의 학 석 사 학 위 논 문

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

결장수술을 받는 환자에서 예방적 항생제로 투여하는 cefoxitin 을 목표농도조절주입방법으로 투여하기 위하여 구축한 약동학 모형의 예측성능평가

울 산 대 학 교 대 학 원

의 학 과

강 현 욱

# 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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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

울 산 대 학 교 대 학 원

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**Abstract**

**Aims:** We aimed to evaluate the predictive performance of previously constructed cefoxitin pharmacokinetic models and the possibility of administering cefoxitin via the target-controlled infusion (TCI) method in clinical practice.

**Methods:** 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. The target total plasma concentration was set to 80 μg $mL^{-1}$, which was 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 minutes after the start of cefoxitin administration. The predictive performance of the TCI system was evaluated using four parameters: inaccuracy, divergence, bias, and wobble.

**Results:** The predictive performance of various pharmacokinetic models of cefoxitin was evaluated using 89 total and 89 free plasma concentration measurements from 30 patients. The pooled median (95% confidence interval) biases and inaccuracies were −16.6 (−18.4 to −14.8) and 18.5 (16.7–20.2) for the total concentration model and −20.9 (−22.7 to −19.1) and 22.4 (20.6–24.2) for the free concentration model, respectively.

**Conclusions:** The pooled biases and inaccuracies of the Choi models were clinically acceptable. However, all models consistently produced negatively biased predictions. Administering cefoxitin via the TCI method with a target total concentration of 80 μg $mL^{-1}$ can maintain a free concentration above 16 μg $mL^{-1}$ throughout the operation.

**Keywords**: Antibiotics, concentration, infection, performance, pharmacokinetics, model

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## 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 dose of 2 g dissolved in normal saline administered intravenously for approximately 10 minutes 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), personalised 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.

## Methods

### *Patients*

This study was approved by the Institutional Review Board of Asan Medical Center (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. 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 CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [9] less than 60 $mL/min^{-1}$ 1.73 $m^{-2}$, pregnancy, or received cefoxitin within 3 days of study enrolment.

### *Study procedure*

General anaesthesia was performed in accordance with the standard operating procedure of Asan Medical Center [10]. 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 Anesthesia 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 model were then programmed into the Asan pump [8]. The target total plasma concentration was set to 80 μg $mL^{-1}$ and administered until the end of surgery. 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.

***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 hours, 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℃ 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 $\mu g/mL^{-1}$ for total cefoxitin and 0.05 to 500 $\mu g/mL^{-1}$ 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, Germany) and centrifuged at 2000×g for 30 min. Twenty μL 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 [11]. 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). 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.

***Performance Analysis***

The predictive performance of the TCI system was evaluated using four parameters: inaccuracy, divergence, bias, and wobble [12]. For each blood sample, the performance error (PE) of the $i^{th}$ patient was calculated as follows:

$$PE_{ij} = \frac{measured_{ij} - predicted_{ij}}{predicted_{ij}} \qquad \text{(equation 1)}$$

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 ($MDAPE_i$):

$$MDAPE_i = \text{median}\left\{ \left| PE_{ij} \right|, j = 1, \ldots\ldots N_i \right\} \qquad \text{(equation 2)}$$

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:

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

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 ($MDPE_i$):

$$MDPE_i = \text{median}\left\{ PE_{ij}, j = 1, \ldots\ldots N_i \right\} \qquad \text{(equation 4)}$$

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

$$Wobble_i = \text{median absolute deviation of } \left\{ PE_{ij}, j = 1, \ldots\ldots N_i \right\} \text{ from } MDPE_i \qquad \text{(equation 5)}$$

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) [13].

***Accuracy test of the syringe pump used in TCI***

The accuracy of the syringe pump (Pilot Anesthesia 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 [14]. 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.

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

***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□second 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 [15], 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 [16]. Therefore, the *Cl* value calculated by the Asan pump is different from that calculated by the original model of cefoxitin (Choi model). 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 total concentration of cefoxitin for calculating predicted concentration with the original model.

***Population pharmacokinetic analysis***

To improve the predictive performance of the Choi model, pharmacokinetic modelling was performed again by combining the total concentrations used in the process of building the Choi model and the total concentrations of cefoxitin measured in the current predictive performance study. 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 [17]. The predictive performance of the new cefoxitin model and the Choi model constructed with free concentration data was also evaluated.

