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Original Article

Pharmacokinetics of cefmetazole in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue of patients scheduled for lower gastrointestinal surgery: Dosing considerations based on site-specific pharmacodynamic target attainment

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ABSTRACT

Introduction: Cefmetazole (CMZ) has gained interest as a carbapenem-sparing alternative to the epidemic of extended-spectrum β-lactamase (ESBL)-producing Enterobacterales (ESBL-E). In this study, we investigated the pharmacokinetics (PK) of CMZ in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue to assess the dosing regimen needed to achieve pharmacodynamic (PD) goals at the target site.

Methods: Patients scheduled for elective lower gastrointestinal surgery were intravenously administered CMZ. Plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue samples were collected after CMZ infusion and during the surgery, and CMZ concentrations were measured. The non-compartmental and compartmental PK parameters were estimated and used to evaluate site-specific PD target attainment.

Results: A total of 38 plasma, 27 peritoneal fluid, 36 peritoneum, and 38 subcutaneous adipose tissue samples were collected from 10 patients. The non-compartmental PK analysis revealed the ratios of the mean area under the drug concentration-time curve ($AUC_{0–3.5\ h}$) of peritoneal fluid-to-plasma, peritoneum-to-plasma, and subcutaneous adipose tissue-to-plasma were 0.60, 0.36, and 0.11, respectively. The site-specific PD target attainment analyses based on the breakpoints for ESBL-E per the Japanese surgical site infection (SSI) surveillance (MIC_{90} = 8 mg/L) revealed that 2 g CMZ every 3.5 h achieved desired bactericidal effect at all sites and 2 g CMZ every 6 h achieved PD goals at peritoneum and peritoneal fluid.

Conclusion: These findings clarify the PK of CMZ in abdominal tissues and could help decide optimal dosing regimens to treat intra-abdominal infection and prophylaxis of SSI.

1. Introduction

The rise in antimicrobial resistance, particularly the spread of extended-spectrum β-lactamases (ESBLs), is a growing problem in intra-abdominal infections and abdominal surgery [1,2]. Overuse of broad-spectrum antibiotics, especially carbapenems, has led to the spread of carbapenemase-producing Enterobacterales [3]. Therefore, alternatives such as carbapenem-sparing strategies are increasingly considered a preferred treatment in patients with ESBL-producing Enterobacterales (ESBL-E) infections [4].

Abbreviations: AUC, Area under curve; C_{max}, Maximum concentration; CMZ, Cefmetazole; ESBL, extended-spectrum β-lactamase; MIC, Minimum inhibitory concentration; PK, Pharmacokinetic; PD, pharmacodynamic; SSI, Surgical site infection.

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Cefmetazole (CMZ) is a cephamycin antibiotic with antibacterial activity against gram-positive and gram-negative aerobic and anaerobic bacteria. In Japan, CMZ is frequently used to treat intra-abdominal infections and is recommended by the practical guideline for appropriate usage of antimicrobial agents to prevent postoperative infections advocated by the Japanese Society of Chemotherapy and Japan Society for Surgical Infection [5] as one of the prophylactic agents for lower gastrointestinal surgery. The characteristics of cephamycin, such as resistance to a variety of ambler class A β-lactamases, especially ESBLs, and antibacterial ability against ESBL-E [6], have led to reconsider their use as carbapenem-sparing alternatives [7–9].

The clinical efficacy of CMZ depends on its ability to reach the target site of infection. However, previous pharmacokinetic (PK) studies have only demonstrated the serum concentration of CMZ [10], and no PK studies have determined its transfer to abdominal tissues. Understanding the PK distribution of CMZ will help clarify the PD effects for treating infections such as intra-abdominal infection and prophylactic antimicrobial dosing during surgery.

Therefore, we investigated the PK of CMZ in plasma, peritoneal fluid, peritoneum, and adipose tissues and performed PK analysis to assess the dosing regimen needed to achieve PD goals at the target site, especially for ESBL-E.

2. Materials and methods

2.1. Study subject

This study was a prospective and open-label study to evaluate the effective dose of CMZ conducted at Hiroshima University Hospital between January 2020 and January 2021. Patients (n = 10) scheduled for elective lower gastrointestinal surgery were chosen as the study subjects. Patients who were hypersensitive to β-lactams, pregnant, or nursing were excluded. Patients with creatinine clearance below 50 mL/min, as estimated by the Cockloft-Gault equation, were also excluded because they would require drug dosage adjustments based on renal dysfunction and therefore confound the analysis of PK parameters. The patients aged >20 years, amenable to antibacterial prophylaxis for postoperative infections, and who provided written informed consent were included in this study (n = 10).

