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Original Article

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

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ABSTRACT

Introduction: Flomoxef is generally used to treat abdominal infections and as antibiotic prophylaxis during lower gastrointestinal surgery. It is reportedly effective against extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* and an increasingly valuable alternative to carbapenems. However, its abdominal pharmacokinetics remain unclear. Herein, pharmacokinetic analysis of flomoxef in the abdominal tissue was conducted to simulate dosing regimens for pharmacodynamic target attainment in abdominal sites.

Methods: Flomoxef (1 g) was administered intravenously to a patient 30 min before commencing elective lower gastrointestinal surgery. Samples of plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue were collected during surgery. The flomoxef tissue concentrations were measured. Accordingly, non-compartmental and compartmental pharmacokinetic parameters were calculated, and simulations were conducted to evaluate site-specific pharmacodynamic target values.

Results: Overall, 41 plasma samples, 34 peritoneal fluid samples, 38 peritoneum samples, and 41 subcutaneous adipose samples from 10 patients were collected. The mean peritoneal fluid-to-plasma ratio in the areas under the drug concentration-time curve was 0.68, the mean peritoneum-to-plasma ratio was 0.40, and the mean subcutaneous adipose tissue-to-plasma was 0.16. The simulation based on these results showed the dosing regimens (q8h [3 g/day] and q6h [4 g/day]) achieved the bactericidal effect (% T > minimum inhibitory concentration [MIC] = 40%) in all tissues at an MIC of 1 mg/L.

Conclusions: We elucidated the pharmacokinetics of flomoxef and simulated pharmacodynamics target attainment in the abdominal tissue. This study provides evidence concerning the use of optimal dosing regimens for treating abdominal infection caused by strains like ESBL-producing bacteria.

1. Introduction

Extended-spectrum beta-lactamase (ESBL)-producing bacteria are antimicrobial bacteria with increasing prevalence [1]. They have increased rapidly worldwide to a level that cannot be overlooked in empiric therapy for abdominal infections [2]. Another problem is the

Abbreviations: AUC, area under the drug concentration-time curve; ESBL, extended-spectrum beta-lactamase; HPLC, high-performance liquid chromatography; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; SD, standard deviation; SSI, surgical site infection.

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increased rate of surgical site infection (SSI) after lower gastrointestinal surgery in ESBL *Enterobacteriaceae* carriers [3]. Carbapenem antibiotics are the first-line therapy for ESBL-producing bacteria, but there are few options for second-line and subsequent therapies [4]. The spread of carbapenemase-producing *Enterobacteriaceae* as resistant bacteria due to carbapenem overuse has become a major concern [5]. The lack of other treatment options for ESBL-producing bacteria is a problem; therefore, finding an alternative antimicrobial to carbapenems is imperative.

Flomoxef is a parenteral β-lactam antibiotic, also called oxacephem, developed in Japan. It is a broad-spectrum antibiotic effective against gram-positive cocci, gram-negative rods, and anaerobic bacteria [6–8]. It has a wide range of indications, including the treatment of pneumonia, urinary tract infections, and abdominal infections, and is used as a prophylactic antibiotic for lower gastrointestinal surgery [6–9]. Furthermore, flomoxef is reportedly effective against ESBL-producing *Enterobacteriaceae* [10–13], with comparable therapeutic efficacy to carbapenems [14–16]. It can be an alternative antimicrobial to carbapenems and may be useful as perioperative prophylactic antibiotic for ESBL-producing *Enterobacteriaceae* carriers.

Currently, no evidence-based criteria have been established for the administration of flomoxef for abdominal infections caused by ESBL-producing *Enterobacteriaceae*. The pharmacokinetics of flomoxef in plasma and peritoneal have been demonstrated to reach adequate therapeutic concentrations [17,18]. However, *in vivo* changes related to the peritoneum and the subcutaneous adipose tissue, which are the primary focus of abdominal infection, remain unknown. In previous reports, the rate of transfer of β-lactam antimicrobials to the peritoneum and adipose tissue has been shown to be low [19,20]. Therefore, dosing regimens based on pharmacokinetics in plasma only would not be expected to maintain adequate therapeutic concentrations in other tissues. To determine the appropriate dosage of flomoxef in each abdominal tissue, it is necessary to confirm its pharmacokinetic distribution in the peritoneum and adipose tissue compared to the corresponding in plasma.

Herein, we investigated the pharmacokinetics of flomoxef in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue. Based on this, a pharmacokinetic analysis was conducted to simulate the optimal dosing regimens to achieve an optimal pharmacokinetic/pharmacodynamic (anti) level against bacteria associated with abdominal infections, including ESBL-producing *Enterobacteriaceae*.

2. Patients and methods

2.1. Study participants

This is a prospective, open trial study on the pharmacokinetics of flomoxef in abdominal tissues. It was conducted at Hiroshima University Hospital between January 2020 and January 2021. The study protocol conformed to the Declaration of Helsinki and was approved by the institutional review board of Hiroshima University Hospital (CRB6180006). This study was registered with the Japan Registry of Clinical Trials (jRCTs061190025). All patients gave informed consent to participate.

The participants were males and females aged ≥20 years who underwent elective lower gastrointestinal surgery for Crohn's disease or colon cancer. The exclusion criteria were previous allergy to flomoxef or other beta-lactam antibiotics, pregnancy or breastfeeding, and organic disease of the brain or spinal cord. Patients whose creatinine clearance estimated by the Cockroft–Gault method was <50 mL/min were also excluded.

