ as well as TAZ concentrations were measured. The noncompartmental and compartmental pharmacokinetic parameters were then estimated. Site-specific pharmacodynamic target attainment analysis using 1.5 g of CTLZ–TAZ was performed.

Results: CTLZ–TAZ was administered to nine patients (once to five patients and twice to four patients). The mean peritoneal fluid-to-plasma ratio (one dose/two doses) for CTLZ was 0.74/1.15, which was slightly higher than the mean peritoneal fluid-to-plasma ratio for TAZ (0.95/1.13). The ratio for subcutaneous adipose was lower than those for peritoneal fluid and peritoneum tissues. We also discovered that the average ratio of CTLZ and TAZ concentrations in all tissues was maintained at or above 2:1. In our investigation of pharmacodynamic target attainment in each tissue, the desired bactericidal effect was attained with all CTLZ–TAZ (1.5 g) administration regimens [q12h (3 g/day), q8h (4.5 g/day), and q6h (6 g/day)].

Conclusion: To the best of our knowledge, this is the first study investigating the optimal pharmacodynamic level of CTLZ–TAZ in the abdominal tissue against cIAI-causing bacteria. This study also serves as a guideline for

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designing an optimal administration regimen based on pharmacodynamic target attainment for cIAI-causing bacteria.

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Keywords: Ceftolozane; Tazobactam; Peritonitis; Lower gastrointestinal disease; Pharmacokinetics; Pharmacodynamics

Key Summary Points

Why carry out this study?

Complicated intra-abdominal infections (cIAI) caused by extended-spectrum β -lactamase (ESBL)-producing Enterobacterales members are increasing worldwide.

Prior studies reported that the therapeutic effect of ceftolozane–tazobactam (CTLZ–TAZ) and metronidazole for cIAI-causing bacteria, including ESBL-producing Enterobacterales members, was not inferior to meropenem.

However, CTLZ–TAZ distribution within the abdominal tissue and its chronological changes have not yet been reported.

Therefore, we investigated the optimal dose and administration duration to achieve an optimal pharmacokinetic/pharmacodynamic target against various cIAI-causing bacteria.

What was learned from this study?

The noncompartmental pharmacokinetic parameters showed the average ratio of CTLZ and TAZ concentrations in all tissues was maintained at or above 2:1.

The simulation curves constructed using the pharmacokinetic parameters were well fitted to all mean measurements of all tissues for CTLZ and TAZ.

Investigation of pharmacodynamic targets attainment in abdominal tissue, CTLZ–TAZ (1.5 g) administration regimens [q12h (3 g/day), q8h (4.5 g/day), and q6h (6 g/day)] could attain the desired bactericidal effect (MIC = 1, 2, 4 mg/L).

However, this study has a small number of patients, who have several creatinine clearances, with various diseases (i.e., inflammatory bowel disease, cancer).

To determine the usefulness and significance of the guidelines in clinical settings, large-scale studies on patients who have several creatinine clearances with cIAI caused by various bacteria should be conducted.

INTRODUCTION

The most common bacteria causing complicated intra-abdominal infections (cIAI) are *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* [1]. However, extended-spectrum β -lactamase (ESBL)-producing Enterobacterales members, which show resistance to several existing antibiotics, are on the rise worldwide [2]. Ceftolozane–tazobactam (CTLZ–TAZ) is an intravenously administered antibiotic, including a cephalosporin CTLZ and a β -lactamase inhibitor TAZ at a 2:1 ratio. CTLZ acts on the penicillin-binding protein of bacteria and exhibits antibacterial action by inhibiting cell wall biosynthesis. Furthermore, CTLZ shows effective therapeutic activity against various bacterial strains, including multiple-drug-resistant *P. aeruginosa* [3]. Additionally, when used in combination with TAZ, hydrolysis of CTLZ is prevented, and CTLZ acts against strains that produce class A β -lactamase (including TEM, SHV, and CTX-M types) and class C β -lactamase (AmpC type) [4]. Thus, CTLZ–TAZ exhibits strong in vitro and in vivo activities against Gram-negative bacteria, including multiple-

drug-resistant *P. aeruginosa* and ESBL-producing Enterobacterales members [5–9].

A prospective, randomized, double-blinded, large-scale trial (phase 3) with cIAI as its primary endpoint discovered that the therapeutic effect of CTLZ–TAZ and metronidazole was not inferior to meropenem [10]. Subsequently, in 2014, the Food and Drug Administration approved CTLZ–TAZ for complicated urinary tract infection (cUTI), as well as cIAI, and in 2019, for hospital-acquired bacterial and ventilator-associated pneumonia [11]. Measurement of plasma concentration of CTLZ–TAZ showed that the combination has a therapeutic effect on cUTI and cIAI [12], whereas the comparison of plasma concentration with lung epithelial lining fluid (ELF) levels simulated the required dose when treating severe pneumonia [13]. These pharmacokinetics studies reported that CTLZ–TAZ blood plasma concentration was rapidly elevated upon initial administration and peaked once administration was completed. However, the therapeutic effect was not achieved unless the drug was sufficiently distributed within the infected tissue site. Therefore, when administering CTLZ–TAZ in clinical settings for treatment purposes, interpreting its pharmacokinetic distribution in tissue is essential for administering the required dose.

The CTLZ–TAZ distribution within the peritoneal fluid, peritoneum, and subcutaneous adipose tissue and its chronological changes have not yet been reported. Thus, in this study, we analyzed the pharmacokinetics of CTLZ–TAZ in the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue collected during lower gastrointestinal surgery. On the basis of the results, we simulated the optimal dose and administration duration to achieve an optimal pharmacodynamic target against various cIAI-causing bacteria.

