

Population pharmacokinetic analysis of the multiple peaks phenomenon in sumatriptan

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The objective of this study was to develop a population pharmacokinetic (PK) model for sumatriptan, which frequently shows an atypical absorption profile with multiple peaks. Sumatriptan, a selective agonist for the vascular serotonin (5-HT₁) receptor that causes vasoconstriction of the cerebral arteries, is used for the acute treatment of migraine attack with or without aura. Despite its relatively high between-subject variability, few reports have addressed PK modeling of sumatriptan. Plasma data obtained after a single 50-mg oral dose of sumatriptan in 26 healthy Korean male subjects were used. Blood samples were collected 0 (predose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after dosing. Plasma sumatriptan concentrations were analyzed using UPLC/MS/MS. Population PK analysis was performed using plasma concentration data for sumatriptan with NONMEM (ver. 7.2). A total of 364 concentrations of sumatriptan were captured by a one-compartment model with first-order elimination, and a combined transit compartment model and first-order absorption with lag time was successful in describing the PK with multiple peaks in the absorption phase of sumatriptan. The creatinine clearance as a covariate significantly ($P < 0.01$) influenced the absorption fraction (f). The final model was validated through a visual predictive check and bootstrapping with no serious model misspecification.

Introduction

Sumatriptan, a selective agonist acting on vascular 5-hydroxytryptamine (5-HT_{1B/1D}) receptors, has been found to be a safe and effective treatment for migraine attacks.[1,2] It is currently marketed as oral, subcutaneous, intranasal, and suppository (limited distribution) formulations.[3]

After oral administration, sumatriptan is rapidly absorbed and eliminated with a half-life of about 2 h.[3-5] The median C_{max} (the maximum plasma drug concentration) following oral dosing with 50 mg of sumatriptan is 29 ng/mL and the t_{max} (the time to reach maximum plasma concentration) generally ranges

from 0.5 to 3 h after administration of 25-, 50-, and 100-mg oral doses.[3] The bioavailability is 100% for the subcutaneous route and 14% for the oral route.[4] This lower bioavailability following oral administration is primarily due to pre-systemic metabolism in the gut wall and in the liver, and partly due to incomplete absorption.[2] It is metabolized by monoamine oxidase (MAO), predominantly the MAO-A isoenzyme, and inhibitors of that enzyme may alter sumatriptan pharmacokinetics (PK) and increase systemic exposure.[3] Sumatriptan and its metabolites are largely renally excreted (about ~60%), with about 40% found in the feces; only 3% of an oral dose can be recovered as unchanged sumatriptan.[3]

Sumatriptan frequently displays a particular absorption profile with multiple peaks in the plasma concentration.[2,4] These multiple peaks produce considerable between-subject variability (BSV) in the t_{max} (0.5-5 h) and influence clinical response by

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altering the rate and extent of absorption in the early absorption phase following oral administration of sumatriptan.[1,4,6] The BSV in plasma concentrations is much greater with the oral route than the parenteral route.[2] Given this complexity, conventional parameters, such as C_{max} and AUC_t (the area under the plasma concentration-time curve from zero until the last sampling time), may be inadequate for PK assessments.

Despite the relatively high BSV of sumatriptan PK, only a few reports have addressed the possible causes of this variability using population PK modeling. Thus, a precise PK assessment using a population approach with a mixed-effects model may be necessary for the evaluation and application of sumatriptan. In this study, we sought to develop a population PK model in healthy Korean male subjects for sumatriptan, which frequently shows an atypical absorption profile with multiple peaks.

Methods

Subjects and Ethical Considerations

Pharmacokinetic data were obtained from a recently performed bioequivalence study evaluating two tablet formulations of sumatriptan that demonstrated the bioavailability of both products. The conditions of clinical trial are described briefly. Healthy Korean male volunteers between 20 and 55 years of age and with a body weight within $\pm 20\%$ of ideal body weight were eligible, provided they had no clinically significant abnormalities, as judged by a clinical history and detailed physical examination that included vital signs, laboratory analyses, and 12-lead electrocardiography. Subjects who had a history of allergic reactions to sumatriptan or hypersensitivity to sulfonamide were excluded. The subjects were admitted to the study site 12 h before drug dosing. All lifestyle factors that may influence PK were controlled.

The study was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH) and was conducted in accordance with the Declaration of Helsinki and Korean good clinical practices. Informed consent was obtained from all participants before any study-related procedure.

Study Design

Subjects who participated in the sumatriptan bioequivalence study with the same protocol design were included in this retrospective analysis. In addition, only data from the reference formulation were used for the current analysis. This single-center, randomized, open-label, two-period, single-dose, comparative cross-over bioequivalence study was performed in 26 healthy Korean male subjects at KNUH Clinical Trial Center, Daegu, Korea. All subjects were randomly allocated to the two sequence groups (reference-test, test-reference) and received a single 50 mg oral dose of sumatriptan succinate (50 mg as sumatriptan) of either the test or reference formulation during each period with a 1-week wash-out period. Blood sampling for PK assessment was performed at 0 (predose), 0.25, 0.5,

0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 h after drug administration. Venous blood (8 mL) was collected into sodium heparin tubes (Vacutainer; BD BioSciences, Franklin Lakes, NJ, USA). The line was flushed with 3 mL of normal saline to ensure patency. The samples were immediately stored in an ice bath and centrifuged (3,000 rpm, 10 min). Plasma (2 mL) was obtained from each sample and transferred to microcentrifuge tubes and stored frozen at -70°C until it was assayed. Plasma concentrations of sumatriptan were assayed by ultra-performance liquid chromatography mass spectrometry mass spectrometry (UPLC/MS/MS). The analytical methods and procedures have been described previously.[7] The observed time-concentration profile is shown in Figure 1.