2.2. Drug administration and sample collection

Flomoxef (1 g) was administered intravenously for 30 min immediately before commencing surgery. The sample collection protocol involved plasma (2 mL), peritoneal fluid (2 mL), peritoneum (4 mm × 4 mm), and subcutaneous adipose tissue (4 mm × 4 mm) at the end of flomoxef administration, and subsequently, every hour until the operation ended. The plasma half-life of flomoxef is short (50 min); hence, a re-dosing interval of every 2 h is recommended [7,21]. At 2 h after the end of the initial administration, we administered re-dosing of flomoxef (1 g) intravenously over a 30-min period after collecting the third set of tissue samples.

Plasma and peritoneal fluid samples were centrifuged, and the supernatant was collected. Peritoneum and subcutaneous adipose tissue samples were washed in physiological saline. All the samples were stored at −40 °C until analysis.

2.3. Flomoxef assay

The total concentration of flomoxef in plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue was measured using high-performance liquid chromatography (HPLC) with minor modifications of the methods of Konaka et al. [22]. 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 mL each) were, then, added to 400 mL of methanol, and the mixture was vortexed and centrifuged. Next, the supernatants (20 mL) were injected into an HPLC system. The HPLC employed a C18 column at a temperature of 40 °C and detected flomoxef at a wavelength of 254 nm ultraviolet absorbance. The mobile phase consisted of a mixture of 60 mmol/L sodium phosphate buffer (pH 6.0) containing 5 mmol/L tetrabutylammonium hydroxide and acetonitrile (85:15 [v/v]) with a flow rate of 1 mL/min. The quantification limits for flomoxef were 0.5 mg/L in plasma and peritoneal fluid, and 0.75 mg/kg in the peritoneum and subcutaneous adipose tissue, respectively. The calibration curves were linear up to 200 mg/L and 100 mg/kg, respectively. The interday and intraday accuracy (as mean absolute values of errors from 100%) and precision (as coefficients of variations) were both within 10%.

2.4. Noncompartmental pharmacokinetic analysis

C_{max} was defined as the maximum observed concentration. The area under the drug concentration-time curve from 0 to 2.5 h ($AUC_{0–2.5}$) was calculated by the trapezoid formula using the MULTI software program (originally developed by Yamaoka et al. and currently maintained by the Department of Biopharmaceutics and Drug Metabolism; Kyoto University, Kyoto, Japan) [23]. For the pharmacokinetic analysis, the specific gravity of the peritoneum and subcutaneous adipose tissues was considered as 1 (kg = L).

2.5. Compartmental pharmacokinetic analysis

The preliminary analysis for flomoxef indicated that a multi-compartment model describing four drug concentrations (i.e., in 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 for the abdominal sites. Therefore, the concentration–time data were fitted to a hypothetical two-compartment model with correction factors [24] to account for concentration differences between the plasma and abdominal sites (Fig. 1). The differential equations for 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:

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

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

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

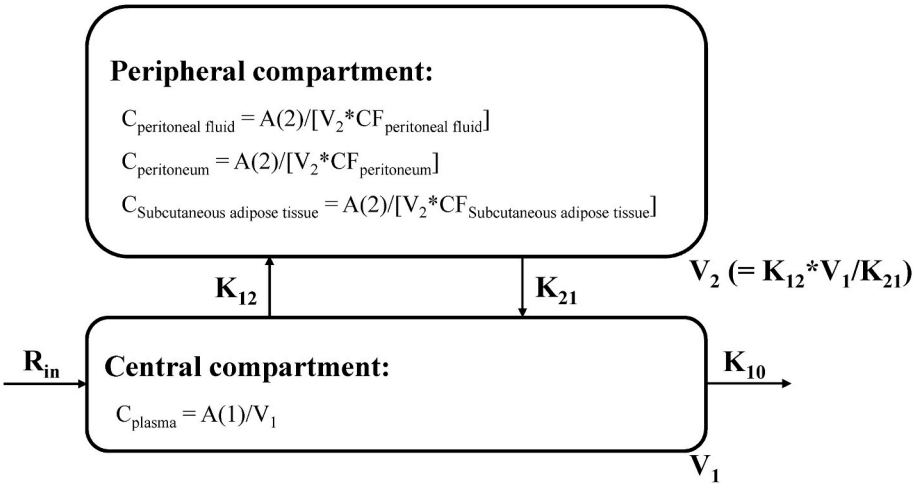

Fig. 1. Hypothetical two-compartment pharmacokinetic model for flomoxef. A(1) and A(2), amounts of drug in the central and peripheral (including abdominal sites) compartments (mg); V1 and V2, volumes of distribution of the central and peripheral compartments (L = kg); C, concentration of drug in plasma 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); CF, correction factors of V2 to account for drug 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 ($CF_{peritoneal\ fluid}$), between the plasma and peritoneum ($CF_{peritoneum}$), and between the 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 pharmacokinetic 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 [23].