The study protocol was per the Declaration of Helsinki and was reviewed and approved by the institutional review board of Hiroshima University Hospital (Approval number: CRB6180006). This study was registered with the Japan Registry of Clinical Trials (jRCTs061190025).

2.2. Drug administration and sample collection

One-gram CMZ was administered intravenously 30 min before surgery. Blood (2 mL), peritoneal fluid (2 mL), peritoneum (4 mm × 4 mm), and subcutaneous adipose tissue (4 mm × 4 mm) were obtained at the end of infusion (30 min), and every hour after that until the completion of surgery. Three hours after the end of the first CMZ administration and 4th collection of tissues, another dose of CMZ (1 g) was administered intravenously for 30 min, and tissues were collected at the end of the second infusion.

Since CMZ displays time-dependent bactericidal activity like other beta-lactam antimicrobials, extended infusion could theoretically effective in terms of pharmacokinetics/pharmacodynamics [11]. However, the guideline indicates that antimicrobials should be started within 1 h of the start of surgery and adequate tissue concentrations should be obtained at the start of surgery [5]. In addition, it is practically difficult to start drug administration exactly 1 h before the start of surgery. Therefore, we administered CMZ for 30 min.

In the guideline, CMZ should be administered 2–3 h after the end of dosing [5]. To avoid overdosing during the long surgery, we readministered CMZ 3 h after the end of dosing. Consequently, the CMZ dosing interval was 3.5 h, including the infusion time of 30 min.

The supernatant of plasma and peritoneal fluid samples were obtained after centrifugation, and the peritoneum and adipose tissue samples were rinsed with saline. All samples were stored at −40 °C until assay.

2.3. Cefmetazole assay

The total concentrations of CMZ in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue were measured using high-performance liquid chromatography (HPLC) following the procedure described by García-Gonzalez et al. [12] with minor modifications. Briefly, peritoneum or subcutaneous adipose tissue samples (0.5 g) were homogenized using an overhead mixer with 4 vol (2 mL [w/v]) of double-distilled water. The tissue homogenate was centrifuged, and the supernatant was collected. The tissue supernatants, plasma, or peritoneal fluid samples (200 μL each) were then added to a solution of 7% perchloric acid (100 μL) and 0.5 mol/L sodium hydroxide (100 μL), and the mixtures were vortexed and centrifuged. Next, the supernatants (20 μL) were injected into an HPLC system fitted with a UV detector. The separation was achieved using a C18 column; the oven temperature and wavelength were set at 40 °C and 272 nm, respectively. The mobile phase comprised a mixture of 20 mmol/L citric acid buffer (pH 5.4) and acetonitrile (91:9 [vol/vol]), and the flow rate was 1 mL/min. The detection limits for CMZ were 0.5 mg/L in plasma and peritoneal fluid and 0.25 mg/kg in the peritoneum and subcutaneous adipose tissues, respectively. The calibration curves were linear up to 300 mg/L and 150 mg/kg, respectively. Interday and intraday accuracy (as mean absolute values of errors from 100%) and precision (as coefficients of variations) were within 10%.

2.4. Noncompartmental PK analysis

The maximum concentration (C_{max}) was the observed maximum concentration after the first intravenous infusion of CMZ for 30 min. According to the guideline [5], an additional dose of CMZ was administered 3.5 h after the first infusion started; therefore, we employed the period from the start of the first dose to 3.5 h. The area under the drug concentration-time curve (AUC) from 0 to 3.5 h ($AUC_{0–3.5}$) was calculated based on the trapezoidal rule using the MULTI software program (originally developed by Yamaoka et al. [13] and currently maintained by the Department of Biopharmaceutics and Drug Metabolism; Kyoto University, Kyoto, Japan). C_{max} or AUC ratio, the indices of drug distribution in tissues, were used to estimate the abdominal tissue penetration ratio of CMZ in each tissue. In the PK analysis, the specific gravity of the peritoneum and subcutaneous adipose tissues was taken as 1 (kg = L).