***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.

**Results**

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 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 predicted total concentration and the measured total concentration of cefoxitin were compared during the target plasma concentration-controlled infusion using the Asan pump software (Figure 1). The measured concentrations were generally less than 80 μg $mL^{-1}$. Comparison of CrCl and clearance calculated by the Cockcroft-Gault formula and the Asan pump software is shown in Figure 2. The clearance calculated by the Asan pump using IBW to calculate CrCl was significantly lower than that calculated by the original Choi model (Choi model: 45. 2 mL $min^{-1}$, Asan pump: 42.2 mL $min^{-1}$, $P$=0.038, Student's $t$-test). 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 3. 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 3C), indicating that the free concentration was maintained above the MIC breakpoints of the major pathogens (i.e, *E. coli*, *S. aureus* and *B. fragilis*), causing SSI during the entire operation period. The results of the re-modelling by adding the total concentration data (n=89) measured in the current study are as follows.

$$V_1\ (\mathrm{L}) = 1.74 \times (Weight / 65)^{0.543}$$
$$V_2\ (\mathrm{L}) = 4.2 \times (Weight / 65)^{0.543}$$
$$Cl\ (\mathrm{L\,min^{-1}}) = 0.11 \times (Weight / 65)^{0.542}$$
$$Q\ (\mathrm{L\,min^{-1}}) = 0.185 \times (Weight / 65)^{0.542}$$

**Table 1.** Characteristics of the study patients (N=30).

| | |
|---|---|
| Male/female | 24/6 |
| ASA PS 1/2 | 5/25 |
| Age, yrs | 62.5 (53–66) |
| Weight, kg | 67.1 (57.7–73.3) |
| Height, cm | 164.4 ± 8.0 |
| Albumin, g $dL^{-1}$ | 3.9 (3.6–4.0) |
| Protein, g $dL^{-1}$ | 7.1 ± 0.5 |
| CrCl, mL $min^{-1}$ | 83.2 ± 16.7 |
| eGFR, mL $min^{-1}$ 1.73 $m^{-2}$ | 90.4 ± 12.2 |
| Operation time*, min | 102.5 (89–144) |
| Cefoxitin dose administered via TCI, g | 1.4 ± 0.3 |

Data are presented as counts, median (25–75%), or means ± SDs as appropriate.

*Time required from skin incision to skin closure.

ASA PS: American Society of Anesthesiologists Physical Status, CrCl: creatinine clearance (calculated using the Cockcroft-Gault formula[14]), eGFR: estimated glomerular filtration rate calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation[9], TCI: target-controlled infusion.

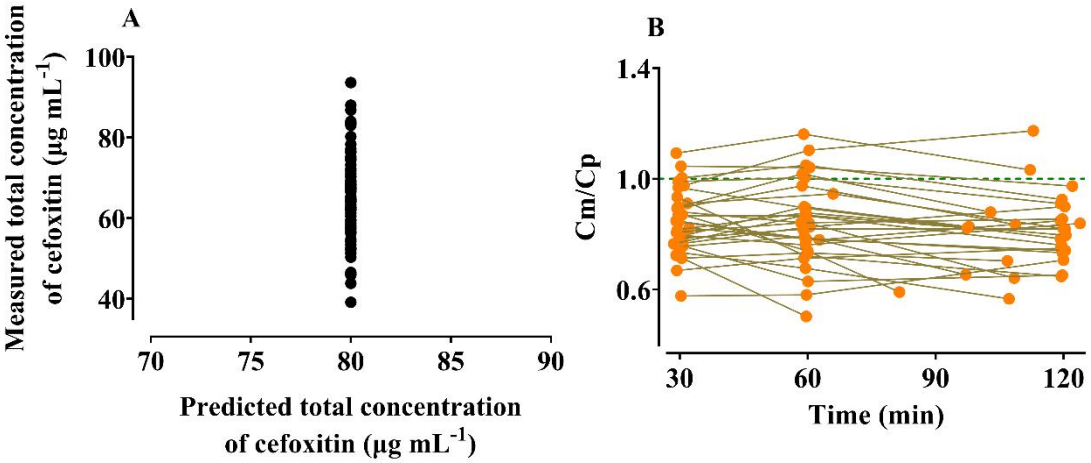


**Figure 1**. Comparison between measured (Cm) and predicted (Cp) total concentration of cefoxitin of the Choi model. A: Cm vs. Cp, B: Cm/Cp over time. Patients (n=30) received cefoxitin via target-controlled infusion (TCI) using a TCI software (Asan pump, version 2.1.3; Bionet Co. Ltd., Seoul, Korea, http://www.fit4nm.org/download, last accessed: August 27, 2012). Target total plasma concentration of cefoxitin was set at 80 μg $mL^{-1}$.