2.6. Site-specific pharmacodynamic target attainment analysis

For each flomoxef regimen (1 g; every 12, 8, or 6 h; 30 min infusion), the duration for which the drug concentration was above the minimum inhibitory concentration (T > MIC) in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue were predicted. An additional simulation was also performed for a regimen (1 g; every 3.5 h [30 min infusion + 3 h interval]) to determine whether re-dosing at 2 h interval, initially recommended [7,21], is appropriate as an intraoperative prophylactic antibiotic. The simulations were conducted according to the previously reported method [19,25–27]. The drug concentration was not adjusted for protein binding but rather treated as the free fraction. Flomoxef protein binding in human plasma is reportedly comparatively low (approximately 35%) [28]. Although the status of flomoxef protein binding in these abdominal sites is currently unknown, even a moderately higher or lower protein binding in the abdominal tissue compared to plasma was not expected to significantly affect this simulation. Using the mean estimates for the seven flomoxef pharmacokinetic model parameters, the time points at which the simulated drug concentrations in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue were consistent with the MIC (0.125–128 mg/L) were determined, and the T > MIC was calculated as the cumulative percentage of a 24-h period.

Based on the analysis of pharmacodynamic target attainment, 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 40% for flomoxef [29,30]. Although the pharmacodynamic targets were derived from the murine model study, correlations of target values of antibiotics containing β-lactams between murine models and humans were presented with the accumulation of PK/PD data to date [31].

3. Results

3.1. Study participants

Five males and five females participated in this study, comprising five patients with Crohn's disease and five with colon cancer. The following surgical procedures were performed: ileocecal resection in four cases, right hemicolectomy in three, left hemicolectomy in two, and subtotal colectomy and partial enterectomy in one.

The patients were aged 56.8 ± 18.5 years (mean ± standard deviation [SD]) and weighed 53.8 ± 7.75 kg, with a body mass index of 21.1 ± 3.57 kg/m^2. The creatinine clearance estimated using the Cockcroft–Gault formula was 85.2 ± 12.4 mL/min, the total bilirubin level was 0.48 ± 0.33 mg/dL, the aspartate transaminase level was 29.9 ± 22.1 IU/L, and the alanine transaminase level was 17.9 ± 6.8 IU/L. Flomoxef was administered once to two participants and twice to eight participants.

3.2. Sample collection and flomoxef assay

Forty-one plasma samples, 34 peritoneal fluid samples, 38 peritoneum samples, and 41 subcutaneous adipose tissue samples were collected. The flomoxef concentration ranges were 6.7–144.4 mg/L in plasma, 10.1–65.4 mg/L in peritoneal fluid, 4.1–60.3 mg/kg in the peritoneum, and 1.2–22.7 mg/kg in subcutaneous adipose tissue. All the measured values were above the determination limits.

3.3. Non-compartmental pharmacokinetic analysis

The non-compartmental pharmacokinetic parameters are shown in Table 1. The mean C_{max} was 75.0 mg/L in plasma, 33.4 mg/L in peritoneal fluid, 23.4 mg/kg in peritoneum, and 10.6 mg/kg in subcutaneous adipose tissue. The mean $AUC_{0\text{-}2.5}$ was 89.1 mg h/L in plasma, 60.7 mg h/L in peritoneal fluid, 35.9 mg h/kg in the peritoneum, and 14.1 mg h/kg in the subcutaneous adipose tissue. The mean peritoneal fluid: plasma ratio of $AUC_{0\text{-}2.5}$ was 0.68. The mean peritoneum: plasma ratio of $AUC_{0\text{-}2.5}$ was 0.40 and the mean subcutaneous adipose tissue: plasma

Table 1
Noncompartmental pharmacokinetic parameters of flomoxef after 30 min intravenous infusion of 1 g.

Sample type and parameter	Value (mean ± SD, n = 10)
Plasma	
C_{max} (mg/L)	75.0 ± 16.3
$AUC_{0\text{-}2.5}$ (mg h/L)	89.1 ± 19.1
Peritoneal fluid	
C_{max} (mg/L)	33.4 ± 9.0
$AUC_{0\text{-}2.5}$ (mg h/L)	60.7 ± 15.0
Peritoneum	
C_{max} (mg/kg)	23.4 ± 10.3
$AUC_{0\text{-}2.5}$ (mg h/kg)	35.9 ± 18.5
Subcutaneous adipose tissue	
C_{max} (mg/kg)	10.6 ± 3.8
$AUC_{0\text{-}2.5}$ (mg h/kg)	14.1 ± 3.6
Peritoneal fluid: plasma ratio	
C_{max}	0.45 ± 0.12
$AUC_{0\text{-}2.5}$	0.68 ± 0.10
Peritoneum: plasma ratio	
C_{max}	0.31 ± 0.12
$AUC_{0\text{-}2.5}$	0.40 ± 0.18
Subcutaneous adipose tissue: plasma ratio	
C_{max}	0.14 ± 0.04
$AUC_{0\text{-}2.5}$	0.16 ± 0.04

AUC, area under the drug concentration-time curve; C_{max}, maximum observed concentration; SD, standard deviation.

ratio of $AUC_{0\text{-}2.5}$ was 0.16, which was lower than that of the peritoneal fluid: plasma ratio.

3.4. Compartmental pharmacokinetic analysis

The pharmacokinetic parameters in the hypothetical two-compartment model (Fig. 1) are summarized in Table 2. The simulation curves drawn using the mean parameter estimates were well fit to all mean measurements of flomoxef in the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue (Fig. 2). The regression equation between the observed concentration (Y) and the individual predicted concentration (X) was $Y = 1.036\ X + 0.073$ ($r = 0.978$, 161 samples). The normalized mean prediction error (as a bias index) and the normalized mean absolute prediction error (as an accuracy index) values were 0.389 and 2.307, respectively.