2.5. Compartmental PK analysis

The preliminary analysis for CMZ indicated that a multicompartment model to describe the four drug concentrations (plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue) was too complicated; rather, a simpler model could be used because of the parallel drug elimination slopes of the abdominal sites. Therefore, the concentration-time data were fitted to a hypothetical two-compartment model with correction factors [14] to account for concentration differences between the plasma and abdominal sites (Fig. 1). The differential equations used to estimate the changes in the amount of drug in the central compartment (A(1), mg) and peripheral compartment (including abdominal sites; A(2), mg) regarding time (t) are as follows:

$$dA(1)/dt = Rin - (K12 + K10) \times A(1) + K21 \times A(2),$$

$$dA(2)/dt = K12 \times A(1) - K21 \times A(2)$$

where Rin is the intravenous infusion rate of drug (mg/h), K12 and K21 are the transfer rate constants (1/h) connecting the central and

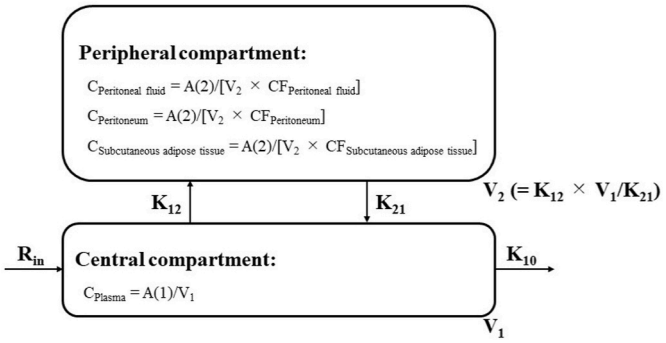

Fig. 1. Hypothetical two-compartment pharmacokinetic model for cefmetazole (CMZ). A(1) and A(2), concentrations of CMZ in the central and peripheral (including abdominal sites) compartments (mg); V1 and V2, volumes of distribution of the central and peripheral compartments (L = kg); C, concentration of CMZ in plasma and peritoneal fluid (mg/L) and peritoneum and subcutaneous adipose tissue (mg/kg); Rin, intravenous infusion rate of CMZ (mg/h), K12 and K21, transfer rate constants (1/h); K10, elimination rate constant (1/h); CF, correction factors of V2 to account for CMZ concentration differences between plasma and abdominal sites (fluid and tissue).

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 correction factors to account for drug concentration differences between the plasma and peritoneal fluid ($CF_{Peritoneal\ fluid}$), plasma and peritoneum ($CF_{Peritoneum}$), and plasma and subcutaneous adipose tissue ($CF_{Subcutaneous\ adipose\ tissue}$), the equations for the drug concentration in plasma (C_{Plasma}, mg/L), peritoneal fluid ($C_{Peritoneal\ fluid}$, mg/L), peritoneum ($C_{Peritoneum}$, mg/kg), and subcutaneous adipose tissue ($C_{Subcutaneous\ adipose\ tissue}$, mg/kg) are expressed as follows:

$$C_{Plasma} = A\ (1)/V1$$

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

$$C_{Peritoneum} = A\ (2) \times K21/\ [K12 \times V1 \times CF_{Peritoneum}]$$

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

These seven PK model parameters (K12, K21, K10, V1, $CF_{Peritoneal\ fluid}$, $CF_{Peritoneum}$, and $CF_{Subcutaneous\ adipose\ tissue}$) were estimated for each patient using the MULTI software program [13].

2.6. Site-specific pharmacodynamic target attainment analysis

We followed six therapeutic (1 or 2 g CMZ at every 12, 8, 6 h; 30 min infusion) and two prophylaxis (1 or 2 g at every 3.5 h; 30 min infusion) regimens. For each CMZ regimen, the duration at which CMZ concentration (T) exceeded the minimum inhibitory concentration (MIC) in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue was predicted. As described in earlier studies [15–18], the drug concentration was not adjusted for protein binding but assumed as the clinically equivalent free concentration; the protein-binding values of CMZ at these abdominal sites are currently unknown. Using the mean estimates for the seven PK model parameters for CMZ (K12, K21, K10, V1, $CF_{Peritoneal\ fluid}$, $CF_{Peritoneum}$, and $CF_{Subcutaneous\ adipose\ tissue}$), the time point at which the predicted drug concentrations in the peritoneal fluid, peritoneum and subcutaneous adipose tissue coincided with a MIC (0.125–128 mg/L) was determined. The time point at which T > MIC was calculated as the cumulative percentage of a 24-h period.

Based on the analysis of pharmacodynamic target attainment, the site-specific PD breakpoint MIC was defined as the highest MIC at which T > MIC in the peritoneal fluid, peritoneum, and subcutaneous adipose tissues was greater than the bactericidal target of 70% for CMZ [9].

