Pharm Res (2014) 31:1801–1812
DOI 10.1007/s11095-013-1284-0

RESEARCH PAPER

Population Pharmacokinetic Analysis of Simvastatin and its Active Metabolite with the Characterization of Atypical Complex Absorption Kinetics

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Received: 10 April 2013 / Accepted: 31 December 2013 / Published online: 19 February 2014

ABSTRACT

Purpose The pharmacokinetics of simvastatin is complex with multiple peaks in the absorption phase, which cannot be adequately described by a conventional first order absorption model. The biotransformation of simvastatin into simvastatin acid, an active metabolite, is reversible. This study evaluated the pharmacokinetics of simvastatin and simvastatin acid, focusing on the absorption kinetics.

Methods Data were collected from three bioequivalence studies, in which subjects were administered 60 mg simvastatin, and from one crossover study, in which subjects were administered two doses randomly selected from 10, 20, 30, 40 to 80 mg simvastatin with washout period. The pharmacokinetics of simvastatin was assessed in 133 healthy males. Plasma concentrations of simvastatin and simvastatin acid were measured in 2,182 and 2,130 samples, respectively, and the pharmacokinetic data were analyzed using NONMEM.

Results The time course of changes in the plasma simvastatin concentration was best described by a two-compartment linear model with three parallel absorption processes, each of which consisted of mixed zero-and first order absorption. Additions of inter-occasional variability to the absorption parameters significantly improved the model's fit. The disposition parameter estimates were significantly different when different absorption models were applied, indicating the importance of the appropriate absorption modeling. Pharmacokinetic modeling preferred the inter-conversion between simvastatin and simvastatin acid.

Conclusion A pharmacokinetic model describing the complex, multiple peak, absorption kinetics of simvastatin was formulated using three parallel, mixed zero and first-order absorptions. This type of absorption model may be applicable to other drugs that show irregular, multiple-peak concentrations during their absorption phase.

KEY WORDS absorption model · multiple peaks · NONMEM · simvastatin · simvastatin acid

ABBREVIATIONS

A(n)	Amount of drug in n^{th} compartment
ALAGn	Absorption lag from n^{th} compartment
CL	Clearance
CV	Coefficient of variation
Dn	Duration of zero order administration to n^{th} Depot compartment

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FM	Fraction that is metabolized to simvastatin acid of total clearance of simvastatin
Fn	Bioavailability to n^{th} depot compartment
FOCE	First-order conditional estimation
GOF	Goodness-of-fit
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IIV	Inter-individual variability
IOV	Inter-occasional variability
K	Transfer rate constant between pharmacokinetic compartment
Ka	Absorption rate constant
LLOQ	Lower limit of quantification
LOWESS	Locally weighted scatterplot smoothing
MAP	Maximum a posteriori probability
OFV	Objective function value
Q	Inter-compartmental clearance between central and peripheral compartment
Vd	Volume of distribution

INTRODUCTION

Simvastatin is a widely prescribed drug based on its effectiveness in the treatment of hypercholesterolemia. As a pro-drug, it undergoes rapid hydrolysis after absorption to several metabolites. One of these, β-hydroxyacid-simvastatin (simvastatin acid) is the active form of the drug, which competitively inhibits 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase (1). The metabolism of simvastatin is complex, involving the inter-conversion between simvastatin and simvastatin acid (2,3). Simvastatin is well absorbed from the gastrointestinal tract but highly extracted by the liver, with subsequent excretion in the bile. Owing to its extensive first-pass hepatic extraction, less than 5% of the drug reaches the systemic circulation (4).

There are very few population pharmacokinetic studies relevant to simvastatin and its metabolites (5). This is probably due in part to the difficulty of developing pharmacokinetic models that fit the multiple peaks during the absorption phase of simvastatin. A multiple-peak plasma concentration-time profile is often observed following the oral administration of several drugs (6–9). This phenomenon might be explained by enterohepatic recirculation (10–12), active intestinal secretion (13), variable gastric emptying and intestinal transit rates, (14,15) oral multi-fractional model (6,16). In general, compartmental analysis that assumes first-order absorption and elimination is often used to fit plasma concentration-time data. However, this conventional model is not appropriate for the description of multiple-peaks. In addition, the use of an inappropriate absorption model could result in the misspecification of the disposition parameter in the pharmacokinetic model and subsequent erroneous prediction of dosing regimens (17).

The objective of this study was to characterize the pharmacokinetics of simvastatin and simvastatin acid by using non-linear mixed effect modeling with focus on the absorption process and interconversion kinetics between simvastatin and simvastatin acid. Various empirical absorption models were therefore compared, including single mixed, zero and first-order absorption, two or three parallel, mixed, zero and first-order absorption, sequential zero- and first-order absorption, and a Weibull type absorption, to describe the irregular multiple-peak concentration-time curves of simvastatin, and their impact on the estimation of disposition kinetics were explored in this study.

MATERIALS AND METHODS

Pharmacokinetic Studies and Data

Plasma simvastatin and simvastatin acid concentration data were collected from a total of four pharmacokinetic studies, three bioequivalence studies, in which subjects were administered 60 mg simvastatin (Zocor®, Merck, NJ, USA) as a reference drug, and another cross-over study, in which two doses randomly selected from 10, 20, 30, 40 to 80 mg simvastatin separated by a 3-day washout period were administered. The pharmacokinetic analysis was based on a total of 2,182 simvastatin and 2,130 simvastatin acid plasma concentration measurements from 133 subjects (Table 1). All four studies were performed at the Clinical Trial Center of Asan Medical Center, Seoul, Korea. They were approved by the institutional review board of Asan Medical Center, and written informed consent was obtained from all the subjects prior to their enrollment.

Crossover Study for Simvastatin Pharmacokinetics

A two sequence and two period, crossover study of simvastatin pharmacokinetics was performed in 20 healthy Korean males. In this study, each subject received two oral doses of simvastatin (Zocor®), separated by a washout period of 3 days with 240 ml of water following an overnight fast. The two doses of simvastatin administered to each subject were randomly selected from doses of 10, 20, 30, 40 to 80 mg. Standard meals were provided 4 and 9 h after each dose. Blood samples were drawn via an indwelling intravenous catheter into a heparinized tube immediately before each dose (0 h) and at 10, 20, 30, 40, and 50 min and 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12 and 24 h after each dose.

