Received: 7 October 2021 | Revised: 20 June 2022 | Accepted: 21 June 2022

DOI: 10.1111/1440-1681.13695

CEPP Clinical and Experimental Pharmacology and Physiology WILEY

ORIGINAL ARTICLE

Predictive performance of pharmacokinetic models for target concentration-controlled infusion of cefoxitin as a prophylactic antibiotic in patients with colorectal surgery

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Funding information
National Research Foundation of Korea, Grant/Award Numbers: 2019K1A3A1A78077783, 2020R1C1C1009976

Abstract

We aimed to evaluate the predictive performance of previously constructed free (C_{free}) and total (C_{total}) cefoxitin pharmacokinetic models and the possibility of administering cefoxitin via the target-controlled infusion (TCI) method in clinical practice. Two external validation studies (N = 31 for C_{free} model, N = 30 for C_{total} model) were conducted sequentially. Cefoxitin (2 g) was dissolved in 50 mL of normal saline to give a concentration of 40 mg mL^{-1}. Before skin incision, cefoxitin was infused with a TCI syringe pump. Target concentrations of free concentration and total concentration were set to 25 and 80 μg mL^{-1}, respectively, which were administered throughout the surgery. Three arterial blood samples were collected to measure the total and free plasma concentrations of cefoxitin at 30, 60 and 120 min, after the start of cefoxitin administration. The predictive performance was evaluated using four parameters: inaccuracy, divergence, bias and wobble. The pooled median (95% confidence interval) biases and inaccuracies were − 45.9 (−47.3 to −44.5) and 45.9 (44.5 to 47.3) for C_{free} model (Choi_F model), and − 16.6 (−18.4 to −14.8) and 18.5 (16.7 to 20.2) for C_{total} model ($Choi\_T_{old}$ model), respectively. The predictive performance of the newly constructed model ($Choi\_T_{new}$ model), developed by adding the total concentration data measured in the external validation, was better than that of the $Choi\_T_{old}$ model. Models constructed with total concentration data were suitable for clinical use. Administering cefoxitin using the TCI method in patients maintained the free concentration above the minimal inhibitory concentration (MIC) breakpoints of the major pathogens causing surgical site infection throughout the operation period.

KEYWORDS
antibiotics, concentration, infection, model, performance, pharmacokinetics

1 | INTRODUCTION

Cefoxitin, a second-generation cephalosporin, is commonly used as a prophylactic antibiotic to prevent surgical site infection (SSI) in patients undergoing colorectal surgery.[1] Adults generally receive a

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TABLE 1 Characteristics of patients enrolled in the two studies

	Study 1 (N = 31)	Study 2 (N = 30)
Male/female	22/9	24/6
ASA PS 1/2	7/24	5/25
Age, years	61.3 ± 10.8	62.5 (53–66)
Weight, kg	65.9 ± 13.7	67.1 (57.7–73.3)
Height, cm	165.5 ± 10.2	164.4 ± 8.0
Albumin, g dL^{-1}	3.9 ± 0.4	3.9 (3.6–4.0)
Protein, g dL^{-1}	7.1 ± 0.4	7.1 ± 0.5
CrCl, mL min^{-1}	84.1 ± 22.1	83.2 ± 16.7
eGFR, mL/min/1.73 m^2	88.8 ± 12.4	90.4 ± 12.2
Operation time*, min	108.4 ± 38.3	102.5 (89–144)
Cefoxitin dose administered via TCI, g	1.4 (1.1–1.6)	1.4 ± 0.3
Amount of crystalloid administered during surgery, mL	1250 (1050–1600)	1200 (1000–1550)
Estimated blood loss, mL	50 (30–50)	50 (40–70)

Note: Data are presented as counts, median (25–75%), or means ± SDs as appropriate. Study 1, study for external validation of free concentration pharmacokinetic model; Study 2, study for external validation of the total concentration pharmacokinetic model.
Abbreviations: ASA PS, American Society of Anesthesiologists Physical Status; CrCl, creatinine clearance (calculated using the Cockcroft–Gault formul[20]); eGFR, estimated glomerular filtration rate calculated using; CKD-EPI, (Chronic Kidney Disease Epidemiology Collaboration) equation;[16] TCI, target-controlled infusion.
*Time required from skin incision to skin closure.

dose of 2 g dissolved in normal saline administered intravenously for approximately 10 min before skin incision.[2] Free concentration can help determine the effectiveness of prophylactic antibiotics and the minimum inhibitory concentration (MIC) of each pathogen causing SSI.[3] Therefore, the period of antibiotic free concentration maintained above the MIC (*f*T>MIC) is used as a surrogate marker for the effectiveness of prophylactic antibiotics.[4,5] We thus expect that target-controlled infusion (TCI) has sufficient potential as a method of administering prophylactic antibiotics.

Target-controlled infusion alters the infusion rate to maintain a user-defined drug concentration constant and has been used in the field of anaesthesia for over 20 years.[6,7] According to the covariates included in the pharmacokinetic parameters (e.g. weight or creatinine clearance), personalized dosing, in which dosage is tailored to the individual patient even at the same target concentration, is possible. If cefoxitin is administered via the TCI method, it is theoretically possible to achieve 100% *f*T>MIC because the desired concentration can be maintained for the desired time. Furthermore, a previous study used a population analysis to develop pharmacokinetic models for administering cefoxitin via TCI (Choi models).[8] In a stochastic simulation based on the results of this study, *f*T>MIC was significantly greater in the TCI method compared with the conventional administration method, even at smaller doses.[8] However, evaluating the predictive performance of the system equipped with Choi models is necessary to administer cefoxitin via TCI in clinical practice. This study aimed to evaluate the predictive performance of previously constructed cefoxitin pharmacokinetic models and determine whether cefoxitin administration via the TCI method may be possible in clinical practice.