3. Results

3.1. Study subjects

Eight male and two female patients were included in this study. Of these ten patients, seven had Crohn's disease, one had ulcerative colitis, and two had ascending colon cancer. Six patients underwent open surgery and four laparoscopic surgeries: one proctocolectomy, five colon resections, and four small bowel resections. Patient demographics were as follows: age, 51.6 ± 15.8 years (mean ± standard deviation [SD]); weight, 55.8 ± 10.4 kg; body mass index, 20.3 ± 2.6 kg/m^2; creatinine clearance estimated by the Cockcroft-Gault formula, 98.3 ± 38.6 mL/min; total bilirubin, 0.6 ± 0.4 mg/dL; aspartate aminotransferase, 21.5 ± 7.9 IU/L; alanine aminotransferase, 27.6 ± 18.3 IU/L; and albumin, 3.77 ± 0.58 g/dL (Table 1).

3.2. Sample collection and CMZ assay

A total of 38 plasma samples, 27 peritoneal fluid samples, 36 peritoneum samples, and 38 subcutaneous adipose tissue samples were collected. CMZ concentrations in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue samples ranged from 4.3 to 246.1 mg/L, 7.5–79.1 mg/L, 3.6–57.6 mg/kg, and 0.7–36.6 mg/kg, respectively. All values exceeded the limit of detection for each.

3.3. Non-compartmental PK analysis

The non-compartmental PK parameters of CMZ are summarized in Table 2. The mean C_{max} in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue was 133.8 mg/L, 60.7 mg/L, 37.7 mg/L, and 12.9 mg/kg, respectively. The mean $AUC_{0–3.5}$ was 201.8 mg h/L in plasma, 121.8 mg h/L in peritoneal fluid, 74.3 mg h/kg in the peritoneum, and 23.2 mg h/kg in subcutaneous adipose tissue. The mean peritoneal fluid $AUC_{0–3.5}$: plasma $AUC_{0–3.5}$, peritoneum $AUC_{0–3.5}$: plasma $AUC_{0–3.5}$, and subcutaneous adipose tissue $AUC_{0–3.5}$: plasma $AUC_{0–3.5}$ were 0.60, 0.36, and 0.11, respectively.

3.4. Compartmental PK analysis

The PK parameters in the hypothetical two-compartment model (Fig. 1) are summarized in Table 3. The prediction curves drawn using the mean parameter estimates fitted to all mean measurements of CMZ in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose

Table 1
Demographic characteristics of the patients.

	Number	Mean ± SD	Range
Gender (male/female)	8/2		
Disease (IBD/cancer)	8/2		
Procedure (open/lap[a])	6/4		
Age (years)		51.6 ± 15.8	22–73
Weight (kg)		55.8 ± 10.4	41.7–71.0
Body mass index (kg/m^2)		20.3 ± 2.6	16.8–24.3
Serum creatinine (mg/dL)		0.72 ± 0.14	0.47–0.89
Creatinine clearance[b] (mL/min)		98.3 ± 38.6	59.2–152.9
Total bilirubin (mg/dL)		0.6 ± 0.4	0.3–1.4
Aspartate aminotransferase (IU/L)		21.5 ± 7.9	13–42
Alanine aminotransferase (IU/L)		27.6 ± 18.3	12–79
Albumin (g/dL)		3.77 ± 0.58	2.7–4.5
Operation time (min)		223.9 ± 66.6	156–343
Bleeding (g)		136 ± 138.0	16–496

SD: standard deviation; IBD: inflammatory bowel disease.
[a] Laparoendoscopic procedure.
[b] Estimated using the Cockcroft-Gault equation.

Table 2
Noncompartmental pharmacokinetic parameters of cefmetazole (CMZ, 1 g) after 30 min intravenous infusion.

Sample type and parameter	Value (mean ± SD, n = 10)
Plasma	
C_{max} (mg/L)	133.8 ± 30.8
$AUC_{0-3.5}$ (mg h/L)	201.8 ± 33.3
Peritoneal fluid	
C_{max} (mg/L)	60.7 ± 16.4
$AUC_{0-3.5}$ (mg h/L)	121.8 ± 33.2
Peritoneum	
C_{max} (mg/L)	37.7 ± 14.1
$AUC_{0-3.5}$ (mg h/L)	74.3 ± 33.0
Subcutaneous adipose tissue	
C_{max} (mg/L)	12.9 ± 6.2
$AUC_{0-3.5}$ (mg h/L)	23.2 ± 8.6
Peritoneal fluid: plasma ratio	
C_{max}	0.46 ± 0.11
$AUC_{0-3.5}$	0.60 ± 0.11
Peritoneum: plasma ratio	
C_{max}	0.28 ± 0.10
$AUC_{0-3.5}$	0.36 ± 0.14
Subcutaneous adipose tissue: plasma ratio	
C_{max}	0.09 ± 0.03
$AUC_{0-3.5}$	0.11 ± 0.03

SD: standard deviation; C_{max}: maximum concentration; $AUC_{0-3.5}$: area under the drug concentration-time curve from 0 to 3.5 h.