Bioequivalence Study for Simvastatin

Pharmacokinetic data were also obtained from three bioequivalence studies of a 2×2 crossover design involving 113 healthy Korean males. Each subject in these studies received single oral dose of simvastatin 60 mg, reference or test drug

Table I Characteristics of the Male Subjects, and Pharmacokinetic Data by Each of the Four Studies Included in this Analysis

	Study I (PK[a])	Study II (BE[b])	Study III (BE[b])	Study IV (BE[b])	Total
No. of subjects	20	30	30	53	133
Age, year	26.6 ± 2.4	25.1 ± 2.7	24.5 ± 2.3	24.7 ± 2.7	25.0 ± 2.6
Weight, kg	69.4 ± 7.3	69.8 ± 6.7	69.7 ± 7.4	70.0 ± 6.9	69.8 ± 6.7
Height, cm	174.4 ± 5.2	174.6 ± 6.1	173.9 ± 5.2	175.6 ± 5.1	174.8 ± 5.4
BMI, kg/m^2	22.8 ± 1.5	22.9 ± 1.6	23.0 ± 1.8	22.7 ± 1.8	22.8 ± 1.7
Simvastatin dose, mg	10, 20, 30, 40, 80[c]	60	60	60	–
No. of simvastatin concentration	717	386	390	689	2,182
No. of simvastatin acid concentration	720	337	390	683	2,130

Data are presented as count or mean ± SD as appropriate

BMI body mass index

[a] PK means 2 × 2 crossover study performed for pharmacokinetic evaluation of simvastatin.

[b] BE means bioequivalence study of simvastatin.

[c] Randomly selected two doses of simvastatin were administered to each subject, separated by a washout period

with 240 ml of water after overnight fast in each period with a 7-day washout period. Standard meals were provided 4 and 9 h after each dose. Blood samples were collected immediately before each dose (0 h) and at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after each dose of simvastatin. For this pharmacokinetic analysis, only the data from the reference formation (Zocor®) were used.

Measurement of Plasma Simvastatin and Simvastatin Acid Concentrations

Plasma concentrations of simvastatin and simvastatin acid were measured using high-performance liquid chromatography (Symbiosis™, Spark Holland Instruments, Emmen, The Netherlands) with tandem mass spectrometry (API 4000; ABSciex, Inc., Foster City, CA) after sample preparation by liquid-liquid extraction. (18)

Modeling Strategy

Pharmacokinetic analysis was performed using NONMEM® VII level 2 (ICON Development Solutions, Dublin, Ireland), employing the first-order conditional estimation (FOCE) with an interaction method. The data were analyzed after changing the units of amount and concentration into molar units. Simvastatin and simvastatin acid were modeled sequentially (19). In the first step the pharmacokinetic model for simvastatin was built. In the second step, the pharmacokinetic model for simvastatin acid was built, using the individual parameter estimates of the pharmacokinetic model for simvastatin. The concentrations lower than the LLOQ (0.2 ng/ml for simvastatin, and 0.1 ng/ml for simvastatin acid) were regarded as the half of the LLOQs. If there are multiple values below LLOQ, during the disposition phase, the first one was fixed at the half of the LLOQ, and the LLOQ values thereafter were removed from the analysis.

Given that the concentration-time profiles of simvastatin showed multiple irregular peaks during the absorption phase, we evaluated five absorption models (20). Model I consisted of a single, mixed, zero- and first-order absorption process. In model II two parallel, mixed zero- and first order absorption models were used, which comprised two absorption processes, each described by mixed zero- and first order kinetics with time delays at the beginning of each of the zero- and first order absorption processes, respectively, such that a fraction of the dose is absorbed by one absorption process and the remainder by another process. Model III was based on three parallel, mixed zero- and first order absorption processes, and was an extension of Model II made by adding one more mixed zero- and first order absorption process to model II together with a corresponding absorption delay. Model IV was a sequential, zero- and first order absorption model, in which a fraction of the dose is absorbed by a zero-order process first, and the remainder by a first-order process. Model V was a Weibull-type absorption model that described the change in the absorption rate constant over time during the absorption phase. In all the five models, onset of the absorption was described as being delayed after drug administration. Inter-occasion variability (IOV) was taken into account with respect to the unexplained differences in pharmacokinetic parameter values among each of the multiple doses within an individual (21). Therefore, random effect parameters were added to the all the pharmacokinetic parameters for absorption and disposition in the model for each period in the crossover design, and tested whether these parameters improve the model significantly. In the disposition model, one-, two-, and three-compartment linear pharmacokinetic models were tested using the ADVAN6 or ADVAN13 subroutines. Potential

covariates of age, body weight, and height were tested to investigate whether they significantly improved the pharmacokinetic model.

Second, for the modeling of simvastatin acid, individual empirical maximum *a posteriori* probability (MAP) Bayes estimates of the simvastatin pharmacokinetics were used as inputs. One- and two-compartment models with linear elimination were fitted to the metabolite plasma concentration-time data. The central volume of distribution (V_d) of simvastatin acid was fixed at 1 L, because of the identifiability problem, and the fraction converted to simvastatin acid relative to the total clearance (CL) of simvastatin was estimated.

We also evaluated the reversibility in the conversion between simvastatin and simvastatin acid, as it may influence the modeling results. Equilibrium and non-equilibrium models in the inter-conversion between simvastatin and simvastatin acid were compared. If the inter-conversion rate is so high that the equilibrium is reached instantaneously, the equilibrium process would not be identifiable from the data, thus favoring the equilibrium model, and vice versa. Age, body weight, and height were tested whether they improved the pharmacokinetic model for the simvastatin acid. Unexplained inter-individual random variability was modeled using a log-normal model (Eq. 1):

$$P_i = P_{TV} \cdot e^{\eta_i} \quad (1)$$

Where P_i is the value of a parameter for the ith individual, P_{TV} is the typical population parameter value, and η is a random variable reflecting unexplainable inter-individual variabilities (IIV) with a mean of 0 and a variance of ω^2. Covariances among IIVs were also considered during the construction of the model. Additve, proportional, and combined residual models were tested for both parent and metabolite pharmacokinetic models.

When applicable, IOV was taken into account in Eq. 1, as follows.

$$\eta = \eta_{IIV} + \eta_{IOV1}*(1-\mathrm{OCC}) + \eta_{IOV2}*\mathrm{OCC}$$

where η_{IIV} is a random variable for unexplained IIV, η_{IOV1}, and η_{IOV21} are random variables for unexplained IOV for period 1 and period 2, respectively, and OCC is an indicator variable with a value in the crossover design of 0 in period 1 and 1 in period 2.

Evaluation and selection of the models were based on graphical as well as statistical methods. Together with a basic goodness-of-fit (GOF) plot, visual predictive checks were performed by simulating 1,000 iterations by each dose group using NONMEM and comparing the simulated median prediction and 95% prediction intervals with the original data. The log likelihood ratio test was used to discriminate among hierarchical models. A P value of 0.05, representing a decrease in objective function value (OFV) of 3.84, was considered to indicate a statistically significant difference (chi-square distribution, degree of freedom = 1) between full and reduced models.

Graphical model diagnosis was performed using R (version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria).. Statistical analyses were performed using R and SigmaStat 3.5 for Windows (Systat Software, Inc., Chicago, IL) software. Data are expressed as counts, percentages, mean ± standard deviation, or medians (ranges) as appropriate.

