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Population pharmacokinetic analysis of cefdinir following a single oral dose in healthy adults
ABSTRACT

Population pharmacokinetic analysis of cefdinir following a single oral dose in healthy adults

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Introduction: Cefdinir is a broad-spectrum oral cephalosporin antimicrobial agent that targets numerous gram-positive and -negative bacteria. (1) Few data are available regarding the pharmacokinetics (PKs) of cefdinir. The aim of this study was to develop a population PK model for cefdinir in healthy adults to aid optimal pharmacotherapy.
Methods: In total, 333 plasma concentration-time data for cefdinir, obtained from 26 healthy males (aged 19-28 years, body weight 54.0–103.0 kg), were used; plasma samples were collected up to 12 h following a single oral dose of cefdinir 100 mg. Plasma concentrations of cefdinir were analyzed using HPLC/MS/MS. The plasma concentration-time data were pooled and a population PK model was developed using the nonlinear mixed-effects method in NONMEM (ver. 7.3). The First-Order Conditional Estimation with Interaction estimation method was implemented, followed by model verification using visual predictive checks (VPCs). Demographic and clinical variables were evaluated as potential covariates for PK parameters.

Results: A one-compartment model with a combined transit compartment and first-order absorption, which described the absorption process well, was selected as the most appropriate model. The population mean estimate for the PK parameters were as follows: apparent clearance (CL/F) was 35.4 L/h, apparent of volume (V/F) was 41.6 L, absorption rate constant from the depot (ka1) was 0.364 /h, absorption rate constant from the final transit compartment to the central compartment (ka2) was 0.488 /h, mean transit time (MTT) was 2.10 h, number of transit compartments (n) was 3.82, and the fraction of the dose absorbed by the transit compartment model (f) was 0.874. Model evaluation by bootstrapping and VPCs suggested that the proposed model was adequate and robust with good precision.
Conclusions: The final population PK model for cefdinir adequately described the observed plasma concentration of cefdinir in healthy adults. This model is expected to promote the understanding of cefdinir PK characteristics. Furthermore, the present model-fitted parameter estimates may be applied to determine the optimal dosage regimen of cefdinir in patients.

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Keywords: Cefdinir, population pharmacokinetics, PK modeling

Student number: 2015-23256
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Cefdinir is a broad-spectrum oral cephalosporin antimicrobial agent that targets numerous gram-positive and -negative bacteria. (1) Cefdinir, a β-lactam agent, binds to penicillin-binding proteins (PBPs), and then causes cell wall damage and lysis at the site of septum formation, finally inducing subsequent death of susceptible bacteria. (2) In this process, cefdinir acts as a mimic for the D-Ala-D-Ala substrate site for inhibiting PBPs by crosslinking for the peptidoglycan irreversibly. (3) This antimicrobial agent is widely used to treat rhinosinusitis, acute chronic bronchitis, and rhinosinusitis. (4) The molecular weight of cefdinir is 395.42 and its chemical structure (Figure 1) provides bactericidal activity against β-lactamase-producing strains such as *Staphylococcus aureus* and *Streptococcus pyogenes*. (5)

![Figure 1. Chemical structure of cefdinir](image-url)
It was discovered by Fujisawa Pharmaceutical Co., Ltd. (now Astellas Pharma Inc.), named as Cefzon in the U.S., and approved by the FDA (Food and Drug Administration, U.S.) under the brand name Omnicef® (Abbott Laboratories, North Chicago, U.S.)

Previous studies in healthy subjects have shown that cefdinir is absorbed with a time-to-peak plasma concentration ($T_{\text{max}}$) of approximately three hours. Furthermore, cefdinir does not undergo a high degree of metabolism, and is eliminated primarily by the kidney as an unchanged form with a half-life of approximately 1.5 hours. (6, 7) A previous study in healthy subjects demonstrated that the oral bioavailability of cefdinir is only 21-25%, which may be attributed to its low aqueous solubility. (4, 8) Despite the popularity of cefdinir as an antibiotic, limited data are available regarding its pharmacokinetics (PKs). In particular, to our knowledge, no studies of cefdinir PKs in the Korean population have been reported to date. (6)

Pharmacodynamics (PD) determinant of β-lactam efficacy, in terms of the bactericidal effect, is best assessed by determining the $T >$ minimum inhibitory concentration (MIC). Organism eradication is time-dependent; therefore, the therapeutic target is to optimize the duration of exposure. This may be achieved by maximizing the duration for which the plasma concentrations of these drugs remain above the MIC. (9) Therefore, the optimization of drug concentrations above pathogen MIC is crucial for the treatment of infection.

The elucidation of the PK characteristics of cefdinir in the Korean population and identification of representative parameters that account for
differences between individuals, via population pharmacokinetics analysis, may enable appropriate dosing regimens to be designed for patients. Accordingly, although the necessity of the population PK analysis approach for cefdinir is evident, this has not been reported in the Korean population to date. The present study is the first report, to our knowledge, of population PK analysis of cefdinir.

The aim of this study was to characterize the PK properties of cefdinir in healthy adults and develop a population model for the PK of cefdinir to inform optimal pharmacotherapy in the Korean population.
METHODS

1. Study design and subjects

A randomized, single-dose, two-treatment, two-period, two-sequence crossover study to evaluate the bioequivalence of a new generic formulation of cefdinir 100 mg was conducted in healthy subjects. All subjects received a single orally administered dose of Omnicef®, a 100-mg capsule of cefdinir provided by Jeil Pharm. Co., Ltd., South Korea (batch number OMHA04) as a reference drug or the new generic capsule, at the same dosage. Plasma samples were collected at pre-dosing and up to 12 h post-dosing. Blood samples were collected in heparin tubes, centrifuged immediately at 4°C for 10 minutes at 1,800 × g, and then stored at -70°C in a deep freezer until analysis.