Table 3
Pharmacokinetic parameters for CMZ in the hypothetical two-compartment model (see Fig. 1).

Parameter	Estimate (mean ± SD, n = 10)
K12 (1/h)	1.27 ± 0.30
K21 (1/h)	5.23 ± 1.89
K10 (1/h)	0.86 ± 0.12
V1 (L)	5.34 ± 1.47
$CF_{peritoneal\ fluid}$	0.33 ± 0.24
$CF_{peritoneum}$	0.54 ± 0.51
$CF_{subcutaneous\ adipose\ tissue}$	1.32 ± 1.09

SD: standard deviation; K12 and K21: transfer rate constants of connecting compartments; K10: elimination rate from the central compartment; V1: distribution volumes for central compartment; $CF_{Peritoneal\ fluid}$, $CF_{Peritoneum}$, and $CF_{Subcutaneous\ adipose\ tissue}$: correction factors to account for drug concentration differences between the plasma and each tissue.

tissue (Fig. 2). The regression equation between the observed concentration (Y) and the individual predicted concentration (X) was $Y = 0.972\ X + 1.046$ ($r = 0.986$). The values of normalized mean prediction error (as a bias index) and normalized mean absolute prediction error (as an accuracy index) were −0.175 and 2.291, respectively.

3.5. Site-specific PD target attainment analysis

Using mean estimates for the seven PK model parameters for CMZ, drug concentrations were predicted for different dosing regimens [1 g at every 12 h (1g q12h), 1 g at every 8 h (1g q8h), 1 g at every 6 h (1g q6h), 2 g at every 12 h (2g q12h), 2 g at every 8 h (2g q8h), 2 g at every 6 h (2g q6h), 1 g at every 3.5 h (1g q3.5h), and 2 g at every 3.5 h (q3.5h)] to determine whether PD target attainment could be achieved in peritoneal fluid (Fig. 3a), the peritoneum (Fig. 3b), and the subcutaneous adipose tissue (Fig. 3c). As the Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing do not report the breakpoint for ESBL-E, desired antibacterial effect was based on the categories of the Japanese surgical site infection (SSI) surveillance (MIC_{90} = 8 mg/L) [19].

Table 4 shows each CMZ regimen needed for site-specific PD breakpoints in a prediction that assumes a T > MIC of 70%. The regimens for prophylaxis doses that achieved the target in all tissue were CMZ 1 g q3.5h for a MIC of 4 mg/L and 2 g q3.5h for a MIC of 8 mg/L. The regimens for therapeutic doses that achieved the target in all tissue were less than MIC of 2 mg/L. The regimens for therapeutic doses that achieved the target except for subcutaneous adipose tissue were 1 g q12h (MIC 0.25 mg/L), 1 g q8h (MIC 2 mg/L), 1 g q6h (MIC of 4 mg/L), 2 g q12 h (MIC 0.5 mg/L), 2 g q8h (MIC 4 mg/L), and 2 g q6h (MIC 8 mg/L).

4. Discussion

Several studies have demonstrated the clinical efficacy of CMZ in treating bacteremia with ESBL-E [8,20]. Although several PK/PD analyses of blood samples to decide its optimal dosage and method of administration have been reported [10,21], the concentration and penetration of CMZ in abdominal tissues where peritonitis and SSIs occur have not been well described. Furthermore, studies that measured CMZ concentrations in subcutaneous adipose tissues have not shown PK/PD analyses which support better dosing consideration [22,23]. In these studies, ratios between blood and subcutaneous adipose tissue concentrations of CMZ were calculated for only a limited time. To the best of our knowledge, the present study is the first to perform a PK/PD