RESULTS

Parent Model

A two-compartment model was chosen as the final disposition model for simvastatin pharmacokinetics based on the OFV changes and GOF plots after testing one through three compartment models. We tested various absorption models to describe the atypical, simvastatin concentration profile during absorption phase. Residual variability incorporated both additive and proportional error terms. The results from some, representative pharmacokinetic models tested in this study are shown in Table 2, where the final PK model (Model III) shows the lowest OFV compared the other models with different absorption kinetics. The pharmacokinetics of simvastatin were best described by the three parallel, mixed zero- and first-order absorption model (Model III in the Methods section), in which the dose of simvastatin was distributed to three depot compartments, with absorption of the drug following mixed zero- and first-order kinetics with lag times in each absorption process. The relative bioavailabilities from each of the three depot compartments are described by the following equations:

$$\begin{aligned} F1 &= \frac{1}{(1 + BA1 + BA2)} \\ F2 &= \frac{BA1}{(1 + BA1 + BA2)} \\ F3 &= \frac{BA2}{(1 + BA1 + BA2)} \end{aligned} \quad (2)$$

where F1, F2, and F3 are the bioavailabilities from each depot compartment, and BA1 and BA2 are parameters in the absorption model that describe the relative bioavailabilities. The population averages of BA1 and BA2 were estimated to be 0.16, and 0.70, respectively, which means that on average, about 53.8%, 8.6%, and 37.6% of total amount of bioavailable simvastatin are absorbed through the 1st, 2nd and 3rd absorption peak, respectively.

Table II Comparison of the Different Absorption Models Tested for Modeling Simvastatin Pharmacokinetics

Model no.	Absorption model	No. of parameters	OFV
Model I	Single mixed, zero- and first-order absorption	17	5,757.0
Model II	Two parallel, mixed zero- and first-order absorption	25	5,652.9
Model III[a]	Three parallel, mixed zero- and first-order absorption	35	5,274.1
Model IV	Sequential zero-order then first-order absorption	21	6,682.5
Model V	Single Weibull function absorption	19	5,999.0

A two-compartment model with first-order elimination (7,615.9 in OFV) was in turn combined with a single mixed zero- and first-order, a two parallel mixed zero- and first-order, a three parallel mixed zero- and first-order, a sequential zero- then first-order and a one Weibull input to fit the absorption profiles

OFV objective function value (−2 log likelihood)

[a] Selected base model of simvastatin

Estimates of the fixed effect parameters, IIV's and IOV's of the final pharmacokinetic model for simvastatin are summarized in Table 3. There was a significant improvement in the model when IOV's were included in the absorption-related parameters. IOVs were significant in BA1, BA2 which are related with the bioavailability of simvastatin, and D_1, D_2, D_3 which are the durations of zero order absorptions from each of the 3 depot compartments. The variance of IOV of each absorption-related parameter was greater than the variance of the IIV of each corresponding absorption related parameters as summarized in Table 3. The apparent central, peripheral $V_{d'ss}$, and CL were estimated to be 199.0 L, 2,710.0 L, and 571.0 L/h, respectively. The plot of the observed plasma simvastatin concentrations versus the model predicted concentration over time showed that the final pharmacokinetic model predicted the observed concentration reasonably well (Fig. 1). Figure 1 shows that the individual predictions are in good agreement with the quite complex observed simvastatin concentrations and are quite different by each subject, reflecting the irregular, complex absorption patterns of kinetics. The other models tested did not satisfactorily predict the multiple peaks during the absorption phase. The diagram for the final pharmacokinetic model, including both the parent and the metabolite, is shown in Fig. 2. The basic goodness-of-fit plots are shown in Fig. 3 (left panel) and predictive check plots of the final model in Fig. 4 (upper 6 plots). Although there seems to be underprediction of the model in the population prediction versus observation plot (Fig. 1a), overall, there was no significant trend as evidenced in the locally weighted scatterplot smoothing (LOWESS) line. No significant trend was observed over time, either (Fig. 1c). Generally, model predicted the observed simvastatin concentration well,

Table III Population Pharmacokinetic Parameter Estimates, 95% Confidence Intervals and Inter-Occasion Variability of the Final Pharmacokinetic Models of Simvastatin and Simvastatin Acid

	Population mean estimate (RSE, %)	95% confidence interval
Parent model		
$V_{central}$ (L)	199.0 (19.1)	124.32–273.68
$IIV_{Vcentral}$, % CV	79.0 (40.8)	31.9–118.1
$V_{peripheral}$ (L)	2,710.0 (17.3)	1,788.8–3,631.2
Cl (L/h)	571.0 (17.1)	379.5–762.5
IIV_{CL}, % CV	66.5 (19.3)	50.6–81.0
$CORRIIV_{Vcentral\text{-}CL}$	0.62 (40.2)[a]	0.08– −0.65[b]
Q (l/h)	199.0 (23.9)	172.68–415.32
IIV_{Q}, % CV	93.6 (32.0)	51.5–133.5
$CORRIIV_{Vcentral\text{-}Q}$	−0.17 (107.8)[a]	−0.13– −0.36[b]
$CORRIIV_{CL\text{-}Q}$	−0.38 (38.1)[a]	−0.40– −0.06[b]
Ka_1 (h^{-1})	0.00126 (54.6)	−0.0001–0.0026
IIV_{Ka1}, % CV	47.1 (68.0)	0–77.1
Ka_2 (h^{-1})	0.964 (0.3)	0.959–0.969
IIV_{Ka2}, % CV	43.9 (0.2)	43.8–43.9
Ka_3 (h^{-1})	0.179 (8.2)	0.150–0.208
IIV_{Ka3}, % CV	50.0 (21.3)	37.2–61.0
BA1	0.636 (49.4)	0.02–1.25
IIV_{BA1}, % CV	47.6 (78.4)	0–82.3
IOV_{BA1}, % CV	59.3 (35.2)	31.3–81.4
BA2	0.662 (13.2)	0.54–0.86
IIV_{BA2}, % CV	45.4 (45.5)	14.3–65.2
IOV_{BA2}, % CV	68.4 (21.6)	49.8–85.3
ALAG2	0.142 (6.9)	0.123–0.161
IIV_{ALAG2}, % CV	46.4 (19.8)	35.6–55.8
ALAG3-ALAG2	0.787 (8.4)	0.657–0.917
$IIV_{ALAG3\text{-}ALAG2}$, % CV	45.2 (28.0)	29.6–57.8
D_1	0.102 (0.06)	0.0594–0.0596
IIV_{D1}, % CV	47.1 (197.5)	0–128.4
IOV_{D1}, % CV	59.2 (118.3)	0–130.7
D_2	0.502 (9.1)	0.413–0.591
IIV_{D2}, % CV	46.3 (80.9)	0–80.7
IOV_{D2}, % CV	59.6 (23.3)	42.4–74.7
D_3	1.38 (5.54)	1.10–1.66
IIV_{D3}, % CV	46.1 (39.7)	20.9–64.0
IOV_{D3}, % CV	57.0 (35.5)	29.9–78.1
ε_1 (*additive*) (nmole/L)	0.118 (6.0)	0.104–0.132
ε_2 (*proportional*)	0.236 (2.8)	0.223–0.245
Metabolite model		
FM	0.236 (0.4)	0.234–0.238
Q_{64}	112.0 (0.2)	111.47–112.53
IIV_{Q64}, % CV	96.5 (12.8)	0.49–0.82
K_{67}	252.0 (6.0)	222.21–281.79
IIV_{K67}, % CV	88.6 (12.8)	0.45–0.71
K_{76}	2.30 (9.0)	1.89–2.71