3.5. Site-specific pharmacodynamic target attainment analysis

Using the mean estimated values for the seven flomoxef pharmacokinetic parameters, we predicted the drug concentrations under various regimens and determined whether the pharmacodynamic targets were attained in the peritoneal fluid (Fig. 3a), peritoneum (Fig. 3b), and subcutaneous adipose tissue (Fig. 3c). Based on the previous study [29], we hypothesized that flomoxef exerts a bactericidal effect when the T > MIC is >40%.

The flomoxef 1 g dosing regimens that achieved the target in the peritoneal fluid, peritoneum, and subcutaneous adipose tissue were in q12 h [2 g/day] for an MIC of 0.5 mg/L, in q8h [3 g/day] for an MIC of 1 mg/L, in q6h [4 g/day] for an MIC of 2 mg/L, and in q3.5 h [6 g/day] for an MIC of 4 mg/L.

Table 3 shows each flomoxef dosing regimen needed for site-specific pharmacodynamic breakpoints in a simulation that assumes a T > MIC of 40% and the MIC distributions of flomoxef for *Escherichia coli*, *Klebsiella* species, *Proteus* species, *Streptococcus* species, and ESBL-producing *Enterobacteriaceae* [32–34]. Based on the categories of the Japanese SSI surveillance (MIC_{90}) [32], the MIC_{90} of flomoxef for ESBL-producing *Enterobacteriaceae* is 1 mg/L. Flomoxef 1 g dosing regimens of q8h [3 g/day], q6h [4 g/day], and q3.5 h [6 g/day] showed sufficient antibacterial effects against ESBL-producing *Enterobacteriaceae* in all abdominal tissues.

Table 2
Pharmacokinetic parameters for flomoxef in the hypothetical two-compartment model (see Fig. 1).

Parameter	Estimate (mean ± SD, n = 10)
K12 (1/h)	2.13 ± 0.51
K21 (1/h)	1.83 ± 0.66
K10 (1/h)	1.49 ± 0.21
V1 (L)	8.83 ± 2.44
$CF_{peritoneal\ fluid}$	0.112 ± 0.081
$CF_{peritoneum}$	0.214 ± 0.199
$CF_{subcutaneous\ adipose\ tissue}$	0.453 ± 0.374

SD, standard deviation; CF, correction factors of V2 to account for drug concentration differences between plasma and abdominal sites (peritoneal fluid, peritoneum, and subcutaneous adipose tissue).

4. Discussion

In this study, we elucidated the pharmacokinetics of flomoxef in abdominal tissues with the aim of facilitating dosing regimen decisions when treating abdominal infections. It showed that the mean ratio of $AUC_{0\text{-}2.5}$ for the subcutaneous adipose tissue: plasma (0.16) was lower than those for peritoneal fluid: plasma (0.68) and the peritoneum: plasma (0.40). Similar to other reports, β-lactam antibiotic was hydrophilic, resulting in a low rate of transfer to the adipose tissue [35–37]. When taking the bactericidal target as T > MIC exceeding 40%, the target attainment regimens in all tissues were q12 h [2 g/day] for an MIC 0.5 mg/L, q8h [3 g/day] for an MIC 1 mg/L, q6h [3 g/day] for an MIC 2 mg/L, and q3.5 h [6 g/day] for an MIC 4 mg/L. The regimens of flomoxef in q8h, q6h, and q3.5 h were shown to achieve bactericidal concentrations against ESBL-producing *Enterobacteriaceae* of MIC 1 mg/L. This study investigated a model simulating abdominal infection in patients subjected to physical invasion in the form of lower gastrointestinal surgery. Thus, although they did not have an established abdominal infection, we believe that this situation was considered to provide an appropriate model of tissue penetration during abdominal infections.

Ikawa et al. [17] measured flomoxef concentrations in the plasma and peritoneal fluid. Moreover, its tissue concentrations in the prostate, lungs, and liver have likewise been reported [18,38–40]. However, to our knowledge, this is the first study investigating the pharmacokinetics of flomoxef in the peritoneum and subcutaneous adipose tissue and simulating site-specific pharmacodynamic target attainment to achieve an optimal dosage for the treatment of abdominal infections.

Flomoxef is also used as antibiotic prophylaxis for lower gastrointestinal surgery, with repeat redosing at 2-h intervals during surgery [7,9,21]. We followed this by repeating flomoxef administration 2 h after the first dose and 3 h after the first dose (30 min infusion + 3 h interval) regimen model was simulated. Consequently, both regimens' pharmacodynamic breakpoints were >4 mg/L (40% T > MIC), indicating that the intraoperative 2 h re-dosing is more than enough to prevent SSI caused by *Escherichia coli*, *Klebsiella* species, *Proteus* species, *Streptococcus* species, and ESBL-producing *Enterobacteriaceae,* and even >3 h re-dosing was well tolerated.

In compartmental pharmacokinetic modeling, the individual predicted concentrations in the plasma, peritoneal fluid, peritoneum, and subcutaneous adipose tissue were in good agreement with the observed drug concentrations, and the simulation curves obtained using pharmacokinetic parameters were all in good agreement with the mean measured values. These results indicated the validity and reliability of the flomoxef pharmacokinetics model and, thus, demonstrated excellent measurement performance for use in pharmacodynamic assessments of flomoxef use for the treatment of abdominal infection.

