의학박사 학위논문

Population PK/PD model to evaluate the effect of uremia on the pharmacokinetics of evogliptin

약동학/약력학 모델을 이용한 요독증의 evogliptin 약동학에 대한 영향 평가

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의학과 협동과정 임상약리학전공

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Ph.D. Dissertation of Medical Science

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Population PK/PD model to evaluate the effect of uremia on the pharmacokinetics of evogliptin

by

Byungwook Kim

A thesis submitted to the Department of Clinical Pharmacology and Therapeutics in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medical Science at Seoul National University College of Medicine

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ABSTRACT

Population PK/PD model to evaluate the effect of uremia on the pharmacokinetics of evogliptin

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Interdisciplinary Program of Clinical Pharmacology Major

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Introduction: Uremia, also known as uremic syndrome, is a pathological condition characterized by the retention of waste products (uremic toxins) in the blood due to inadequate kidney function. Uremic toxins can accumulate in the body and affect various physiological processes, including drug metabolism and elimination mediated by cytochrome P450 enzymes such as CYP3A4. Evogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor used to treat type 2 diabetes and is primarily metabolized by the liver enzyme CYP3A4. Uremia may affect the function of CYP3A4, which may have significant implications for

the metabolism and elimination of evogliptin. By conducting population pharmacokinetics (PK) and pharmacodynamics (PD) modeling on evogliptin in patients with renal impairment, it is possible to predict the PK of drugs that are mainly metabolized by CYP3A4 in renal impairment conditions. This study aimed to construct a population PK and PD model of evogliptin in patients with varying degrees of kidney disease.

Methods: This study implemented data from two clinical studies of evogliptin: an open-label, parallel-group clinical study conducted in patients with varying degrees of renal impairment and normal renal function (NCT02214693) and a single-dose, open-label, parallel-group study conducted in patients with end-stage renal disease (ESRD) and normal renal function (NCT04195919). In both studies, subjects were administered 5 mg evogliptin in a fasting state. A total of 46 subjects with 688 evogliptin concentration measurements and 598 DPP-4 activity measurements were available for analysis. PK/PD data for evogliptin, as well as potential covariate information including hematology, blood chemistry, and demographic data, were used to construct a population PK/PD model. The model construction used nonlinear mixed-effects modeling software (NONMEM®

version 7.4) with first-order conditional estimation with interaction (FOCE-I). Each parameter was added to the structural model in a stepwise approach with forward and backward elimination, employing significance levels of 0.01 and 0.001, respectively. Nonparametric bootstrap resampling was used to evaluate model stability and to estimate confidence intervals (CIs) for the model parameters by repeatedly fitting the final model to bootstrap replicates (n = 1000) of the dataset. Prediction-corrected visual predictive checks (pcVPCs; 500 simulation replicates) were conducted to validate the final model. The final PK model was used to simulate concentration-time profiles, and the area under the concentration-time curve (AUC) from time zero to 120 h was derived, and the maximum plasma concentration (C_{max}) was calculated, assuming a single dose of 5 mg in various covariate conditions.

Results: A total of 46 participants with varying degrees of renal impairment and healthy subjects were enrolled. All subject groups had comparable demographic characteristics but different levels of renal impairment. A nonlinear mixed-effects model was developed to describe the population PK of evogliptin using 688 plasma PK samples. A two-compartment model with first-order absorption was selected as the base PK model on the basis of the

Akaike information criterion (AIC), diagnostic plots, and objective function values (OFVs). The base PK model demonstrated reliable parameter estimation and a strong agreement between observed and predicted data without systematic bias. The significant covariates retained in the final model included chloride and amylase on F_r (relative bioavailability), age on CL/F (apparent clearance) and body weight on V3/F (peripheral volume of distribution). Varying chloride and amylase levels contributed to increasing the bioavailability of evogliptin. Lower clearance was observed in older patients, and body weight correlated with increasing V3/F. The goodness-of-fit plots indicated an adequate model structure for predicting evogliptin concentrations. The pcVPC showed an overlap between simulated and observed evogliptin concentrations, and bootstrapping resulted in 93.1% successful replication among 1000 replicates. The potential effects of relevant covariates on CYP3A4-mediated evogliptin PK were evaluated using Monte Carlo simulation. The simulation findings, in conjunction with previously reported PK data of evogliptin, provided evidence of a significant inhibition of first-pass metabolism in severe renal impairment conditions. A direct-link sigmoidal E_{max} model was developed to describe the relationship

between plasma evogliptin concentration and DPP-4 inhibition. The final model robustly estimated PD parameters. The PK/PD model of evogliptin predicted near complete inhibition of DPP-4 at the maximum effect (E_{max}: 95.7%) and exhibited a low EC_{50} value (0.837 μg/L), suggesting the high potency and efficacy of evogliptin.

Conclusion: The developed PK/PD model of evogliptin accurately predicted absorption, systemic exposure, and elimination variability in individuals with renal impairment. This study indicates that renal impairment and the resulting biochemical changes may impact the relative bioavailability of CYP3A4-metabolized drugs. This model serves as a basis for future evaluations of uremia's effect on nonrenal drug clearance and aids in optimizing dosing regimens for patients with renal impairment.

* Part of this work has been published in Diabetes, Obesity and Metabolism (Byungwook Kim et al. 2023-02-28. doi: 10.1111/dom.15034)

Keywords: evogliptin, dipeptidyl peptidase-4 inhibitor, type 2 diabetes mellitus, pharmacokinetic pharmacodynamic modeling
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List of Abbreviations

%DR	Percentage hemodialysis recovery
AE	Adverse events
A_{elast}	Amount excreted in urine until the time of the last measurable concentration
AIC	Akaike information criterion
Amyl	Amylase
AST	Aspartate aminotransferase
AUC_{0-120}	AUC from 0 to 120 hours after administration
AUC_{inf}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to the last observation
$AUEC_{last}$	Area under the % inhibitory effect−time curve until the time of last measurable concentration
BMI	Body mass index
BMI	Body mass index
Chl	Blood chloride level
CI	Confidence interval
CKD	Chronic kidney disease
CL/F	Total apparent clearance
CL_{NR}	Non−renal clearance
CL_R	Renal clearance
CL/R	Renal clearance
C_{max}	Maximum plasma concentration
CPK	Creatine phosphokinase
C_{pred}	Predicted concentration
CWREs	Conditional weighted residuals
CYP	Cytochrome P450
DPP−4	Dipeptidyl peptidase−4
E_{max}	Maximum % inhibitory effect
ESRD	End−stage renal disease
ETA	Individual random effect
f_e	Fraction of dose excreted unaltered in urine
Fi80	Time duration of ≥ 80% DPP−4 inhibition

FOCE-I	First-order conditional estimation with interaction
Fr	Relative bioavailability
fu	Unbound fraction
GAM	Generalized additive model
GFR	Glomerular filtration rat
HD	Hemodialysis
IIV	Interindividual variability
IRB	Institutional Review Board
Ka	First order absorption rate constant
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDH	Lactate dehydrogenase
MDRD	Modification of Diet in Renal Disease
NCA	Non-compartmental analysis
OFV	Objective function
pcVPC	Prediction-corrected visual predictive checks
PD	Pharmacodynamic
PK	Pharmacokinetics
RSE	Relative standard error
SCM	Stepwise covariate model
TG	Triglyceride
T_{max}	Time to reach maximum plasma concentration
V2/F	Apparent volume of distribution of central compartment
V3/F	Apparent volume of distribution of peripheral compartment
Vz/F	Apparent volume of distribution
Wt	Weight
λ_z	Terminal elimination rate constant

Chapter 1. Introduction

1.1. Study Background

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are some of the most prevalent and debilitating conditions worldwide [1]. Patients with CKD are at increased risk of comorbidities, which often require pharmacotherapy for effective management [2, 3]. However, the pharmacokinetics (PK) of drugs in patients with CKD may be altered due to changes in drug metabolism, protein binding and renal clearance. Consequently, a comprehensive understanding of the alterations in drug PK in renal impairment patients is pivotal in the optimization of drug dosage regimens [4, 5].

It is well known that CKD can affect both the renal (CL_R) and nonrenal (CL_{NR}) clearance of drugs. Changes in CL_{NR} are thought to be mediated by uremia, a pathological condition characterized by the retention of uremic toxins in the blood due to inadequate kidney function. The inhibition of CL_{NR} by uremic toxins is still poorly understood, and proposed mechanisms include interference with enzyme transcriptional activation, downregulation of gene expression, and direct inhibition of the

activity of cytochrome P450s and drug transporters [6] (Figure 1).

Among the cytochrome P450 enzymes involved in drug metabolism, CYP3A4 is particularly important due to its broad substrate specificity and high expression in the liver and intestines [7]. Due to its widespread expression and high metabolic activity, CYP3A4 is involved in the metabolism of approximately 50% of all drugs on the market, making it one of the most important drug-metabolizing enzymes in the human body.

In patients with uremia, alterations in the expression and activity of CYP3A4 may significantly affect drug exposure and clinical response to pharmacotherapy. In most cases where CYP3A4-mediated drug metabolism is altered by CKD status, CL_{NR} is reduced and/or bioavailability is increased [6]. In ESRD patients who are undergoing hemodialysis (HD), previous studies have reported that the metabolic activity of CYP3A4 is improved, possibly through the removal of uremic toxins [8]. However, elucidating the effect of CKD on CYP3A4-mediated drug metabolism is challenging, particularly due to multiple clearance pathways and overlapping substrate specificity of

various CYP450 enzymes and drug transporters [9, 10].

Evogliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor used as an antidiabetic drug. Evogliptin exhibits linear PK, and the main route of elimination is CL_{NR}, predominantly through metabolism by CYP3A4 [11, 12]. The clinical pharmacology of evogliptin has been assessed in patients with various degrees of renal impairment and ESRD patients undergoing HD [13, 14]. The CL_{NR} of evogliptin was reduced and bioavailability was increased in CKD patients, correlating with the extent of renal impairment [13]. When the PK of evogliptin was assessed in ESRD patients, the CL_{NR} and bioavailability were comparable to those in mild to moderate renal impairment patients, indicating a lower inhibitory effect from uremia [14].

In evaluating the impact of CKD on CYP3A4-mediated drug metabolism, population pharmacokinetic/pharmacodynamic (PK/PD) modeling is a valuable tool. Population PK/PD modeling allows for the quantitative analysis of the relationships among drug exposure, drug response, and patient-specific factors. By conducting population PK and PD modeling on a drug that is predominantly metabolized by CYP3A4, such as evogliptin, in renal impairment patients, it is possible to predict the PK of other

drugs that are mainly metabolized by CYP3A4 in renal impairment conditions.

1.2. Purpose of Research

In this paper, I aimed to construct a population PK/PD model of evogliptin to evaluate the impact of uremia on the metabolism of evogliptin. A PK/PD model was developed using data from healthy individuals, patients with varying degrees of CKD and ESRD patients on HD. My model will provide a quantitative assessment of the changes in drug metabolism due to uremia and facilitate the optimization of drug dosing regimens for patients with renal impairment.