Table III (continued)

	Population mean estimate (RSE, %)	95% confidence interval
IIV_{K76}, % CV	130.2 (12.2)	0.75–1.23
$CORRIIV_{K67\text{-}K76}$	−0.90 (8.9)[a]	−0.81– −0.56[b]
Cl_m	0.035 (41.4)	0.01–0.06
IIV_{CLm}, % CV	41.0 (30.2)	0.06–0.25
ε_3 (*additive*) (nmole/L)	0.27 (0.7)	0.26–0.27
ε_4 (*proportional*)	0.43 (1.0)	0.42–0.43

Inter-individual and residual random variabilities were modeled using a log-normal model, and a combined additive and proportional model, respectively

IOV inter-occasion variability; *IIV* inter-individual variability; *CORRIIV* correlation between IIVs; ε_1 *and* ε_3 standard deviation; ε_2 *and* ε_4 coefficient of variation; *RSE* relative standard error = SE/estimate × 100 (%); *% CV* unexplained inter-individual variation expressed as a percentage of the coefficient of variance; $V_{central}$ central volume of distribution (L) which is V4 in the model; $V_{peripheral}$ peripheral volume of distribution (L) which is V5 in the model; *Cl* total clearance of simvastatin (L/h); *Q* inter-compartmental clearance (L/h); Ka_1 absorption rate constant of the first depot compartment (h^{-1}); Ka_2 absorption rate constant of the second depot compartment (h^{-1}); Ka_3 absorption rate constant of the third depot compartment (h^{-1}); *BA1 and BA2* parameters describing the relative bioavailabilities in each of the three depot compartments $\left(\mathrm{F1}=\frac{1}{(1+BA1+BA2)}, \mathrm{F2}=\frac{BA1}{(1+BA1+BA2)}, \mathrm{F3}=\frac{BA2}{(1+BA1+BA2)}\right)$; *ALAG2* absorption lag-time of the second depot compartment (h); *ALAG3* absorption lag-time of the third depot compartment (h); *ALAG3-ALAG2* difference between *ALAG3* and *ALAG2*; D_1 duration of zero order absorption into the first depot compartment (h); D_2 duration of zero order absorption into the second depot compartment (h); D_3 duration of zero order absorption into the third depot compartment (h); *FM* fractional metabolic clearance for the conversion of simvastatin to simvastatin acid; Q_{64} inter-compartmental clearance for reversible conversion between simvastatin acid to simvastatin; K_{67} *and* K_{76} inter-compartmental rate constants; Cl_m apparent clearance of simvastatin acid (L/h)

[a] Relative standard error of covariance

[b] 95% confidence interval of covariance

although there was underprediction in 60 mg group (E of Fig. 4).

Metabolite Model

The disposition of simvastatin acid was best described by a two-compartment model with combined error model based on the OFV changes and GOF plots. The model preferred the model with inter-conversion with a non-equilibrium between simvastatin and simvastatin acid to that with equilibrium after a single oral dose of simvastatin (the OFVs of the non-equilibrium and equilibrium models were 13,140.4 and 16,274.5, respectively). The population pharmacokinetic parameter estimates of the metabolite model are summarized in Table 3. Metabolic fraction from simvastatin to simvastatin acid (FM) was estimated to be 0.236, when we fixed the central V_d of simvastatin acid at 1 L, and apparent clearance of simvastatin acid was 0.035 L/h. Interindividual variations of intercompartmental clearance from simvastatin acid to simvastatin (Q_{64}) was relatively larger (112.0% in CV) than those of the other pharmacokinetic parameters. The GOF's are shown in Fig. 3 (right panel) and predictive checks of the metabolite model in Fig. 4 (lower 6 plots).

Age, body weight, and height had not improved any model for simvastatin and simvastatin acid.

DISCUSSION

After oral administration, some drugs exhibit atypical, complex absorption patterns that do not follow simple first-order kinetics. The absorption process of such drugs might be affected by many factors, including the characteristics determined by oral dosage formulations, such as the nature of the excipients, and coatings, which could affect the rate of disintegration, its dissolution in the gastrointestinal tract, and the properties of the active ingredient itself, such as its solubility. An appropriate absorption model can lead to a better understanding of the mechanisms underlying the atypical absorption profiles, and may prevent bias in estimations of the disposition pharmacokinetic parameters. Erroneous estimates can lead to inaccurate predictions of the pharmacokinetic profile over time for various dosing regimens.

In this study, high and multiple-peak plasma concentration-time profiles of simvastatin were observed following oral administration of simvastatin tablets to fasted subjects. This phenomenon has been observed in many other drugs, including diclofenac sodium (6), etintidine (7), bumetanide (8), and zolmitriptan (9). Conventional analysis which assumes single, first-order absorption, is not appropriate to describe the multiple-peak data during the absorption phase of these drugs. Multi-fraction absorption models, in which drugs during their passage in the gastrointestinal tract, were divided into several fractions (each with its own lag time and absorption rate constant) have recently been evaluated for drugs with irregular absorption profiles (16). A previous study in animals suggested that 61–85% of a dose of simvastatin is absorbed from the stomach. The multiple-peak absorption profile of simvastatin might result from site-specific absorption, with the different rates and lag times due to the different rates and lag times of site-specific absorption (22). We applied our pharmacokinetic model, based on three-site discontinuous absorption, to fit the multiple-peak absorption profiles of simvastatin. The pharmacokinetic results obtained for simvastatin in this study are similar to those described in a previous report (5), although direct comparison is not feasible owing to the difference in the structural pharmacokinetic models adopted. In the previous study, the typical values of V_d, and CL are 8,980 L, and 1,740 L/h, respectively, compared to 2,909 L (central V_d + peripheral V_d), 571 L/h, respectively in this study. When we adopted the conventional first-order