METHODS

Study Participants

This is a prospective, open-trial study on the pharmacokinetics of CTLZ–TAZ in plasma, peritoneal fluid, peritoneum, and subcutaneous

adipose tissue. It was conducted at the Hiroshima University Hospital between January 2020 and January 2021. The study protocol was carried out in accordance with the Helsinki Declaration of 1964 and its later amendments [14] and was reviewed/approved by the institutional review board of Hiroshima University Hospital (CRB6180006). This study was registered with the Japan Registry of Clinical Trials (jRCTs061190025). All participants provided written informed consent before enrollment. The study involved patients selected from men and women aged 20 years and older who were scheduled to undergo elective surgery for lower gastrointestinal diseases and received prophylactic antibacterial administration against post-operative infection. The exclusion criteria were (1) pregnant or breastfeeding, (2) a history of allergy to cephem or β -lactam antibiotics, (3) a history of cerebrospinal diseases, and (4) a creatinine clearance (Ccr) level below 50 mL/min according to the Cockcroft–Gault formula. This study used methods of sample collection or antibiotic assays similar to those of our previous studies [15–18]. However, our study differs significantly from the previous studies in that it newly analyzed concentrations in subcutaneous adipose tissue.

Drug Administration and Sample Collection

Antibacterial administration was started 1 h and 20 min before surgery. Metronidazole (0.5 g) was prophylactically administered via a 20-min intravenous infusion. Subsequently, CTLZ–TAZ (1 g CTLZ and 0.5 g TAZ) was administered via a 1-h intravenous infusion. For surgeries lasting longer than 4 h, the same infusion regimen of CTLZ–TAZ was additionally administered. Specifically, it was administered via a 1-h intravenous infusion 3 h after the end of the first administration. The samples collected during surgery included plasma (2 mL), peritoneal fluid (2 mL), peritoneum (4 mm \times 4 mm), and subcutaneous adipose tissue (4 mm \times 4 mm \times 4 mm). Sample collection was performed once the first administration of CTLZ–TAZ was concluded. The second samples were collected 0.5 h

later, whereas the third and subsequent samples were collected every subsequent hour following the conclusion of administration. The supernatant was removed from the plasma and peritoneal fluid samples following centrifugation for 20 min at 10,000 rpm. The peritoneum and subcutaneous adipose tissue samples were washed using a physiological saline solution. All samples were stored at -40°C until analysis.

CTLZ and TAZ Assays

The total concentration of CTLZ and TAZ in the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue was measured using high-performance liquid chromatography, as previously reported [19, 20]. For CTLZ, the peritoneum and subcutaneous adipose tissue samples were homogenized using an overhead mixer with four volumes (w/v) of double-distilled water. The homogenate was centrifuged for 20 min at 10,000 rpm, and the supernatant was collected. The plasma, supernatant peritoneal fluid, peritoneum, and subcutaneous adipose tissue samples (200 μL each) were added to 400 μL of 30 mmol/L potassium dihydrogen phosphate buffer (pH 3.0). The resulting solution was mixed using a vortex mixer and transferred to a centrifugal filter device (Nanosep 10 K; Pall Corporation, Port Washington, NY, USA) and centrifuged for 20 min at 10,000 rpm. A total of 20 μL of the filtered solution was injected into a chromatograph with a reversed-phase column (Xbridge C18; 5 $\mu\text{m} \times 4.6 \text{ mm} \times 150 \text{ mm}$; Waters Corporation, Milford, MA, USA) and detected by measuring the ultraviolet absorbance at 220 nm. The mobile phase consisted of a mixture of 30 mmol/L potassium dihydrogen phosphate buffer (pH 3.0) and acetonitrile (96:4) at a flow rate of 1.0 mL/min.

The quantification ranges for CTLZ were 0.5–250 mg/L for plasma and peritoneal fluid and 0.5–250 mg/kg for peritoneum and subcutaneous adipose tissue samples. For intra- and interday assays, the precision was 1.01–4.79%, and the accuracy was 88.7–114%. Additionally, the quantification ranges for TAZ were 0.25–125 mg/L for plasma and peritoneal fluid

and 0.25–50 mg/kg for peritoneum and subcutaneous adipose tissue samples. For intra- and interday assays, the precision was 0.96–7.08%, and the accuracy was 89.4–113%.

Noncompartmental Pharmacokinetic Analysis

For each drug, the C_{max} was defined as the observed maximum concentration after a single or repeated 1-h intravenous infusion. The area under the drug concentration–time curve from 0 to infinity ($\text{AUC}_{0-\infty}$) was calculated on the basis of the trapezoidal rule using MULTI software (originally developed by Yamaoka et al. [21] and currently maintained by the Department of Biopharmaceutics and Drug Metabolism; Kyoto University, Kyoto, Japan). For the pharmacokinetic analysis, the specific gravity of the tissue (peritoneum and subcutaneous adipose) was considered as 1 ($\text{kg} = \text{L}$).

Compartmental Pharmacokinetic Analysis

The preliminary analysis for each drug indicated that a multicompartment model for describing the four drug concentrations (plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue) was complicated. A simpler model could be used owing to the parallel drug elimination slopes for the abdominal sites. Therefore, the concentration–time data were fitted to a hypothetical two-compartment model with correction factors [22] to account for concentration differences between the plasma and the abdominal sites (Fig. 1). The differential equations for the changes in the amount of drug in the central compartment [$A(1)$, mg] and peripheral compartment (including abdominal sites) [$A(2)$, mg] with time (t) are as presented as Eqs. (1) and (2):

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

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

where R_{in} is the intravenous drug infusion rate (mg/h), K_{12} and K_{21} are the transfer rate