This study has several limitations First, the sample size was small (10 patients). Second, the study participants did not suffer from an infection. Therefore, flomoxef permeation in patients with abdominal infections may differ. Tissue permeation depends on vascular permeability, which

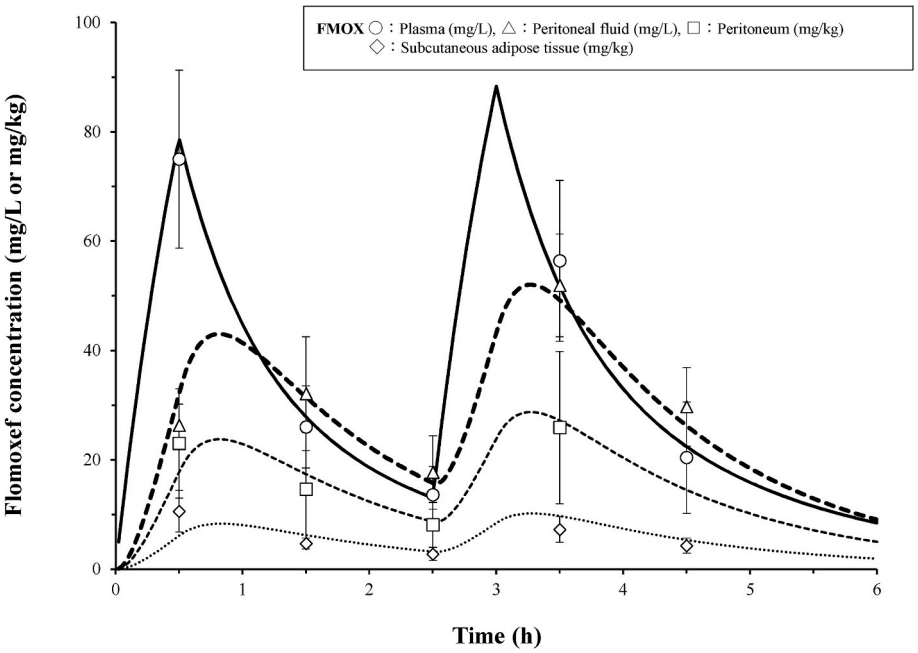

Fig. 2. Observed concentrations (mean ± SD, n = 10) and simulation curves for flomoxef in plasma, peritoneal fluid, peritoneal tissue, and subcutaneous adipose tissue after single or re-dose 30-min infusions of 1 g. The simulation curves were drawn using the mean pharmacokinetic model parameters (K12 = 2.13 1/h, K21 = 1.83 1/h, K10 = 1.49 1/h, V1 = 8.83 L, $CF_{peritoneal\ fluid}$ = 0.112, $CF_{peritoneum}$ = 0.214, and $CF_{subcutaneous\ adipose\ tissue}$ = 0.453).

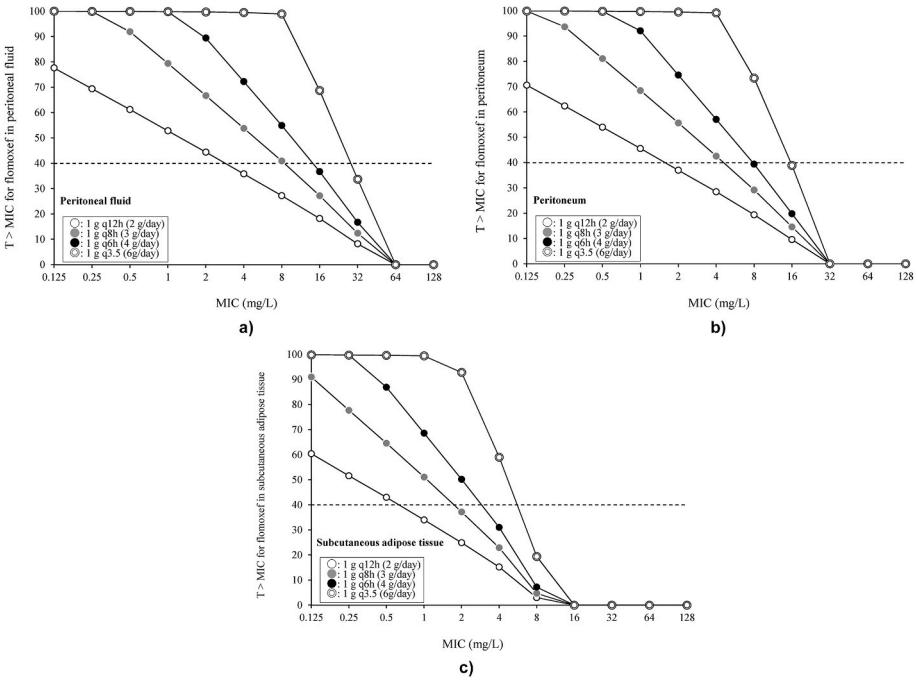

Fig. 3. Site-specific time that the drug concentration was above the minimum inhibitory concentration (T > MIC) in the peritoneal fluid (a), peritoneum (b), and subcutaneous adipose tissue (c) at a MIC of 0.125–128 mg/L, using four flomoxef regimens. The T > MIC values were predicted using the mean pharmacokinetic model parameters for flomoxef (Table 2). The dashed lines represent the bactericidal target (40% T > MIC).