2 | RESULTS

2.1 | Study 1 (external validation of Choi_F model)

Thirty-one patients were screened and included in the analysis (Table 1). Seven scheduled blood samples could not be obtained because of the time constraints of the surgery. Thus, 86 total and 86 free plasma concentration measurements from 31 patients were used to evaluate the predictive performance of the free concentration pharmacokinetic model. The predicted free and the measured free concentrations of cefoxitin were compared (Figure 1), and of the total samples, five (5.8%) were less than 16 μg mL^{-1}. Pooled biases, inaccuracies, divergences, and wobbles of the Choi_F model are depicted in Table 2. Using the measured total plasma concentration data and dosing regimens, the performances of Choi_T_{old} model and Choi_T_{new} model were also evaluated. The pooled biases and inaccuracies of the Choi_F model were not clinically acceptable. SSI did not occur in any patient.

2.2 | Study 2 (external validation of Choi_T_{old} model)

Thirty-two patients were screened, of whom two were excluded after not meeting the inclusion criteria. Hence, 30 patients were included in the current study, and their characteristics are summarized in Table 1. When cefoxitin was administered via the TCI method, the average dose could be reduced by approximately 30% compared with the

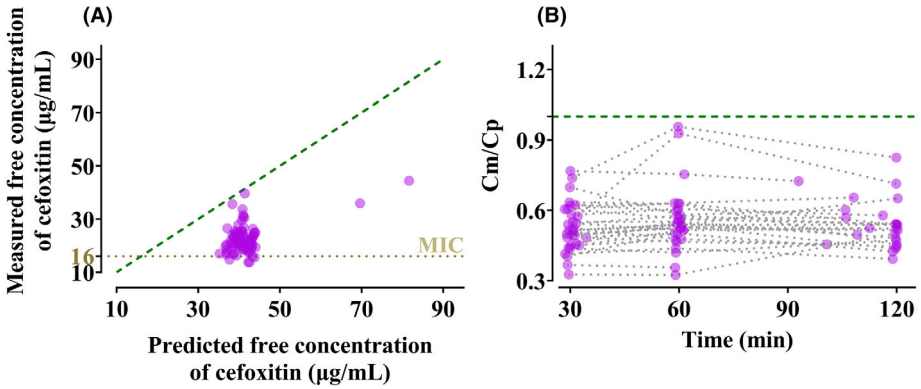

FIGURE 1 Comparison between measured (Cm) and predicted (Cp) free concentration of cefoxitin based on the concentration data measured in the external validation study of Choi_F model. A, Cm vs. Cp; B, Cm/Cp over time. Patients ($n = 31$) received cefoxitin via target-controlled infusion (TCI) method using Choi_F model

TABLE 2 Pooled biases, inaccuracies, divergences, and wobbles of various models based on the concentration data measured in the external validation study of the Choi_F model. Values are median (95% confidence interval)

Model	Choi_F model	Choi_T_{old} model*	Choi_T_{new} model*
Bias (%)	−45.9 (−47.3 to −44.5)†	−21.3 (−23.7 to −19.0)†	−10.2 (−12.9 to −7.4)†
Inaccuracy (%)	45.9 (44.5–47.3)	22.8 (20.8–24.8)	16.4 (13.9–19.0)
Divergence (% h^{-1})	0.3 (−1.9–2.5)	−2.2 (−5.3–0.9)	−3.2 (−7.8–1.4)
Wobble (%)	2.0 (0.9–3.0)	3.7 (1.9 to 5.4)	4.5 (2.5–6.5)

Note: Choi_F model, Choi model constructed from free concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal;[8] Choi_T_{old} model, Choi model constructed from total concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal;[8] Choi_T_{new} model, a newly constructed model by combining the total concentrations (297 samples) used in the process of building the Choi_T_{old} model and the total concentrations of cefoxitin (89 samples) measured in the external validation study of Choi_T_{old} model; Bias, median performance error (MDPE); Inaccuracy, median absolute performance error (MDAPE).
*Calculated using the plasma concentrations retrospectively estimated for each model.
†Significant bias.

TABLE 3 Pooled biases, inaccuracies, divergences, and wobbles of various models based on the concentration data measured in the external validation study of the Choi_T_{old} model. Values are median (95% confidence interval)

Model	Choi_T_{old} model	Choi_F model*	Choi_T_{new} model*
Bias (%)	−16.6 (−18.4 to −14.8)†	−20.9 (−22.7 to −19.1)†	−6.1 (−8.1 to −4.2)†
Inaccuracy (%)	18.5 (16.7–20.2)	22.4 (20.6–24.2)	13.1 (11.3–14.9)
Divergence (%/h)	5.5 (3.8–7.2)	3.2 (0.3–6.0)	2.9 (0.9–4.9)
Wobble (%)	4.2 (2.9–5.4)	3.3 (1.9–4.7)	4.4 (2.9–5.6)

Note: Choi_T_{old} model, Choi model constructed from total concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal;[8] Choi_F model, Choi model constructed from free concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal;[8] Choi_T_{new} model, a newly constructed model by combining the total concentrations (297 samples) used in the process of building the Choi_T_{old} model and the total concentrations of cefoxitin (89 samples) measured in the external validation study of Choi_T_{old} model; Bias, median performance error (MDPE); Inaccuracy, median absolute performance error (MDAPE).
*Calculated using the plasma concentrations retrospectively estimated for each model.
†Significant bias.