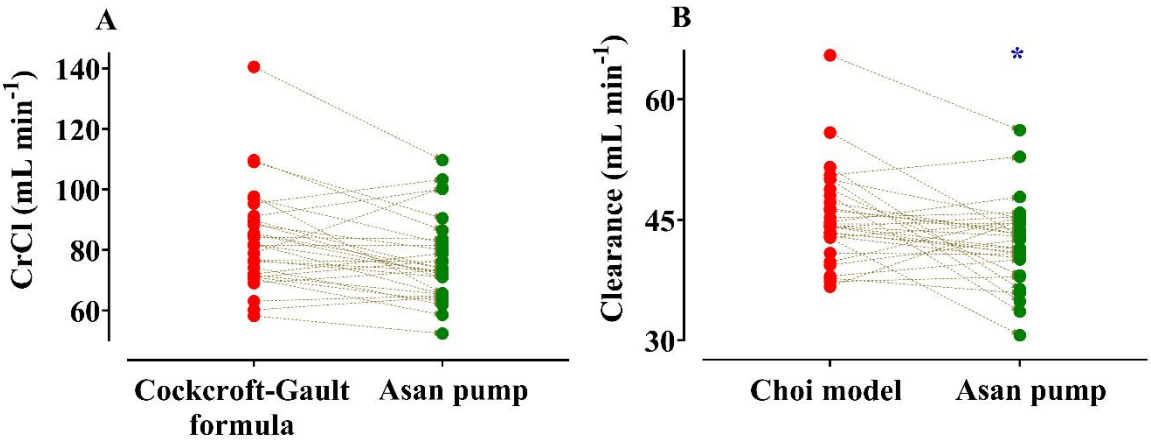


**Figure 2**. Comparison of creatinine clearance (CrCl, A) and clearance (B) calculated by Cockcroft-Gault formula and Asan pump software. CrCl was calculated using the Cockcroft-Gault formula and Asan pump software as follows: Cockcroft-Gault formula[15]: For men, CrCl = (140 – age) × weight / (serum creatinine × 72), for women, CrCl × 0.85. Asan pump software: for men, CrCl = (140 – age) × IBW / (serum creatinine × 72), for women, CrCl × 0.85. The units of serum creatinine was mg/dL$^{-1}$. IBW: ideal body weight calculated by the Devine formula[16]. The pharmacokinetic parameter, the clearance (*Cl*), was calculated as follows by the Choi model. *Cl* (L min$^{-1}$) = 0.02 × (weight/64)$^{0.75}$ + (CrCl/82) × 0.0246.

*P < 0.05 vs. clearance reflecting CrCl calculated by Cockcroft-Gault formula.