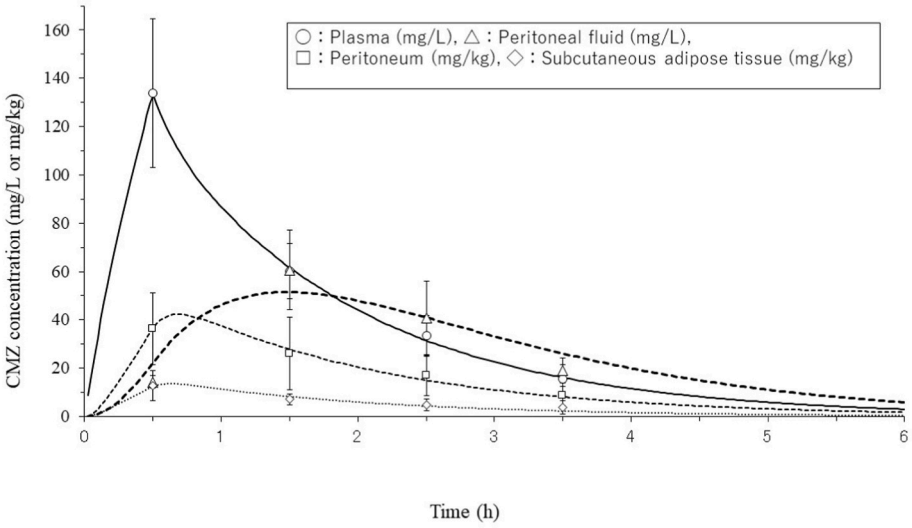

Fig. 2. Observed concentrations (mean ± standard deviation [SD], n = 10) and prediction curves for CMZ in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue after a single 0.5 h infusion of 1 g CMZ. The prediction curves were drawn using the mean pharmacokinetic model parameters (K12 = 1.27 1/h, K21 = 5.23 1/h, K10 = 0.858 1/h, V1 = 5.34 L, $CF_{Peritoneal\ fluid}$ = 0.330, $CF_{Peritoneum}$ = 0.542, and $CF_{Subcutaneous\ adipose\ tissue}$ = 1.32). (K12 and K21: transfer rate constants of connecting compartments, K10: elimination rate from the central compartment, V1: distribution volumes for central compartment, $CF_{Peritoneal\ fluid}$, $CF_{Peritoneum}$, and $CF_{Subcutaneous\ adipose\ tissue}$: correction factors to account for drug concentration differences between the plasma and each tissue.)