standard dose (2 g). SSI did not occur in any patient. The third blood sample could not be obtained from one patient (ID12) because the end time of the operation coincided with the second blood collection time. As such, 89 total and 89 free plasma concentration measurements from 30 patients were used to evaluate the predictive performance of various pharmacokinetic models of cefoxitin. The pooled biases, inaccuracies, divergences and wobbles of various models for cefoxitin are depicted in Table 3. The pooled biases and inaccuracies of all models were clinically acceptable; however, all models consistently produced negatively biased predictions. The predictive performance of the model constructed with total concentration was better than that of the model constructed with free concentration data. Comparison of the predicted concentration calculated by correcting clearance using the infusion history of the Asan pump software and the measured concentration of cefoxitin is presented in Figure 2. A slight improvement in predictive performance was observed in the model built with total concentration. Additionally, all free concentration measurements were greater than 16 μg mL^{-1} (Figure 2C), indicating that the free concentration was maintained above the MIC breakpoints of the major pathogens (i.e. *Escherichia coli*, *Staphylococcus aureus* and *Bacteroides fragilis*),

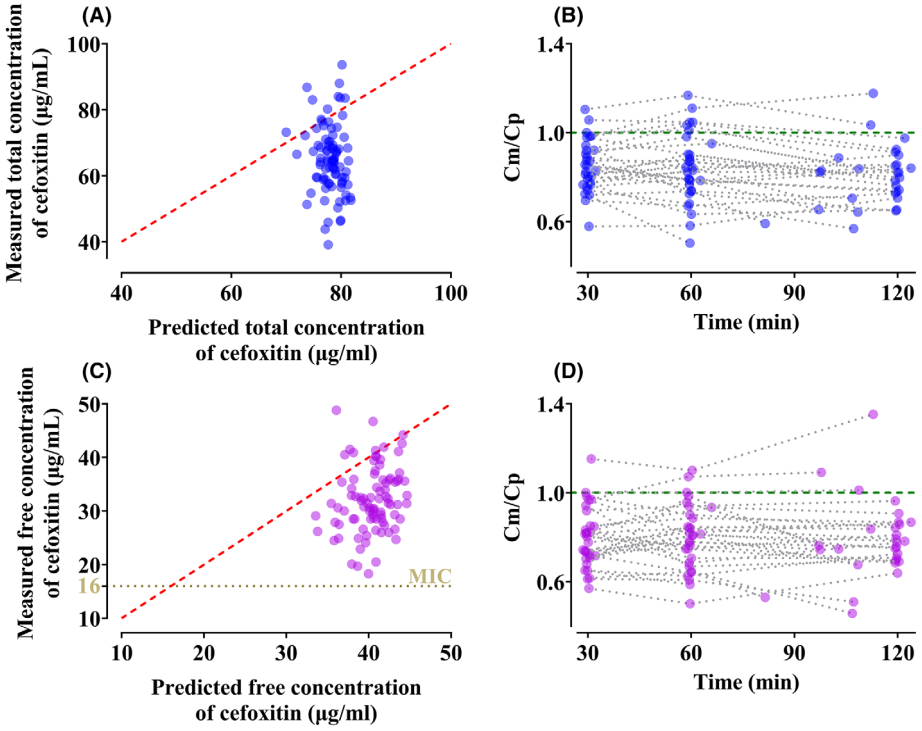

FIGURE 2 Comparison between measured (Cm) and predicted (Cp) total or free concentration of cefoxitin based on the concentration data measured in the external validation study of Choi_T_{old} model. A, Cm vs. Cp based on Choi_T_{old} model; B, Cm/Cp based on total concentration over time, C, Cm vs. Cp based on Choi_F model; D, Cm/Cp based on free concentration over time; MIC, minimal inhibitory concentration

TABLE 4 Population pharmacokinetic parameter estimates, inter-individual variability (IIV) and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of the Choi_T_{new} model

Parameters		Estimates (RSE, %)	IIV (CV %)	η Shrinkage	Median (2.5–97.5%)
V_1 (L) $= \theta_{V1} \times (WT/65)^{\theta 1}$	θ_{V1}	1.74 (4.2)	-	-	1.75 (1.68–1.83)
V_2 (L) $= \theta_{V2} \times (WT/65)^{\theta 1}$	θ_{V2}	4.2 (9.1)	17.3	35.8	4.26 (3.98–4.54)
Cl (L min^{-1}) $= \theta_{Cl} \times (WT/65)^{\theta 2}$	θ_{Cl}	0.11 (4.0)	24.3	3.3	0.114 (0.109–0.119)
θ_Q (L min^{-1}) $= \theta_Q \times (WT/65)^{\theta 2}$	θ_Q	0.185 (4.0)	-	-	0.185 (0.175–0.198)
	θ_1	0.543 (33.1)	-	-	0.572 (0.351–0.809)
	θ_2	0.542 (38.7)	-	-	0.576 (0.310–0.761)
σ_1		0.28 (47.5)	-	-	0.319 (0.174–0.446)
σ_2		0.129 (11.6)	-	-	0.123 (0.101–0.144)

Note: Choi_T_{new} model, a newly constructed model by combining the total concentrations (297 samples) used in the process of building the Choi_T_{old} model and the total concentrations of cefoxitin (89 samples) measured in the external validation study of Choi_T_{old} model; Choi_T_{old} model, Choi model constructed from total concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal.[8] A log normal distribution of inter-individual random variability was assumed. Residual random variability was modelled using an additive (σ_1) plus proportional (σ_2) error model. Non-parametric bootstrap analysis was repeated 2000 times. RSE indicates relative standard error = SE mean^{-1} × 100 (%).Abbreviations: *Cl*, clearance; CV, coefficient of variation; *Q*, inter-compartmental clearance of peripheral compartment; V_1, central volume of distribution; V_2, peripheral volume of distribution; WT, weight.