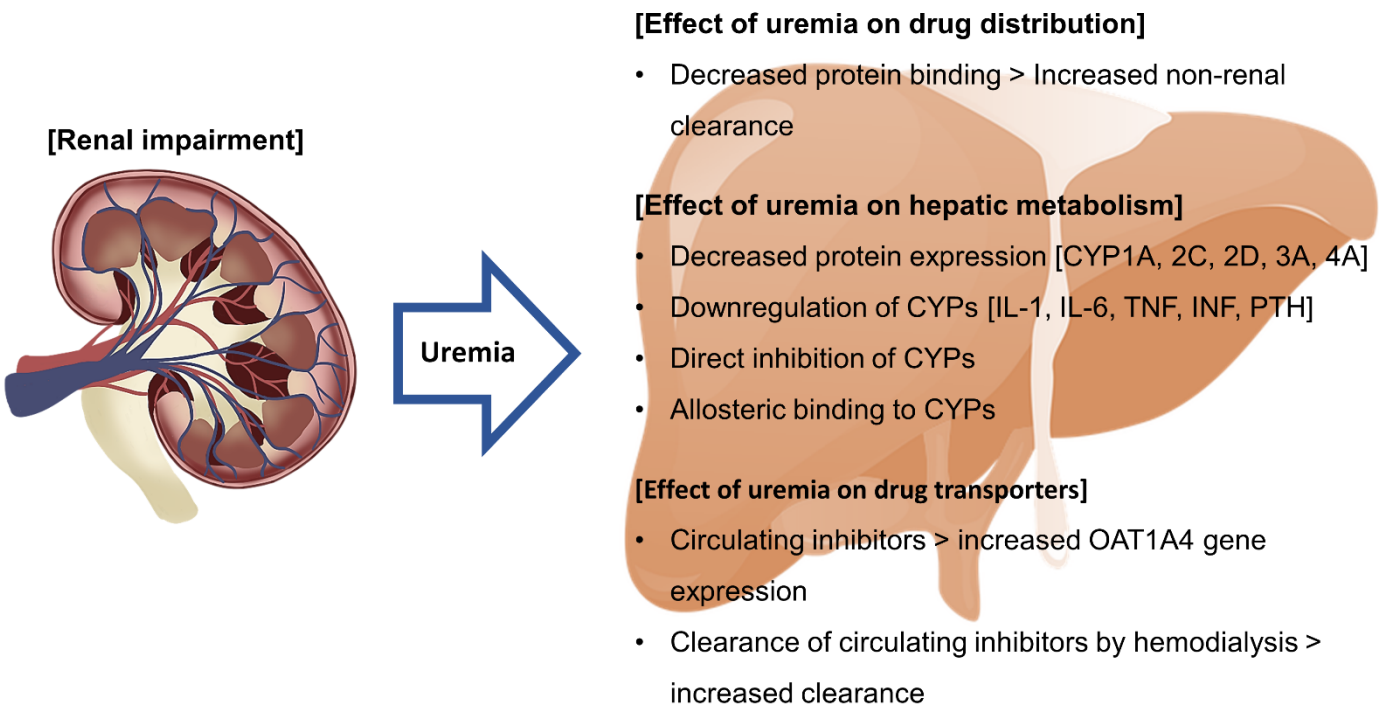


Figure 1. Proposed mechanisms for the effect of uremia on the non-renal clearance [6]

Chapter 2. Methods

2.1. Clinical Study and Data Collection

2.1.1. Study Design and Population

Evogliptin concentration and DPP-4 inhibition data were obtained from two phase I studies: DA1229_RI_I and DA1229_ESRD_I (Table 1).

PART I. A single-dose, open-label, parallel-group clinical trial was conducted in healthy subjects and patients with varying degrees of renal impairment. Study subjects were stratified according to glomerular filtration rate (GFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation. A total of 8 subjects each with healthy renal function (eGFR≥ 90 mL/min) and mild (60 mL/min ≤ eGFR < 90 mL/min), moderate (30 mL/min ≤ eGFR < 60 mL/min), and severe (15 mL/min ≤ eGFR < 30 mL/min) renal impairment were enrolled in the study. Patients with uncontrolled or unstable comorbidities, those taking any medication that could affect the PK and PD characteristics of evogliptin, and those requiring renal replacement therapy were not included in this study. The demographic characteristics of the participants with normal renal function (NRF) were matched with

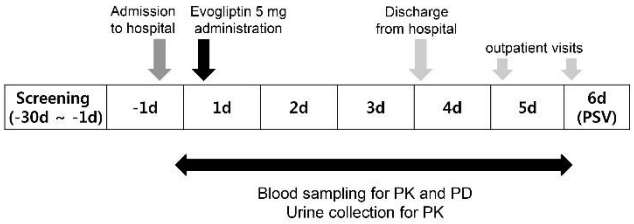
those of the participants with renal impairment with regard to age (±5 years), body mass index (BMI, ±10%) and sex. All subjects received a single treatment of 5 mg evogliptin (Dong-A ST Co. Ltd., Seoul, Korea) in the fasting state (Figure 2).

PART II. A single-dose, open-label, parallel-group study was conducted in healthy subjects and ESRD patients on HD. The study population was Korean patients with a confirmed diagnosis of ESRD aged 20 to 80 years and healthy subjects matched for patient age (±5 years), BMI (±20%) and sex. ESRD patients were eligible for the study if their MDRD-calculated eGFR rate was ≤ 15 mL/min and they were on HD on the day of screening. Subjects were excluded from the study if they had any medical history or condition that may have affected the PK and/or PD of the study drug, such as gastrointestinal disease or aspartate aminotransferase (AST) levels 1.5 times higher than the upper normal limit. ESRD patients were also screened for any concomitant medications that may interact with the study drug. ESRD patients received the treatment at two time points: 1 hour after (period 1) and 1 hour before (period 2) a 4-hour HD session. Healthy subjects (cohort 2) were administered the same treatment in a single period (Figure 2).

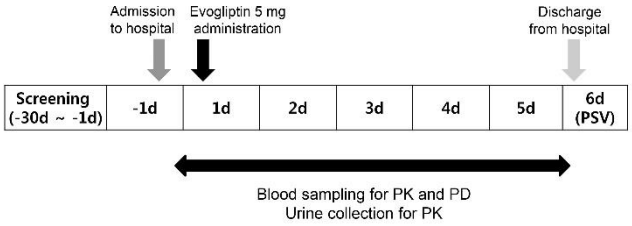
All clinical studies were reviewed and approved by the Institutional Review Board of Seoul National University Hospital, Republic of Korea. The clinical studies were registered at ClinicalTrials.gov (NCT02214693 and NCT04195919) and conducted in accordance with the Declaration of Helsinki and the Guidelines of Good Clinical Practice. Written informed consent was obtained from all subjects prior to participation in the study.

(A)

[Renal impairment patients]

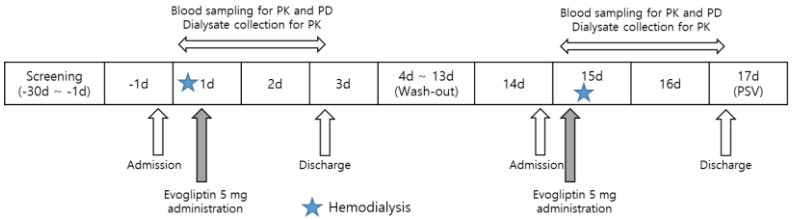


[Healthy subjects]



(B)

[ESRD patients]



[Healthy subjects]

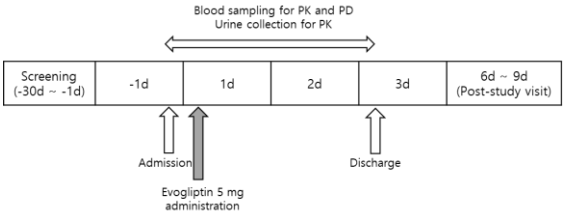


Figure 2. Clinical study design of (A) Part I, and (B) Part II

2.1.2. PK Sample Collection and Bioanalytical Assay

[PK sample collection]

PART I. Serial blood samples were collected to determine the evogliptin concentrations at the following time points: predose (0 h) and 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 96, and 120 h after 5 mg evogliptin oral administration. Urine samples were collected at 24 h intervals to determine the renal clearance of evogliptin as follows: predose (0 h), 0–24, 24–48, 48–72, 72–96, and 96–120 h after 5 mg evogliptin oral administration. In addition, samples for the detection of fraction unbound evogliptin (f_u) were collected at 1, 24 and 48 h post-dose.

PART II. Blood samples for plasma PK assessment were collected at the following time points: predose (0 h) and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, and 48 h after 5 mg evogliptin oral administration. Urine samples for PK analysis were collected at 24 h intervals to determine the renal clearance of evogliptin as follows: predose (0 h), 0–24, and 24–48 h after 5 mg evogliptin oral administration. Dialysate samples from ESRD patients were collected throughout the entire duration of the 4-h HD process. Blood samples for evogliptin f_u determination were collected at 1, 24, and 48 hours after evogliptin administration.

Safety and tolerability profiles were evaluated throughout the duration of both studies based on the occurrence of adverse events (AEs), the results of clinical laboratory tests, ECGs and physical examinations, and vital signs.

[PK bioanalytical methods]

Part I. The total and unbound evogliptin concentrations in plasma and the total evogliptin concentration in urine were determined by liquid chromatography–tandem mass spectrometry (Agilent 1260 HPLC system and Agilent 6490 Triple Quadrupole; Agilent Technologies, Santa Clara, California). Sitagliptin was used as an internal standard for quantifying evogliptin. The mobile phase consisted of 5 mM ammonium formate buffer and acetonitrile. Evogliptin and sitagliptin were separated on a Zorbax extend-C18 column (50×2.1 mm, 1.8 μm; Agilent Technologies, Santa Clara, CA, USA). The calibration curves were linear over the ranges of 0.5 to 50 μg/L for the plasma samples, 0.2 to 25 μg/L for the unbound plasma samples, and 50 to 5000 μg/L for the urine samples.

Part II. Validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) was used to determine the concentrations of evogliptin. LC was performed with a Shimadzu

UFLC system (Shimadzu, Japan), and MS/MS was performed with API 5000(2) (SCIEX, USA). DA-1229-d_9 tartrate was used as the internal standard for the quantification of evogliptin. Evogliptin was separated on an ACQUITY UPLC BEH C_{18} (2.1 mm, i.d. x 100 mm, ℓ; particle size, 1.7 μm) column. For plasma analysis, the calibrations were validated over the range of 0.1 to 60 ng/mL ($r^2 \geq 0.9950$); for urine analysis, the calibrations were validated over the range of 5~5000 ng/mL ($r^2 \geq 0.9950$); for unbound evogliptin analysis, the calibrations were validated over the range of 50~5000 pg/mL ($r^2 \geq 0.9950$); and for dialysate analysis, the calibrations were validated over the range of 50~5000 pg/mL ($r^2 \geq 0.9950$).

[Noncompartmental analysis]

PK parameters were calculated by a noncompartmental analysis (NCA) method using validated software (Phoenix WinNonlin®; Version 8.3; Certara, St Louis, MO, USA). For NCA, plasma PK samples up to 48 h post-administration were used for comparison between the two studies. Primary PK parameters included the area under the concentration-time curve from time 0 to the last point of measurement (AUC_{last}) and maximum concentration (C_{max}). Secondary PK parameters were the area

under the concentration-time curve from time 0 to infinity (extrapolated) (AUC_{inf}), time to C_{max} (T_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), apparent renal clearance (CL_R/F), apparent hemodialysis clearance (CL_{HD}/F), percentage hemodialysis recovery (%DR), unbound fraction (f_u), amount excreted in urine until the time of the last measurable concentration (A_{elast}), fraction of dose excreted unaltered in urine (f_e), and apparent volume of distribution (V_z/F).

CL/F, CL_R/F, CL_{HD}/F and Vz/F were calculated using the following equations:

$CL/F = dose/AUC_{inf}$; $CL_R/F = A_{elast}/AUC_{last}$; $CL_{HD}/F = (\%DR/100) \cdot Dose/AUC_{last}$; $V_z/F = (CL/F)/\lambda_z$

where λ_z is the terminal elimination rate constant and %DR is the percent recovered in hemodialysis.

2.1.3. PD Sample Collection and Bioanalytical Assay

[PD sample collection]

Part I: Blood samples for PD assessment were collected at the following time points: predose (baseline) and 1, 3, 5, 8, 12, 24, 36, 48, 60, 72, 96, and 120 h.

Part II: Blood samples for PD assessment were collected at the following time points in each period: predose (baseline) and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, and 48 h.

In both studies, plasma DPP-4 activity before and after drug administration was measured by using a validated method that employed a semiquantitative enzyme activity assay with fluorescence detection using I-1225-H-Gly-Pro-AMC (Bachem, Bubendorf, Switzerland) as a substrate; all procedures were conducted at the Biomedical Research Institute of SNUH. Fluorescence was detected at 465 nm (emission) using a 360-nm excitation wavelength after 10 minutes of incubation at an amplification/gain of 60 using a microplate reader (SpectraMax M5, Molecular Devices Korea, Seoul, Korea). Assay performance was confirmed by using 6 standards, and the precision of the assay was between 0.4% and 5.0%. The measurement of DPP-4 activity was expressed as the percentage change from the baseline DPP-4 activity:

$$[\text{DPP-4 inhibition (\%)}] = \left(1 - \frac{[\text{DPP-4 activity}]}{[\text{Baseline DPP-4 activity}]}\right) \text{x } 100$$

The individual PD parameters were calculated with the NCA method. PD parameters included in the analysis were the area under the % inhibitory effect-time curve until the time of last

measurable concentration ($AUEC_{last}$), maximum % inhibitory effect (E_{max}), and duration of ≥ 80% DPP-4 inhibition (Fi80). $AUEC_{last}$ was calculated by the linear trapezoidal method, and E_{max} was directly observed from the study data. For the purpose of NCA, PD samples up to 48 h post-administration were used for comparison between the two studies.