The study was conducted at the Clinical Trials Center (CTC), Kyung Hee University Hospital (KHUH), Seoul, South Korea in compliance with the ethical principles of the Declaration of Helsinki, all International Conference on Harmonization Good Clinical Practice Guidelines, and local laws and regulations.(10) The protocol was approved by the Institutional Review Board (IRB) of KHUH. Written informed consent was obtained from all subjects after a detailed explanation of the study was provided, and before the screening test for eligibility was performed.
2. Plasma concentration analysis

Plasma concentrations of cefdinir were analyzed using high-performance liquid chromatography (HPLC, Agilent 1200 series, Agilent Technologies, CA, USA) coupled with tandem mass spectrometry (LC-MS/MS, Agilent 6410 Triple Quad, Agilent Technologies, CA, USA). The sample preparation for plasma involved a simple protein precipitation with methanol. Ramipril was used as an internal standard (IS) for quantitation of cefdinir. The plasma samples were separated under gradient conditions using a mobile phase that consisted of 0.2% formic acid and 100% acetonitrile (20:80, v/v), and the samples were run at a flow rate of 0.3 mL/min. Cefdinir and IS were separated on an XTerra MS C18 column (2.1 x 100 mm, 5 µm; Waters, USA) and detected in positive electrospray ionization mode with multiple reaction monitoring. The MRM was based on the transition of m/z 396.1 > 226.7 for cefdinir and 417.3 > 234.2 for ramipril (IS).

The lower limit of quantification (LLOQ) was 20 ng/mL, and the calibration curve was linear over a concentration range of 20.00–1,500 ng/mL following administration of cefdinir five times daily for 5 days. The coefficient of variance (% CV) for the intra-day and inter-day precision for cefdinir was 2.61–15.63% and 3.52–6.94%, respectively, whereas the intra-day and inter-day accuracies (%) were 93.04–101.30% and 97.69–111.48%, respectively. These data indicate that the analytical method used was accurate and precise.
3. Non-compartmental pharmacokinetic analysis

The PK parameters following a single oral administration of Omnicef® in healthy males in the bioequivalence study were calculated and estimated using a non-compartmental analysis program (Phoenix® WinNonlin®, version 7.0, Pharsight, Mountain View, CA, USA).

The $C_{\text{max}}$ and the time taken to achieve $C_{\text{max}}$ ($T_{\text{max}}$) were derived from the drug plasma concentration-time data.(4) The half-life ($t_{1/2}$) was calculated by dividing $\ln 2$ by $\lambda z$, where $\lambda z$ represents the elimination rate constant determined by regression analysis of the log-linear part of the time-concentration curves.(4) The area under the plasma concentration-time curve, from time zero to the last observed time point (AUC$_{\text{last}}$), was calculated according to the non-compartmental method using the linear trapezoidal, linear interpolation rule. The AUC from time zero to infinity (AUC$_{\text{inf}}$) was determined as the sum of the AUC$_{\text{last}}$ and the extrapolated area beyond the final plasma concentration. The apparent volume of distribution during the terminal phase (Vz/F) was estimated as CL/$\lambda z$, and the total apparent clearance (CL/F) was calculated using the following formula: CL/F = dose/AUC$_{\text{inf}}$.

4. Basic population PK model development

Time-concentration data were obtained following oral administration of Omnicef® in healthy subjects, and 333 blood samples were pooled for this population PK analysis. A population PK model was developed using the nonlinear mixed-effects method in NONMEM (version 7.3; Icon
Development Solutions, Ellicott City, MD, USA). The basic PK model was implemented in the PREDPP library subroutine ADVAN6 in NONMEM, and the First-Order Conditional Estimation (FOCE) method with the interaction estimation method was used. For graphical visualization, R (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) was used.

The inter-individual variability of the PK parameters was applied exponentially, as follows:

\[ P_{ij} = TVP_j \exp(\eta_{ij}) \]

where \( P_{ij} \) is the value of the \( j \)th parameter for the \( i \)th subject, \( TVP_j \) represents the population typical value of \( j \)th parameter value, and \( \eta_{ij} \) is a random variable for the \( j \)th parameter for the \( i \)th subject following a normal distribution with a mean of 0 and variance of \( \omega^2 \). For intra-individual variability (residual error), the combination of proportional error and additional error form was used, as follows (11, 12):

\[ C_{ij} = C_{\text{ipred},ij} \cdot (1 + \varepsilon_{\text{prop},ij}) + \varepsilon_{\text{add},ij} \]

where \( C_{ij} \) is the \( j \)th observed concentration of cefdinir for the \( i \)th subject, \( C_{\text{ipred},ij} \) is the \( j \)th predicted value for the \( i \)th subject, and \( \varepsilon_{\text{prop},ij} \) and \( \varepsilon_{\text{add},ij} \) represent intra-individual variability with a mean of 0 and variance of \( \sigma_{\text{prop}}^2 \) and \( \sigma_{\text{add}}^2 \), respectively. When the correlation in the random variables was significant, the relationship was reflected using the OMEGA BLOCK option in the model.(11, 12)

A single-compartmental model was used to describe cefdinir distribution, and first-order kinetics were assumed for all PK processes except
absorption. Various absorption models were estimated to identify the one that best described the absorption of cefdinir. (Figure 2) The structural model development strategies included first-order absorption followed by zero-order absorption, zero-order absorption followed by first-order absorption, and a combined transit compartment model, and enterohepatic recycling models were considered and explored for the PK model. (11) Absorption was assumed to follow a first-order absorption process, and inclusion of transit compartment absorption was also tested. (12)