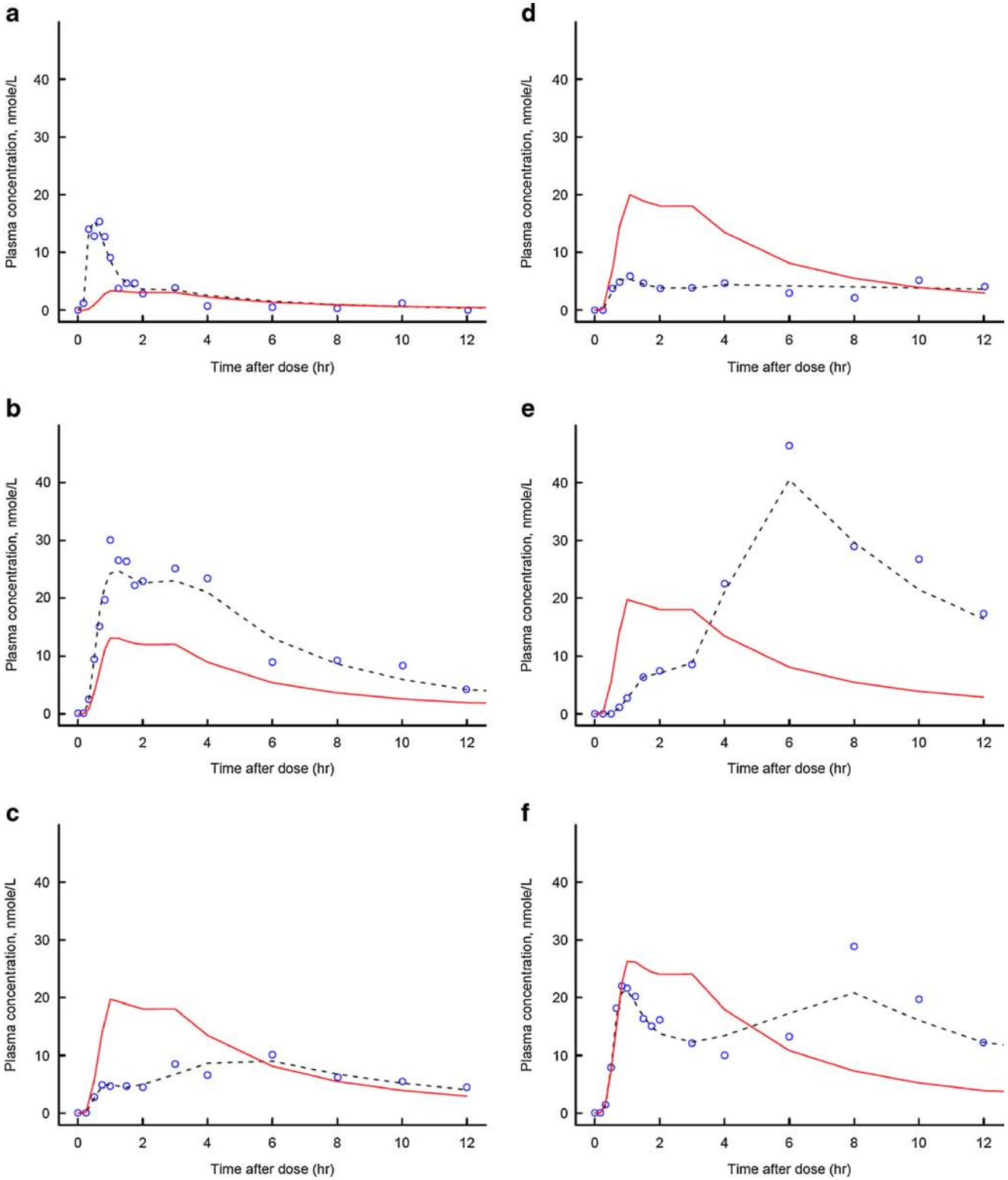

Fig. 1 Plasma simvastatin concentrations, individual predictions of simvastatin concentration and population predictions of simvastatin concentration vs. time in six subjects from different dose groups. (**a**) 30 mg, (**b**) 40 mg, (**c**, **d** and **e**) 60 mg, (**f**) 80 mg; *Empty circles* are observed simvastatin concentrations; *Red solid lines* are population predictions of simvastatin concentrations; *Blue dashed lines* are individual predictions of simvastatin concentrations.

absorption model with an absorption lag, as in the previous study, the parameter estimates increased to 4,827 L in central V_d+peripheral V_d, and CL of 1,000 L/h, more in line with the results of that study. Absorption related parameters and V_d are often hard to determine accurately because of relatively sparse sampling for pharmacokinetics during the absorption