Table 1. Summary of clinical studies and available data from CKD, ESRD patients and healthy subjects

Study (ClinicalTrials.gov identifier)	Number of subjects *		Plasma PK sampling	Urine PK sampling	PD sampling schedule
DA1229_RI_I † (NCT02214693)	Severe renal impairment	N = 6	Pre-dose (0 h), 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, 72, 96, and 120 h Additionally, 1, 24 and 48 h for unbound concentration	Pre-dose (0 h), 0 – 24, 24 – 48, 48 – 72, 72 – 96, 96 – 120 h	Pre-dose(baseline), 1, 3, 5, 8, 12, 24, 36, 48, 60, 72, 96, 120 h
	Moderate renal impairment	N = 8			
	Mild renal impairment	N = 8			
	Healthy subjects	N = 8			
DA1229_ESRD_I (NCT04195919)	ESRD group	N = 8	Pre-dose (0 h), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, and 48 h	Pre-dose (0 h), 0 – 24, 24 – 48 h (Healthy subjects only)	Pre-dose(baseline), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 36, 48 h
	Healthy subjects	N = 8			

Notes: * Patients were classified in to each treatment group using MDRD-eGFR. EPI-GFR was recalculated for the purpose of population PK model. † Subjects were administered a single dose of evogliptin 5 mg in both studies. ESRD patients were administered a single dose of evogliptin 5 mg before (period 2) and after (period 1) HD.

Abbreviations: EPI-GFR, estimated Glomerular Filtration Rate using the CKD-EPI equation; ESRD, end-stage renal disease; HD, hemodialysis; MDRD-eGFR, Modification of Diet in Renal Disease- estimated glomerular filtration rate; PD pharmacodynamics; PK pharmacokinetics

2.2. Development of the Population PK Model

2.2.1. Base PK model development

Population PK models were developed according to recommendations in the guidance from the FDA [15]. Dataset preparation, exploration and visualization were performed using R (version 4.3.0 or higher). Population PK analysis was performed with nonlinear mixed-effects modeling software (NONMEM® version 7.5) with first-order conditional estimation with interaction (FOCE-I).

Following graphical assessment, compartmental models were evaluated to optimally describe the pharmacokinetics of evogliptin. The interindividual variability (IIV) of the structural model parameters was modeled using the following log-normal model:

$$\theta_i = \theta_{TV} \cdot \exp(\eta_i)$$

where θ_i is the individual value of the parameter (e.g., CL/F), θ_{TV} is the typical value of the parameter, and η_i is the interindividual random effect accounting for the i^{th} individual's deviation from the typical value. A combined (proportional and

additive) residual error model was used to describe the random variability in the serum concentrations. PK samples with concentrations below the lower limit of quantification were excluded from the analysis.

Base model selection was based on goodness-of-fit indicators, including visual inspection of diagnostic plots, biological plausibility of the parameter estimates, precision of the parameter estimates, objective function value (OFV) and Akaike information criterion (AIC) value. Additionally, estimation of individual random effect (ETA) shrinkage was considered.

2.2.2. Covariate PK model

A covariate analysis was conducted to explore the potential covariates affecting the metabolism of evogliptin. Clinical laboratory tests, demographic data, CKD stratified by EPI-GFR, and HD status were initially screened as potential covariates. Covariate candidates were selected from the available biochemistry data, considering the list of potential uremic toxins investigated in previous studies [16]. To mitigate the impact of transient variability, the arithmetic mean values from the clinical laboratory tests from the initial screening and on Day 1 (prior to the administration of evogliptin) were used for analyses.

Among the tested covariates, glomerular filtration rate (GFR) was calculated using the 2021 CKD-EPI Creatinine Equation:

$$EPI\text{-}GFR = 141 * \min(Scr/\kappa, 1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018\ [\text{if female}] * 1.159\ [\text{if black}]$$

where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum Scr/κ or 1, and max indicates the maximum Scr/κ or 1.

The list of all considered covariates is presented in Table 2. During the covariate screening process, a stepwise covariate model (SCM) and generalized additive model (GAM) were implemented with a significant relationship at the .01 level. Demographic data and other laboratory results, including hematology, were broadly investigated through SCM and GAM analysis, and significant results were also included in the evaluation.

For the stepwise selection of covariates, a forward addition and backward elimination of covariates was performed at significance levels of .01 (⊿OFV 6.63, df=1) and .001 (⊿OFV 10.8, df=1), respectively. Continuous covariates were included in the model using power functions, whereas categorical

covariates were implemented using a reference category to determine the effect of other categories.

Table 2. Potential covariates and considered covariates in the stepwise analysis

Parameters	Considered covariates *
CL/F (L/h)	Size (Weight, BMI, age) Sex Renal function impairment covariates: Creatinine MDRD−eGFR EPI−GFR HD (hemodialysis) ESRD status Liver function tests (AST, ALT, ALP, bilirubin) Biochemistry (Albumin, LDH, TG, CPK) Blood electrolytes (Ca, K, Na, Chl)
V2/F, V3/F (L)	Size (Weight, BMI, age) Sex Renal function impairment covariates: (see above) Biochemistry (Albumin, TG)
F_r	BMI Renal function impairment covariates: (see above) Liver function tests (AST, ALT, ALP, bilirubin) Biochemistry (Albumin, amylase, CPK, LDH, lipase, TG, urate) Blood electrolytes (Ca, K, Na, Chl)
Ka (/h)	Size (Weight, BMI, age)

Parameters	Covariates tested in stepwise analysis *
CL/F (L/h)	Size (Weight, age) Liver function tests (AST, ALT, ALP, bilirubin) Biochemistry (Albumin)
V2/F, V3/F (L)	Size (Weight) Biochemistry (Albumin, TG)
F_r	Liver function tests (AST, ALT, ALP, bilirubin) Biochemistry (Albumin, amylase, CPK, LDH, lipase, TG, urate) Blood electrolytes (Ca, K, Na, Chl)

Notes: * Covariates are selected based on visual inspection, COSSAC, and SCM
Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; Chl, blood chloride level; CL/F, clearance; COSSAC, conditional sampling for stepwise approach based on correlation tests; CPK, creatine phosphokinase; EPI−GFR, estimated Glomerular Filtration Rate using the CKD−EPI equation; ESRD, end−stage renal disease; F_r, relative bioavailability; HD, hemodialysis; LDH, lactate dehydrogenase; MDRD−eGFR, Modification of Diet in Renal Disease−estimated glomerular filtration rate; SCM, stepwise covariate model; TG, triglyceride; V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution.

2.2.3. Model validation

The assessment of model stability and estimation of confidence intervals (CIs) for the model parameters were carried out using nonparametric bootstrap resampling. Specifically, the final model was repeatedly fitted to bootstrap replicates (n = 1000) of the dataset to evaluate the stability and estimate the CIs of the model parameters. Prediction-corrected visual predictive checks (pcVPCs; 500 simulation replicates) were conducted to validate the final model. Categorical covariates were assessed at each level of the covariate, while continuous covariates were assessed at the reference value (i.e., median) and the 5th and 95th percentiles.

2.2.4. PK simulation in renal impairment patients

To assess the effect of covariates on the pharmacokinetics of evogliptin, covariates implemented in the PK model were tested using Monte Carlo simulation. The median levels of significant covariates were used as the reference. Categorical covariates were incorporated into the simulation design to create various simulation scenarios. The range of the influencing continuous covariate factors was stratified into median, upper and lower

boundary (5%, 95% percentile) values and incorporated into different simulation scenarios. Each scenario was simulated with 1000 sets of virtual data. Pharmacokinetic parameters were calculated, and descriptive statistical and graphical analyses were performed. The C_{max} and AUC_{0-120} of the drug exposure in each simulation scenario were compared with the reference.

2.2.5. PD model of evogliptin

Pharmacodynamic data were analyzed using a sigmoidal E_{max} model. Visual analysis of plasma concentration–DPP−4 inhibition profiles (pooled data from all subjects) suggested that the relationship could be characterized by a sigmoid E_{max} model as follows:

$$E = \frac{E_{max} \times Cp^{\gamma}}{EC_{50}{}^{\gamma} + Cp^{\gamma}}$$

where E is the pharmacodynamic effect [DPP-4 inhibition (%)], E_0 is the baseline effect, E_{max} is the maximum % DPP−4 inhibitory effect, Cp is the plasma evogliptin concentration, EC_{50} is the concentration that produces 50% of the maximum effect, and gamma (γ) is a coefficient constant that describes the steepness of the concentration–response curve.

The PK–DPP−4 inhibition model was developed using the

following equation:

$$\text{DPP-4 inhibition (\%)} = \frac{E_{max} \times {C_{pred}}^{\gamma}}{{EC_{50}}^{\gamma} + {C_{pred}}^{\gamma}}$$

A directly linked model was implemented, where DPP-4 inhibition (%) was directly linked to the predicted concentration (C_{pred}) of evogliptin.

The developed PK/PD model was tested through a visual predictive check using 500 simulation replicates. PK/PD parameters from the developed model were used to simulate DPP-4 activity inhibition according to the original subject conditions. The simulated and observed data were plotted together for visual predictive checks.

Chapter 3. Results

3.1. Clinical Study and Data Collection

3.1.1. Clinical study results

PART I. A total of 30 participants were enrolled, including 22 renal impairment patients and 8 healthy subjects, and all completed the study. The patients were divided into groups according to varying degrees of renal impairment. The patient groups had comparable demographic characteristics but had varying degrees of renal impairment: the mean values of creatinine were 0.96, 1.23 and 2.65 mg/dL for the mild, moderate, and severe renal impairment groups, respectively (Table 3).

Part II. A total of 9 ESRD patients and 8 matching healthy subjects were enrolled, and 7 and 8 subjects completed the study, respectively. One subject in cohort 1 withdrew consent before evogliptin administration, and another subject withdrew consent after the first period. Demographic characteristics, including age, height, weight, and BMI, were comparable between the two cohorts. The mean MDRD eGFR was lower and the mean creatinine level was higher in ESRD patients than in healthy subjects (Table 3).

With the exception of the covariates and their corresponding characteristics evaluated in the PK model, the subjects in each group had comparable medical status, demographic profiles, and laboratory results, including biochemistry parameters.

Table 3. Summary of demographics and baseline characteristics

Variable	DA1229_RI_I				DA1229_ESRD_I	
	Severe renal impairment (N=6)	Moderate renal impairment (N=8)	Mild renal impairment (N=8)	Healthy subject group ‡ (N=8)	ESRD patients on HD * (N=9)	Healthy Subjects group † (N=8)
Sex						
Male	2 (33.3)	4 (50.0)	4 (50.0)	4 (50.0)	6 (66.7)	5 (62.5)
Female	4 (66.7)	4 (50.0)	4 (50.0)	4 (50.0)	3 (33.3)	3 (37.5)
Age (years)	56.5 ± 12.19	59.13 ± 6.20	48.25 ± 13.51	53.00 ± 12.32	48.78 ± 15.18	45.63 ± 15.59
Height (m)	1.6 ± 0.1	1.61 ± 0.04	1.65 ± 0.09	1.62 ± 0.13	1.65 ± 0.10	1.68 ± 0.09
Weight (kg)	60.75 ± 11.59	64.43 ± 6.40	66.41 ± 10.47	62.56 ± 12.65	66.73 ± 10.28	69.84 ± 12.39
BMI (kg/m^2)	23.6 ± 3.21	24.83 ± 1.89	24.34 ± 2.07	23.61 ± 1.78	24.28 ± 1.91	24.68 ± 2.18
MDRD-eGFR ($mL/min/1.73\ m^2$)	22.4 ± 5.32	50.51 ± 4.05	70.80 ± 5.75	101.28 ± 9.15	6.44 ± 2.93	99.06 ± 5.10
EPI-GFR ($mL/min/1.73\ m^2$)	23.04 ± 6.16	55.84 ± 4.62	83.47 ± 8.87	103.50 ± 10.13	4.81 ± 1.63	106.57 ± 10.3
Creatinine (mg/dL)	2.65 ± 0.86	1.23 ± 0.13	0.96 ± 0.25	0.70 ± 0.13	9.31 ± 3.57	0.78 ± 0.13

Notes: Percentages are based on the subjects within each cohort. Data are presented as number (%) for sex and mean ± SD for others. * One subject in ESRD group dropped out before treatment. † Subjects in healthy subject groups were recruited to match age, BMI and sex of the patient groups.