(A) 1001: One-compartment model with first-order absorption

(B) 2001: One-compartment model followed by first-order absorption with lag time

Notes: ka, first-order absorption rate constant; CL, clearance
(C) 3001: One-compartment model with zero-order absorption

![Diagram for 3001](image)

Notes: CL, clearance

(D) 3002: One-compartment model followed by zero-order absorption with lag time

![Diagram for 3002](image)

Notes: CL, clearance; T_{lag}, lag time

(E) 4001: One-compartment model with zero-order and first-order absorption

\[
F_z \cdot F \cdot Dose \\
(1 - F_z) \cdot F \cdot Dose
\]

Notes: F, the total fraction of the administered dose; F_z, the fraction of the dose absorbed by the first-order rate; 1-F_z, the fraction of the dose absorbed by the zero-order rate; k_a, first-order absorption rate constant; CL, clearance
(F) 4002: One-compartment model with zero-order absorption followed by first-order absorption with lag time

Notes: $k_a$, first-order absorption rate constant; $T_{lag}$, lag time for $k_a$; $CL$, clearance

(G) 4003: One-compartment model with zero-order absorption lag time followed by first-order absorption with lag time

$F_Z \cdot F \cdot Dose : k_a$

$(1 - F_Z) \cdot F \cdot Dose : zero$-order

Notes: $F$, the total fraction of the administered dose; $F_Z$, the fraction of the dose absorbed by the first-order rate; $1 - F_Z$, the fraction of the dose absorbed by the zero-order rate; $k_a$, first-order absorption rate constant; $T_{lag,1}$, lag time for $k_a$; $T_{lag,2}$, lag time for zero-order; $CL$, clearance
(H) 5001: One-compartment model with combined transit compartment absorption

Notes: \( k_a \), first-order absorption rate constant; \( k_{tr} \), identical transfer rate constant of the transit compartment model; \( n \), number of transit compartments placed before the central compartment; \( a_n \), the drug amount in the \( n \)th compartment; CL, clearance

(I) 6001: One-compartment model with combined transit compartment absorption and first-order absorption (Figure 4)
(J) 6002: One-compartment model with combined transit compartment absorption followed first-order absorption with lag time

![Diagram](image1.png)

Notes: $k_{a1}$, absorption rate constant from the depot; $k_{a2}$, absorption rate constant from the final transit compartment to the central compartment; $k_{tr}$, identical transfer rate constant of the transit compartment model; $T_{lag}$, lag time for $k_a$; $f$, fraction of the dose absorbed through the absorption compartment; $n$, number of transit compartments placed before the central compartment; $a_n$, the drug amount in the $n^{th}$ compartment; CL, clearance.

(K) 7001: One-compartment model with first-order absorption and enterohepatic recirculation

![Diagram](image2.png)

Notes: $k_a$, first-order absorption rate constant; $k_{23}$, absorption rate constant from the central compartment to the bile compartment; $T_{lag}$, lag time for $k_a$; $T_{32}$, times for release from bile compartment; CL, clearance
Figure 2. Structure of population pharmacokinetic models in development process

(A) 1001: One-compartment model with first-order absorption. (B) 2001: One-compartment model followed by first-order absorption with lag time. (C) 3001: One-compartment model with zero-order absorption. (D) 3002: One-compartment model followed by zero-order absorption with lag time. (E) 4001: One-compartment model with zero-order and first-order absorption. (F) 4002: One-compartment model with zero-order absorption followed by first-order absorption with lag time. (G) 4003: One-compartment model with zero-order absorption lag time followed by first-order absorption with lag time. (H) 5001: One-compartment model with combined transit compartment absorption. (I) 6001: One-compartment model with combined transit compartment absorption and first-order absorption. (J) 6002: One-compartment model with combined transit compartment absorption followed first-order absorption with lag time. (K) 7001: One-compartment model with first-order absorption and enterohepatic
The combined transit compartment and first-order absorption model included $k_{tr}$, which is the identical transfer rate constant from the $n^{th} - 1$ compartment to the $n^{th}$ compartment, and $n$ is the number of transit compartments placed before the central compartment. $k_{tr}$ was calculated using mean transit time ($MTT$) and the number of transit compartments ($n + 1$) as follows (11, 12):

$$k_{tr} = \frac{n + 1}{MTT}$$

The fraction of the dose absorbed through the transit compartment ($f$) could only assume values between 0 and 1, such that $f$ was applied to logit transformation using the bioavailability fraction as the source (BIOFs), described as (13):

$$f = \frac{\exp(\text{BIOFs})}{1 + \exp(\text{BIOFs})}$$

The various models were diagnosed based on visual criteria, including goodness-of-fit plots, individual plots, and precision of numerical estimates within NONMEM.(11) To evaluate model improvement, statistical significance was assessed based on the decrease in objective function value (OFV) in the two nested models using 3.84 units. ($P < 0.05$, $df = 1$).(12) Therefore, when the difference in the OFV was < 3.84, it was assumed that there was no significant difference between the two models.
5. Covariate selection

After development of the basic structural model, potential covariates were screened using both visual and numerical methods. (11) The potential covariates for PK parameters were age, height, body weight, blood creatinine level, estimated creatinine clearance (CLcr), and estimated glomerular filtration rate (eGFR). CLcr and eGFR were calculated using the Cockcroft-Gault equation and Modification of Diet in Renal Disease (MDRD) Study equation. For visual screening, individual PK parameter versus variable scatterplots were used. For numerical screening, a generalized additive model (GAM) implemented by Xpose (version 4.5.3) was used. Once significant covariates were selected using GAM, a stepwise forward and backward approach was applied such that each covariate was added (p < 0.05) or deleted (p < 0.01) one at a time in the model. (11)