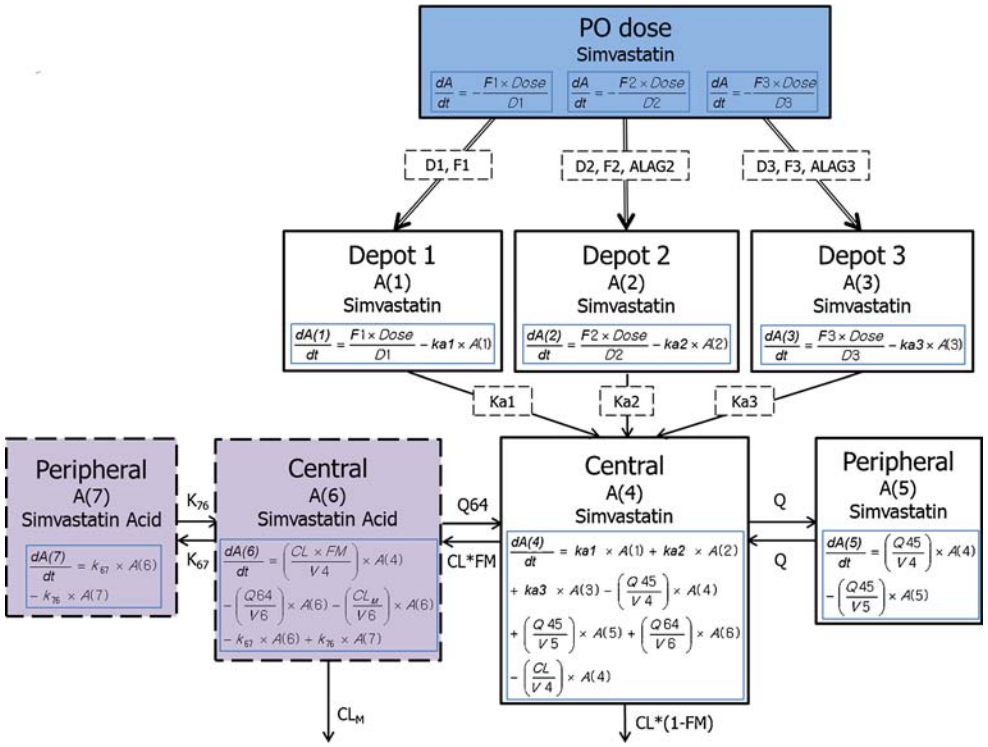

Fig. 2 Diagram for final pharmacokinetic model of simvastatin and simvastatin acid. Differential equations in $DES block in NONMEM are displayed. Concentrations of simvastatin and simvastatin acid are A(4)/V4, and A(6)/V6, respectively. *A(n)* amount of drug in nth compartment; *Dn* duration of zero order administration to nth Depot compartment; *Fn* bioavailability to nth depot compartment (F1 + F2 + F3 = 1); *ALAGn* absorption lag from nth compartment, which means that the absorption from nth compartment begins after ALAGn; *Kan* absorption rate constant from nth depot compartment; *Q* inter-compartmental clearance between central and peripheral compartment of simvastatin; *CL* total clearance of simvastatin; *FM* fraction that is metabolized to simvastatin acid out of total clearance of simvastatin (CL); *Q64* clearance of simvastatin acid to simvastatin; CL_M total clearance of simvastatin acid; *Vn* volume of distribution of nth compartment; K_{67} transfer rate constant of simvastatin acid from central to peripheral compartment; K_{76} transfer rate constant of simvastatin acid from peripheral to central compartment.

phase. In 2 × 2 crossover trial in 20 subjects as a part of current study, more dense sampling during absorption phase than usual was conducted (predose (0 h), and at 10, 20, 30, 40, 50 min and 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12 and 24 h after each dose), which would make this complex absorption modeling possible.

Enterohepatic recirculation refers to the process in which a drug from the systemic circulation accumulates in the gall-bladder, and is then released into the gastrointestinal tract in response to food intake. This process has been shown to contribute to the occurrence of multiple peaks in the plasma concentration-time profile of various drugs, with the extent of the enterohepatic circulation affecting the bio-availability of a drug (10,11,23). We did not observe a definite enterohepatic circulation pattern for simvastatin, given that most of the peaks occurred before the first meal, was consumed, 4 h after administration of the drug. In a previous report, multiple peaks in the concentration-time profile have not been observed after intravenous administration of simvastatin (24).

The absorption model in the final pharmacokinetic model describes multiple, irregular peaks during absorption phase using 3-depot compartment with mixed zero-order and first-order absorption from each compartment, Individual predictions in Fig. 1 are in good agreement with the observed concentraton, and the large differences between population and individual predictions are due to the high random effect parameters for the inter-individual and intra-individual variability in this model, which reflects the irregular absorption phenomena of simvastatin. The addition of IOV to the absorption parameters for zero-order absorptions and bioavailabilities in our model significantly improved the model's fit. When IOVs were introduced to disposition parameters of simvastatin and parameters for simvastatin acid, there was no significant improvement of the model. This indicates that, even within an individual, the absorption patterns may differ each time he or she takes simvastatin. The estimated variances in the IOV's in the absorption parameters were even larger than those of the unexplained IIV for the corresponding absorption parameters, which implies that the uncertainty in absorption kinetics within a subject is larger than that between subjects (Table 3). The variances of IOVs displayed in the Table 3 give us the quantitative information on the inter-subject variability of simvastatin pharmacokinetics. Compounds with very low aqueous solubility are believed to

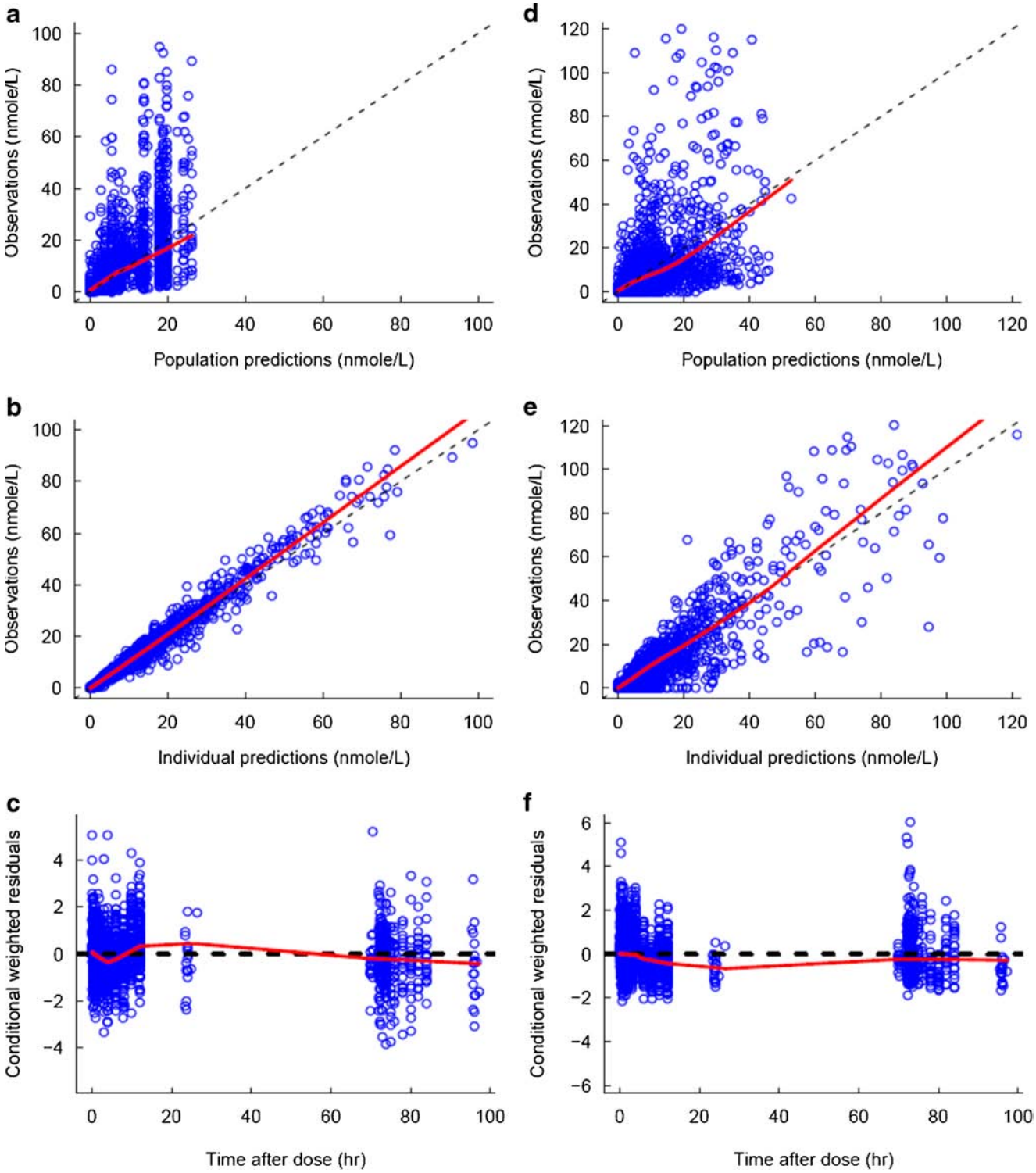

Fig. 3 Basic goodness of fit plots. **a** and **d** Population predictions vs. observations of simvastatin (**a**) and simvastatin acid (**d**); (**b** and **e**) Individual predictions vs. observations of simvastatin (**b**) and simvastatin acid (**e**); (**c** and **f**) Conditional weighted residuals vs. time of simvastatin (**c**) and simvastatin acid (**f**). *Open circles* are observed and predicted concentrations of simvastatin or simvastatin acid. *Solid lines* are locally weighted scatterplot smoothing (LOWESS) lines.