is associated with inflammation, and this may increase tissue penetration in patients with abdominal infections. However, under conditions of impaired perfusion, such as sepsis and septic shock, the flomoxef concentration may decrease. Third, the renal function of the study participants was normal, with a mean creatinine clearance of 85.2 ± 12.4 mL/min. However, as flomoxef is mainly excreted via the kidneys, and patients with severe infection often develop renal impairment, clearance may decrease, maintaining the drug concentration in the plasma and abdominal tissue and, thus, increasing T > MIC. Therefore, in some patients, flomoxef may be effective at a lower dose than the pharmacokinetic and pharmacodynamic values estimated from the dosing regimen tested in this study. Fourth, the site-specific T > MIC (Fig. 3) and the breakpoint MIC (Table 3) 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 (Table 2) with a variation

Table 3
The flomoxef regimens needed for site-specific pharmacodynamic breakpoints and minimum inhibitory concentration (MIC) values against *Escherichia coli*, *Klebsiella* species, *Proteus* species, *Streptococcus* species, and ESBL-producing *Enterobacteriaceae*.

Regimen (30 min infusion)	Peritoneal fluid	Peritoneum	Subcutaneous adipose tissue	References
1 g q12 h [total 2 g/day]	2	1	0.5	Nationwide susceptibility surveillance data in Japan [28,29] - 0.25 mg/L for *E. coli* and *Klebsiella* species - 0.5 mg/L for *Proteus* species - 1 mg/L for *Streptococcus* species Japanese SSIs surveillance MIC_{90} [27] - 1 mg/L for ESBL-producing *Enterobacteriaceae*
1 g q8h [total 3 g/day]	8	4	1	
1 g q6h [total 4 g/day]	8	4	2	
1 g q3.5 h [total 6 g/day]	16	8	4	

coefficient (SD/mean) of 14.1–93.0% and the observed concentrations at 0.5–4.5 h (Fig. 2) with a variation coefficient of 14.8–71.2%. This study did not find significant factors (i.e., sex, age, weight, body mass index, creatinine clearance) that correlated well with the individual pharmacokinetic parameters. The covariates that explain the interindividual variability in flomoxef pharmacokinetics should be identified to personalize dosing regimen. Fifth, the pharmacodynamic results were based on simulated bactericidal effects rather than on clinical effects or outcomes. Although our results provide valuable information, we have not established the optimum dosing regimen for the treatment of patients with abdominal infections. Considering these limitations, further clinical studies in larger populations involving a wider variety of patients with intraperitoneal infections are required to confirm the pharmacokinetic results and ascertain its clinical importance by investigating the relationship between peritoneal permeation and flomoxef pharmacodynamic exposure.

In conclusion, the results of this study may help support the clinical effectiveness of flomoxef against abdominal infection. It is very meaningful to lead to the rationalization and optimization of flomoxef regimens as an alternative treatment to carbapenems against ESBL-producing *Enterobacteriaceae* strains.

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Author statement

TH and HO participated in the study design, drafting of the article, analysis, and interpretation of data. KI was the chief investigator and responsible for the data analysis. SU, YW, and NS participated in the study design, interpretation of data, and revision of the article for intellectual content. KY, HK, YK, and NM developed the trial design. ST had full access to all of the data in the study and takes responsibility for the integrity of the data. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

None.