6. Population PK model evaluation

Goodness of fit was assessed by plotting observed concentration data versus individually predicted data and population predicted concentration data and population predicted concentration data and time after dose versus conditionally weighted residuals using the program Xpose4 (version 4.5.3). (12) For the final model, verification was performed using bootstrapping and visual predictive checking (VPC). A bootstrap was performed using 1,000 re-sampled datasets from the original dataset for the final model to obtain standard errors for parameter estimates and the non-
parametric confidence interval, and repeatedly run using each of the resampled datasets. (14) Using VPC, the observed data points were overlaid with the median and 90% confidence intervals (CIs, 5\textsuperscript{th}, and 95\textsuperscript{th} percentiles) of 1,000 simulated datasets from the final model.
RESULTS

1. Demographic characteristics

In total, 30 healthy Korean male subjects were enrolled in this study; four dropped out due to personal reasons leading to non-compliance. Twenty-six healthy males (aged 19-28 years, height 166.0-188.5 cm, and body weight 54.0-103.0 kg) completed the study and they were included in the population PK analysis. The demographic characteristics of these subjects are summarized in Table 1.

Table 1. Demographic characteristics of subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Median (min - max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)$^a$</td>
<td>26/0</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>24.5 ± 2.4</td>
<td>24.5 (19 – 28)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175.6 ± 5.1</td>
<td>174.6 (166.0 – 188.5)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.0 ± 11.3</td>
<td>71.5 (54.0 – 103.0)</td>
</tr>
</tbody>
</table>

$^a$ number of subjects
SD, standard deviation
2. **Pharmacokinetic analysis**

The individual time-concentration data displayed absorption and distribution profiles with double peaks, or flat profiles. These profiles showed high variability between subjects (Figure 3, Appendix 1).

![Figure 3. Individual plasma concentration versus time plots for cefdinir.](image)

The bold red line represents the median value.
Calculation of the PK parameters of cefdinir in healthy male subjects by non-compartmental analysis following a single orally administered dose, indicated that approximately 4 hours was required to reach $C_{\text{max}}$, and cefdinir was eliminated with a mean half-life of 1.7 hours. The mean ± standard deviation (SD) for $C_{\text{max}}$ (range) and $\text{AUC}_{\text{last}}$ (range) was $651.5 \pm 238.3 \ \mu\text{g}\,/\text{L}$ ($354.9 \ - \ 1258.7 \ \mu\text{g}\,/\text{L}$) and $3087.6 \pm 1171.1 \ \text{h} \cdot \mu\text{g}\,/\text{L}$ ($1189.4 \ - \ 5662.8 \ \text{h} \cdot \mu\text{g}\,/\text{L}$), respectively. In addition, the mean ± SD for $V_d/F$ (range) and $\text{CL/F}$ (range) was $86.9 \pm 38.2 \ \text{L}$ ($40.0 \ - \ 222.4 \ \text{L}$) and $36.2 \pm 14.5 \ \text{L}/\text{h}$ ($17.4 \ - \ 79.6 \ \text{L}/\text{h}$), respectively (Table 2).

Table 2. Pharmacokinetic parameters following a single oral dose of 100 mg of cefdinir in healthy Korean volunteers ($n = 26$), estimated by non-compartmental analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Range (min – max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (μg/L)</td>
<td>$651.5 \pm 238.3$</td>
<td>$354.9 \ - \ 1258.7$</td>
</tr>
<tr>
<td>$T_{\text{max}}$ a (h)</td>
<td>4.0</td>
<td>$2.5 \ - \ 5.0$</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{last}}$ (h·μg/L)</td>
<td>$3087.6 \pm 1171.1$</td>
<td>$1189.4 \ - \ 5662.8$</td>
</tr>
<tr>
<td>$\text{AUC}_{\text{inf}}$ (h·μg/L)</td>
<td>$3173.8 \pm 1183.6$</td>
<td>$1255.5 \ - \ 5753.6$</td>
</tr>
<tr>
<td>$V_d/F$ (L)</td>
<td>$86.9 \pm 38.2$</td>
<td>$40.0 \ - \ 222.4$</td>
</tr>
<tr>
<td>$\text{CL/F}$ (L/h)</td>
<td>$36.2 \pm 14.5$</td>
<td>$17.4 \ - \ 79.6$</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>$1.7 \pm 0.2$</td>
<td>$1.3 \ - \ 2.3$</td>
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Abbreviations: $\text{AUC}_{\text{last}}$, area under the serum concentration-time curve to the last observation; $\text{AUC}_{\text{inf}}$, area under the serum concentration from 0 to infinity; $C_{\text{max}}$, maximum serum concentration; $T_{\text{max}}$, time to reach $C_{\text{max}}$; $\text{CL/F}$, apparent clearance; $V_d$, apparent volume of distribution; $t_{1/2}$, terminal half-life; CI, confidence interval; SD, standard deviation

a Median value
3. Population pharmacokinetic analysis

In total, 333 plasma concentration-time data for cefdinir in 26 subjects were obtained; these were pooled and used to develop a population PK model using the nonlinear mixed-effects method in NONMEM (ver. 7.3). The most adequate PK model capable of explaining the observed time-concentration profiles of cefdinir was a one-compartment model with a combined transit compartment and first-order absorption (Figure 4).
Figure 4. Structural representation of the final model describing cefdinir population pharmacokinetics in healthy male Korean subjects