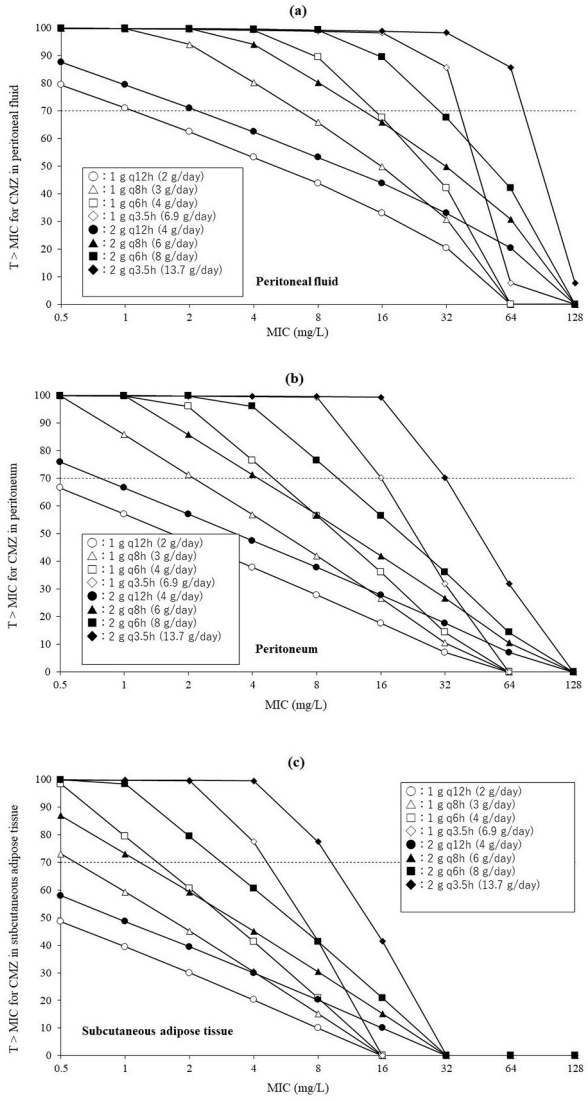

Fig. 3. Site-specific time that drug concentration (T) was above the minimum inhibitory concentration (MIC) for CMZ in the peritoneal fluid (a), peritoneum (b), and subcutaneous adipose tissue (c) at a MIC of 0.125–128 mg/L, using eight regimens; 1 g at every 12 h (1g q12h), 1 g at every 8 h (1g q8h), 1 g at every 6 h (1g q6h), 2 g at every 12 h (2g q12h), 2 g at every 8 h (2g q8h), 2 g at every 6 h (2g q6h), 1 g at every 3.5 h (1g q3.5h), and 2g q3.5h. The T > MIC values were predicted using the mean pharmacokinetic model parameters (Table 3). The dashed lines represent the bactericidal target (T > MIC = 70%).

analysis, where an estimation of non-compartmental PK parameters, compartmental PK parameters, and site-specific PD target attainment was performed by measuring the CMZ concentrations of the abdominal tissues (peritoneal fluid, peritoneum, and subcutaneous adipose).

The PK analysis demonstrated a lower concentration of CMZ in subcutaneous adipose tissues (mean $AUC_{0–3.5}$ ratio, 0.11) than those in peritoneal fluid (mean $AUC_{0–3.5}$ ratio, 0.60) and peritoneum (mean $AUC_{0–3.5}$ ratio, 0.36). Concordant to our study, previous studies have shown that the penetration of other cephems, such as cefazolin [24] and cefotetan [25] is low in adipose tissues compared with that in other abdominal tissues. SSI occurs more frequently in subcutaneous adipose tissue than in intra-abdominal tissue. Moreover, the lower concentration of cephem in subcutaneous adipose tissue is considered a risk factor for SSI [26]. Therefore, subcutaneous adipose tissue penetration is important for antimicrobial agents to prevent SSI. A previous study evaluating the concentration of CMZ in serum, subcutaneous adipose tissues, and mesenteric adipose tissues of patients who underwent colorectal surgery

Table 4
The CMZ regimens for the estimation of site-specific pharmacodynamic breakpoints and minimum inhibitory concentration (MIC) values against ESBL-producing Enterobacterales.

Regimen (30 min infusion)	Peritoneal fluid (mg/L)	Peritoneum (mg/L)	Subcutaneous adipose tissue (mg/L)
For treatment			
1g q12h (2 g/day)	1	0.25	0.0625
1g q8h (3 g/day)	4	2	0.5
1g q6h (4 g/day)	8	4	1
2g q12h (4 g/day)	2	0.5	0.125
2g q8h (6 g/day)	8	4	1
2g q6h (8 g/day)	16	8	2
For prophylaxis			
1g q3.5h (6.9 g/day)	32	16	4
2g q3.5h (13.7 g/day)	64	32	8

1g q12h: 1 g at every 12 h; 1g q8h: 1 g at every 8 h; 1g q6h: 1 g at every 6 h; 2g q12h: 2 g at every 12 h; 2g q8h: 2 g at every 8 h; 2g q6h: 2 g at every 6 h; 1g q3.5h: 1 g at every 3.5 h; 2g q3.5h: 2 g at every 3.5 h.

has shown that CMZ concentration in subcutaneous adipose tissue was lower in patients with SSI than in those without SSI [22]. These findings suggest that when using cephems for antimicrobial prophylaxis during surgery, maintaining the drug concentration in subcutaneous adipose tissues at sufficient bactericidal levels is essential to reduce SSI.

The site-specific PD target attainment analysis showed that the regimen 2g q3.5h achieved the desired bactericidal effect in all abdominal tissues. As intra-abdominal infections rarely occur in the subcutaneous adipose tissue, CMZ concentrations in the peritoneum and peritoneal fluid were important for therapeutic purposes. In addition, a therapeutic dose of 2g q6h achieved the desired bactericidal effect in the peritoneum and peritoneal fluid. Following these results, 2 g CMZ q3.5h in the perioperative period would require 6 g in the third dose for surgery over 7 h, and 2 g q6h for intra-abdominal infections would result in total 8 g/day. In previous studies, CMZ has been administered up to 8 g [27]. However, in Japan, CMZ has been approved to use up to 4 g. Since the safety at a dose of more than 4 g has not been established in Japan, careful attention to the risk of side effects is needed especially elderly and low-weight patients. Previous studies performing PK/PD analysis based on plasma concentration of CMZ indicated that the optimal dosage should be determined based on renal function [10,21]. In our study, 5 of the 10 patients had good renal function with creatinine clearance >100 mL/min (102, 104.2, 127.5, 151.5, and 172.4 mL/min), which may have led to early drug excretion and lower tissue concentrations. In this study, desired antibacterial effect for ESBL-E was based on the surveillance program monitoring the antibacterial susceptibility in Japan (MIC_{90} = 8 mg/L) [19]. However, for ESBL-E in Japan and China, MIC_{90} for CMZ varied by genotypes, ranging from 2 to 8 mg/L [6,28]. Therefore, depending on the MIC for CMZ of the ESBL-E, the dosing regimen can be decided. For example, if the ESBL-E had a MIC <8 before treatment, a smaller dosing regimen (2g q3.5h or 2g q6h) could be effective.