Abbreviations: BMI, body-mass index; EPI-GFR, estimated Glomerular Filtration Rate using the CKD-EPI equation; MDRD-eGFR, Modification of Diet in Renal Disease- estimated glomerular filtration rate; SD, standard deviation.

3.1.2. Pharmacokinetic results

A total of 779 plasma samples for evogliptin PK analysis collected from 46 participants were available for analysis.

Part I. After 5 mg evogliptin oral administration, the areas under the concentration-time curves for plasma evogliptin extrapolated to infinity (AUC_{inf}) were 1.26-, 1.85- and 1.97-fold higher in the mild, moderate, and severe RI groups, respectively, compared to the NRF group (Table 4). The CL/F and apparent volume of distribution (Vz/F) decreased as the eGFR decreased.

Part II. The AUC_{inf} of evogliptin was 1.48-fold higher in ESRD patients on HD than in matching healthy subjects (Table 4). The overall clearance (CL/F) was lower in ESRD patients by approximately 0.78-fold.

Table 4. Summary of PK parameters

Pharmacokinetic parameters	DA1229_RI_I				DA1229_ESRD_I	
	Severe renal impairment group	Moderate renal impairment group	Mild renal impairment group	Healthy subject group	ESRD patients on HD group †	Healthy Subject group
	(N=6)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)
C_{max} (μg/L)	8.30 ± 1.43	7.37 ± 2.54	5.81 ± 1.81	5.45 ± 0.93	6.40 ± 0.99	5.45 ± 1.52
AUC_{last} (μg · h/L)	215.98 ± 24.13	195.43 ± 37.48	144.05 ± 32.97	133.78 ± 23.07	150.75 ± 44.17	105.97 ± 22.67
AUC_{inf} (μg · h/L)	373.96 ± 61.98	350.36 ± 64.4	238.75 ± 97.04	189.45 ± 43.49	262.71 ± 110.73	176.81 ± 46.41
T_{max} (h)	5.01 (5.00–6.02)	5.00 (2.00–8.05)	5.00 (1.98–8.00)	5.00 (1.00–6.00)	1.51 (1.00–3.00)	1.51 (1.00–3.00)
$t_{1/2}$ (h)	38.31 ± 7.64	40 ± 8.29	34.66 ± 11.55	26.02 ± 4.96	36.26 ± 9.64	37.42 ± 10.90
CL/F (L/h)	13.74 ± 2.69	14.7 ± 2.72	23.03 ± 6.14	27.89 ± 7.55	23.86 ± 15.54	30.67 ± 10.90
V_z/F (L)	741.60 ± 106.37	834.06 ± 156.82	1070.69 ± 198.4	1017.53 ± 185.31	1108.59 ± 388.29	1586.05 ± 455.76

Notes: Data are presented as the arithmetic mean ± standard deviation, except for T_{max}, which were presented as median (min–max). † ESRD patients were administered evogliptin 5 mg after hemodialysis.

Abbreviations: AUC_{inf}, area under the concentration–time curve extrapolated to infinity; AUC_{last}, area under the concentration–time curve from time 0 to time of the last quantifiable concentration; C_{max}, maximum concentration; CI, confidence interval; CL/F, apparent clearance; ESRD, end–stage renal disease; max, maximum; $t_{1/2}$, terminal half–life; T_{max}, time to maximum concentration; V_z/F, apparent volume of distribution during terminal phase.

3.1.3. Pharmacodynamic results

A total of 689 samples for evogliptin PD (DPP-4 activity) analysis collected from 46 participants were available for analysis.

Part I. Plasma DPP-4 activity inhibition increased after the administration of 5 mg evogliptin, and the effect was sustained up to 120 h post-dose. The mean DPP-4 inhibition reached a maximum value (E_{max}) of 87-89%, and the mean durations of ≥ 80% DPP-4 inhibition were 39.30, 22.94, 16.49, and 20.24 hours in the severe, moderate, and mild RI patients and healthy subjects, respectively (Table 5).

Part II. After a single oral administration of 5 mg evogliptin, an immediate increase in DPP-4 inhibition was observed in all subjects. The mean DPP-4 inhibition reached an E_{max} of 86-87%, and the effect was sustained up to 48 hours after administration. The mean durations of ≥80% DPP-4 inhibition were 28.84 and 17.87 hours in the ESRD patients and healthy subjects, respectively.

Table 5. Summary of PD parameters

Pharmacodynamic parameters	DA1229_RI_I				DA1229_ESRD_I	
	Severe renal impairment group	Moderate renal impairment group	Mild renal impairment group	Healthy subject group	ESRD patients on HD group †	Healthy Subject group
	(N=6)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)
$AUEC_{last}$ [(%) · h]	3990.00 ± 120.79	3745.39 ± 218.46	3526.56 ± 195.30	3596.12 ± 200.43	3797.09 ± 195.10	3525.25 ± 139.80
E_{max} (%)	88.92 ± 0.55	85.94 ± 3.71	87.21 ± 1.47	87.66 ± 1.94	86.05 ± 1.62	86.95 ± 2.05
Fi80 (h)	39.30 ± 7.90	22.94 ± 12.62	16.49 ± 4.76	20.24 ± 7.68	28.84 ± 16.22	17.87 ± 4.48

Notes: Data are presented as the arithmetic mean ± standard deviation. Cohort 1 Period 1: † ESRD patients were administered evogliptin 5 mg after hemodialysis.

Abbreviations: $AUEC_{last}$, area under the % DPP−4 inhibitory effect−time curve until the time of last measurable concentration; DPP−4, dipeptidyl peptidase−4; E_{max}, maximum % DPP−4 inhibitory effect; ESRD, end−stage renal disease; Fi80, time duration of ≥ 80% DPP−4 inhibition

3.2. Development of the Population PK Model

3.2.1. Base model

A nonlinear mixed-effects model was developed to describe the population PK of evogliptin. Among the collected plasma PK samples, 688 samples from 8 ESRD patients; 6 severe, 8 moderate, and 8 mild RI patients; and 16 NRF subjects were used for model development (Figure 3). The administration data before HD (period 2) of ESRD patients on HD were excluded.

For the base model, one- and two-compartment models with first-order absorption structures were evaluated to find the best fit for the observed PK data based on the AIC. The 2-compartment model was selected as the base PK model after comparing diagnostic plots, AIC and OFV from the initial modeling results (Table 6).

The 2-compartment base PK model had the following parameters: F_r, relative bioavailability; Ka, first-order absorption rate constant; CL/F, apparent clearance; V2/F, apparent volume of distribution of the central compartment; V3/F, apparent volume of distribution of the peripheral compartment; and Q/F, apparent intercompartmental clearance (Figure 4).

Residual variability was modeled with a combined error model. Inclusion of IIV for CL/F, V2/F and Q/F significantly improved the model fit. Inclusion of IIV for Ka improved the model (⊿OFV=−9.168) but resulted in RSEs on PK parameters >50% and was discarded. Likewise, inclusion of IIV for F_r improved the model (⊿OFV=−63.102) but resulted in RSEs on PK parameters >80% and distortion in typical values (V2/F = 110 L) and was discarded.

The base population pharmacokinetic (PK) model demonstrated a reliable estimation of all PK parameters, as evidenced by relative standard error (RSE) values below 20% and ETA shrinkage values under 20%. The goodness−of−fit diagnostic plots for the base model revealed a strong concordance between observed and predicted data, with no indication of systematic bias.

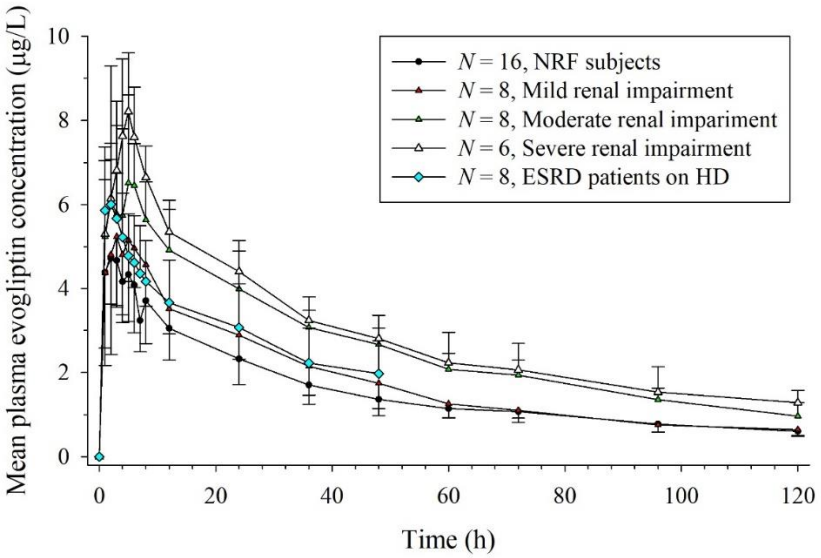


Figure 3. Mean plasma evogliptin concentration-time profile after a single oral administration of evogliptin 5 mg.

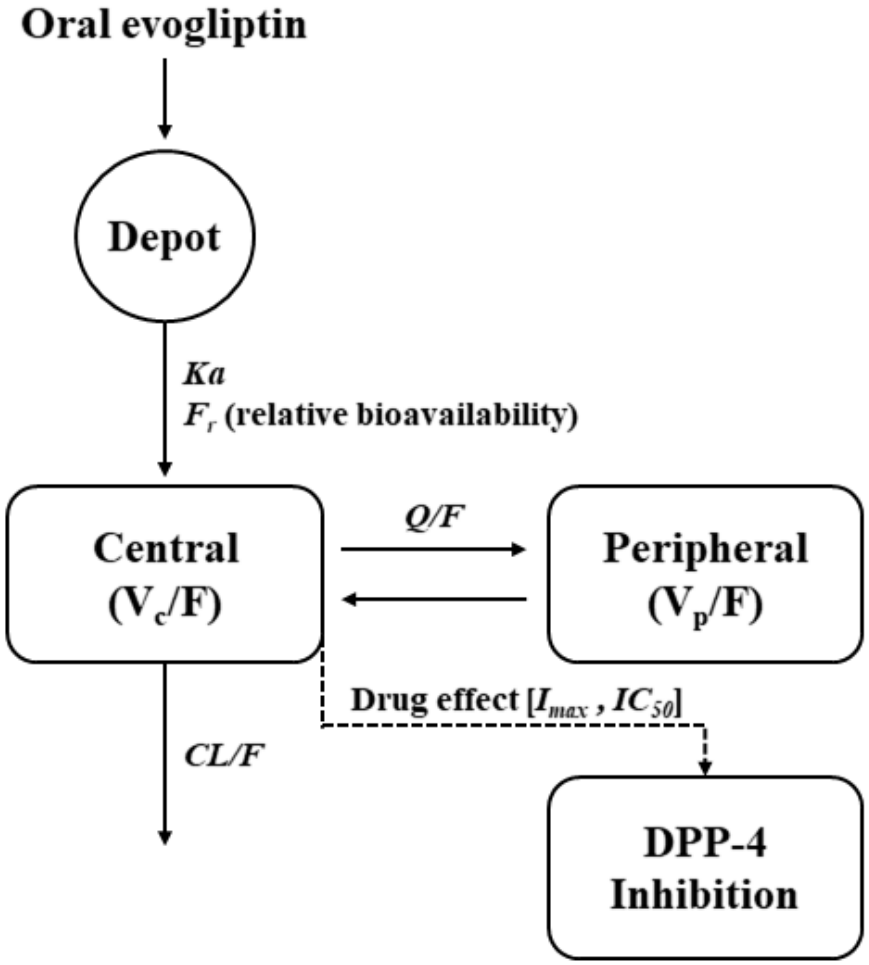


Figure 4. Pharmacokinetic/pharmacodynamic model of evogliptin.
Notes: DPP-4 activity is directly inhibited by evogliptin.