causing SSI during the entire operation period. The results of the remodelling by adding the total concentration data (n = 89) measured in study 2 are as follows.

$$V_1\,(\mathrm{L}) = 1.74 \times (Weight/65)^{0.543}$$
$$V_2\,(\mathrm{L}) = 4.2 \times (Weight/65)^{0.543}$$
$$Cl\,(\mathrm{L/min}) = 0.11 \times (Weight/65)^{0.542}$$
$$Q\,(\mathrm{L/min}) = 0.185 \times (Weight/65)^{0.542}$$

Population pharmacokinetic parameter estimates and the results of the non-parametric bootstrap replicates are summarized in Table 4. A two-compartment mammillary model described the time concentration curves of cefoxitin. Comparison of pharmacokinetic parameters of the Choi_T_{old} model and Choi_T_{new} model are summarized in Table S1. The goodness-of-fit plots of the Choi_T_{new} model are shown in Figure 3. Bias is observed at low concentrations of ≤10 μg mL^{-1}; however, it can likely be used in clinical practice considering the target concentration of 80 μg mL^{-1} when administering cefoxitin. Predictive cheques of the Choi_T_{new} model are shown in Figure 4. In order to compare the total concentration models, the difference in cumulative dose was compared when cefoxitin was administered for 2 h with a target concentration of 80 μg mL^{-1} in both models (Figure 5, cumulative

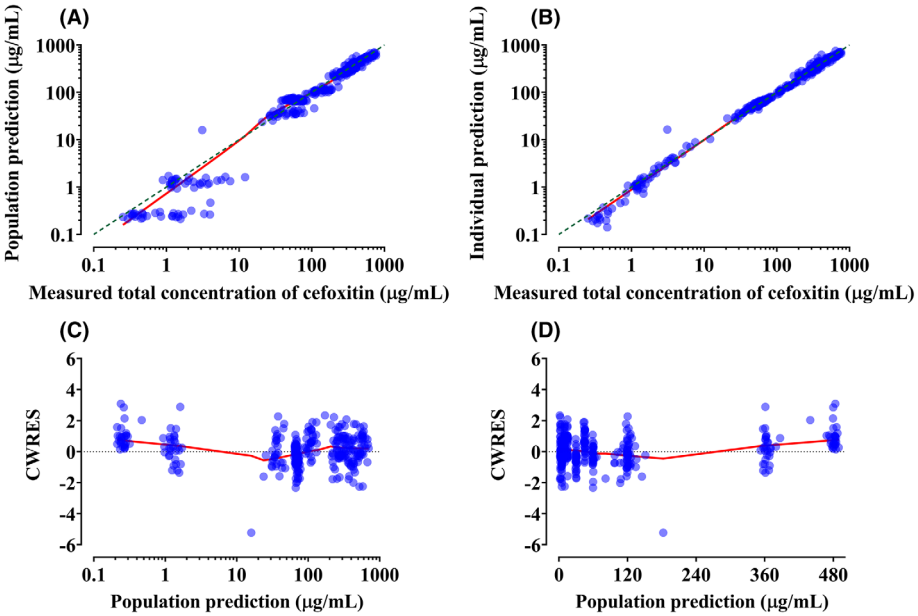

FIGURE 3 Goodness-of-fit plots of the Choi_T_{new} model of cefoxitin. A, Population-predicted total concentration of cefoxitin vs. the measured total concentration of cefoxitin; B, Individual predicted total concentration of cefoxitin vs. measured total concentration of cefoxitin; C, Conditional weighted residuals (CWRES) vs. population-predicted total concentration of cefoxitin; D, CWRES over time at the total concentration. Identity and locally weighted scatterplot smoothing (LOWESS) lines are presented in green and red, respectively

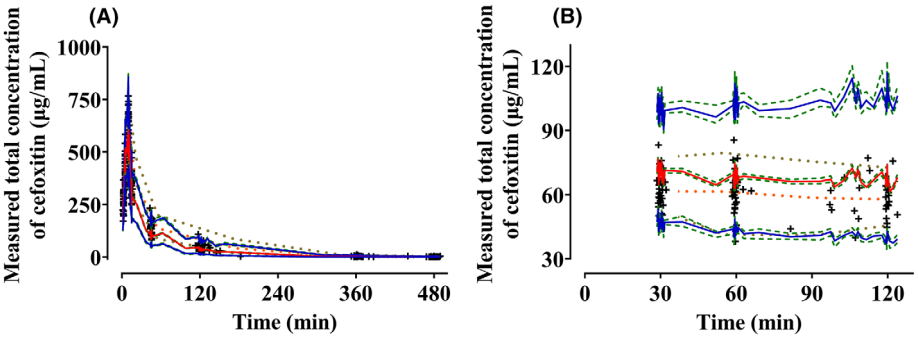

FIGURE 4 Predictive checks of the Choi_T_{new} model of cefoxitin. Stratification was performed according to study type. A, Data ($n = 297$) used to build the Choi_T_{old} model; B, Data ($n = 89$) used for external validation of the Choi_T_{old} model. The solid red line and the solid blue line indicate the 50% prediction line and 95% prediction lines, respectively. The green dotted lines indicate the 95% confidence intervals of the 2.5%, 50% and 97.5% prediction lines. $^{+}$measured total concentration of cefoxitin. The gold dotted lines represent the 95th percentile lines of the observations, and the orange dotted line depicts the 50th percentile line of the observations. In total, 5.7% of the data (A: 6.5%, B: 3.4%) were distributed outside of the 95% prediction intervals