$k_{a1}$, absorption rate constant from the depot; $k_{a2}$, absorption rate constant from the final transit compartment to the central compartment; $k_{tr}$, identical transfer rate constant of the transit compartment model; $f$, fraction of the dose absorbed through the absorption compartment; $n$, number of transit compartments placed before the central compartment; $a_n$, drug amount in the $n^{th}$ compartment; $CL$, clearance
Various models were evaluated to identify the one that best described the cefdinir absorption profile (Table 3, Figure 2). These structural models included one- and two-compartment models with first-order elimination, and various absorption approaches were tested. The estimation of the two-compartment model with first-order elimination was minimization-terminated due to rounding errors; (error=134) therefore, the two-compartment model was excluded and a single-compartmental model was used to describe cefdinir distribution in this study. First-order absorption (1001), zero-order absorption (3001), and lag time were joined to 1001 and 3001 (2001 and 3002), combined zero-order and first-order absorption (4001), and model 4001, followed by first-order absorption with lag time (4002), both zero- and first-order absorption with lag time (4003), combined transit compartment absorption (5001), model 5001 with first-order absorption (6001), model 6001 with lag time (6002), and model 1001 with enterohepatic recirculation (7001).

A summary of typical values for population PK parameter estimates of cefdinir is shown in Table 4. The population mean estimates for apparent clearance (CL/F) and the apparent central volume of distribution (V/F) of the final model were 35.4 L/h and 41.6 L, respectively, with moderate inter-individual variability (IIV) corresponding to the CV (33.9% and 38.3%, respectively), where F is the bioavailability. The residual variability of the proportional error was 0.238 (13.0% for relative standard error). In addition, the other population mean estimates for the PK parameters of the final model were as follows: the absorption rate constant from the depot (k_{a1}) was 0.364 /h,
the absorption rate constant from the final transit compartment to the central compartment \( (k_{a2}) \) was 0.488 /h, the mean transit time (MTT) was 2.10 h, the number of transit compartments \( (n) \) was 3.82, and the fraction of the dose absorbed by the transit compartment model \( (f) \) was 0.874, which under transformation according to the equation using bioavailability fraction as the source (BIOFs) became 1.94.
Table 3. Pharmacokinetic model development process

<table>
<thead>
<tr>
<th>Model</th>
<th>Model tested</th>
<th>Objective function value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1001</td>
<td>One-compartment model with first-order absorption</td>
<td>3655.656</td>
</tr>
<tr>
<td>2001</td>
<td>One-compartment model followed by first-order absorption with lag time</td>
<td>3428.889</td>
</tr>
<tr>
<td>3001</td>
<td>One-compartment model with zero-order absorption</td>
<td>3351.251</td>
</tr>
<tr>
<td>3002</td>
<td>One-compartment model followed by zero-order absorption with lag time</td>
<td>3272.646</td>
</tr>
<tr>
<td>4001</td>
<td>One-compartment model with zero-order and first-order absorption</td>
<td>3622.981</td>
</tr>
<tr>
<td>4002</td>
<td>One-compartment model with zero-order absorption followed by first-order absorption with lag time</td>
<td>3314.004</td>
</tr>
<tr>
<td>4003</td>
<td>One-compartment model with zero-order absorption lag time followed by first-order absorption with lag time</td>
<td>3278.419</td>
</tr>
<tr>
<td>5001</td>
<td>One-compartment model with combined transit compartment absorption</td>
<td>3238.657</td>
</tr>
<tr>
<td>6001</td>
<td>One-compartment model with combined transit compartment absorption and first-order absorption</td>
<td>3214.143</td>
</tr>
<tr>
<td>6002</td>
<td>One-compartment model with combined transit compartment absorption followed first-order absorption with lag time</td>
<td>3247.709</td>
</tr>
<tr>
<td>7001</td>
<td>One-compartment model with first-order absorption and enterohepatic recirculation</td>
<td>3655.681</td>
</tr>
</tbody>
</table>
Table 4. Parameter estimates and variability for the population pharmacokinetic model of cefdinir

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Definition</th>
<th>Estimates (% RSE)</th>
<th>Bootstrap median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structural model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>Apparent oral clearance</td>
<td>35.4 (7.0)</td>
<td>35.0 (30.6 – 40.3)</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>Apparent volume of distribution</td>
<td>41.6 (54.3)</td>
<td>31.9 (13.6 – 65.7)</td>
</tr>
<tr>
<td>$k_a$ (h$^{-1}$)</td>
<td>Absorption rate constant of first-order absorption</td>
<td>0.364 (28.8)</td>
<td>0.32 (0.21 – 0.52)</td>
</tr>
<tr>
<td>$k_{a2}$ (h$^{-1}$)</td>
<td>Absorption rate constant from the final transit compartment to the central compartment</td>
<td>0.488 (17.5)</td>
<td>0.48 (0.44 – 1.00)</td>
</tr>
<tr>
<td>MTT (h)</td>
<td>Mean transit time</td>
<td>2.1 (15.7)</td>
<td>2.33 (1.91 – 2.68)</td>
</tr>
<tr>
<td>n</td>
<td>Number of transit compartments</td>
<td>3.82 (31.7)</td>
<td>3.53 (2.71 – 5.31)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td>Mean (RSE)</td>
<td>Lower Limit (RSE)</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>------------</td>
<td>------------------</td>
</tr>
<tr>
<td>BIOFs</td>
<td>Bioavailability fraction as the source</td>
<td>1.94 (29.8)</td>
<td>1.92 (0.94 – 3.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIV for CL/F</td>
<td>Inter-individual variability (IIV)</td>
<td>0.115 (21.4)</td>
<td>0.112 (0.065 – 0.164)</td>
</tr>
<tr>
<td>IIV for V/F</td>
<td></td>
<td>0.147 (76.2)</td>
<td>0.224 (0.057 – 0.934)</td>
</tr>
<tr>
<td>IIV for MTT</td>
<td></td>
<td>0.0357 (88.5)</td>
<td>0.023 (0.001 – 0.068)</td>
</tr>
<tr>
<td>IIV for n</td>
<td></td>
<td>0.0002 (115.1)</td>
<td>0.0002 (0 – 0.513)</td>
</tr>
<tr>
<td>IIV for BIOFs</td>
<td></td>
<td>0.344 (51.5)</td>
<td>0.325 (0.126 – 1.018)</td>
</tr>
<tr>
<td>Correlation between IIV on CL/F and V/F</td>
<td></td>
<td>0.125 (49.3)</td>
<td>0.147 (0.065 – 0.288)</td>
</tr>
<tr>
<td>Residual error</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive error</td>
<td></td>
<td>0.0001 fix</td>
<td>NA</td>
</tr>
<tr>
<td>Proportional error</td>
<td></td>
<td>0.238 (13.0)</td>
<td>0.230 (0.164 – 0.290)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not applicable; RSE, relative standard error
4. Covariate selection