Table 6. Base model and stepwise covariate selection

No.	Reference model	Base model selection	OFV	⊿OFV	Notes
1	–	2−compartment oral, linear elimination, proportional error model	325.808	–	AIC: 343.808
2	1	2−compartment oral, linear elimination, additive error model	92.304	−233.504	AIC: 112.304
3	2	2−compartment oral, linear elimination, combined error model	−115.303	−207.607	Base model; AIC: −95.303
No.	**Reference model**	**Stepwise covariate selection**	**OFV**	**⊿OFV**	**Notes** [*]
4	3	Age:CL/F	−123.187	−7.884	
5	4	Age:CL/F; Wt:V2/F	−139.161	−15.974	
6	5	Age:CL/F; Wt:V2/F; Amyl:F_r	−162.653	−23.492	
7	6	Age:CL/F; Wt:V2/F; Amyl, Chl:F_r	−179.120	−16.467	Final model

Notes: Models which are successful minimization or significant OFV reduction from the reference models are presented. [*] Unless stated otherwise, df = 1.

Abbreviations: AIC, Akaike information criterion; Amyl, amylase level; Chl, chloride level; CL/F, drug clearance; F_r, relative bioavailability; OFV, objective function value; Wt, body weight

3.2.2. Covariate model

The parameter estimates for the final model are summarized in Table 7.

According to plots of individual Eta (random effects) vs. covariates, the covariates were formally tested as part of the stepwise analysis (Table 6). Following the stepwise forward addition and backward elimination processes, the statistically significant covariates retained in the final model were blood chloride level (Chl) and blood amylase level (Amyl) on F_r; age on CL/F and body weight (Wt) on V3/F. F_r (relative bioavailability) was defined as 1 (100%) in a reference scenario of Chl=100 mmol/L and Amyl=83.75 IU/L:

$$F_r = \left(\frac{Chl}{100}\right)^{2.43} \times \left(\frac{Amyl}{83.75}\right)^{0.313}$$

The exponent of the Chl effect on F_r was 2.43, suggesting a significant correlation. Estimates of typical CL/F and V2/F were 18.9 L/h and 36.7 L, respectively:

$$CL/F\ (L/h) = 18.9 \times \left(\frac{Age}{56}\right)^{-0.338}$$

$$V2/F\ (L) = 36.7 \times \left(\frac{Wt}{64.5}\right)^{0.695}$$

The exponent for the effect of age on CL/F was −0.338, suggesting lower clearance in older patients. The IIV of V2/F was relatively high at 84.6%, and covariates including demographic characteristics and biochemistry did not significantly affect the variability of V2/F.

All PK parameters were robustly estimated, with the largest RSEs belonging to the effect of age on CL/F (55.6%) and the effect of Wt on V3/F (34.2%). All other RSEs were less than 30%, and ETA shrinkage was less than 19%. When the model-predicted individual evogliptin concentration-time profiles overlapped with the observed concentration, the data showed good agreement (Figure 5).

Table 7. Parameter estimates of the population PK and PD parameters

Parameter	Final model		Bootstrap median (95% CI)
	Estimate	RSE (%)	
Population PK parameters *			
CL/F (L/h)	18.9	5.8	18.93 (16.93−21.57)
V2/F (L)	36.7	12.8	37.84 (26.78−57.94)
Ka (/h)	0.0721	11.9	0.0737 (0.0563−0.1154)
Q/F (L/h)	41.1	14.9	42.19 (29.43−70.87)
V3/F (L)	920	4.0	924.14 (847.71−1013.60)
F_r ‡	1 (FIX)	NA	NA
Chl~F_r	2.43	26.1	2.431 (1.020−3.996)
Amyl~F_r	0.313	24.3	0.310 (0.146−0.489)
Age~CL/F	−0.338	55.6	−0.349 (−0.789−0.058)
Wt~V3/F	0.695	34.2	0.649 (0.182−1.173)
PK IIV			
CL/F (%)	37.4	12.6	35.96 (26.56−45.7)
V2/F (%)	84.6	12.2	83.57 (61.54−104.44)
Q/F (%)	23.7	12.0	22.91 (16.51−28.4)
PK Residual variability			
Additive Error (SD)	0.0895	13.2	0.1139 (0.1002−0.1302)
Proportional Error (SD)	0.1150	6.1	0.0876 (0.0292−0.1306)
Population PD parameters †			
E_{max} (%inhibition)	95.7	1.8	95.7 (92.4~99.4)
EC_{50} (μg/L)	0.837	15.8	0.845 (0.574~1.128)

γ (Hill coefficient)	1.38	9.2	1.38 (1.16~1.67)
PD IIV			
E_{max} (%)	9.4	15.0	9.2 (6.7~12.1)
EC_{50} (%)	79.4	25.8	79.1 (37.5~119.6)
γ (Hill coefficient)	40.2	15.9	39.5 (27.2~53.0)
Residual variability			
Additive Error (SD)	8.34	21.0	8.19 (5.15~12.28)

Notes: Total of 1000 bootstrap replications were conducted using the raw PK and PD data. Summary statistics were obtained from 931 (93.1 %) and 992 (99.2 %) replicates for PK (*) and PD (†), respectively. ‡Relative bioavailability was set as 1 (100%) for a reference patient (Chloride=100 mmol/L and Amylase=83.75 IU/L).

Abbreviations: Amyl, blood amylase level; Chl, blood chloride level; CI, confidence interval; CL/F, apparent clearance; EC_{50}, plasma concentration of evogliptin that achieves 50% of the maximum drug effect; E_{max}, maximum DPP-4 %inhibition; F_r, relative bioavailability; IIV, Inter-individual variability; Ka, first-order absorption rate constant; Q/F, apparent intercompartmental clearance; RSE, relative standard error (%); SD, standard deviation; V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution; Wt, weight; γ (hill coefficient), steepness of the concentration-response curve.

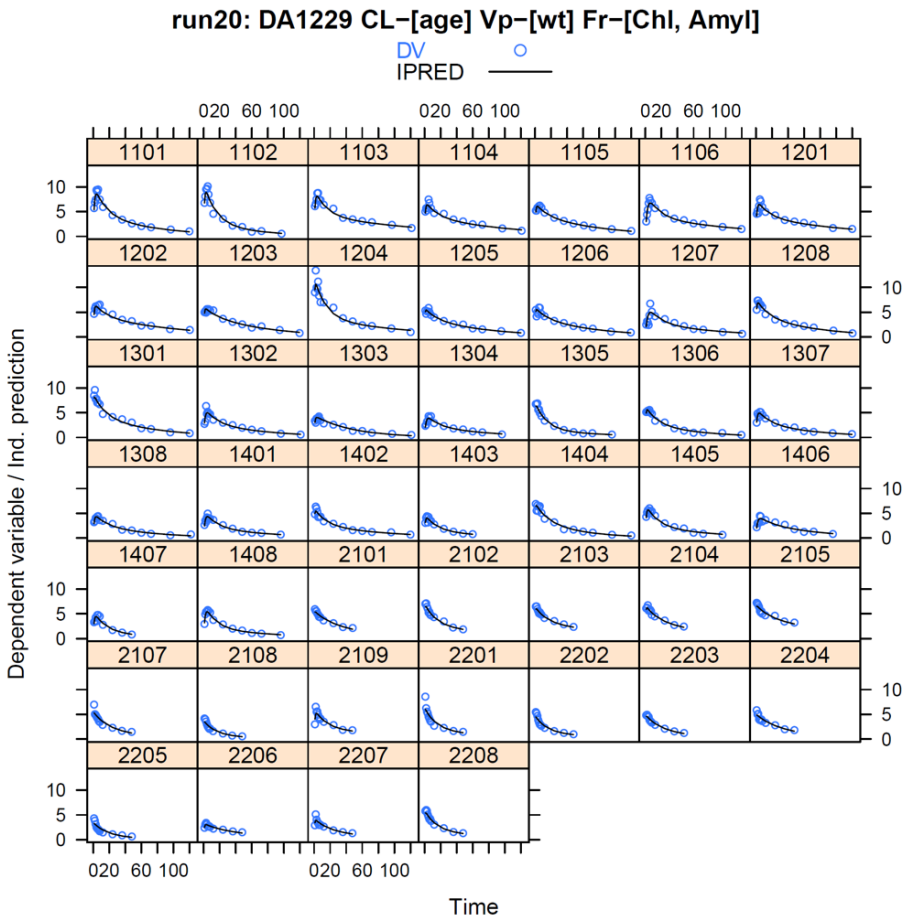


Figure 5. Individual predicted evogliptin concentration vs time overlapped with observed data

3.2.3. Model validation

The goodness-of-fit plots demonstrated an adequate model structure for predicting evogliptin concentrations, exhibiting an even distribution of high and low concentration values around the line of identity on both linear and logarithmic scales (Figure 6). The majority of the conditional weighted residuals (CWREs) primarily ranged from −2 to 2, demonstrating an equitable distribution both above and below the y = 0 coordinate. Upon inspection of the CWRE distribution in relation to population predictions and temporal factors, no significant trends were observed that would indicate model insufficiency. These findings suggest that the model describes the observed data well.

A pcVPC demonstrated an acceptable overlap between the simulated and observed evogliptin concentrations (Figure 7). A total of 1,000 bootstrap replications were conducted using the original PK data, with 93.1% (931) of the replicates converging successfully with a covariance step. The medians and 95% confidence intervals (CIs) of the PK parameters generated by the bootstrap analysis were consistent with the final PK parameter estimates, indicating model stability. In summary, the model was robust, adequate, and precise in characterizing the pharmacokinetic properties of evogliptin.

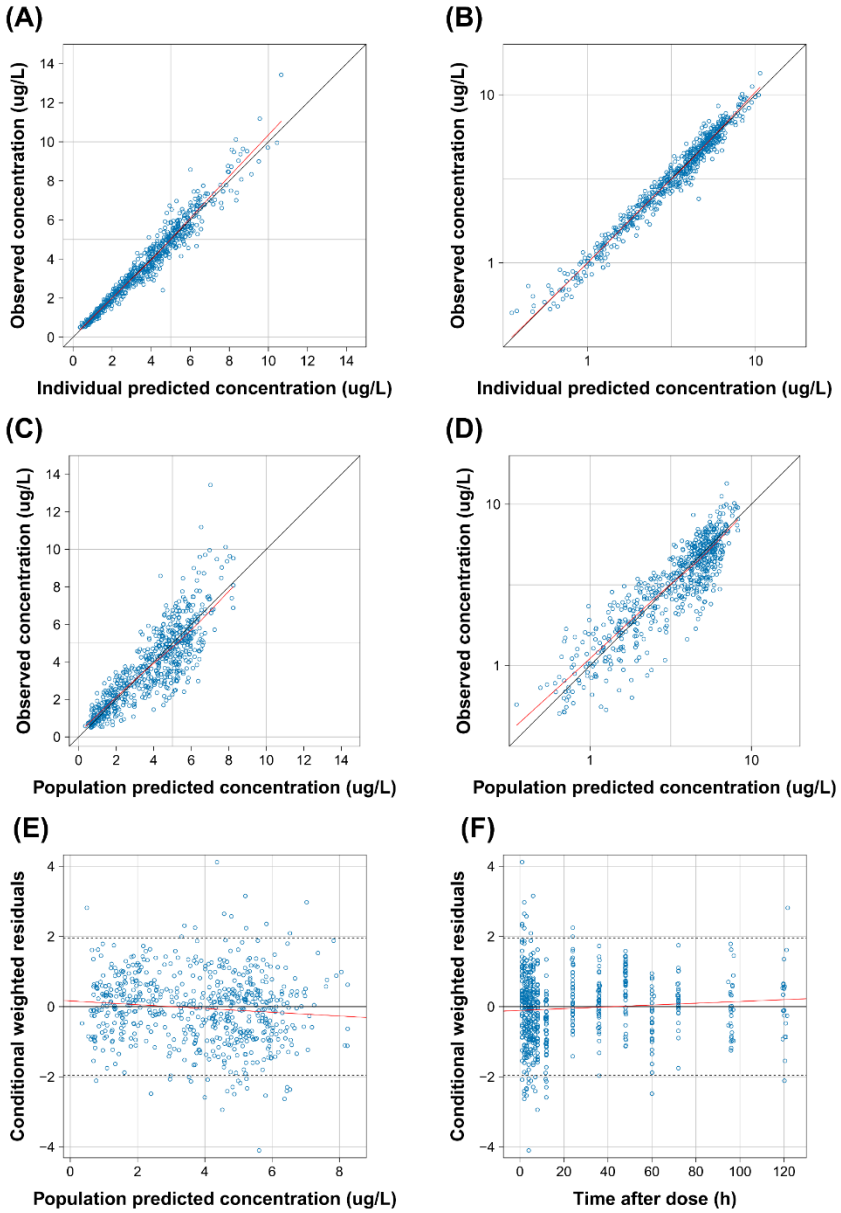
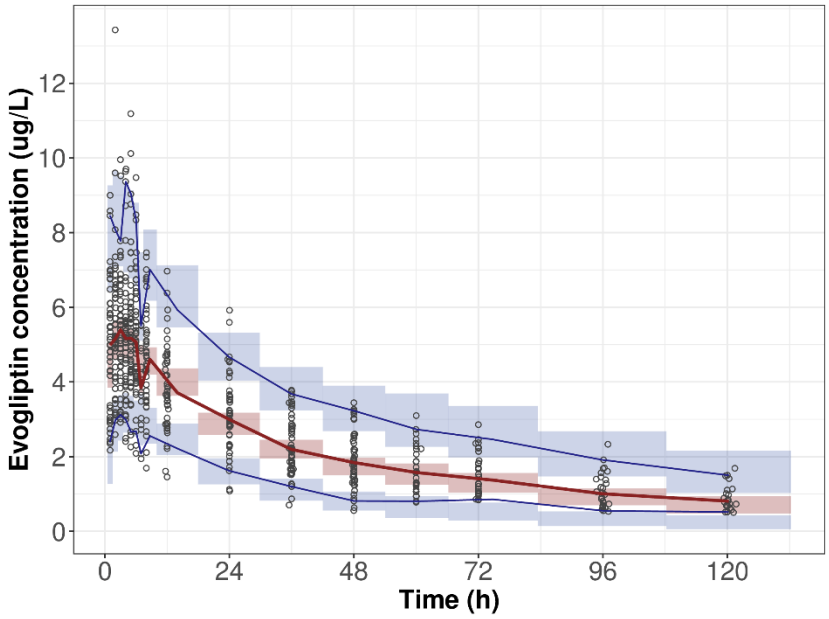