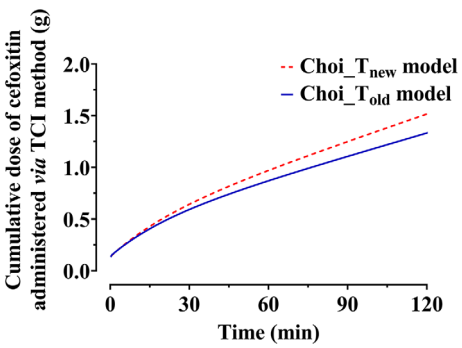

FIGURE 5 Differences in cumulative dose according to models when cefoxitin was administered with a target concentration-controlled infusion method. The target total concentration was set at 80 μg mL^{-1}. The body weight and creatinine clearance (CrCl) were set at 64 kg and 82 mL min^{-1}, respectively

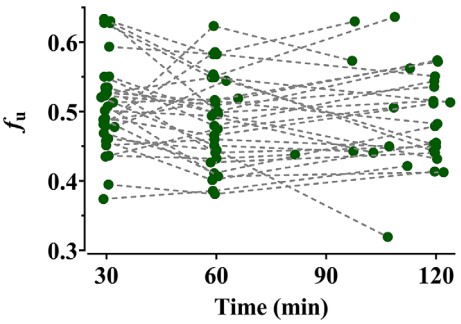

FIGURE 6 Changes in the free fraction of cefoxitin (f_u) over time for each individual

dose for 2 h: 1.32 g for Choi_T_{old} model, 1.51 g for Choi_T_{new} model). Changes in f_u over time for each individual are presented in Figure 6. The mean (SD, range) f_u was 0.496 (0.067, 0.319–0.636), with a large

inter-individual variability of f_u. The primary sources of uncertainty regarding the syringe pump are balance, time, density, syringe pump input digits, buoyancy and repeat measurement uncertainty. The uncertainty budget at a flow rate of 60 mL h^{-1} is listed in the supplementary material (Table S2). When the flow rate is 60 mL h^{-1}, the measured syringe pump had an error of − 0.135% with an uncertainty of 0.119% ($k = 2$).

3 | DISCUSSION

It was observed that the models constructed with total concentration data were suitable for clinical use in terms of bias and inaccuracy when cefoxitin was administered via a TCI method. However, overprediction was observed across all tested models. Nevertheless, administering cefoxitin using the TCI method in patients undergoing colorectal surgery maintained the free concentration above the MIC breakpoints of the major pathogens causing SSI throughout the operation period.

Performing TCI based on total concentration rather than free concentration may yield better results in maintaining the cefoxitin concentration constant, whilst reducing the number of confounding factors will help retain the target concentration constant. Free concentration is primarily influenced by plasma proteins,[9,10] the levels of which vary across individuals. In particular, TCI administration may cause variation in the plasma protein concentration, depending on the fluids and anaesthetic administered during surgery or bleeding. Therefore, variability of *fu* is inevitably large in patients undergoing surgery (Figure 6). Moreover, the coefficients of variation (CV) of measured total concentrations were less than that of the free concentration (CV=SD/mean×100; total concentration, 15.1%; free concentration, 18.9%). We can therefore interpret that the predictive performance of the total concentration model was greater than that of the free concentration model in terms of bias and inaccuracy (see Tables 2 and 3). Thus, an appropriate target total concentration to administer cefoxitin by the TCI method should be determined using a total concentration model. Amongst the major pathogens causing SSI in patients undergoing colorectal surgery, *B. fragilis* had the highest MIC, with a corresponding breakpoint of 16 μg mL^{-1} based on free concentration.[3] Since the TCI system does not reflect inter-individual and intra-individual variabilities, the target free concentration should be set to ensure the measured free concentration is 16 μg mL^{-1} or higher in most patients. Using this target could theoretically maintain the concentration above 16 μg mL^{-1} in approximately 50% of patients. In the previous stochastic simulation, if a target concentration of 25 μg mL^{-1} was set, 16 μg mL^{-1} was maintained in 97.5% of patients.[8] When considering f_u, the target total concentration can be established ($C_{total} = C_{free} / f_u$). In a previous study that constructed pharmacokinetic models of cefoxitin, the mean (SD, range) f_u was 0.503 (0.114, 0.237–0.887).[8] To best achieve a free concentration of ≥25 μg mL^{-1} in all patients, a value (=0.312) corresponding to 2.5% of the distribution of f_u values was used and converted to the total concentration. Therefore, the target concentration when performing TCI based on the total concentration was 80 (=25 μg/mL/0.312) μg mL^{-1}.

The Choi_T_{old} model described the disposition of the total concentration of cefoxitin with the three-compartment;[8] however, the Choi_T_{new} model was more suitable for two-compartment. We aimed to fit the data to the three-compartment mammillary model, but only the estimation step was successful, whilst the covariance step failed. Furthermore, the objective function value was similar to that of the two-compartment model (2COM, 2101.533; 3COM, 2121.807). A two-compartment mammillary model was selected as the base model to avoid over-parameterization. Allometric expression was applied to account for inter-individual variability in the pharmacokinetic parameters. In general, the allometric exponents of volumes and clearances had been fixed at one and 0.75[11]; however, estimating these exponents occasionally further reduced the objective function value.[12] Moreover, estimating the allometric exponent reduced the objective function value further throughout our study (Objective function value: 2064.775 for model for estimating the allometric exponent, 2091.407 for model fixed at the traditional value). Creatinine clearance was not a significant covariate for clearance. Since weight is included in the CrCl calculation process, collinearity problems may have occurred.