In total, six covariates were explored to determine subject-specific characteristics that could best describe the model and explain variability. The effects of demographic factors and laboratory indicators, including age, height, body weight, creatinine, estimated CLcr, and eGFR, on PK parameters were tested. Visual exploration using parameter versus variable scatter plots was performed for screening of the effects of covariates on the PK parameters; then, GAM was evaluated. Results did not indicate a significant interaction between each covariate and PK parameters (Appendix 2).

5. Model evaluation

The basic goodness-of-fit plots for the final model were generated (Figure 5). Bootstrap and VPCs were performed to assess the predictive performance of the base population PK model; the results suggested that the proposed model was adequate and robust with good precision (Figure 6). The VPCs showed that the observed plasma concentration data fit well within the 5th – 95th percentiles of the simulated 1,000-replicate population data. In addition, the individual plots predicted using the final PK model were in good agreement with the observed data (Figure 7).
Figure 5. Basic goodness-of-fit diagnostics of the final pharmacokinetic model

(A) Observed concentrations (DV) vs. individual predictions (IPRED). (B) DV vs. population predictions (PRED). (C) Conditional weighted residuals (CWRES) vs. PRED and (D) CWRES vs. time (TIME); open circles indicate observations; solid black lines are lines of identity. Red lines are LOESS (locally weighted regression)-smoothed lines.
Figure 6. Visual predictive check plot of the final model 0 and 12 h after administration of a single oral dose of 100 mg of cefdinir.

In total, 1,000 datasets were simulated using the final PK parameter estimates. Circles represent the observed cefdinir plasma concentrations. Blue and red areas indicate the 90% confidence interval of the simulated concentrations, and the solid lines represent the 5th (blue line), median (red line), and 95th percentiles (blue line) of the observed concentration.
Figure 7. Individual fitting plot for the final pharmacokinetic model

Open circles are observations (DV). Red lines are individual predictions (IPRED).

Black dotted lines are population predictions (PRED).
All PK parameter estimates obtained from the final model using original datasets were consistent with the median values obtained after 1,000 bootstrap runs and within the 95% bootstrap CIs of the corresponding parameters. The final model adequately represented the data (see Table 4). The predicted time-concentration profile was highly correlated with the raw data.
DISCUSSION

In this study, a nonlinear mixed-effects model was used to estimate population PK parameters via comparison of various absorption models. Although cefdinir is widely used in the form of the antibiotic Omnicef®, cefdinir PK studies have not been performed in the Korean population to date. Here, we elucidated the PK characteristics of cefdinir in healthy Korean adults; the present model best described the PK profiles and successfully fit flat absorption profiles of cefdinir by a one-compartment with combined transit compartment model and first-order absorption.

After oral administration, there exists a time period for the drug to reach systemic circulation; it reflects the time required for various mechanisms related to absorption to occur, including transit to absorption site(s), transfer of drug through the absorbing site tissue, disintegration of the delivery system, and/or modified drug dissolution and/or release formulation.(12) Thus, we developed a model by using a transit compartment model to describe the flat or double peak absorption profile to pursue mechanistic PK modeling approaches.(11)

In a previous study, oral cefdinir was found to show bactericidal activity and clinical efficacy. Accordingly, the clinical use of this drug for treatment of patients with infections, such as pneumonia and rhinosinusitis, was approved; the US approved dosage regimen involved once-daily dosing of cefdinir 600 mg or twice-daily dosing of cefdinir 300 mg for 5-10 days.(5,
8) The PD parameters and clinical efficacy of cefdinir, which is a β-lactam agent, are best assessed by measurement of T > MIC, which is a determinant of in vivo potency; these characteristics may be improved by maximizing the duration for which the plasma concentrations of the drug remains above the MIC for the pathogen. (9) The present approach provides representative values of population PK parameters for cefdinir in Korean subjects. Therefore, we additionally performed visual exploration to identify consistency of T > MIC at various dosages using time versus predicted concentration dataset from final PK model and MIC for *Haemophilus influenzae* and *Streptococcus pneumoniae*, which causes pneumonia or rhinosinusitis. These datasets comprised 100 subjects who were administered cefdinir once at various dosages approved for daily dose. (i.e., 100 mg, 300 mg, and 600 mg) (Figure 8) The MIC at which 90% of the isolates were inhibited in standardized susceptibility tests for *H. influenzae* and *S. pneumoniae* was 120-500 μg/L. (5,7) The time above the minimum MIC$_{90}$ of *H. influenzae* and *S. pneumoniae* was 7.5 h, 8.5 h, and 9.0 h at 100 mg, 300 mg, and 600 mg, respectively. (Figure 8)
In addition, through further investigation such as simulation studies for multiple administration of cefdinir based on our final model, $T > MIC$ can be predicted in the Korean population. According to the results of these further studies, the duration of effective treatment required to achieve maximum serum cefdinir concentrations ($C_{\text{max,ss}}$) over the MIC at steady state can be predicted. The results of such simulation studies are expected to indicate the minimum duration for treatment and establish the duration of treatment for optimal clinical efficacy in patients.