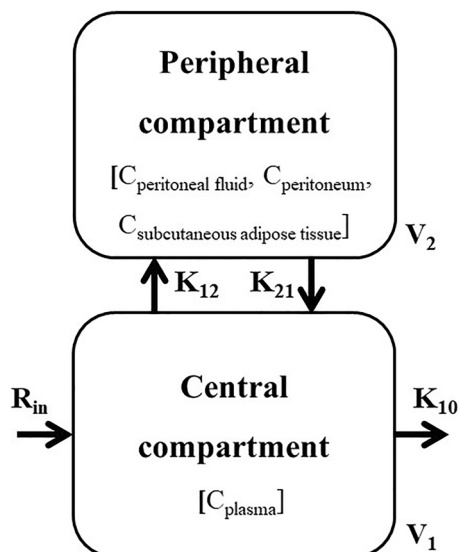


Fig. 1 Hypothetical two-compartment pharmacokinetic model for ceftolozane and tazobactam. V1 and V2, volume of distribution in the central and peripheral compartments (L = kg); C, concentration of drug in the plasma and peritoneal fluid (mg/L) and peritoneum and subcutaneous adipose tissue (mg/kg); Rin, intravenous infusion rate of drug (mg/h); K12 and K21, transfer rate constants (1/h); K10, elimination rate constant (1/h)

constants (1/h) connecting the central and peripheral compartments, respectively, 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) ($V2 = K12 \times V1 / K21$). Assuming that the correction factors account for drug concentration differences between the plasma and peritoneal fluid ($CF_{\text{peritoneal fluid}}$), the plasma and peritoneum ($CF_{\text{peritoneum}}$), and the plasma and subcutaneous adipose tissue ($CF_{\text{subcutaneous adipose tissue}}$), the equations for the drug concentration in plasma (C_{plasma} , mg/L), peritoneal fluid ($C_{\text{peritoneal fluid}}$, mg/L), peritoneum ($C_{\text{peritoneum}}$, mg/kg), and subcutaneous adipose tissue ($C_{\text{subcutaneous adipose tissue}}$, mg/kg) are expressed as Eqs. (3, 4, 5, 6):

$$C_{\text{plasma}} = A(1)/V1 \tag{3}$$

$$C_{\text{peritoneal fluid}} = A(2)/[V2 \times CF_{\text{peritoneal fluid}}] = A(2) \times K21/[K12 \times V1 \times CF_{\text{peritoneal fluid}}] \tag{4}$$

$$C_{\text{peritoneum}} = A(2) \times K21/[K12 \times V1 \times CF_{\text{peritoneum}}] \tag{5}$$

$$C_{\text{subcutaneous adipose tissue}} = A(2) \times K21/[K12 \times V1 \times CF_{\text{subcutaneous adipose tissue}}] \tag{6}$$

The seven pharmacokinetics model parameters (K12, K21, K10, V1, $CF_{\text{peritoneal fluid}}$, $CF_{\text{peritoneum}}$, and $CF_{\text{subcutaneous adipose tissue}}$) were estimated for each patient using the MULTI software [15].

Site-Specific Pharmacodynamic Target Attainment Analysis

For each CTLZ-TAZ regimen (1 g CTLZ and 0.5 g TAZ, every 12, 8, 6, or 4 h; 1 h infusion), the duration for which the drug concentration was above the minimum inhibitory concentration ($T > MIC$) for CTLZ in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue was predicted. Using the same method as that described for previous simulations [15–18], the drug concentration was not adjusted for protein binding but instead treated as the free fraction. The protein-binding levels of CTLZ in these abdominal sites are currently unknown. Using the mean estimates for the seven CTLZ pharmacokinetic model parameters, the timepoint at which the simulated drug concentration in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue coincided with a minimum inhibitory concentration (MIC) of 0.125–128 mg/L was determined. The $T > MIC$ was calculated as the cumulative percentage of a 24-h period.

On the basis of the findings of the pharmacodynamic target attainment analysis, the site-specific pharmacodynamic breakpoint MIC was defined as the highest MIC at which $T > MIC$ in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue was greater than the bactericidal target of 30% [6, 23, 24] for CTLZ.

RESULTS

Study Participants

Among the nine patients (six men and three women), five suffered from inflammatory bowel disease (IBD; four with Crohn's disease and one with ulcerative-colitis-associated colorectal cancer), two had colorectal cancer, and two suffered from other ileal diseases. The following surgical procedures were performed: colectomy ($n = 6$), abdominoperineal rectal resection ($n = 2$), and ileal resection ($n = 1$). The mean age was 51.7 ± 17.2 years [mean \pm standard deviation (SD)], body weight was 57.8 ± 3.4 kg, body mass index (BMI) was 21.1 ± 3.4 kg/m², Ccr according to the Cockcroft–Gault formula was 93.8 ± 27.2 mL/min, total bilirubin was 0.7 ± 0.3 mg/dL, aspartate transferase (AST) level was 30.3 ± 14.5 IU/L, and alanine transaminase (ALT) level was 53.8 ± 45.5 IU/L. The antibiotics were administered once and twice to five and four participants, respectively. Detailed characteristics of the patients are summarized in Table 1.

Sample Collection and CTLZ and TAZ Assays

A total of 54 plasma, 39 peritoneal fluid, 45 peritoneum, and 52 subcutaneous adipose tissue samples were collected. The CTLZ levels in each sample were as follows: plasma, 16.9–112.7 mg/L; peritoneal fluid, 8.6–188.9 mg/L; peritoneum, 7.4–46.3 mg/kg; subcutaneous adipose tissue, 3.9–25.2 mg/kg. The TAZ levels in each sample were as follows: plasma, 0.6–31.6 mg/L; peritoneal fluid, 1.6–69.5 mg/L; peritoneum, 0.7–22.5 mg/kg; subcutaneous adipose tissue, 0.4–11 mg/kg. All measured values exceeded the determination limits.