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References

[1] Chong Y, Shimoda S, Shimono N. Current epidemiology, genetic evolution and clinical impact of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Infect Genet Evol 2018;61:185–8. https://doi.org/10.1016/j.meegid.2018.04.005.
[2] Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M β-lactamases: temporal and geographical shifts in genotype. J Antimicrob Chemother 2017;72:2145–55. https://doi.org/10.1093/jac/dkx146.
[3] Dubinsky-Pertzov B, Temkin E, Harbarth S, Fankhauser-Rodriguez C, Carevic B, Radovanovic I, et al. Carriage of extended-spectrum beta-lactamase-producing Enterobacteriaceae and the risk of surgical site infection after colorectal surgery: a prospective cohort study. Clin Infect Dis 2019;68:1699–704. https://doi.org/10.1093/cid/ciy768.
[4] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of Infections caused by extended-spectrum-beta-lactamase-, ampc-, and carbapenemase-producing Enterobacteriaceae. Clin Microbiol Rev 2018;31. https://doi.org/10.1128/CMR.00079-17. e00079–17.
[5] van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence 2017;8:460–9. https://doi.org/10.1080/21505594.2016.1222343.
[6] Tsuji T, Satoh H, Narisada M, Hamashima Y, Yoshida T. Synthesis and antibacterial activity of 6315-S, a new member of the oxacephem antibiotic. J Antibiot 1985;38:466–76. https://doi.org/10.7164/antibiotics.38.466.
[7] Ito M, Ishigami T. The meaning of the development of flomoxef and clinical experience in Japan. Infection 1991;19:S253–7. https://doi.org/10.1007/BF01645536.
[8] Darlow CA, da Costa RMA, Ellis S, Franceschi F, Sharland M, Piddock L, et al. Potential antibiotics for the treatment of neonatal sepsis caused by multidrug-resistant bacteria. Paediatr Drugs 2021;23:465–84. https://doi.org/10.1007/s40272-021-00465-z.
[9] Kobayashi M, Takesue Y, Kitagawa Y, Kusunoki M, Sumiyama Y. Antimicrobial prophylaxis and colon preparation for colorectal surgery: results of a questionnaire survey of 721 certified institutions in Japan. Surg Today 2011;41:1363–9. https://doi.org/10.1007/s00595-010-4511-x.
[10] Partina I, Kalinogorskaya O, Kojima S, Gostev V, Volkova M, Ageevets V, et al. Surveillance of antimicrobial susceptibility of Enterobacteriaceae pathogens isolated from intensive care units and surgical units in Russia. Jpn J Antibiot 2016;69:41–51.
[11] Santanirand S, Kojima T, Yamaguchi K, Wongnak S, Thokaew S, Chiaranaicharoen S. Antimicrobial activity of flomoxef against Enterobacteriaceae including extended spectrum beta-lactamases-producing strains isolated at Ramathibodi Hospital: a 1000-bed tertiary care hospital in Bangkok, Thailand. J Infect Dis Ther 2018;6:378. https://doi.org/10.4172/2332-0877.1000378.
[12] Ito A, Tatsumi YM, Wajima T, Nakamura R, Tsuji M. Evaluation of antibacterial activities of flomoxef against ESBL producing Enterobacteriaceae analyzed by Monte Carlo simulation. Jpn J Antibiot 2013;66:71–86.
[13] Jung Y, Lee SS, Song W, Kim HS, Uh Y. In vitro activity of flomoxef against extended-spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in Korea. Diagn Microbiol Infect Dis 2019;94:88–92. https://doi.org/10.1016/j.diagmicrobio.2018.11.017.
[14] Matsumura Y, Yamamoto M, Nagao M, Komori T, Fujita N, Hayashi A, et al. Multicenter retrospective study of cefmetazole and flomoxef for treatment of extended-spectrum-β-lactamase-producing Escherichia coli bacteremia. Antimicrob Agents Chemother 2015;59:5107–13. https://doi.org/10.1128/aac.00701-15.
[15] Lee CH, Chen IL, Li CC, Chien CC. Clinical benefit of ertapenem compared to flomoxef for the treatment of cefotaxime-resistant Enterobacteriaceae bacteremia. Infect Drug Resist 2018;11:257–66. https://doi.org/10.2147/idr.s146923.
[16] Lee CH, Su LH, Chen FJ, Tang YF, Li CC, Chien CC, et al. Comparative effectiveness of flomoxef versus carbapenems in the treatment of bacteraemia due to extended-spectrum β-lactamase-producing Escherichia coli or Klebsiella pneumoniae with emphasis on minimum inhibitory concentration of flomoxef: a retrospective study. Int J Antimicrob Agents 2015;46:610–5. https://doi.org/10.1016/j.ijantimicag.2015.07.020.
[17] Ikawa K, Morikawa N, Ikeda K, Ohge H, Sueda T. Development of breakpoints of cephems for intraabdominal infections based on pharmacokinetics and pharmacodynamics in the peritoneal fluid of patients. J Infect Chemother 2008;14:141–6. https://doi.org/10.1007/s10156-008-0598-z.
[18] Nakamura K, Ikawa K, Nishikawa G, Kobayashi I, Tobiume M, Sugie M, et al. Clinical pharmacokinetics of flomoxef in prostate tissue and dosing considerations for prostatitis based on site-specific pharmacodynamic target attainment. J Infect Chemother 2020;26:236–41. https://doi.org/10.1016/j.jiac.2019.08.019.
[19] Murao N, Ohge H, Ikawa K, Watadani Y, Uegami S, Shigemoto N, et al. Pharmacokinetics of piperacillin-tazobactam in plasma, peritoneal fluid and peritoneum of surgery patients, and dosing considerations based on site-specific pharmacodynamic target attainment. Int J Antimicrob Agents 2017;50:393–8. https://doi.org/10.1016/j.ijantimicag.2017.03.025.