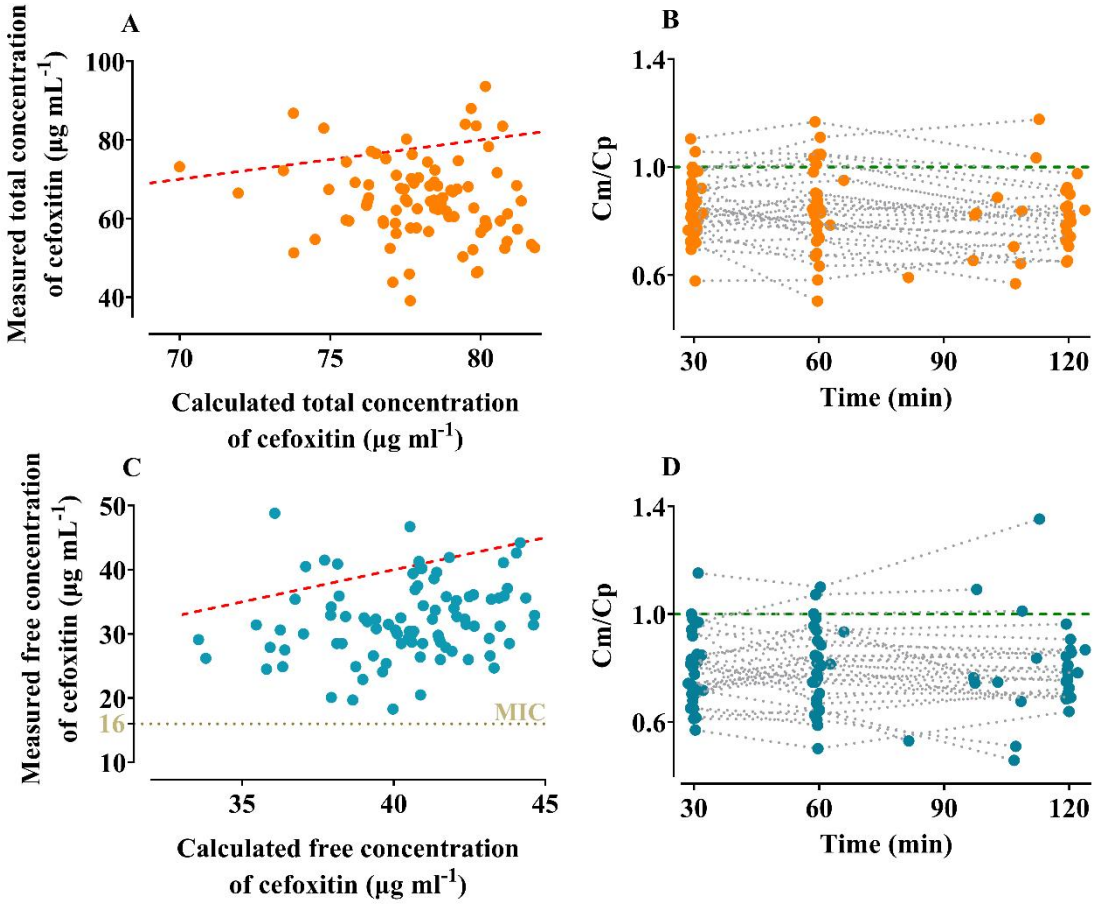


**Figure 3**. Comparison of the predicted concentration (Cp) calculated by correcting clearance using the infusion history of the Asan pump software and the measured concentration (Cm) of cefoxitin. A: Cm vs. Cp based on total concentration, B: Cm/Cp based on total concentration over time, C: Cm vs. Cp based on free concentration, D: Cm/Cp based on free concentration over time.

Population pharmacokinetic parameter estimates and the results of the non-parametric bootstrap replicates are summarized in Table 2. A two-compartment mammillary model described the time concentration curves of cefoxitin. The goodness-of-fit plots of this new pharmacokinetic model of cefoxitin are shown in Figure 4. Bias is observed at low concentrations of $\leq$10 μg/mL$^{-1}$; however, it can likely be used in clinical practice considering the target concentration of 80 μg/mL$^{-1}$ when administering cefoxitin. Predictive checks of the new pharmacokinetic model of cefoxitin are shown in Figure 5. Comparison between measured and predicted total concentration of cefoxitin of a new model is shown in Figure 6, and 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. The newly constructed model that added data achieved the greatest predictive performance. Changes in $f_u$ over time for each individual are presented in Figure 7. 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 Table 4. 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).

**Table 2**. Population pharmacokinetic parameter estimates, inter-individual variability (IIV) and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of a new pharmacokinetic model of the total plasma concentrations of cefoxitin

| Parameters | | Estimates (RSE, %) | IIV (CV %) | η Shrinkage | Median (2.5–97.5%) |
|---|---|---|---|---|---|
| $V_1$ (L) = $\theta_{V1} \times (WT/65)^{\theta 1}$ | $\theta_{V1}$ | 1.74 (4.2) | – | – | 1.75 (1.68–1.83) |
| $V_2$ (L) = $\theta_{V2} \times (WT/65)^{\theta 1}$ | $\theta_{V2}$ | 4.2 (9.1) | 17.3 | 35.8 | 4.26 (3.98–4.54) |
| $Cl$ (L min$^{-1}$) = $\theta_{Cl} \times (WT/65)^{\theta 2}$ | $\theta_{Cl}$ | 0.11 (4.0) | 24.3 | 3.3 | 0.114 (0.109–0.119) |
| $\theta_Q$ (L min$^{-1}$) = $\theta_Q \times (WT/65)^{\theta 2}$ | $\theta_Q$ | 0.185 (4.0) | – | – | 0.185 (0.175–0.198) |
| | $\theta_1$ | 0.543 (33.1) | – | – | 0.572 (0.351–0.809) |
| | $\theta_2$ | 0.542 (38.7) | – | – | 0.576 (0.310–0.761) |
| $\sigma_1$ | | 0.28 (47.5) | – | – | 0.319 (0.174–0.446) |
| $\sigma_2$ | | 0.129 (11.6) | – | – | 0.123 (0.101–0.144) |

A log normal distribution of inter-individual random variability was assumed. Residual random variability was modelled using an additive ($\sigma_1$) plus proportional ($\sigma_2$) error model. Non-parametric bootstrap analysis was repeated 2000 times. RSE indicates relative standard error = SE mean$^{-1}$ × 100 (%). *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.