exhibit dissolution-rate limited absorption with reduced systemic absorption, and simvastain is practically not soluble in water (30 μg/mL), and 0.1 M HCl (60 μg/mL) (25). Multiple peak concentrations observed during absorption phase, and the model improvement after the inclusion of IOVs to zero-order absorption and bioavailability related parameters, may

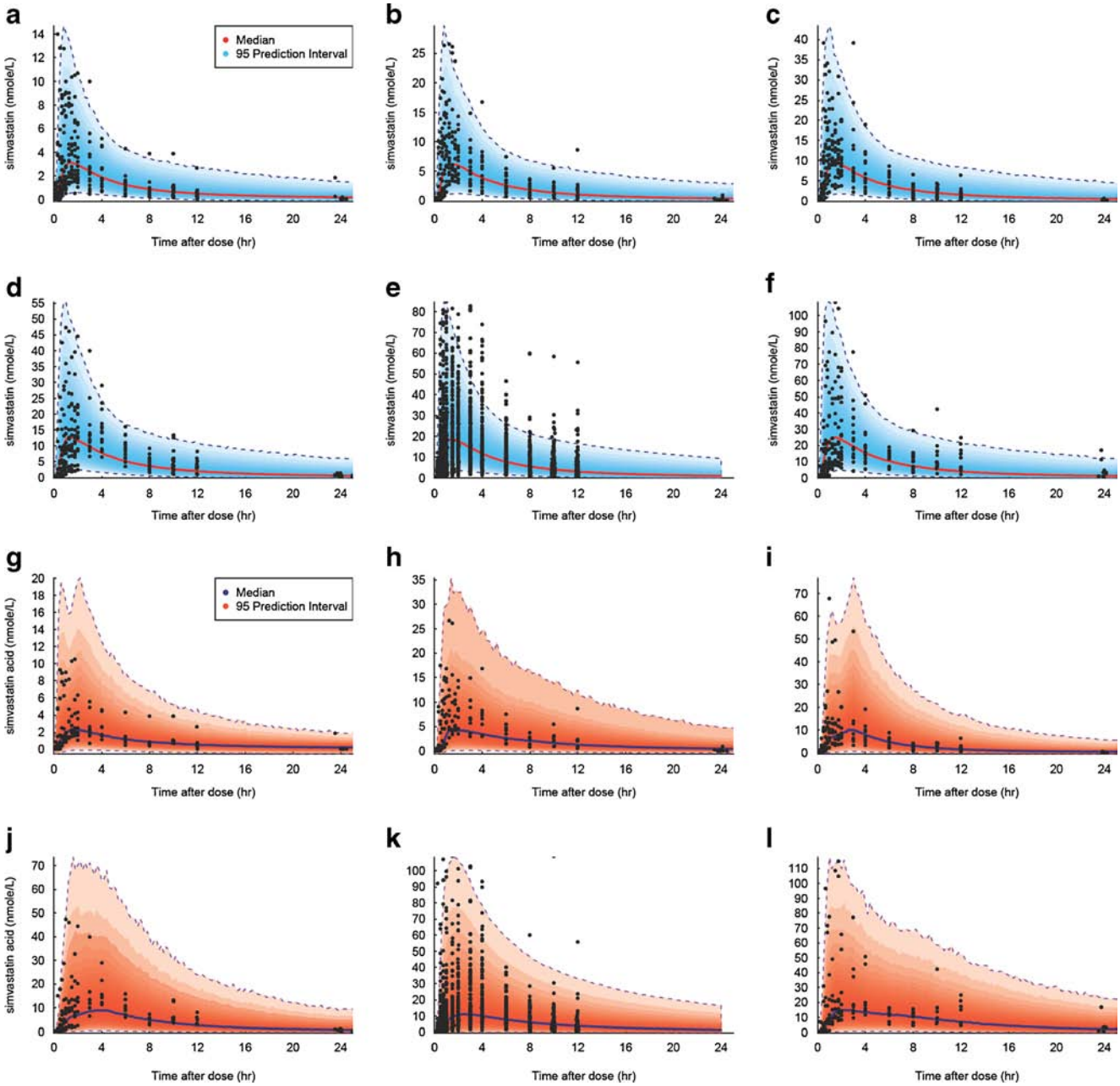

Fig. 4 Predictive checks of the final pharmacokinetic models of each dose groups. (**a** and **g**) 10 mg; (**b** and **h**) 20 mg; (**c** and **i**) 30 mg; (**d** and **j**) 40 mg; (**e** and **k**) 60 mg; (**f** and **l**) 80 mg; The *blue and orange filled area* represents the 95% prediction intervals by pharmacokinetic models for simvastatin and simvastatin acid, respectively. *Red and black solid lines* are median predictions by the pharmacokinetic models for simvastatin and simvastatin acid, respectively.

suggest that the irregularities in the absorption processes of simvastatin could result from the dynamically changing environment for dissolution of simvastatin in gastrointestinal tract at each time of administration even within each individual.

As described in the Materials and Methods section, pharmacokinetic models were tested by using various absorption models including models I–V. The resulting dispositions of the parameter estimates of simvastatin were quite different, especially regarding the central V_d, which ranged from 157 to 3,520 L, and was 214 L in the final model. By contrast, there was little change in the other major disposition parameters. Thus, the CL ranged from 750 to 1,000 L/h (750 L/h in the final model) and the peripheral V_d from 3,510 to 4,540 L (3,510 L in the final model). This suggests that the absorption model affects the characterization of not only the absorption process but also the disposition process of the drug, underlying the importance of appropriate absorption modeling during pharmacokinetic analyses. The models I–V did not predicted the observed concentration well in goodness of fit plots, which was improved a lot in the final pharmacokinetic model.

Simvastatin undergoes extensive first-pass hepatic extraction by phase I enzyme like CYP3A during absorption, significantly limiting the bioavailability (4). During modeling process, the first effect model was tested by implementing direct transfer of simvastatin acid to the central V_d of the metabolite from Depot compartments. However, the model did not improved significantly.