Figure 8. Simulated mean plasma concentration of cefdinir in subjects ($N=100$) following a single oral dose of 100 mg (○), 300 mg (▲), and 600 mg (□) using the final pharmacokinetic model. Max MIC, maximum MIC at which 90% of the isolates are inhibited. Min MIC, minimum MIC.
The individual time-concentration data indicated an absorption and distribution phase with flat or double peak profile in a number of subjects. The objective of developing the model with covariates was to clarify subject-specific characteristics and reduce variability in the model. Accordingly, we explored covariates after developing the structure model. Although the data used in this study were obtained from healthy male subjects aged between 19 and 45 years, and demographic variables were selected as potential covariates for any PK parameter, relatively high between-subject variability in cefdinir PK was observed. We additionally tested several laboratory variables such as the levels of creatinine, CLcr, and eGFR, which may affect cefdinir PK characteristics because cefdinir is eliminated mainly via renal excretion (5); however, these variables were not found to exert significant effects on the PK model. This may be attributed to the enrollment of healthy subjects and the strict inclusion and exclusion criteria applied in this study. However, as shown in previous studies,(8) the impact of these variables on the PKs of cefdinir in adults is presumed to have a smaller influence on the variability of cefdinir exposure, and is not clinically significant. Further studies using individual data with higher variability are required to explain the high variability in cefdinir exposure in the Korean population.

In this study, 26 healthy subjects were administered a single oral dose of 100 mg cefdinir in a capsule formulation. PK parameters were estimated using non-compartmental analysis to elucidate the PK characteristics and profiles of cefdinir. The PK parameters in the Korean population, which were similar to those reported for Chinese and Caucasian
populations in previous studies (4, 7), showed the presence of absorption and elimination, such that approximately 4 hours were required to reach $C_{\text{max}}$, with an average half-life of 1.7 hours. These were found to be consistent with the findings of previous studies (4, 5, 7) with regard to the PK parameters elucidated using non-compartmental analysis, including CL and half-life of cefdinir with respect to race. However, the recommended dosages of oral cefdinir for treatment of adult patients with bacterial infections differ between the US Food and Drug Administration and the Korea Ministry of Food and Drug Safety guidelines, i.e., 300 mg of cefdinir every 12 h (or 600 mg every 24 h) vs. 100 mg every 8 h, respectively (5, 15). Although the recommended dosage is different between the US and Korea, the maximum total daily dose for infections is identical in both countries: 600 mg. (5) Therefore, we expect that our study result can be applied regardless of race.

In a previous study of healthy adults, cefdinir was not found to accumulate in the plasma of individuals with normal renal function who received multiple doses of cefdinir once or twice daily; PK parameters were similar for multiple administration and single administration (13). Accordingly, we suggest that the final population PK model (6001 in Table 3), which used single-dose study data, should be useful for assessment of cefdinir exposure in patients receiving multiple doses of the drug.

To our knowledge, this study is the first to report cefdinir PK characteristics in the Korean population and a population PK model of cefdinir using a combined transit compartment model and first-order absorption using NONMEM. The final population PK model of cefdinir
adequately described the observed plasma concentration of cefdinir in healthy adults. Consequently, the present model may enable accurate estimation of cefdinir PK characteristics. Furthermore, our model-fitted parameter estimates may be utilized to determine optimal dosage regimens of cefdinir in patients.

DISCLOSURE

The present study was sponsored by a research grant from Aju Pharm. Co., Ltd., Seoul, Republic of Korea and Dongkwang Pharm. Co. Ltd., Seoul, Republic of Korea.
REFERENCES


8. Perry CM, Scott LJ. Cefdinir: a review of its use in the management


APPENDICES

1. Individual plots for plasma concentration versus time for cefdinir. (n=26)
Individual plots for plasma concentration versus time for cefdinir. (continued)
Individual plots for plasma concentration versus time for cefdinir. (continued)
Individual plots for plasma concentration versus time for cefdinir. (continued)
Individual plots for plasma concentration versus time for cefdinir. (continued)
2. Scatterplots for estimated parameter versus covariate

Scatterplot matrix of covariates
Scatterplots for estimated parameter versus covariate (continued)
Scatterplots for estimated parameter versus covariate

(continued)
Scatterplots for estimated parameter versus covariate

(continued)
Scatterplots for estimated parameter versus covariate
(continued)
Scatterplots for estimated parameter versus covariate

(continued)
Scatterplots for estimated parameter versus covariate

(continued)
Scatterplots for estimated parameter versus covariate

(continued)
Scatterplots for estimated parameter versus covariate

(continued)
3. NONMEM control code for the final pharmacokinetic model

S$PROB Cefdinir PopPK simple 1-compartment first + transit
SINPUT ID AMT TIME DV CMT EVID MDV
SDATA Cefdinir_PK_3.csv IGNORE=#
SSUBROUTINE ADVAN6 TOL=3

$MODEL
COMP = (DEPOT1)
COMP = (DEPOT2)
COMP = (CENTRAL)

$PK
CL = THETA(1)*EXP(ETA(1))
V = THETA(2)*EXP(ETA(2))
KA1 = THETA(3)*EXP(ETA(3))
KA2 = THETA(4)*EXP(ETA(4))
MTT = THETA(5)*EXP(ETA(5))
NN = THETA(6)*EXP(ETA(6))