Noncompartmental Pharmacokinetic Analysis

The noncompartmental pharmacokinetic parameters are presented in Table 2. The mean peritoneal fluid-to-plasma ratio (one dose/two

Table 1 Characteristics of the patients

	<i>n</i> = 9
Gender (male/female; <i>n</i>)	6 (67%)/3 (33%)
Age (years; mean \pm SD)	51.7 ± 17.2
Body weight (kg; mean \pm SD)	57.8 ± 3.4
BMI (kg/m ² ; mean \pm SD)	21.1 ± 3.4
<i>Preoperative blood examinations</i>	
T.Bil (mg/dl; mean \pm SD)	0.7 ± 0.3
AST (IU/L; mean \pm SD)	30.3 ± 14.5
ALT (IU/L; mean \pm SD)	53.8 ± 45.5
Ccr (mL/min; mean \pm SD)	93.8 ± 27.2
<i>Co-medications (including duplicates)</i>	
Sodium ferrous citrate; <i>n</i>	4 (44%)
Famotidine; <i>n</i>	3 (33%)
Prednisone; <i>n</i>	2 (22%)
5-ASA; <i>n</i>	2 (22%)
<i>Preoperative diagnosis</i>	
IBD (CD/UCAC; <i>n</i>)	5 (56%)
Cancer; <i>n</i>	2 (22%)
Others; <i>n</i>	2 (22%)
<i>Surgical procedure</i>	
Colectomy; <i>n</i>	6 (67%)
APR; <i>n</i>	2 (22%)
Ileal resection; <i>n</i>	1 (11%)
Antibiotic administration (once/twice; <i>n</i>)	5 (56%)/4 (44%)

SD standard deviation, *BMI* body mass index, *T.Bil* total bilirubin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *Ccr* creatinine clearance, *5-ASA* 5-aminosalicylate, *IBD* inflammatory bowel disease, *CD* Crohn's disease, *UCAC* ulcerative-colitis-associated colorectal cancer, *APR* abdominoperineal resection

doses) for CTLZ was 0.74/1.15, which was slightly higher than the mean peritoneal fluid-to-plasma ratio for TAZ (0.95/1.13). For CTLZ,

Table 2 Noncompartmental pharmacokinetic parameters of ceftolozane and tazobactam after 1-h intravenous infusion of 1 g CTLZ and 0.5 g TAZ

Sample type and parameter	Value (mean ± SD, n = 9)	
	Ceftolozane (1 g)	Tazobactam (0.5 g)
Plasma		
C_{max} (mg/L)		
1 administration	73.7 ± 12.1	25.1 ± 4.8
2 administrations	74.7 ± 16.4	21.3 ± 2.0
$AUC_{0-\infty}$ (mg·h/L)		
1 administration	274.8 ± 35.0	45.9 ± 13.9
2 administrations	400.3 ± 27.0	65.9 ± 5.0
Peritoneal fluid		
C_{max} (mg/L)		
1 administration	69.7 ± 21.0	19.7 ± 7.2
2 administrations	65.1 ± 9.9	16.8 ± 2.4
$AUC_{0-\infty}$ (mg·h/L)		
1 administration	203.0 ± 45.3	41.9 ± 11.4
2 administrations	457.2 ± 117.3	74.8 ± 15.2
Peritoneum		
C_{max} (mg/L)		
1 administration	32.3 ± 9.5	14.1 ± 5.9
2 administrations	34.7 ± 10.3	14.3 ± 1.5
$AUC_{0-\infty}$ (mg·h/L)		
1 administration	114.9 ± 65.6	29.6 ± 16.7
2 administrations	170.2 ± 24.3	46.1 ± 13.8
Subcutaneous adipose tissue		
C_{max} (mg/L)		
1 administration	17.5 ± 5.9	5.4 ± 3.6
2 administrations	15.3 ± 3.9	3.3 ± 1.3
$AUC_{0-\infty}$ (mg·h/L)		
1 administration	46.1 ± 8.8	8.6 ± 3.9
2 administrations	80.8 ± 26.4	15.1 ± 6.3

Table 2 continued

Sample type and parameter	Value (mean ± SD, n = 9)	
	Ceftolozane (1 g)	Tazobactam (0.5 g)
Peritoneal fluid:plasma ratio		
C_{max}		
1 administration	0.95 ± 0.22	0.78 ± 0.20
2 administrations	0.88 ± 0.06	0.79 ± 0.05
$AUC_{0-\infty}$		
1 administration	0.74 ± 0.15	0.95 ± 0.25
2 administrations	1.15 ± 0.34	1.13 ± 0.15
Peritoneum:plasma ratio		
C_{max}		
1 administration	0.44 ± 0.10	0.56 ± 0.23
2 administrations	0.46 ± 0.06	0.67 ± 0.10
$AUC_{0-\infty}$		
1 administration	0.41 ± 0.22	0.64 ± 0.33
2 administrations	0.42 ± 0.04	0.69 ± 0.17
Subcutaneous adipose tissue:plasma ratio		
C_{max}		
1 administration	0.24 ± 0.06	0.21 ± 0.11
2 administrations	0.21 ± 0.05	0.15 ± 0.05
$AUC_{0-\infty}$		
1 administration	0.17 ± 0.03	0.19 ± 0.06
2 administrations	0.20 ± 0.07	0.23 ± 0.08

the mean peritoneum-to-plasma ratio was 0.41/0.42, and the mean subcutaneous adipose-to-plasma ratio was 0.17/0.20. In contrast, for TAZ, the mean peritoneum-to-plasma ratio was 0.64/0.69, and the mean subcutaneous adipose-to-plasma ratio was 0.19/0.23, which was lower than the peritoneal fluid-to-plasma ratios measured for CTLZ and TAZ.