The model was in favor of interconversion between simvastatin and simvastatin acid in agreement with previous study (3), and preferred non-equilibrium model than equilibrium one for the interconversion with wider interindividual variation (112.0% in CV), which indicates that the interconversion is not fast enough to be indistinguishable, compared the other pharmacokinetic processes.

The V_d of a metabolite cannot be identified without knowing the fraction of a parent compound converted into a particular metabolite out of the total CL of the parent compound, unless the pharmacokinetic data collected following administration of metabolite alone, are available. In the absence of these data, the value of either the metabolic fraction, or the V_d of the metabolite should be fixed to an arbitrary value. In the metabolite modeling described herein, the V_d of simvastatin acid was fixed at 1 L. Although 1 L is not physiological as the V_d of simvastatin acid, this model could be used to describe and predict the simvastatin acid concentration over time, under the assumption about the V_d. The final pharmacokinetic model with three parallel, mixed zero- and first order absorption model was then able to describe the quite complex absorption patterns of simvastatin better than any of the other assessed models. The model finally selected in this study to assess the absorption kinetics of simvastatin and simvastatin acid is an empirical one, and more concentration data during the absorption phase are needed owing to the increased number of parameters compared to a conventional absorption model. Nonetheless, it is useful in describing the absorption phase of many other drugs having complex absorption pattern with multiple peaks.

CONCLUSION

Current modeling analysis describes the pharmacokinetics of simvastatin which shows multiple, irregular peaks during absorption phase using the absorption modelwith three parallel, mixed zero- and first-order absorption processes. The model also describes the non-equilibrium reversible conversion between simvastatin and its active metabolite. The proposed model may be useful for characterizing the absorption and disposition processes of many drugs showing complex absorption kinetics with multiple peaks, and it may help in designing proper dosage regimens by more accurately estimating pharmacokinetic parameters related to disposition.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was supported by Daewoong Corporation, South Korea, and a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI07C0001). The authors declare they have no conflict of interest.

REFERENCES

1. Alberts AW, Chen J, Kuron G, Hunt V, Huff J, Hoffman C, *et al.* Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. Proc Natl Acad Sci U S A. 1980;77:3957–61.
2. Prueksaritanont T, Subramanian R, Fang X, Ma B, Qiu Y, Lin JH, *et al.* Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization. Drug Metab Dispos. 2002;30:505–12.
3. Prueksaritanont T, Qiu Y, Mu L, Michel K, Brunner J, Richards KM, *et al.* Interconversion pharmacokinetics of simvastatin and its hydroxy acid in dogs: effects of gemfibrozil. Pharm Res. 2005;22:1101–9.
4. Merck Sharpe & Dohme. Manufacturer Information, Zocor: simvastatin. PA: West Point; 1991.
5. Kim J, Ahn BJ, Chae HS, Han S, Doh K, Choi J, *et al.* A Population Pharmacokinetic-PharmacodynamicModel for Simvastatin that Predicts Low-Density Lipoprotein-Cholesterol Reduction in Patients with Primary Hyperlipidaemia. Basic Clin Pharmacol Toxicol. 2011;109:156–63.
6. Mahmood I. Pharmacokinetic analysis of the absorption characteristics of diclofenac sodium in man by use of a multi-segment absorption model. J Pharm Pharmacol. 1996;48:1260–3.
7. Huang SM, Marriott TB, Weintraub HS, Arnold JD, Boccagno J, Abels R, *et al.* Clinical pharmacokinetics of etintidine. Biopharm Drug Dispos. 1988;9:477–86.
8. Lee SH, Lee MG, Kim ND. Pharmacokinetics and pharmacodynamics of bumetanide after intravenous and oral administration to rats: absorption from various GI segments. J Pharmacokinet Biopharm. 1994;22:1–17.
9. Dixon R, Warrander A. The clinical pharmacokinetics of zolmitriptan. Cephalalgia. 1997;17 Suppl 18:15–20.
10. Ezzet F, Krishna G, Wexler DB, Statkevich P, Kosoglou T, Batra VK. A population pharmacokinetic model that describes multiple peaks due to enterohepatic recirculation of ezetimibe. Clin Ther. 2001;23:871–85.
11. Funaki T. Enterohepatic circulation model for population pharmacokinetic analysis. J Pharm Pharmacol. 1999;51:1143–8.
12. Plusquellec Y, Efthymiopoulos C, DuthilP HG. A pharmacokinetic model for multiple sites discontinuous gastrointestinal absorption. Med Eng Phys. 1999;21:525–32.
13. Lennernas H, Regardh CG. Dose-dependent intestinal absorption and significant intestinal excretion (exsorption) of the beta-blocker pafenolol in the rat. Pharm Res. 1993;10:727–31.
14. Oberle RL, Amidon GL. The influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation for the double peak phenomenon. J Pharmacokinet Biopharm. 1987;15:529–44.
15. Savic RM, Jonker DM, Kerbusch T, Karlsson MO. Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2007;34:711–26.

16. Murata K, Noda K, Kohno K, Samejima M. Pharmacokinetic analysis of concentration data of drugs with irregular absorption profiles using multi-fraction absorption models. J Pharm Sci. 1987;76:109–13.
17. Wade JR, Kelman AW, Howie CA, Whiting B. Effect of misspecification of the absorption process on subsequent parameter estimation in population analysis. J Pharmacokinet Biopharm. 1993;21:209–22.
18. Jemal M, Ouyang Z, Powell ML. Direct-injection LC-MS-MS method for high-through put simultaneous quantitation of simvastatin and simvastatin acid in human plasma. J Pharm Biomed Anal. 2000;23:323–40.
19. Zhang L, Beal SL, Sheiner LB. Simultaneous vs. sequential analysis for population PK/PD data I: best-case performance. J Pharmacokinet Pharmacodyn. 2003;30:387–404.
20. Ette EI, Williams PJ. Pharmacometrics: The Science of Quantitative Pharmacology. New York: Wiley-Interscience; 2007.
21. Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses. J Pharmacokinet Biopharm. 1993;21:735–50.
22. Vickers S, Duncan CA, Chen IW, Rosegay A, Duggan DE. Metabolic disposition studies on simvastatin, a cholesterol-lowering prodrug. Drug Metab Dispos. 1990;18:138–45.
23. Miller R. Pharmacokinetics and bioavailability of ranitidine in humans. J Pharm Sci. 1984;73:1376–9.
24. Ogasawara A, Utoh M, Nii K, Ueda A, Yoshikawa T, Kume T, *et al.* Effect of oral ketoconazole on oral and intravenous pharmacokinetics of simvastatin and its acid in cynomolgus monkeys. Drug Metab Dispos. 2009;37:122–8.
25. Murtaza G. Solubility enhancement of simvastatin: a review. Acta Pol Pharm. 2012;69:581–90.