Figure 6. Goodness-of-fit of the final PK model for evogliptin.
Notes: (A, B) Observed vs individual predicted evogliptin concentrations on the linear and logarithmic scales. (C, D) Observed vs population predicted evogliptin concentrations on the linear and logarithmic scales. (E) Conditional weighted residuals over time. (F) Conditional weighted residuals over population predicted concentrations. Red lines represent the regression fit, whereas solid grey lines represent the lines of identity.

(A)



(B)

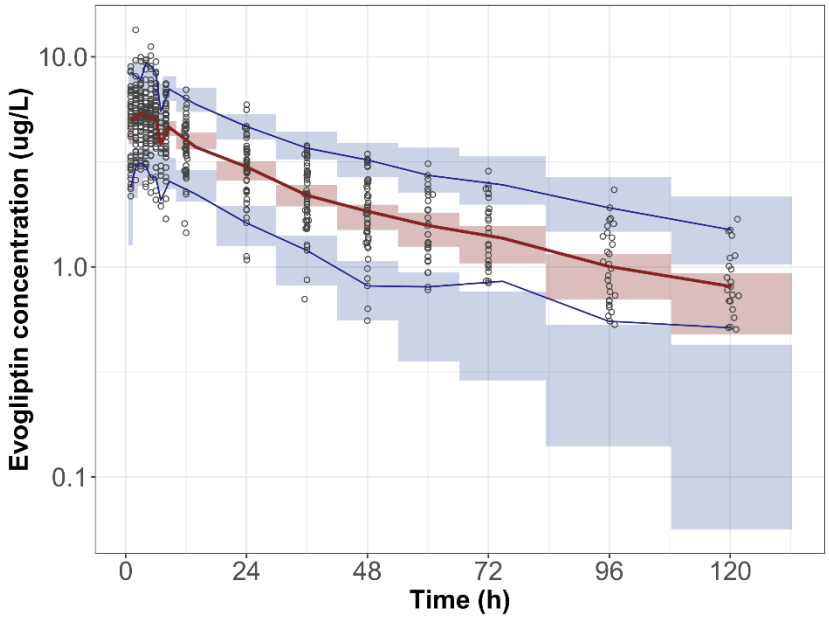


Figure 7. Simulation results for the time-concentration profile of evogliptin after a single oral administration. (A) linear, (B) log scale.
Notes: Red line indicate the median, and blue lines indicate 5 and 95% prediction intervals. Dots represent individual observations.

3.2.4. PK simulation

To evaluate the potential effects of relevant covariates on the PK of evogliptin, covariates implemented in the PK model were tested using Monte Carlo simulation.

Scenario A was set as the reference scenario and represented healthy subjects. The median values from healthy subjects were used: Amyl, 59.5 IU/L; Chl, 102 mmol/L; age, 53.5 years; and Wt, 64.5. Scenario B was set as a representative for aged patients with severe CKD not undergoing HD. The 95th percentile values for Amyl (59.5 IU/L), Chl (108 mmol/L) and age (67 years) were used. Wt was fixed at 64.5 kg. Scenarios C1 to C3 were set to test the effect of Chl on the systemic exposure of evogliptin. The 95th percentile, median and 5th percentile values of Chl were used for C1, C2 and C3, respectively. Notably, the median values for the ESRD participants on HD had a median Chl value of 96, and scenario C3 was similar to ESRD patients on HD. Scenarios D1 and D2 were set to test the effect of high Chl levels with normalized Amyl levels. Detailed scenarios and the resulting PK parameters are summarized in Table 8.

The C_{max}, AUC_{0-120} and CL/F were investigated to assess the

change in evogliptin PK according to each influencing factor. Each scenario simulated 1000 sets of virtual data, and the PK parameters were calculated. As expected, in the PK model, C_{max} and AUC_{0-120} were both significantly affected by blood chloride and amylase levels. AUC_{0-120} showed a 1.8-fold increase in scenario B, where maximum boundary levels of amylase and chloride levels were implemented. In contrast, the C3 scenario with lower boundary levels of chloride displayed much lower drug exposure (1.25-fold of the reference scenario A) (Figure 8).

Table 8. Simulated PK parameter of evogliptin in severe CKD and ESRD patients on HD

Scenario	Amyl	Chl	Age	C_{max} (μg/L) *	AUC_{0-120} (μg·h/L)	CL/F (L/h)
A †	59.5	102	53.5	5.28 (3.79~7.45)	202.15 (120.5~301.42)	21.28 (11.8~39.4)
B	191.5	108	67.0	8.97 (6.31~12.41)	359.4 (219.9~518.64)	11.65 (6.47~21.18)
C1	191.5	108	53.5	8.8 (6.17~12.23)	336.56 (206.23~506.36)	12.68 (6.91~22.73)
C2	191.5	102	53.5	7.63 (5.42~10.54)	292.6 (176.29~448.95)	14.62 (7.93~27.09)
C3	191.5	96	53.5	6.56 (4.72~9.15)	250.63 (154.24~381.91)	17.02 (9.27~30.4)
D1	59.5	108	67.0	6.18 (4.38~8.73)	250.59 (153.36~363.91)	16.41 (9.33~30.27)
D2	59.5	108	53.5	6.07 (4.31~8.76)	238.13 (136.06~355.73)	17.78 (10.08~34.86)

Notes: * Data are presented as median (0.05−95.0 percentile). † Median age, chloride and amylase levels of healthy subjects were used in the reference scenario A.
Scenario A: represents healthy subjects
Scenario B: represents severe renal impairment patients
Scenario C1~3: C3 represents ESRD patients on HD; effects of varying levels of chloride
Scenario D1~2: effects of high chloride level in normal amylase levels, in different age
Abbreviations: Amyl, blood amylase level; AUC_{0-120}, area under the concentration–time curve from time 0 to 120 h; Chl, blood chloride level; CL/F, apparent clearance; C_{max}, maximum concentration; CPK, creatine phosphokinase; ESRD, end−stage renal

disease on hemodialysis; LDH, lactate dehydrogenase; NRF, normal renal function.

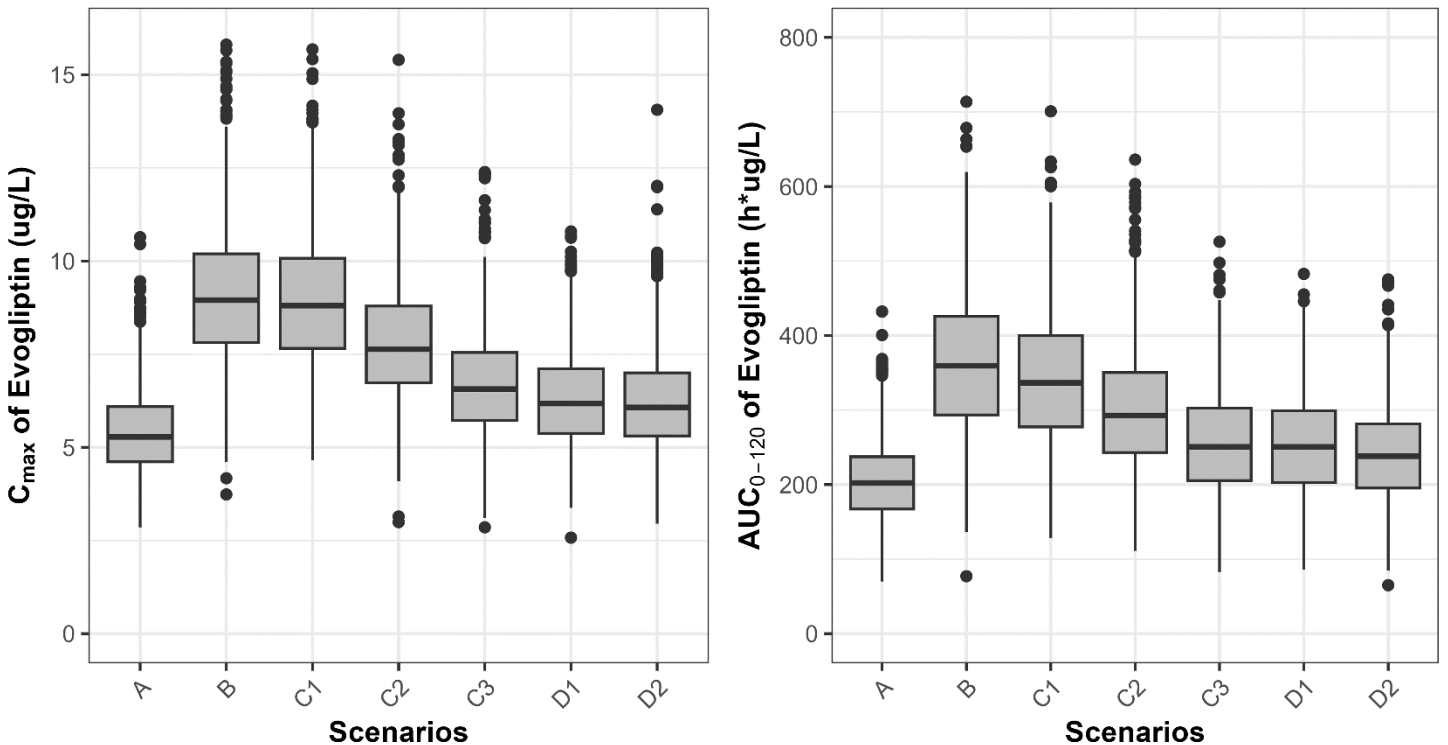


Figure 8. The box diagram of C_{max} and AUC_{0-120} simulated in different scenarios.
Notes: The bold horizontal line is the median level. Scenario A was used as a reference. Details of the dosing scenarios are presented in Table 8.

3.2.5. PD model of evogliptin

Similar to the PK model, the before-HD administration data of ESRD patients on HD (period 2) were excluded, and 598 samples were used for the PD model (Figure 9).