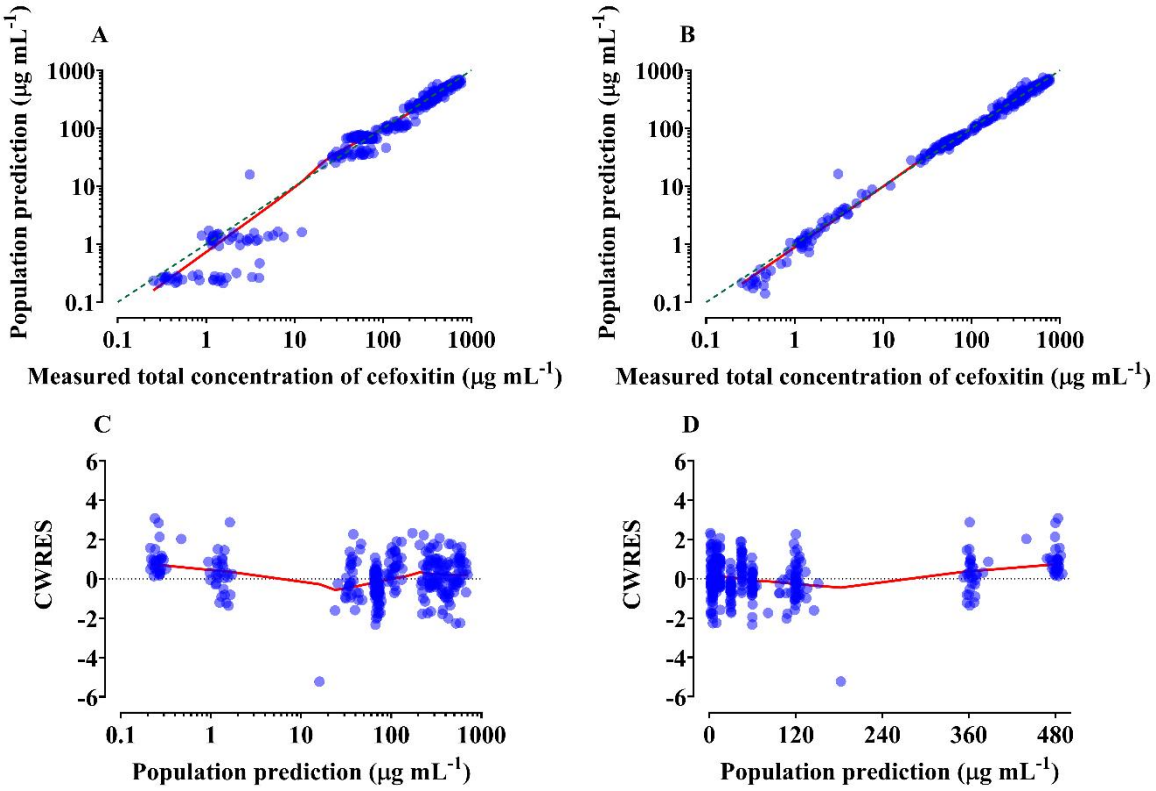


**Figure 4**. Goodness-of-fit plots of the new pharmacokinetic models of total concentrations of cefoxitin. The new model was constructed by combining the total concentrations (297 samples) used in the process of building the Choi model and the total concentrations of cefoxitin (89 samples) measured in the current predictive performance study. (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.