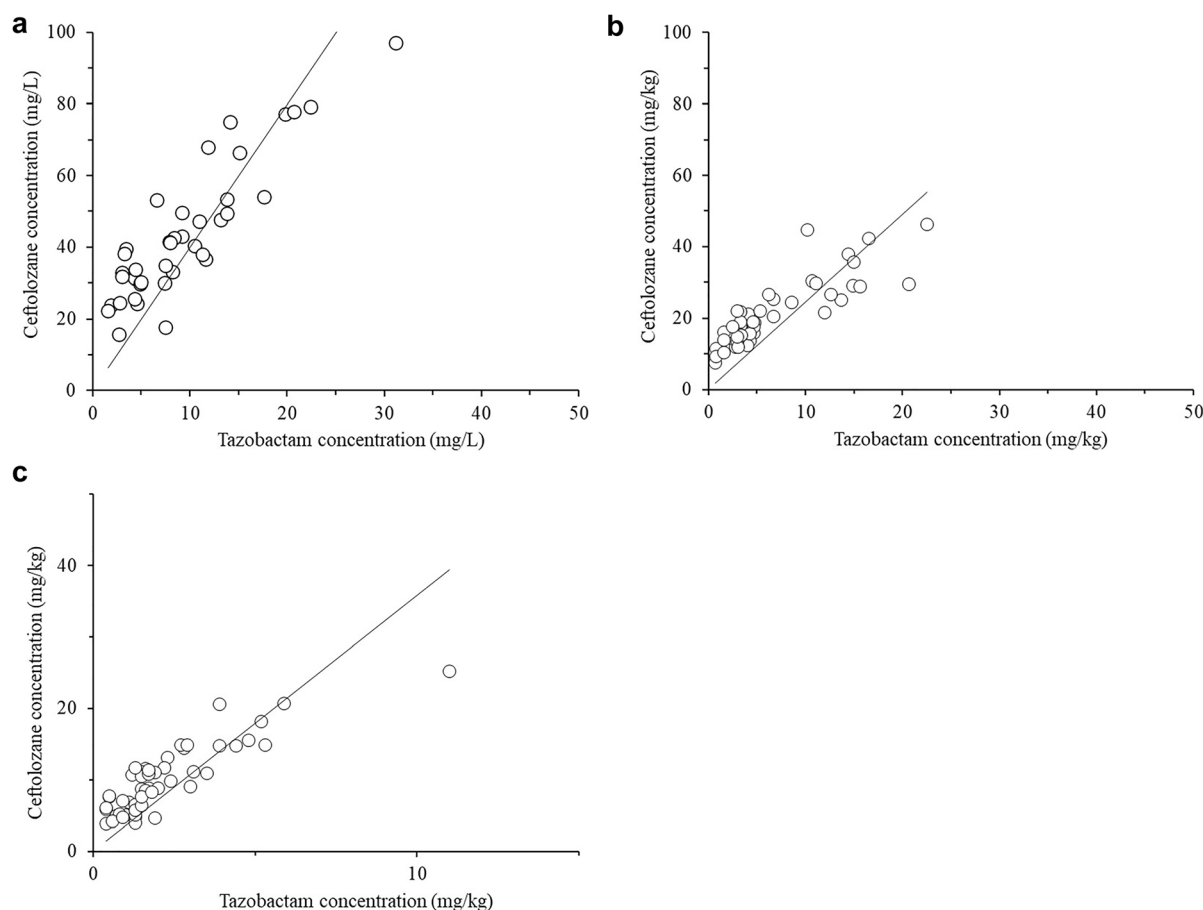


Fig. 2 Relationship between the observed concentrations of ceftolozane and tazobactam in the peritoneal fluid (a), peritoneum (b), and subcutaneous adipose tissue (c) after 1 h intravenous infusion of 1 g CTLZ and 0.5 g TAZ.

The mean CTLZ:TAZ ratio (one dose/two doses) was 6.4/6.1, 4.9/6.1, 4.2/3.9, and 5.8/5.5 for plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue, respectively. Similarly, when these data were expressed as regression equations for the observed concentrations, the CTLZ:TAZ ratios were 3.99 for peritoneal fluid (Fig. 2a), 2.45 for peritoneum (Fig. 2b), and 3.59 for subcutaneous adipose tissues (Fig. 2c). These values exceeded the 2:1 CTLZ and TAZ composition.

Compartmental Pharmacokinetic Analysis

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

Lines represent regression equations. The CTLZ:TAZ ratios were 3.99 for peritoneal fluid, 2.45 for peritoneum, and 3.59 for subcutaneous adipose tissues

summarized in Table 3. The simulation curves constructed using the mean parameter estimates were well fit to all mean measurements of the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue for CTLZ (Fig. 3a) and TAZ (Fig. 3b). The regression equations between the observed concentration (Y) and individual predicted concentration (X) were $Y = 0.967X + 0.720$ ($r = 0.971$, 190 samples) for CTLZ and $Y = 0.966X - 0.242$ ($r = 0.984$, 190 samples) for TAZ. The normalized mean prediction error (as a bias index) and the normalized mean absolute prediction error (as an accuracy index) were -0.492 and 2.670 for CTLZ and -0.296 and 1.142 for TAZ, respectively.