BIOFs = THETA(7)*EXP(ETA(7))
FR = EXP(BIOFs)/(1+EXP(BIOFs)) ; fraction of the dose absorbed by the transit compartment model
\[ F_1 = 1 - FR \]
\[ F_2 = 0 \]

\[ KTR = \frac{NN+1}{MTT} \]

\[ \text{LNFAC} = \log(2.5066) + (NN+0.5) \log(NN) - NN \]

\[ S_3 = V \]
\[ K30 = \frac{CL}{V} \]

\[ \text{SDES} \]

\[ \text{DADT}(1) = -KA1 \cdot A(1) \]
\[ \text{DADT}(2) = \exp \left( \log(FR \cdot 100000 + 0.00001) + \log(KTR) + \right. \]
\[ \left. NN \log(KTR \cdot T + 0.00001) - KTR \cdot T - \text{LNFAC} \right) - KA2 \cdot A(2) \]
\[ \text{DADT}(3) = KA1 \cdot A(1) + KA2 \cdot A(2) - K30 \cdot A(3) \]

\[ \text{SERROR} \]

\[ \text{IPRED} = F \]
\[ \text{IRES} = DV - \text{IPRED} \]
\[ W = \sqrt{\text{THETA}(8)^2 + \text{THETA}(9)^2 \cdot \text{IPRED}^2} \]
\[ \text{IWRES} = \frac{\text{IRES}}{W} \]
\[ Y = F + W \cdot \text{EPS}(1) \]
\textbf{STHETA}

(0, 30) ; 1CL
(0, 70) ; 2V
(0, 0.7) ; 3KA1
(0, 0.7) ; 4KA2
(0, 1) ; 5MTT
(0, 3) ; 6NN
0.5 ; 7BIOFs
0.00001 FIX ; 8ADD
(0, 0.5) ; 9PRO

\textbf{SOMEga BLOCK(2)}

0.5
0.3 0.5

\textbf{SOMEga}

0 FIX ; 3KA1
0 FIX ; 4KA2
0.5 ; 5MTT
0.5 ; 6NN
0.5 ; 7BIOFs

\textbf{SSIGMA}
1 FIX

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INTER PRINT=5
$COV PRINT=E
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ONEHEADER NOPRINT FILE = sdtab6001
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ETA(3) ETA(4) ETA(5) ETA(6) ETA(7) ONEHEADER
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국문 초록

서론: Cefdinir 는 경구 cephalosporin 계 3 세대 항생제로 그람 양성균과 그람 음성균에 작용하며 넓은 범위에서 치료제로 이용된다. Cefdinir 는 넓은 범위의 각종 염증이나 세균성 질환에 작용하는 만큼 오랜 기간 동안 사용되어 왔지만 이용 기간에 비해 약동학에 대한 연구 결과는 많지 않다. 본 연구는 건강한 성인에서 cefdinir 의 집단 약동학 모델을 구축하고 이를 통해 적절한 약물 요법에 대한 부가적인 정보를 제공하기 위하여 수행되었다.

방법: 기존에 수행된 cefdinir 의 제네릭 의약품(또는 복제약)의 생물학적 동등성 연구에서 대조약(Omnicef®)의 결과 데이터만을 이용하여 집단 약동학 모델을 개발하였다. 26 명의 건강한 남성(나이:19 – 28 세, 체중:54.0 – 103.0 kg)에게 cefdinir 100 mg 을 단회 경구 투여한 후 12 시간까지 수집한 총 333 개의 시간에 따른 혈장 농도 데이터를 이용하였다. 이용된 cefdinir 의 혈장 농도는 HPLC/MS-MS 를 이용하여 분석하였으며, NONMEM (ver 7.3)의 비구획모형을 이용하여 집단 약동학 모델을 개발하였다. First-Order Conditional Estimation with Interaction 평가 방법을 이용하였으며, visual predictive checks (VPC)를 통해 모델의 적절성을 확인하였다. 아울러, 인구통계 자료와 임상 변수들을 약동학 parameter 의 잠재적인 공변량으로 평가하였다.
결과: Transit compartment 와 1 차 흡수 모델이 포함된 1 구획 모델이 cefdinir 의 흡수 단계에서의 변동성을 가장 잘 설명하였고, 본 연구에서는 이 모델이 가장 적합한 모델로 선택되었다. 최종 모델로부터 측정된 약동학 parameter 들의 집단 대표 평균 값은 다음과 같다: 겉보기 청소율(CL/F)은 35.4 L/h, 겉보기 용적(V/F)은 41.6 L, 투약 구획으로부터의 흡수 속도 상수(Ka1)는 0.364 /h, 최종 transit compartment 로부터 중심 구획으로의 흡수 속도 상수(Ka2)는 0.488 /h, 평균 통과 시간 (MTT)는 2.10 h, transit compartment 의 개수 (n)는 3.82, 그리고 transit compartment 모델에서의 투약 흡수 fraction (f)은 0.874 로 나타났다. Bootstrapping 과 VPC 를 통하여 제안된 최종 모델이 좋은 예측력 을 가지고, 데이터를 설명하기에 적절하다고 평가되었다.

결론: 본 연구에서 최종 선택된 transit compartment 와 1 차 흡수 모델이 포함된 1 구획 약동학 모델은 건강한 성인에서 관찰된 cefdinir 의 약동학을 적절하게 잘 설명하였다. 이 모델은 cefdinir 의 약동학 특성 이해를 증진시킬 수 있으며, 이 모델을 통해 예측된 parameter 들은 환자에서 적정 약물 요법을 결정하는데 응용될 수 있을 것이다.

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주요어: 세프디니르, 집단 약동학, 약동학 모델링
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