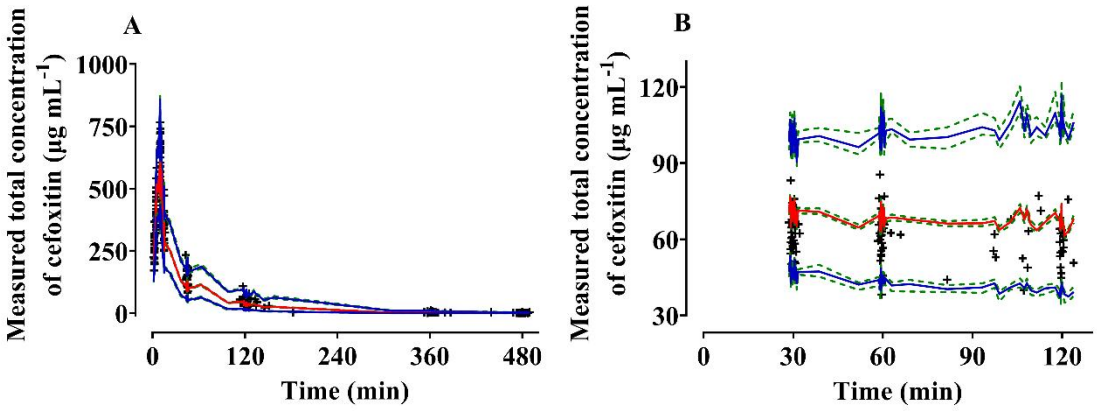


**Figure 5**. Predictive checks of the new pharmacokinetic model of total concentrations of cefoxitin. Stratification was performed according to the two data sets. A: Data (n=297) used to build the Choi model, B: Data (n=89) used for performance evaluation of the Choi model. The solid red line and the 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. In total, 5.7% of the data (A: 6.5%, B: 3.4%) were distributed outside of the 95% prediction intervals.

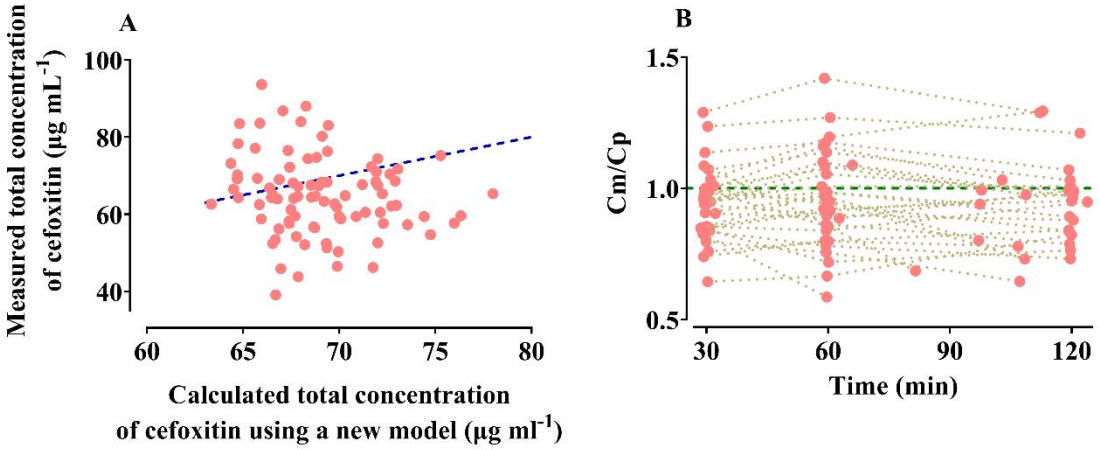


**Figure 6**. Comparison between measured (Cm) and predicted (Cp) total concentration of cefoxitin of a new model. A: Cm vs. Cp, B: Cm/Cp over time. The new model was constructed by combining the total concentrations (297 samples) used in the process of building the Choi model and the total concentrations of cefoxitin (89 samples) measured in the current predictive performance study.

**Table** 3. Pooled biases, inaccuracies, divergences, and wobbles of various models for cefoxitin. Values are median (95% confidence interval).

| Model | Model A (n=30) | Model A* (n=30) | Model B* (n=30) | Model C* (n=61) |
|---|---|---|---|---|
| Body size parameter used for CrCl calculation | IBW calculated by the Devine formula | Actual body weight | Actual body weight | Actual body weight |
| Type of cefoxitin concentrations used in the model building process | Total | Total | Free | Total |
| Bias (%) | −18.6 (−20.4 to −16.9)† | −16.6 (−18.4 to −14.8)† | −20.9 (−22.7 to −19.1)† | −6.1 (−8.1 to −4.2)† |
| Inaccuracy (%) | 20.0 (18.3–21.7) | 18.5 (16.7–20.2) | 22.4 (20.6–24.2) | 13.1 (11.3–14.9) |
| Divergence (% $h^{-1}$) | 5.2 (3.4–7.0) | 5.5 (3.8–7.2) | 3.2 (0.3–6.0) | 2.9 (0.9–4.9) |
| Wobble (%) | 3.8 (2.6 to 5.0) | 4.2 (2.9–5.4) | 3.3 (1.9–4.7) | 4.4 (2.9–5.6) |

* Calculated using the plasma concentrations retrospectively estimated for each model. †: significant bias.