[20] Takayama Y, Komatsu T, Nakamura K, Tomoda Y, Toda M, Miura H, et al. Association of serum and fat tissue antibiotic concentrations with surgical site infections in lower gastrointestinal surgery. Surgery 2022;171:1000–5. https://doi.org/10.1016/j.surg.2021.10.013.
[21] Bratzler DW, Dellinger EP, Olsen KM, Perl TM, Auwaerter PG, Bolon MK, et al. American society of health-system pharmacists; infectious disease society of America; surgical infection society; society for healthcare epidemiology of America. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195–283. https://doi.org/10.2146/ajhp120568.
[22] Konaka R, Hashimoto H, Nishimura R, Kuruma K, Hirauchi K. Assays of 6315-S (flomoxef) and its metabolites in body fluids by high-performance liquid chromatography. Jpn J Chemother 1987;35:137–44. https://doi.org/10.11250/chemotherapy1953.35.Supplement1_137.
[23] Yamaoka K, Tanigawara Y, Nakagawa T, Uno T. A pharmacokinetic analysis program (multi) for microcomputer. J Pharmacobio-Dyn 1981;4:879–85. https://doi.org/10.1248/bpb1978.4.879.
[24] Barbour AM, Schmidt S, Zhuang L, Rand K, Derendorf H. Application of pharmacokinetic/pharmacodynamic modelling and simulation for the prediction of target attainment of ceftobiprole against meticillin-resistant *Staphylococcus aureus* using minimum inhibitory concentration and time-kill curve-based approaches. Int J Antimicrob Agents 2014;43:60–7. https://doi.org/10.1016/j.ijantimicag.2013.08.016.
[25] Kobayashi I, Ikawa K, Nakamura K, Nishikawa G, Kajikawa K, Yoshizawa T, et al. Penetration of piperacillin-tazobactam into human prostate tissue and dosing considerations for prostatitis based on site-specific pharmacokinetics and pharmacodynamics. J Infect Chemother 2015;21:575–80. https://doi.org/10.1016/j.jiac.2015.04.015.
[26] Ikawa K, Morikawa N, Hayato S, Ikeda K, Ohge H, Sueda T. Pharmacokinetic and pharmacodynamic profiling of cefepime in plasma and peritoneal fluid of abdominal surgery patients. Int J Antimicrob Agents 2007. https://doi.org/10.1016/j.ijantimicag.2007.04.012. 270–3.
[27] Ikawa K, Morikawa N, Matsuda S, Ikeda K, Ohge H, Takesue Y, et al. Peritoneal penetration and pharmacodynamic exposure of intravenous cefozopran in abdominal surgery patients. Int J Antimicrob Agents 2007;30:352–5. https://doi.org/10.1016/j.ijantimicag.2007.06.001.
[28] Yasunaga K, Okamoto Y, Maehara K, Mase K, Iida Y, Yoshioka S, et al. Phase-1 clinical study on 6315-S (Flomoxef). Chemotherapy 1987;35:494–517. https://doi.org/10.11250/chemotherapy1953.35.Supplement1_494.
[29] Tashiro S, Hayashi M, Takemura W, Igarashi Y, Liu X, Mizukami Y, et al. Pharmacokinetics/pharmacodynamics evaluation of flomoxef against extended-spectrum beta-lactamase-producing Escherichia coli in vitro and in vivo in a murine thigh infection model. Pharm Res (N Y) 2021;38:27–35. https://doi.org/10.1007/s11095-020-02977-8.
[30] Darlow CA, Hope W. Flomoxef for neonates: extending options for treatment of neonatal sepsis caused by ESBL-producing Enterobacterales. J Antimicrob Chemother 2022;77:711–8. https://doi.org/10.1093/jac/dkac072.
[31] Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis 2007;44:79–86. https://doi.org/10.1086/510079.
[32] Ueda T, Takesue Y, Matsumoto T, Tateda K, Kusachi S, Mikamo H, et al. Change in antimicrobial susceptibility of pathogens isolated from surgical site infections over the past decade in Japanese nation-wide surveillance study. J Infect Chemother 2021;27:931–9. https://doi.org/10.1016/j.jiac.2021.03.010.
[33] Yamaguchi K, Ishii Y, Tateda K, Iwata M, Watanabe N, Shinagawa M, et al. [Nationwide surveillance of parenteral antibiotics containing meropenem activities against clinically isolated strains in 2012]. Jpn J Antibiot 2014;67:73–107.
[34] Shinagawa N, Taniguchi M, Hirata K, Furuhata T, Mizuguchi T, Osanai H, et al. [Bacteria isolated from surgical infections and its susceptibilities to antimicrobial agents - special references to bacteria isolated between April 2011 and March 2012]. Jpn J Antibiot 2014;67:339–83.
[35] Alobaid AS, Hites M, Lipman J, Taccone FS, Roberts JA. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents 2016;47:259–68. https://doi.org/10.1016/j.ijantimicag.2016.01.009.
[36] Chen X, Brathwaite CEM, Barkan A, Hall K, Chu G, Cherasard P, et al. Optimal cefazolin prophylactic dosing for bariatric surgery: no need for higher doses or intraoperative redosing. Obes Surg 2017;27:626–9. https://doi.org/10.1007/s11695-016-2331-9.
[37] Lillico R, Sayre CL, Sitar DS, Davies NM, Baron CM, Lakowski TM. Quantification of cefazolin in serum and adipose tissue by ultra high performance liquid chromatography-Tandem mass spectrometry (UHPLC-MS/MS): application to a pilot study of obese women undergoing cesarean delivery. J Chromatogr, B: Anal Technol Biomed Life Sci 2016;1031:94–8. https://doi.org/10.1016/j.jchromb.2016.07.032.
[38] Hoshi S, Kuwahara M, Orikasa S, Nakano S, Onuma T, Chiba R, et al. Diffusion into human prostate and clinical evaluation of 6315-S (flomoxef) in urinary tract infection. Jpn J Chemother 1987;35:968–78.
[39] Imaizumi M, Watanabe H, Ojika T, Fujita K, Sakakibara M, Kondo D, et al. A clinical study on pulmonary tissue uptake of flomoxef. Jpn J Antibiot 1991;44:22–34.
[40] Komatsu T, Tsumuraya S, Takayama Y, Kaizu T, Okamoto M, Tajima H, et al. Population pharmacokinetic-pharmacodynamic target attainment analysis of flomoxef in the serum and liver tissue of patients undergoing hepatic resection. Antimicrob Agents Chemother 2022;66:e0230321. https://doi.org/10.1128/aac.02303-21.