A direct-link sigmoidal E_{max} model was developed to describe the plasma evogliptin concentration and DPP-4 inhibition profiles. The decision to employ a direct link model was based on the close alignment between the time points of maximum DPP-4 inhibition and the T_{max} of evogliptin concentration within each subject, as well as the absence of hysteresis when plotting evogliptin concentration against DPP-4 inhibition. Furthermore, no discernible pattern in DPP-4 inhibition emerged when stratifying the DPP-4 inhibition profiles by subject groups, thus affirming the suitability of the PK-PD direct link model (Figure 10). The individual *post hoc* estimates of the final PK model were used to develop the DPP-4 inhibition model. Inclusion of IIV for E_{max} and EC_{50} improved the model fit and was implemented. The typical values in the final model were E_{max}, 95.7%; EC_{50}, 0.837 μg/L; and γ, 1.38. All PD parameters were robustly estimated, with the largest RSE among parameters being 25.8% for EC_{50}, and all ETA shrinkages were below 13%.

A bootstrap analysis was conducted to confirm the precision of the parameter estimates (Table 7). A total of 1000 bootstrap replications were conducted using the original PK and PD data, and 992 (99.2%) replicates converged with a successful covariance step. All the typical PD parameter values were within the 95% confidence intervals of the bootstrap results. This confirmed the precision of the final model parameters. When observed PD data were overlaid with the PD prediction by the PK/PD model, the results showed an acceptable overlap (Figure 11).

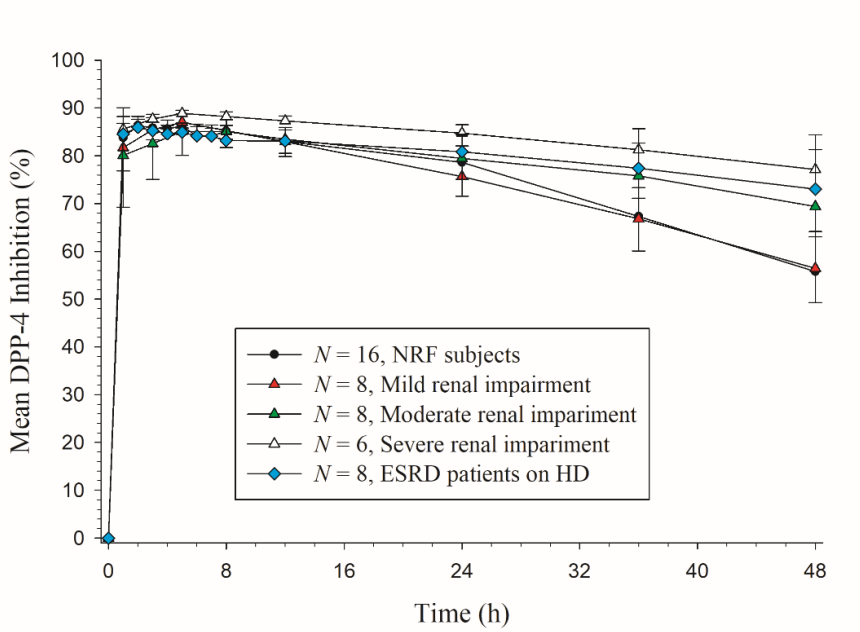


Figure 9. Mean E(DPP-4 % inhibition)-time profiles after a single oral administration of evogliptin 5 mg.
Abbreviations: DPP-4, dipeptidyl peptidase-4; ESRD, end-stage renal disease; HD, hemodialysis; NRF, normal renal function.

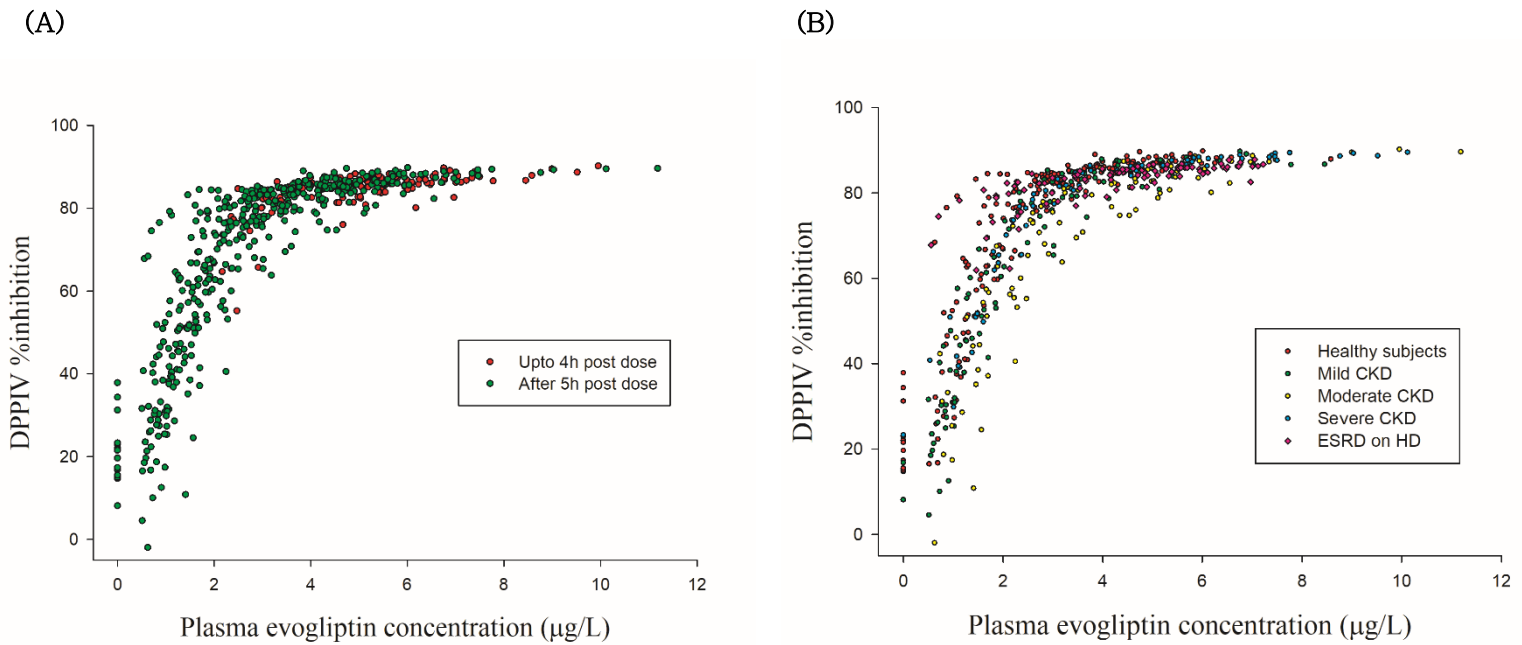


Figure 10. Observed DPP-4 inhibition and pharmacokinetic profiles, stratified by (A) time and (B) subject group

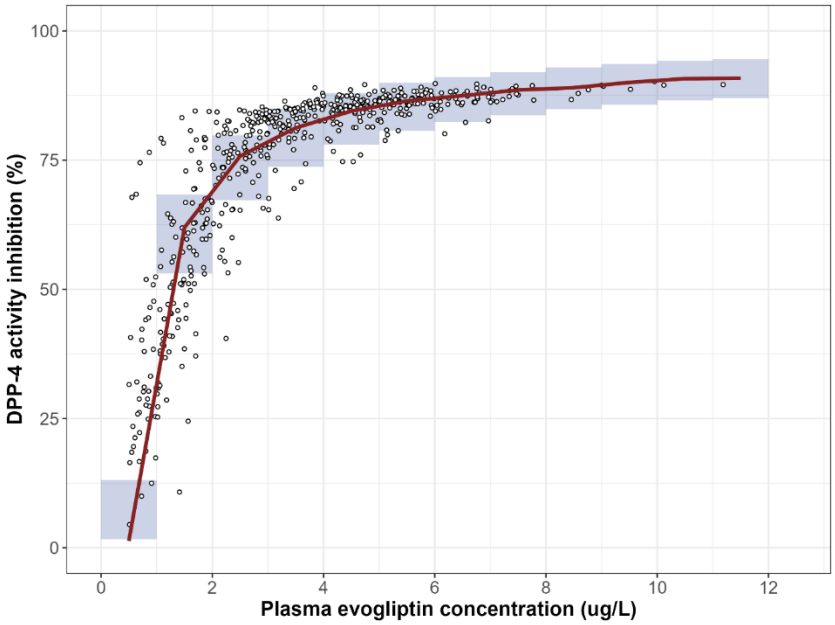


Figure 11. Observed data overlaid with simulated data of the PD model. Red line indicates the median, and blue box indicate 5 and 95% prediction intervals. Dots represent individual observations.

Chapter 4. Discussion

In this study, a population PK/PD model for evogliptin was developed. Utilizing a range of routinely employed laboratory tests, my objective was to construct a PK model of evogliptin under uremic conditions. To my knowledge, this is the first population PK/PD analysis of evogliptin, a CYP3A4 substrate, in patients with renal impairment. By performing a prospective study on patients with varying degrees of renal impairment and HD status, the impact of contributing covariates on the metabolism of evogliptin was evaluated. The results from this study also further supported the safe use of evogliptin in the renal impairment population.

Evogliptin PK was best described by a two-compartment, first-order absorption model with linear elimination. The final model of evogliptin was robust and adequate with good precision based on the goodness-of-fit plots, visual predictive checks, and bootstrap results. Evogliptin displayed an apparent first-order elimination (CL/F) of 18.9 L/h, and an apparent central distribution volume of 36.7 L.

A significant correlation was identified when Chl was

incorporated into the relative bioavailability F_r, with a power of 2.43 and a ΔOFV of −16.437. Blood chloride levels displayed an increasing tendency according to the degree of renal impairment (103, 106 and 107 mmol/L for mild, moderate and severe renal impairment, respectively) but showed lower boundary levels in ESRD patients on HD (before and after HD, median 97 and 96 mmol/L, respectively). This is probably due to the chloride levels being stabilized through the HD process in ESRD patients. This influence of HD (and the resulting low blood chloride level) on decreased relative bioavailability F_r may be attributed to the periodic removal of uremic toxins in patients undergoing HD. Prior research has indicated that HD can acutely enhance the metabolic activity of CYP3A4, potentially through the elimination of uremic toxins that inhibit the enzyme's activity [8]. While blood chloride is not classified as a uremic toxin, its correlation with the observed drug exposure suggests that it may be used to represent the clearance of uremic toxins in RI patients.

Blood chloride levels are known to be associated with acute kidney injury [17, 18]. In two randomized control trials, both critically ill and noncritically ill patients who received fluids with higher chloride concentrations showed worsened renal outcomes

[19, 20]. This further suggests that blood chloride levels may be correlated with renal dysfunction and the resulting uremic state.

Blood amylase levels were also significantly correlated with F_r (⊿OFV = −23.492). Amylase levels are known to be associated with the degree of renal impairment due to a decrease in renal clearance [21]. In the current study, amylase displayed a tendency to increase with decreasing renal function and showed the highest value in ESRD patients: 75.75, 102.5, 113.75, and 150.5 IU/L in mild, moderate, and severe renal impairment and ESRD patients, respectively.

Among the pharmacokinetic parameters of evogliptin, the relative bioavailability F_r was most substantially influenced by the presence of covariates. While CL/F was influenced by covariates such as blood triglyceride and LDH levels (⊿OFV = −4.984 and −3.881), this parameter was discarded due to identifiability issues and lack of significance at .01 (⊿OFV = −6.63). Previous studies have reported increased oral bioavailability and decreased systemic clearance in CYP3A-selective substrates in renal impairment conditions, such as the antidepressant reboxetine and the dihydropyridine calcium channel blockers nicardipine, nimodipine, and nitrendipine [6].

The proposed mechanism of this increased bioavailability includes a reduction in the first-pass metabolism by CYP3A4. As a selective substrate of cytochrome CYP3A4, evogliptin exhibited pharmacokinetic properties similar to those of the aforementioned drugs.

When the PK model was simulated with different patient scenarios, maximum boundary levels of amylase, chloride and age (scenario B) displayed the highest drug exposure, with approximately 1.8-fold greater AUC_{0-120} than in reference scenario A. In contrast, drug exposures were significantly lower in the scenario where blood chloride was low (scenario C3), reflecting decreased bioavailability in patients undergoing HD. While the simulation outcomes suggest an increased likelihood of elevated evogliptin exposure in patients with higher amylase and chloride levels (scenario B), the observed variance in evogliptin exposure (~1.8-fold) is unlikely to be clinically significant. This is due to the broad safety margin associated with evogliptin's pharmacological profile [22].