Table 3 Pharmacokinetic parameters of ceftolozane and tazobactam in the hypothetical two-compartment model (Fig. 1)

Parameter	Estimate (mean \pm SD, $n = 9$)	
	Ceftolozane	Tazobactam
K12 (1/h)	0.478 \pm 0.102	3.29 \pm 0.88
K21 (1/h)	1.48 \pm 0.51	2.86 \pm 1.08
K10 (1/h)	0.508 \pm 0.066	1.56 \pm 0.23
V1 (L)	10.2 \pm 2.7	8.05 \pm 2.31
CF _{peritoneal fluid}	0.0865 \pm 0.0615	0.107 \pm 0.079
CF _{peritoneum}	0.187 \pm 0.174	0.194 \pm 0.181
CF _{subcutaneous adipose tissue}	0.366 \pm 0.305	0.398 \pm 0.326

Site-Specific Pharmacodynamic Target Attainment Analysis

Using the mean estimated values of the seven CTLZ pharmacodynamic model parameters, we predicted the drug concentration in several administration regimens. We investigated whether the pharmacodynamic targets could be attained in peritoneal fluid (Fig. 4a),

peritoneum (Fig. 4b), and subcutaneous adipose tissue (Fig. 4c). The percentage of $T > MIC$ for CTLZ in humans has not yet been established. Thus, as previously described [6, 23, 24], we hypothesized the percentage of $T > MIC$ to be 30%. On the basis of the categories of the Clinical and Laboratory Standards Institute (CLSI) [25] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [26], we identified sufficient antibacterial effects in all three CTLZ-TAZ (1 g CTLZ and 0.5 g TAZ) administration regimens [q12h (3 g/day), 1.5 g q8h (4.5 g/day), and 1.5 g q6h (6 g/day)], against *E. coli*, *K. pneumoniae*, *E. cloacae* (MIC 2 mg/L), and *P. aeruginosa* (MIC 4 mg/L) in all abdominal tissues. Although the CLSI and EUCAST do not report the breakpoint for ESBL-producing Enterobacterales members, based on the categories of the Japanese surgical site infection (SSI) surveillance (MIC₉₀) [23], all three CTLZ-TAZ (1 g CTLZ and 0.5 g TAZ) administration regimens [q12h (3 g/day), q8h (4.5 g/day), and q6h (6 g/day)] in all abdominal tissues showed sufficient antibacterial effects against ESBL-producing Enterobacterales members (MIC₉₀ 1 mg/L).

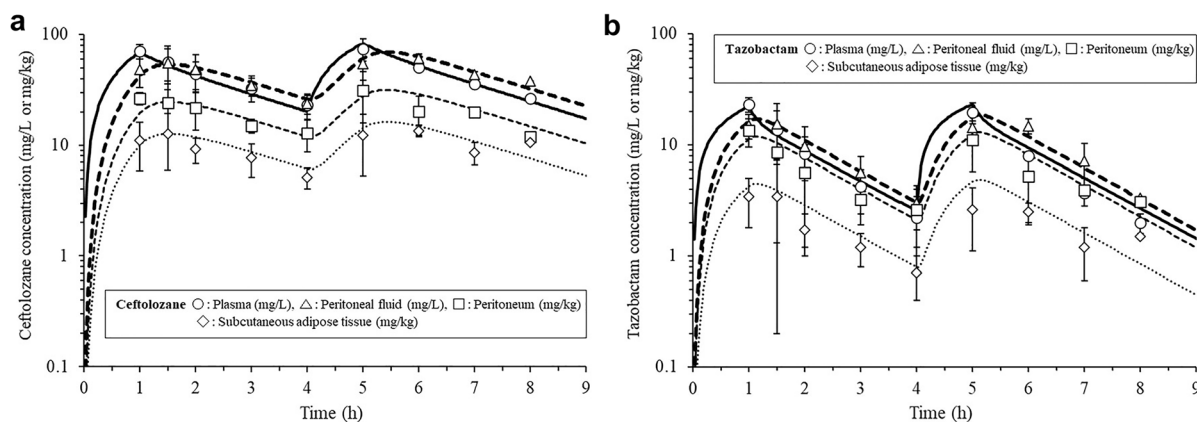


Fig. 3 Observed concentrations (mean \pm SD, $n = 9$) and simulation curves for ceftolozane (CTLZ) (a) and tazobactam (TAZ) (b) in the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue after a single or repeated 1 h infusion of 1 g CTLZ and 0.5 g TAZ. The simulation curves were drawn using the mean pharmacokinetics model parameters (K12 = 0.478 1/h, K21 = 1.48 1/h,

K10 = 0.508 1/h, V1 = 10.2 L, CF_{peritoneal fluid} = 0.0865, CF_{peritoneum} = 0.187, and CF_{subcutaneous adipose tissue} = 0.366 for CTLZ; K12 = 3.29 1/h, K21 = 2.86 1/h, K10 = 1.56 1/h, V1 = 8.05 L, CF_{peritoneal fluid} = 0.107, CF_{peritoneum} = 0.194, and CF_{subcutaneous adipose tissue} = 0.398 for TAZ)