The serum albumin in the study patients were 3.77 ± 0.58 g/dL (Table 1). The degrees of the protein levels did not correlate with the penetration ratio values of CMZ (Table 2). Generally, protein binding (unbound fraction) of drugs is a determinant of their penetrability into biological fluids ad tissues. However, the free drug concentration in plasma does not always represent the drug level in biological fluids ad tissues, as shown in our previous studies [15–18]. Therefore, it is important to directly use the drug level at a specific site of action in order to accurately estimate the site-specific pharmacodynamic target

attainment.

Our study had several limitations. (1) The number of study patients was small (n = 10). (2) The PD results of CMZ in the various tissues examined in this study are only predictions of bactericidal effects and do not indicate therapeutic or clinical results. The PD results may provide useful information for treating intra-abdominal infections and antimicrobial prophylaxis during surgery, but it does not confirm the optimal method of administration in actual clinical practice. (3) In general, healthy subjects are recruited to study drug tissue penetration; however, peritoneal cavity conditions of patients with intra-abdominal infection or surgical patients are assumed to differ markedly from those of healthy subjects. The present study was conducted to investigate drug distribution during bowel resection surgery. As these patients had an inflamed condition due to surgical invasion, we considered them suitable as an inflamed peritoneal cavity model. (4) The majority of our study was IBD patients with chronic gastrointestinal inflammation. Inflammation in abdominal tissues can change the physiochemical environment, such as capillary permeability, fluid balance and blood flow [29]. These changes can affect the ability of drugs to reach sites of action. Therefore, PK parameters may be different in cases with no inflammation. (5) The site-specific T > MIC and the breakpoint MIC were representative values derived from the mean predicted concentrations at the abdominal sites based on the mean pharmacokinetic parameters. However, there was a wide variability in the parameter estimates with a variation coefficient (SD/mean) of 13.9–93.2% and in the observed concentrations at 0.5–3.5 h with a variation coefficient of 18.9–71.1%. This study did not find significant factors (e.g., sex, age, weight, body mass index, creatinine clearance) that correlated well with the individual pharmacokinetic parameters. The covariates that explain the interindividual variability in CMZ pharmacokinetics should be identified to personalize dosing regimen based on the breakpoint MIC for each patient. Considering these limitations, it is necessary to validate our CMZ PD results by conducting a large clinical study in patients with a variety of intra-abdominal infections and clarify its therapeutic significance by examining the relationship between CMZ peritoneal permeability and PD exposure and therapeutic efficacy.

5. Conclusion

A comparison of CMZ concentrations in plasma and the various tissues based on PK analysis showed that the mean $AUC_{0–3.5}$ ratio for subcutaneous adipose was lower than those for peritoneal fluid and peritoneum tissues. In our investigation of site-specific PD target attainment analyses based on the breakpoints for ESBL-E in the Japanese SSI surveillance (MIC_{90} = 8 mg/L), 2 g CMZ q3.5h achieved bactericidal effect at all sites, and 2 g q6h achieved the target at peritoneum and peritoneal fluid. Our results would help optimize the dosing regimen when using CMZ as a carbapenem-sparing alternative in treating intra-abdominal infections and antimicrobial prophylaxis during surgery, especially for ESBL-E based on the site-specific PD target attainment. Further studies are needed to confirm the present findings and clarify their therapeutic significance.

Authorship statement

All authors meet the ICMJE authorship criteria. YK, HO, KI, NS, TH, KY, HK, and NM conceptualized and designed the study. YK, KI, HO, SU, YW, TH, KY, and NM were responsible for sample collection. YK, KI, and NM participated in the data analysis and interpretation. YK prepared the initial draft manuscript, which was critically reviewed and revised by all authors. All authors approved the final manuscript and shared responsibility for the work.

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Declaration of competing interest

None.

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