Model A: Choi model constructed with the total concentration of cefoxitin[8], Model B: Choi model constructed with the free concentration of cefoxitin[8]. Model C: A newly constructed model by combining the total concentrations (297 samples) used in the process of building model A and the total concentrations of cefoxitin (89 samples) measured in the current predictive performance study. In the current study, cefoxitin was infused with a target-controlled infusion (TCI) syringe pump (Pilot Anesthesia 2, Fresenius vial, France), which was connected to a personal computer (PC) with an RS232c cable and controlled by a TCI software (Asan pump, version 2.1.3; Bionet Co. Ltd., Seoul, Korea, http://www.fit4nm.org/download, last accessed: August 27, 2012). Ideal body weight (IBW) was set in the Asan pump software when calculating creatinine clearance (CrCl). In the original paper, CrCl was calculated from the actual body weight[15]. Bias: median performance error (MDPE), Inaccuracy: median absolute performance error (MDAPE).

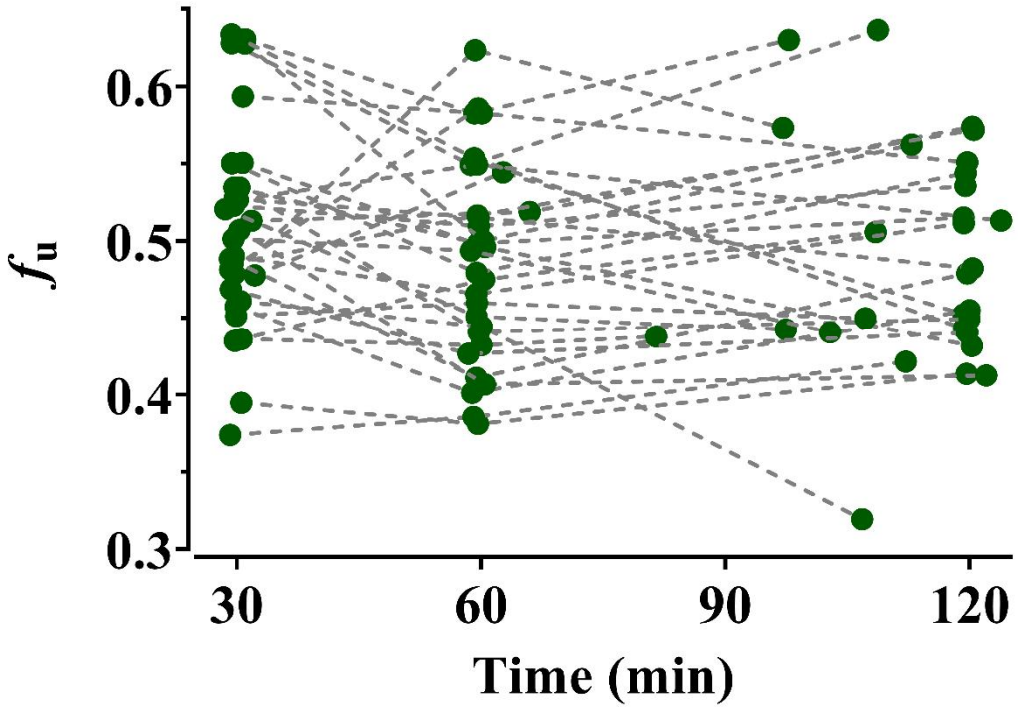


**Figure 7**. Changes in the free fraction of cefoxitin ($f_u$) over time for each individual.

**Table 4**. Uncertainty budget for evaluating the syringe pump accuracy.

| Quantity (Xi) | Uncertainty factor | Value of uncertainty | $C_i = \frac{\partial f}{\partial x_i}$ | Uncertainty contribution | Degree of freedom |
|---|---|---|---|---|---|
| Mass | $u(\delta W)$ | *5.17E-04* | 2.49E-04 | 1.29E-07 | 289 |
| Time | $u(\delta t)$ | *9.80E-04* | 4.159E-07 | 4.07E-09 | 210 |
| Density | $u(\delta \rho)$ | *3.75E-03* | 3.746E-09 | 3.74E-09 | 107 |
| Pump input digits | $u(\delta q_{PUMP})$ | *3.40E-04* | 1.00E+00 | 3.74E-04 | 354 |
| Buoyancy correction | $u(\delta \varepsilon)$ | *2.89E-06* | –9.96E-04 | -2.88E-09 | 3873 |
| Relative error | $u(E_A)$ | *5.97E+00* | 1.00E+00 | 0.05 | 9 |

$u(\delta W)$: the uncertainty of a weighing system, $u(\delta t)$: uncertainty of a timer, $u(\delta \rho)$: uncertainty of liquid density, $u(\delta q_{PUMP})$: uncertainty of a syringe pump input digits, $u(\delta \varepsilon)$: uncertainty of buoyancy correction factor, $u(E_A)$: type A uncertainty of error (E) (%). The combined uncertainty ($u_c(E)$) was determined to be 0.06%. When the coverage factor ($k$) was set to 2, the expanded uncertainty was 0.12%.