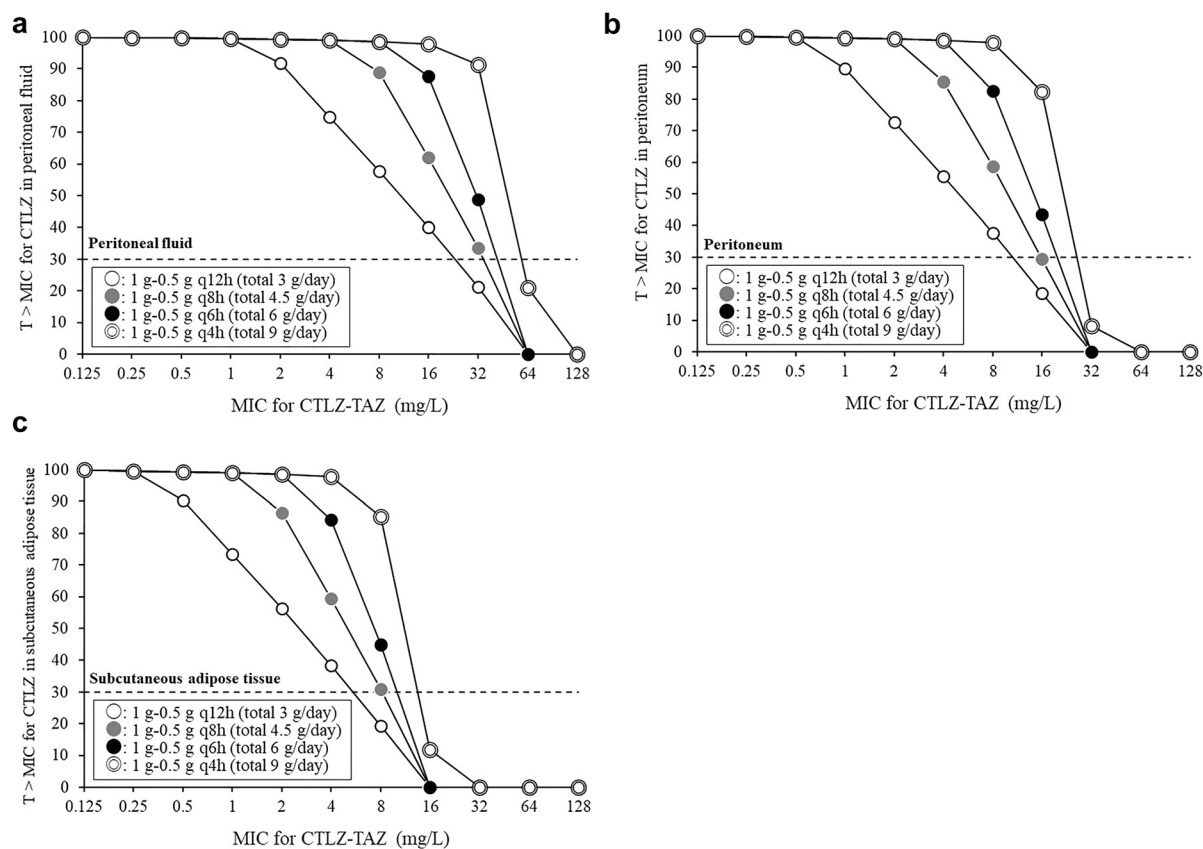


Fig. 4 Site-specific time for which the drug concentration was above the minimum inhibitory concentration ($T > MIC$) for ceftolozane (CTLZ) in the peritoneal fluid (**a**), peritoneum (**b**), and subcutaneous adipose tissue (**c**) at a MIC of 0.125–128 mg/L, using four CTLZ–tazobactam

DISCUSSIONS

In this study, we investigated the optimal pharmacokinetics/pharmacodynamics of CTLZ–TAZ in the abdominal tissue (peritoneal fluid, peritoneum, and subcutaneous adipose) against cIAI-causing bacteria. A comparison of CTLZ plasma concentration with various tissue concentrations showed that the ratio for subcutaneous adipose was lower than those for peritoneal fluid and peritoneum tissues. We also discovered that, in all tissues, the average ratio of CTLZ to TAZ concentrations was maintained at or above 2:1. In our investigation of pharmacodynamic target attainment in each tissue, we observed that the desired bactericidal effect was attained with all CTLZ–TAZ (1 g CTLZ and

regimens. The $T > MIC$ values were predicted using the mean pharmacokinetics model parameters for CTLZ (Table 3). Dashed lines represent the bactericidal target ($T > MIC$ 30%) for CTLZ

0.5 g TAZ) administration regimens [q12h (3 g/day), q8h (4.5 g/day), and q6h (6 g/day)] based on the breakpoints for each cIAI-causing bacterium listed in the CLSI, EUCAST, and Japanese SSI surveillance (MIC_{90}). Although this study investigated drug distribution in the abdominal tissue of patients in whom cIAI was not established, it was performed under conditions in which the patients experienced physical invasiveness in the form of lower gastrointestinal surgery. Thus, we believe that CTLZ–TAZ represents an appropriate model for tissue distribution in cIAI cases.

CTLZ–TAZ is considered to exhibit therapeutic effects against cUTI as well as cIAI [11, 27]. Subsequently, the drug combination was confirmed to have therapeutic effects

against severe hospital-acquired bacterial [13] and ventilator-associated pneumonia [28, 29] on the basis of pharmacokinetic/pharmacodynamic estimates using lung ELF. Nevertheless, only a few studies investigated the tissue concentrations of antibiotics in tissues directly affected by cIAI (i.e., peritonitis), such as peritoneal fluid, peritoneum, and subcutaneous adipose tissue. Murao et al. [18] performed a simulation of the optimal administration regimen of piperacillin-TAZ (PIPC-TAZ) used against cIAI by measuring the PIPC-TAZ concentrations in the peritoneal fluid and peritoneum samples collected during surgery of patients with IBD. However, to the best of our knowledge, this is the first study in which a simulation of noncompartmental pharmacokinetic parameters, compartmental pharmacokinetic parameters, and site-specific pharmacodynamic target attainment has been performed by measuring the tissue concentration of CTLZ-TAZ.

As the main antibacterial activity of CTLZ-TAZ depends on CTLZ, the $AUC_{0-\infty}$ of CTLZ is considered to reflect the antibacterial effect and site-specific permeability of CTLZ-TAZ. For the treatment of cIAI, CTLZ-TAZ is approved at a dose of 1.5 g (1 g of CTLZ and 0.5 g of TAZ) q8h, adjusted on the basis of renal function [30]. In other words, for the cIAI treatment, a 2:1 ratio of CTLZ to TAZ is considered optimal. In the present study, the mean value of the $AUC_{0-\infty}$ for CTLZ (one dose/two doses) was 0.74/1.15 for peritoneal fluid to plasma, 0.41/0.42 for peritoneum to plasma, and 0.17/0.20 for subcutaneous adipose to plasma (Table 2). The CTLZ-to-TAZ dose in all tissues was maintained at a compound ratio of at least 2:1 (Fig. 2). These results provide evidence from a pharmacodynamic perspective of the validity of CTLZ-TAZ use for the treatment of cIAI.