In general, the predictive performance of the TCI system is primarily evaluated by bias (MDPE) and inaccuracy (MDAPE) amongst the four parameters suggested by Varvel et al.[13] If MDPE and MDAPE are less than 20% and 30%, respectively, the TCI system is considered applicable to clinical practice.[14,15] The purpose of evaluating the predictive performance of a TCI system is to examine how effectively the target concentration is maintained. In particular, when a drug with a narrow therapeutic range is administered via the TCI method, maintaining the target concentration is important. However, although maintaining the target concentration is important in the case of prophylactic antibiotics, maintaining the free concentration above the MIC may be of higher importance given their need to prevent infection. In this study, the target concentration of 80 μg mL^{-1}, based on the pharmacokinetic model built with the total concentration data, led to the free concentration of 16 μg mL^{-1} or higher across all measured values. Furthermore, all total concentration models evaluated in this study satisfy the Varvel criteria. Based on the pharmacokinetic model constructed from the total concentration data, it was confirmed that cefoxitin can be administered in the clinical field using the TCI method.

There was no identified cause for the significant negative bias observed across all the models. Model misspecification was possible, but there were no problems in the internal validation (i.e. bootstrap and predictive cheque) and the goodness-of-fit plots.[8] Additionally, since two medical personnel administered cefoxitin together, errors in the dosing process are less likely to have occurred. However, ruling out the possibility of an unintentional error in the concentration measurement process is not difficult. We asked the persons in charge of the company who requested the concentration analysis (U Min Seo and Yeri Park, PhD from the International Scientific Standards, Inc. [Chuncheon-si, Gangwon-do, South Korea]) to reconfirm the validity of the concentration measurement process. We also requested that the concentration be measured again using the remaining plasma

samples. However, the result of the second concentration measurement did not differ from the first. We could therefore confirm that there was no error in the concentration measurement process. Although unlikely, the inaccuracy of the syringe pump could also have been the cause. We therefore could evaluate the accuracy of the syringe pump. An error of approximately 0.14% at an infusion rate of 60 mL h^{-1} indicates an error of approximately 3 mg of cefoxitin, which is negligible. The accuracy of the pump is largely guaranteed because the measurement uncertainty is also taken into account. The cause of the model overprediction remains unclear; however, administration of cefoxitin via the TCI method with a target total concentration of 80 μg mL^{-1} maintained a free concentration above 16 μg mL^{-1} during the entire operation period at a dose reduced by approximately 30% from the standard dose.

As a limitation of this study, it was assumed that the relationship between total concentration and free concentration was always linear. The relationship may not be linear in situations in which massive bleeding occurs. However, it is rare for a large amount of bleeding to occur in colorectal surgery. In fact, the average estimated blood loss of patients enrolled in this study was 50 mL (Table 1). Redosing of prophylactic antibiotics is recommended if prolonged surgery exceeds two drug half-lives or if there is excessive blood loss (> 1500 mL).[2] If excessive bleeding occurs, there is a high possibility that the free concentration cannot be maintained above the MIC even when administered by the TCI method. Antibiotics should be administered by the conventional method rather than the TCI method in the event of excessive bleeding.

In conclusion, the pooled biases and inaccuracies of models built from total concentration data were clinically acceptable. However, all models consistently produced negatively biased predictions. In the case of intraoperative administration of cefoxitin by TCI method, it is more effective to maintain a constant concentration by setting the total concentration to the target concentration rather than the free concentration. Administration of cefoxitin via the TCI method with a target total concentration of 80 μg mL^{-1} maintained a free concentration above 16 μg mL^{-1} during the elective surgery.

4 | METHODS

4.1 | Cefoxitin models evaluated in this study

- Choi_T_{old} model: Choi model constructed from total concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal.[8]
- Choi_F model: Choi model constructed from free concentration data of cefoxitin and published in the *Br J Clin Pharmacol* journal.[8]
- Choi_T_{new} model: a newly constructed model by combining the total concentrations (297 samples) used in the process of building the Choi_T_{old} model and the total concentrations of cefoxitin (89 samples) measured in the external validation study of the Choi_T_{old} model.

4.2 | Patients

4.2.1 | External validation of the free concentration pharmacokinetic model (study1)

The model constructed with the free concentration data was used when administering cefoxitin via the TCI method.[8] This study was approved by the Institutional Review Board of Asan Medical Centre (Seoul, South Korea; approval number, 2020–1462; approval date, September 23, 2020) and registered on an international clinical trials registry platform (http://cris.nih.go.kr, KCT0005456, principal investigator, Byung-Moon Choi; date of registration, October 08, 2020) before enrolment began. Written informed consent was obtained from all patients participating in the study. The patients were enrolled between December 2020 and January 2021. Patients meeting the following criteria were included: aged 20–80 years, body weight > 40 kg, American Society of Anesthesiologists Physical Status Classification 1–3, and scheduled to undergo elective colorectal surgery. Exclusion criteria were as follows: a history of allergic response to cefoxitin, haemoglobin level less than 8 g dL^{-1}, estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[16] less than 60 mL/min/1.73 m^2, pregnancy, or received cefoxitin within 3 days of study enrolment.

4.2.2 | External validation of the total concentration pharmacokinetic model (study 2)

The model used when administering cefoxitin via the TCI method was the model constructed with total concentration.[8] This study was approved by the Institutional Review Board of Asan Medical Centre (Seoul, South Korea; approval number, 2021–0665; approval date, May 04, 2021) and registered on an international clinical trials registry platform (http://cris.nih.go.kr, KCT0006148; principal investigator, Byung-Moon Choi; date of registration, May 18, 2021) before first enrolment. Written informed consent was obtained from all patients participating in the study. The patients were enrolled between May 2021 and June 2021. The criteria for patient inclusion were the same as that of the free concentration model validation study.