A previous microdosing study conducted in healthy individuals revealed an absolute bioavailability of 0.502 for evogliptin. Therefore, it was anticipated that the healthy subject

group in the current study would exhibit a similar bioavailability of 0.5 [23]. However, in the severe renal impairment group, the mean AUC_{last} and AUC_{inf} were approximately 1.61- and 1.97-fold higher, respectively, than in the corresponding healthy subjects. Likewise, in scenario B of the PK simulation, which represents a severe renal impairment condition, the AUC_{0-120} was 1.8-fold higher than in reference scenario A. Considering that the only significant covariate in clearance was age in the PK model, these findings suggest that in severe renal impairment conditions, there is a notable inhibition of the hepatic first-pass metabolism and/or gut wall metabolism, resulting in higher bioavailability (0.80 to 0.99, approximated from the above AUC values and the reported bioavailability of 0.5). This inhibition of first-pass metabolism can be considered a distinctive characteristic that can be affected by the presence of the uremic state for drugs exhibiting a significant first-pass effect. However, it should be noted that the same approach may not be applicable to drugs with high bioavailability, as these drugs are expected to exhibit limited variability in bioavailability in response to the uremic state.

Drug PK may be affected by their unbound concentration, so

it can be hypothesized that the uremic state affects blood albumin concentration, which in turn will affect evogliptin clearance. However, a clear trend in albumin concentration was not observed among the different subject groups. The average albumin levels of each subject group were 4.3, 4.3, 4.1, 3.9, and 4.5 g/dL in healthy individuals and patients with mild, moderate, and severe CKD and ESRD, respectively. In severe CKD patients with low albumin levels, exposure to the drug seemed to be increased, which is counterintuitive since increased unbound concentration should contribute to increased clearance. Overall, the effect of altered albumin concentration on the clearance of evogliptin was not clear.

An approximation of the hepatic extraction ratio of evogliptin was performed to evaluate the potential impact and magnitude of the uremic state on hepatic clearance. If evogliptin is a drug with a low hepatic extraction ratio, it is plausible that the clearance of evogliptin may be significantly influenced by the unbound fraction and hepatic CYP3A4 activity. Assuming an equal distribution of evogliptin between plasma and red blood cells (RBCs), the following equation can be utilized to estimate the blood clearance.

$$CL_P/(1-HCT) = CL_B$$

According to the findings from the previous microdosing study, the observed absolute clearance in healthy subjects was 12.96 L/h, while a similar trend was observed in severe renal impairment patients in the current study (CL/F = 13.74 L/h), where the highest bioavailability was anticipated. Therefore, CL_P was assumed to be 13 L/h. Assuming HCT to be 0.4, CL_B was calculated [13/(1−0.4) = 21.7 L/h]. The following equation can be utilized to determine the hepatic extraction ratio:

$$CL_B = E_H \times Q$$

where E_H=hepatic extraction ratio, and Q=hepatic blood flow. Assuming a hepatic blood flow of Q=1 L/min (60 L/h), E_H is 21.7/60 = 0.36 [24]. This ratio corresponds to an intermediate to low hepatic extraction ratio. Hence, if CYP3A4 activity is assumed to be inhibited by uremia, it is anticipated that the clearance of evogliptin, which displays an intermediate to low extraction ratio, would undergo some degree of modulation according to the unbound fraction and CYP3A4 activity.

When the absolute clearance values were estimated, the NCA findings of this study revealed a CL/F (clearance to bioavailability ratio) ranging from approximately 28 to 30 L/h in healthy individuals, which, considering the previously determined

bioavailability of 0.5 for healthy subjects from a microdosing study, corresponds to an absolute CL of approximately 14 to 15 L/h. Conversely, in the case of severe renal impairment, incorporating the observed AUC values derived from NCA and the relative bioavailability obtained through the PK model, an absolute bioavailability of approximately 0.8 to 0.99 can be approximated. Assuming an F (bioavailability) value of 0.9, the adjusted CL for severe renal impairment patients can be calculated as 0.9 x 13.74 = 12.4 L/h. Hence, renal impairment patients demonstrate a somewhat diminished clearance profile, potentially attributed to the presence of uremia. However, the disparity in clearance rates was not substantial, potentially owing to evogliptin's positioning near the boundary between a low and intermediate extraction ratio.

The present study successfully fitted an E_{max} pharmacodynamic model to the observed data, illustrating a strong correlation between evogliptin concentration and DPP-4 inhibition. The E_{max} model parameters, including E_{max}, EC_{50}, and γ, were estimated with good precision, and bootstrap replications achieved a 99.2% success rate. The typical E_{max} value of 95.7% indicates near-complete DPP-4 inhibition at

maximum drug effect. The EC_{50} of 0.837 μg/L is lower than that of most existing DPP-4 inhibitors, such as linagliptin (EC_{50} = 1.42 μg/L), highlighting the high potency of evogliptin [25].

There were several limitations to the study. First, while the study aimed to elucidate the effect of the uremic state on the CYP3A4-mediated metabolism of evogliptin, it is still unclear whether the observed PK characteristics of evogliptin are a direct result of inhibition of CYP3A4 metabolism by uremic toxins. It is possible that the increased bioavailability is due to an unknown factor that independently inhibits first-pass metabolism. Second, most of the previously proposed uremic toxins and endogenous metabolic markers for CYP3A activity (e.g., 4beta-hydroxycholesterol in plasma) were not investigated in the current study, which, if measured, could potentially be statistically better covariates for the PK model [16]. Third, it cannot be ruled out that the observed variation in the PK of evogliptin was due to other factors, such as undetected hepatic impairment. However, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values in the participants were mostly within the normal range (<40 U/L), except for one healthy subject with an ALT of 49 U/L. Given the

AST and ALT values, the presence of undetected hepatic damage is unlikely. Finally, the possibility of the observed PK variation being attributed to an unidentified drug interaction resulting from concomitant medications cannot be completely dismissed. However, a thorough assessment of the concomitant medications was carried out, and no noteworthy potential drug interactions were found.

Chapter 5. Conclusion

The established PK/PD model of evogliptin, a selective substrate of CYP3A4, adequately predicted the variability of absorption, systemic exposure and elimination in the renal impairment population. This study suggests that the extent of renal impairment and the resulting biochemistry may be used to predict the PK of drugs metabolized by CYP3A4. My model will provide a basis for future assessments of the effect of uremia on the nonrenal clearance of drugs and facilitate the optimization of drug dosing regimens for patients with renal impairment.

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Abstract in Korean

서론: 요독증(uremia) 또는 요독증후군(uremic syndrome)은 신기능 저하로 인해 혈액 중 노폐물(요독소)이 축적되는 병리학적 상태이다. 요독소는 몸에 축적되어 사이토크롬 P450 효소(CYP3A4 등)를 통해 이루어지는 약물 대사 및 배설과 같은 여러 생리 과정에 영향을 준다. 에보글립틴(evogliptin)은 2형 당뇨병 치료에 사용되는 디펩티딜 펩티다제-4(DPP-4) 억제제로, 주로 간에서 CYP3A4 효소에 의해 대사된다. 요독증은 CYP3A4의 기능에 영향을 미칠 수 있으며, 이는 에보글립틴의 대사 및 배설에 중요한 영향을 미칠 수 있다. 신장 손상 환자에서 CYP3A4를 주로 대사시키는 에보글립틴과 같은 약물에 대한 인구 약동학(PK) 및 약력학(PD) 모델링을 수행하면, CYP3A4를 주로 대사시키는 약물의 약동학을 예측할 수 있다. 본 연구는 다양한 정도 신장 질환을 가진 환자에서 에보글립틴의 인구 PK 및 PD 모델을 구축하는 것을 목표로 하였다.

방법: 본 연구에서는 에보글립틴의 두 가지 임상 연구 데이터를 사용하였다. 하나는 다양한 정도의 신장 손상 환자와 정상 신장 기능을 가진 환자를 대상으로 한 임상 연구(NCT02214693)이고, 다른 하나는 말기 신장 질환(ESRD) 환자와 정상 신장 기능을 가진 환자를 대상으로 한 단회 투여 연구(NCT04195919)이다. 두 연구에서 대상자들은 공복 상태에서 5mg의 에보글립틴을 투여 받았다. 총

46명의 대상자로부터 취득한 688건의 에보글립틴 농도 및 598건의 DPP-4 활성 데이터가 분석에 사용되었다. 에보글립틴의 PK/PD 데이터와 혈액학, 혈액화학, 인구통계학 데이터 등의 잠재적 공변량 정보를 사용하여 인구 PK/PD 모델을 구축하였다. 모델 구축에는 비선형 혼합효과 모델링 소프트웨어(NONMEM® 버전 7.4)를 사용하였으며, 일차 조건부 추정과 상호 작용(FOCE-I)을 이용하였다. 각 매개변수는 전진 선택 및 후진 제거 방식을 사용하여 구조 모델에 순차적으로 추가되었으며, 각각 0.01과 0.001의 유의 수준을 적용하였다. 비모수적 부트스트랩 재표본 추출법을 사용하여 모델의 안정성과 모델 매개변수의 신뢰구간(CI)을 평가하였으며, 데이터 세트의 부트스트랩 복제본(n=1000)에 대해 최종 모델을 반복적으로 적용하였다. 예측 수정 시각 예측 검증(pcVPCs; 500회 시뮬레이션 복제본)을 수행하여 최종 모델을 검증하였다. 최종 PK 모델을 사용하여 5 mg 단회 투여를 가정한 농도-시간 곡선 하 면적(AUC) 및 최대 혈장 농도(C_{max})를 계산하였으며, 다양한 정도의 신장 기능을 가진 환자들의 시나리오를 평가하였다.

결과: 다양한 정도의 신장 손상을 가진 환자와 건강한 대상자들로 구성된 총 46명의 참여자가 연구에 참여하였다. 각 연구의 환자 그룹은 인구통계학적 특성이 비슷했으며, 환자군의 신장 손상의 정도는 달랐다. 총 688개의 혈장 PK 샘플을 사용하여 에보글립틴의 인구 약동학(PK)을 설명하는 비선형 혼합효과 모델을 개발하였다. 아

카이케 정보 기준(AIC), 각종 진단 플롯 및 목표 함수 값(OFV)에 기반하여 2-구획 모델과 일차 흡수가 선택된 기본 PK 모델이 선택되었다. 기본 PK 모델은 신뢰할 수 있는 매개변수 추정 및 관찰된 데이터와 예측된 데이터 간의 강한 일치성을 보였다. 최종 모델에 유지된 중요한 공변량은 혈중 chloride 및 amylase 수치가 F_r(상대적 생체이용률)에, 나이가 CL/F (외적 청소율)에, 그리고 체중이 V3/F (말초 분포량)에 영향을 미쳤다. pcVPC는 시뮬레이션된 에보글립틴 농도와 관찰된 농도 간의 중첩을 보여주었으며, 부트스트랩은 1000회 복제본 중 93.1%의 성공률을 보였다. 에보글립틴의 약동학에 관련된 공변량의 잠재적 영향을 몬테카를로 시뮬레이션을 통해 평가하였다. 시뮬레이션 결과와 이전에 보고된 evogliptin의 PK 데이터를 종합하였을 때, 중증 신장 기능 저하 환자에서 초회통과효과 대사 억제가 유의미하게 나타나는 것이 예측되었다. Direct link sigmoidal E_{max} 모델을 개발하여 혈장 evogliptin 농도와 DPP-4 억제 간의 관계를 설명했다. Evogliptin의 PK/PD 모델은 최대 효과 시에 DPP-4의 거의 완전한 억제를 예측하였으며 (E_{max}: 95.7%), 낮은 EC_{50} 값 (0.837 μg/L)을 보여주어 evogliptin의 높은 효력과 효능을 나타내었다.

결론: 개발된 에보글립틴의 PK/PD 모델은 신장 기능 저하가 있는 개체에서 흡수, 체내 노출, 배설 변동성을 정확하게 예측하였다. 본 연구는 신장 손상의 정도가 CYP3A4를 통해 대사되는 약물의 상대

생체이용률에 영향을 줄 수 있음을 시사한다. 이 모델은 앞으로 신장 기능 저하 환자에서 비 신장 약물 청소에 대한 요독증의 영향을 평가하는 근거로 사용될 수 있으며, 신장 기능 저하 환자를 위한 용량 조정 방안을 최적화하는 데 도움을 주리라 판단된다.

주요어: 에보글립틴, 디펩티딜 펩티다제-4 억제제, 제2형 당뇨병, 약동학 약력학 모델링

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