The common Gram-negative bacteria that cause cIAI are *E. coli*, *K. pneumoniae*, *E. cloacae*, and *P. aeruginosa* [1]. In addition, cases of cIAI caused by ESBL-producing Enterobacterales members are increasing worldwide [2]. In the present study, we investigated whether the pharmacodynamic concentration that is effective against various cIAI-causing bacteria can be

attained using the estimated parameters of a pharmacodynamic model. Table 4 presents the MIC for each CTLZ-TAZ administration regimen in abdominal tissues and the MIC values for cIAI-causing bacteria that have been reported by the CLSI [25], EUCAST [26], and Japanese SSI surveillance (MIC_{90}) [23] in a simulation that assumes a percentage of $T > MIC$ of 30%. With reference to the CLSI and EUCAST, CTLZ-TAZ (1 g CTLZ and 0.5 g TAZ) demonstrated optimal antibacterial effect against *E. coli*, *K. pneumoniae*, *E. cloacae*, and *P. aeruginosa* not only at q8h (4.5 g/day) and q6h (6 g/day) but also at q12h (3 g/day). Furthermore, we observed adequate antibacterial effects against ESBL-producing Enterobacterales members (MIC 1 mg/L) while following the Japanese SSI surveillance (MIC_{90}) category. These results provide evidence from the perspective of estimated pharmacodynamic model parameters for the validity of CTLZ-TAZ use as a treatment against cIAI or SSI.

Nevertheless, this study has several limitations. First, the number of patients who participated in the study was small ($n = 9$). Second, the patients who underwent elective surgery for lower gastrointestinal disease were hypothesized to be comparable to patients with peritonitis. However, these conditions were not exactly equal, especially because this study included IBD in addition to colorectal cancer. Apparently, there were no significant differences in pharmacokinetic values between the IBD ($n = 5$) and non-IBD ($n = 4$) groups. However, inflammatory reactions within tissues can change the physiochemical environment, such as capillary permeability, and can affect the ability of drugs to reach sites of action [31–33]. Perea [34] investigated the distribution of ofloxacin in bronchoalveolar tissue of patients with acute purulent exacerbations of chronic bronchitis. They reported higher ofloxacin concentrations in inflamed tissues than in non-inflamed tissues due to the promotion of vascular permeability by inflammation. The same may be true for CTLZ-TAZ penetration into peritoneal fluid and peritoneum in the presence of inflammation. Conversely, the CTLZ-TAZ concentrations in abdominal tissues may be lower if patients suffer from peripheral

Table 4 Ceftolozane and tazobactam administration regimens needed for site-specific pharmacodynamic breakpoints and minimum inhibitory concentrations against *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and ESBL-producing Enterobacterales members

Regimen (1-h infusion)	Peritoneal fluid	Peritoneum	Subcutaneous adipose tissue	References
1 g CTLZ and 0.5 g TAZ q12h (total 3 g/day)	16	8	4	
1 g CTLZ and 0.5 g TAZ q8h (total 4.5 g/day)	32	8	8	CLSI breakpoint, EUCAST epidemiological cutoff 2 mg/L for <i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. cloacae</i> 4 mg/L for <i>P. aeruginosa</i>
1 g CTLZ and 0.5 g TAZ q6h (total 6 g/day)	32	16	8	Japanese SSI surveillance (MIC ₉₀) 1 mg/L for ESBL-producing Enterobacterales members
1 g CTLZ and 0.5 g TAZ q4h (total 9 g/day)	32	16	8	

circulatory failure such as sepsis or septic shock. Third, all patients had a normal renal function and a Ccr mean value of 93.8 mL/min. However, numerous patients suffering from severe infections exhibit low Ccr due to kidney dysfunction. As CTLZ-TAZ is primarily metabolized by the kidneys [30], the drug concentrations in plasma and abdominal tissues may be maintained longer than expected, that is, the $T > MIC$ may be extended. Forth, a CTLZ-TAZ percentage of $T > MIC$ of 30% was assumed. However, as the percentage of $T > MIC$ for humans has not yet been established, different simulation results may have been obtained through the use of other assumed values. Finally, considering that we performed our simulation in patients under an invasive procedure—that is, surgery—this study provides data that are useful in the treatment of cIAI. However, the pharmacodynamic results for CTLZ-TAZ in all tissues investigated were the product of simulated antibacterial effects; therefore, these results do not indicate therapeutic effect or clinical results. Considering these limitations, there is a need for further research to elucidate the therapeutic significance by investigating our CTLZ-TAZ

pharmacodynamic results through a large-scale clinical study with patients suffering from cIAI and by investigating the peritoneal permeability of CTLZ-TAZ as well as the relationship between pharmacodynamic exposure and therapeutic effect.

CONCLUSIONS

The simulation performed to assess CTLZ-TAZ pharmacokinetics in abdominal tissue samples collected during lower gastrointestinal surgery established a guideline for designing an optimal administration regimen based on pharmacodynamic target attainment for cIAI-causing bacteria. To determine the usefulness and significance of these guidelines in clinical settings, large-scale studies on patients with cIAI caused by various bacteria should be conducted.

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Disclosures. Kosuke Yoshimura, Hiroki Ohge, Kazuro Ikawa, Shinnosuke Uegami, Yusuke Watadani, Norifumi Shigemoto, Toshinori Hirano, Hiroki Kitagawa, Yuki Kaiki, Norifumi Morikawa, and Shinya Takahashi declare that they have no competing interest.

Compliance with Ethics Guidelines. The study protocol was carried out in accordance with the Helsinki Declaration of 1964 and its later amendments and was reviewed/approved by the Institutional Review Board of Hiroshima University Hospital (CRB6180006). This study was registered with the Japan Registry of Clinical Trials (jRCTs061190025).

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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