4.3 | Study procedure

General anaesthesia was performed in accordance with the standard operating procedure of Asan Medical Centre.[17] After the induction of anaesthesia, a 20-gauge catheter was inserted into a radial artery for blood sampling. Two grams of cefoxitin were dissolved in 50 mL of normal saline to give a concentration of 40 mg mL^{-1}. Before skin incision, cefoxitin was infused with a TCI syringe pump (Pilot Anaesthesia 2, Fresenius vial, France), which was connected to a personal computer by an RS232c cable and controlled with TCI software (Asan pump, version 2.1.3; Bionet Co. Ltd., Seoul, Korea, http://www.fit4nm.org/download; last accessed, 27 August, 2012). Pharmacokinetic parameters of the

Choi models were then programmed into the Asan pump.[8] Target concentrations of free and total concentrations were set to 25 μg mL^{-1} and 80 μg mL^{-1}, respectively. Based on the data from previous studies,[3,8] a target total concentration was set to give a free cefoxitin concentration of 16 μg mL^{-1} or greater. During surgery, Ringer's lactate solution was administered. Intraoperative estimated blood loss was calculated as the sum of the volume of blood contained in suction systems and gauze.[17]

4.4 | Blood sampling and measurement of total and free cefoxitin concentrations

Total and free plasma concentrations of cefoxitin were measured by three arterial blood samples (5 mL each) collected at 30, 60 and 120 min after the start of cefoxitin administration. If the operation was completed within 2 h, the last blood sample was obtained at the end of the operation. The collected blood was placed in ethylenediaminetetraacetic acid-containing tubes and centrifuged at 1500 × g for 10 min. The resulting plasma was then stored at −70 °C until use. The liquid chromatography with tandem mass spectrometry (LC–MS/MS) method was developed to determine the total and free plasma concentrations of cefoxitin. Chromatographic retention of cefoxitin and donepezil-d7, internal standard (IS), was obtained on an ACE Excel 3 AQ, 50 × 2.1 mm, 3 μm column (Aberdeen, Scotland) under isocratic elution with a flow rate of 0.4 mL min^{-1}. The mobile phase consisted of water with 0.1% formic acid and acetonitrile with 0.1% formic acid. Cefoxitin and IS were detected by multiple reaction monitoring using an MDS SCIEX API 4000 mass spectrometer (Applied Biosystems/MDS Sciex, Concord, Ontario, Canada) in positive electrospray ionization (ESI+) mode. The mass transitions monitored for cefoxitin and IS were 445.1 > 215.0 m/z and 387.5 > 98.1 m/z, respectively. Assays ranged from 0.1 to 1,000 μg mL^{-1} for total cefoxitin and 0.05 to 500 μg mL^{-1} for free cefoxitin. Protein precipitation was used to extract total cefoxitin from the plasma. Briefly, 20 μL of calibration standard, quality control, or specimen was added with 5 μL of internal standard working solution (ISWS) and 750 μL of acetonitrile, vortexed, and then centrifuged. Next, a portion of supernatant was injected onto the LC–MS/MS system. Free cefoxitin was extracted from plasma through ultrafiltration followed by protein precipitation. The specimens were then loaded onto a Centrifree Ultrafiltration Device with Ultracel PL membrane (Merck, Darmstadt, Germany) and centrifuged at 2000 × g for 30 min. Twenty microlitres of calibration standard, quality control, or filtered specimen was added with 5 μL of ISWS and 800 μL of acetonitrile, vortexed and then centrifuged. A portion of supernatant was subsequently injected onto the LC–MS/MS system. The biggest limitation of the ultrafiltration technique, largely used for plasma protein binding assay, is the non-specific binding (NSB) of substances to the filter membrane, the material of the ultrafiltration device, and the ultrafiltration compartment in the absence of plasma, thus leading to an inaccurate concentration of the free fraction.[18] A test sample (prepared by passing a post-filtration spiked sample through a filter membrane applied with blank plasma proteins in six replications) was compared with a control sample (i.e. post-filtration spiked sample, in six replications, to represent 100% recovery) to evaluate the NSB of free cefoxitin in plasma. The actual free cefoxitin concentration was calculated by dividing the measured concentration by a correction factor of 0.523 (i.e. the recovery rate of free cefoxitin against the losses on plasma ultrafiltration, recovery rates of six replicates: 0.563, 0.526, 0.497, 0.516, 0.482, 0.552, 0.523 ± 0.031). The free fraction of cefoxitin in the plasma (f_u) was calculated using the following equation:

$$f_u = C_{free}/C_{total}.$$

where C_{total} and C_{free} indicate the total and free concentration of cefoxitin, respectively.

4.5 | Performance analysis

The predictive performance of the TCI system was evaluated using four parameters: inaccuracy, divergence, bias, and wobble.[13] For each blood sample, the performance error (PE) of the i^{th} patient was calculated as follows:

$$PE_{ij} = \frac{measured_{ij} - predicted_{ij}}{predicted_{ij}} \quad (1)$$

where $predicted_{ij}$ is the predicted total or free cefoxitin concentration at the j^{th} sampling point from the i^{th} patient, and $measured_{ij}$ is the measured total or free cefoxitin concentration.

The inaccuracy of a TCI system for the i^{th} individual was calculated as the median absolute PE ($MDAPE_i$):

$$MDAPE_i = \text{median}\{|PE_{ij}|, j = 1, \ldots\ldots N_i\} \quad (2)$$

where N_i is the number of blood sampling points for the i^{th} individual.