**Discussion**

Various pharmacokinetic models of cefoxitin to determine bias and inaccuracy are suitable for clinical use. 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. This is because free concentration is primarily influenced by plasma proteins [18, 19], and plasma protein levels vary across individuals. Notably, a large inter-individual variability of $f_u$ was observed throughout this study (Figure 7). Additionally, it is important to note the intra-individual variability of $f_u$ in patients undergoing surgery involving fluids and anaesthetics, wherein bleeding may occur. 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 Table 3). Thus, an appropriate target total concentration to administer cefoxitin by the TCI method should be determined using a total concentration model. Among 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 $mL^{-1}$/0.312) μg $mL^{-1}$.

The previously constructed model explained the disposition of the total concentration of cefoxitin with the three-compartment [8]; however, the newly constructed model with the addition of data in this study 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, and the covariance step failed. Furthermore, the objective function value was similar to that of the two-compartment model (2COM: 2101.533, 3COM: 2121.807). To avoid over-parameterization, a two-compartment mammillary model was selected as the base model. 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 1 and 0.75 [20]; however, estimating these exponents occasionally further reduced the objective function value [21]. Moreover, estimating the allometric exponent reduced the objective function value further throughout our study. 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) among the four parameters suggested by Varvel et al. [12]. If MDPE is less than 20% and MDAPE is less than 30%, the TCI system is considered clinically usable [13, 22]. All models evaluated in this study satisfy these criteria, so they could be expected to be used in clinical practice. Although the newly constructed model achieved the greatest predictive performance, some improvements would be expected because the predictive performance data are included in the model-building data. Conducting a performance evaluation of the new model in a new population not related to the model building process may be helpful.

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 check) 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.

In conclusion, the pooled biases and inaccuracies of the various pharmacokinetic models of cefoxitin were clinically acceptable. However, all models consistently produced negatively biased predictions. In particular, performing the target concentration-controlled infusion based on the total concentration rather than TCI based on the free concentration more effectively maintained the concentration constant.

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**22** Yi JM, Doh I, Lee SH, Kim SY, Lee YH, Lee EK*, et al.* Predictive performance of a new pharmacokinetic model for propofol in underweight patients during target-

**Abstract (Korean)**

**목적:** 본 연구는 이전 연구를 통해 구축된 cefoxitin 의 약동학 모형의 예측성능을 평가하고, 임상에서 cefoxitin 의 목표농도조절주입방법(TCI)을 적용할 수 있을 지 평가하기 위해 진행되었다.

**방법:** Cefoxitin 2 g 을 생리식염수 50 mL 에 용해시켜 40 mg $mL^{-1}$ 제제를 준비하였다. 피부절개 전, cefoxitin 은 TCI 용 시린지 펌프를 통해 주입되었다. 목표 혈장 총약물농도는 80 μg $mL^{-1}$ 으로 설정하여 수술 종료시까지 유지하였다. Cefoxitin 투여 시작 이후 30, 60, 120 분 시점에 각각 혈액을 채취하여 혈장 내 총약물농도와 유리약물농도를 측정하였다. TCI 시스템의 예측성능은 inaccuracy, divergence, bias, wobble 의 네 가지 지표로 평가하였다.

**결과:** 30 명의 환자에게서 측정한 89 개의 총약물농도와 89 개의 유리약물농도 검체를 이용하여 cefoxitin 의 다양한 약동학모형의 예측성능을 평가하였다. 총약물농도 모형의 치우침 중앙값(95% 신뢰구간)은 −16.6 (−18.4 to −14.8), inaccuracy 는 18.5 (16.7–20.2)였으며 유리약물농도 모형의 치우침 중앙값(95% 신뢰구간)은 –20.9 (–22.7 to –19.1), inaccuracy 는 22.4 (20.6–24.2)였다.

**결론:** 이전 연구를 통해 구축된 Choi 모형의 치우침과 inaccuracy 는 임상적으로 수용 가능하였다. 한편, 모든 모형에서 예측값이 음의 방향으로 편향되어 있었다. Cefoxitin 을 목표 혈장 총약물농도 80 μg mL-1 로 설정하여 TCI 로 투여함으로서 수술 중 cefoxitin 의 혈중 유리약물농도를 16 μg $mL^{-1}$ 이상으로 유지할 수 있다.