Divergence, a measure of the expected systematic time-related changes in performance, was calculated for the i^{th} individual through the slope obtained from the linear regression of the $|PE_{ij}|$ values of that individual against time:

$$Divergence_i\left(\% \cdot h^{-1}\right) = 60 \times \frac{\sum_{j=1}^{N_i}|PE_{ij}| \times t_{ij} - \left(\sum_{j=1}^{N_i}|PE_{ij}|\right) \times \left(\sum_{j=1}^{N_i} t_{ij}\right)/N_i}{\sum_{j=1}^{N_i}(t_{ij})^2 - \left(\sum_{j=1}^{N_i} t_{ij}\right)^2/N_i} \quad (3)$$

where t_{ij} is the time (in min) at which the corresponding PE_{ij} was determined.

Bias for the i^{th} individual, was calculated as the median PE ($MDPE_i$):

$$MDPE_i = \text{median}\{PE_{ij},\ j = 1, \ldots\ldots N_i\} \quad (4)$$

$Wobble_i$ for the i^{th} individual was a measure of the variability of the PE_{ij} in that individual:

$$Wobble_i = \text{median absolute deviation of} \{PE_{ij},\ j = 1,.....N_i\} \ \text{ from } MDPE_i \quad (5)$$

Population estimates for MDAPE, divergence, bias and wobble were obtained using a pooled data approach (fit4NM 3.3.3, Eun-Kyung Lee and Gyu-Jeong Noh, https://cran.r-project.org/src/contrib/Archive/fit4NM/, last accessed 29 October 2012).[14]

4.6 | Accuracy test of the syringe pump used in TCI

The accuracy of the syringe pump (Pilot Anaesthesia 2, Fresenius vial, France) was evaluated using a gravimetric facility. Deionized water was passed through the syringe pump with a 50 mm diameter syringe at a constant flow rate. The reference flow rate was obtained using a micro balance (XPE 206 DR, Mettler-Toledo LLC, Columbus, OH, USA). Details of the gravimetric facility are described in a previously published paper.[19] The reference flow rate (q_{ref}) measured by the gravimetric facility and the target flow rate (q_{target}) of the syringe pump were compared to determine the accuracy, as shown in the following equation.

$$Error\ (\%) = \frac{q_{target} - q_{ref}}{q_{ref}} \times 100 \quad (6)$$

4.7 | Post-correction of creatinine clearance (CrCl) calculation error in Asan pump software

The pharmacokinetic model of cefoxitin is not included in the commercialized TCI pump; therefore, the target total plasma concentration-controlled infusion of cefoxitin was performed using Asan pump software, which allows users to freely add new pharmacokinetic models. Plasma concentration, dose infused, and infusion rate data were recorded at 10 s intervals and stored in the 'csv' format. Creatine clearance was included as a covariate in the clearance (*Cl*) of the cefoxitin pharmacokinetic parameter ($Cl = 0.02 \times [\text{weight}/64]^{0.75} + [\text{CrCl}/82] \times 0.0246$).[8] In the original paper,[20] body weight was used to calculate CrCl (Cockcroft–Gault formula); however, the Asan pump instead uses ideal body weight (IBW) calculated with the Devine formula.[21] Therefore, the *Cl* value calculated by the Asan pump is different from that calculated by the original model of cefoxitin (Choi models). Therefore, if cefoxitin were to be administered at a target concentration of 80 μg mL^{-1} using the Asan pump software, the actual predicted concentration would not be 80 μg mL^{-1}. The infusion profiles of the Asan pump for each patient were applied as inputs to the Choi model constructed with the free or total concentration of cefoxitin for calculating predicted concentration with the original model.

4.8 | Population pharmacokinetic analysis

To improve the predictive performance of the Choi_T_{old} model, pharmacokinetic modelling was performed again by combining the total concentrations used in the process of building the Choi_T_{old} model and the total concentrations of cefoxitin measured in the study 2 (external validation study of total concentration pharmacokinetic model). NONMEM VII level 4 (ICON Development Solutions, Dublin, Ireland) was used for the population pharmacokinetic analysis. Total cefoxitin concentrations were fitted to one-, two-, or three-compartment models using the ADVAN 13 subroutines and first-order conditional estimation with interaction. A more detailed modelling process has been described previously.[22] The predictive performance of the new cefoxitin model and the Choi model constructed with free concentration data was also evaluated.

4.9 | Simulation

The Asan Pump software was used to simulate the required amount of cefoxitin according to the different models when cefoxitin was administered via the TCI method for 2 h at a target total plasma concentration of 80 μg mL^{-1}.

4.10 | Statistical analysis

Statistical analyses were conducted using the SigmaStat software version 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation (range) for normally distributed continuous variables, median (25–75%) for non-normally distributed continuous variables, or count.

AUTHOR CONTRIBUTIONS

B.M.C. and S.H.L. conceived and designed the study. H.U.K., K.M.K., J.M.C., E.K.L., and G.J.N. performed the data analysis and interpretation. All authors contributed to, and have approved, the final manuscript.

ACKNOWLEDGEMENTS

We are grateful to U Min Seo and Yeri Park, PhD from the International Scientific Standards, Inc. (Chuncheon-si, Gangwon-do, South Korea) for measuring the plasma concentrations of cefoxitin. We are also grateful to Jeong-Sim Yang, AS (Asan Medical Center, Seoul, South Korea) and Do-Yang Park, AS (Asan Medical Center, Seoul, South Korea) for their efforts as clinical research coordinators.

FUNDING INFORMATION

This work performed under MeDDII project has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme. This research was also supported by the National Research Foundation of Korea (NRF) (Grant 2019K1A3A1A78077783 and 2020R1C1C1009976).

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The datasets generated or analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kang H-U, Kim KM, Choi JM, et al. Predictive performance of pharmacokinetic models for target concentration-controlled infusion of cefoxitin as a prophylactic antibiotic in patients with colorectal surgery. *Clin Exp Pharmacol Physiol*. 2022;1-10. doi:10.1111/1440-1681.13695