Population PK Model Development

A population PK analysis was performed using nonlinear mixed-effects modeling (NONMEM, ver. 7.2; Icon Development Solutions, Ellicott City, MD, USA). The dataset consisted of a total of 364 sumatriptan concentration measurements. Demographic characteristics, including the age, sex, weight, and height of subjects, are shown in Table 1.

Base PK model

The basic pharmacokinetic model was implemented in the PREDPP library subroutine ADVAN6 in NONMEM and estimated using the first-order conditional estimation (FOCE)

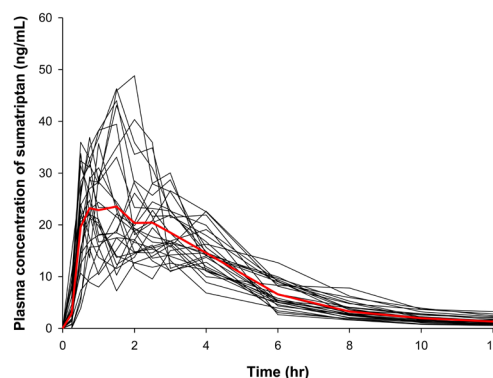


Figure 1. Individual plasma concentration versus time plots of sumatriptan. The bold red line is the median value.

Table 1. Demographic characteristics of subjects

Variable	Distribution ^a
Age (years)	23.9 (22-28)
Sex (male/female)	26 / 0
Weight (kg)	66.7 (51-84)
Height (cm)	174.2 (166.2-184.8)

^aMean (range) is presented for continuous variables and number of subjects for categorical variables.

method with η - ϵ interaction. Both single- and multi-compartmental models were used to describe the sumatriptan distribution. First-order kinetics was assumed for all PK processes other than absorption. The BSV of each of the structural parameters of the basic model was modeled exponentially:

$$P_i = P_{TV} \cdot \exp(\eta_i)$$

where P_i is the value of the parameter for the i^{th} individual, P_{TV} is the population typical value of the according parameter, and η_i is a random variable for the i^{th} individual following a Gaussian distribution with the mean of zero and variance of ω^2 . For intraindividual variability (residual error), both additive and proportional characteristics were allowed:

$$C_{ij} = C_{\text{pred},ij} \cdot (1 + \epsilon_{\text{pro},ij}) + \epsilon_{\text{add},ij}$$

where C_{ij} is the j^{th} observed value in the i^{th} subject, $C_{\text{pred},ij}$ is the j^{th} predicted value in the i^{th} subject, and $\epsilon_{\text{pro},ij}$ and $\epsilon_{\text{add},ij}$ are the intraindividual variability with means of zero and variances of σ_{pro}^2 and σ_{add}^2 , respectively. When one of the characteristics was not estimable, it was excluded from the model. When the correlation between the random variables was significant, the relationship was reflected in the model using the OMEGA BLOCK option.

The structural model included a one- and two-compartment model combined with first-order elimination and nonlinear elimination (Michaelis-Menten equation), which considered the potential for saturable elimination.

Various absorption models were evaluated to find the one that best described the absorption of sumatriptan, which showed multiple peaks in many subjects (Table 2). These included first-order absorption followed by zero-order absorption, zero-order absorption followed by first-order absorption, and a combined transit compartment model with first-order absorption.[8]

The combined transit compartment model and first-order absorption is shown schematically in Figure 2. k_{tr} is the transit

rate constant from the n^{th} -1 compartment to the n^{th} compartment and n is the number of transit compartments. k_{tr} was calculated from the estimate of the mean transit time (MTT) and number of transit compartments ($n+1$). MTT represents the average time for a drug molecule to transit from the first transit compartment to the absorption compartment. The relationship between MTT , n and k_{tr} is shown [8,9]:

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

The rate of change of the amount of drug in the n^{th} compartment is given by:

$$\frac{da_n}{dt} = k_{tr} \cdot a_{(n-1)} - k_{tr} \cdot a_n$$

da_n/dt represents the rate of change of substance a in compartment n at time t ; a_n is the drug amount in the n^{th} compartment at time t . For estimating the optimal number of transit compartments, the analytical solution for a_n is given by the function:

$$a_n(t) = F \cdot Dose \cdot \frac{(k_{tr} \cdot t)^n}{n!} \cdot e^{-k_{tr} \cdot t}$$

F denotes drug bioavailability and $n!$ is the n factorial function with argument n . To compute this function numerically, the approximation of Stirling to $n!$ was used:

$$n! \approx \sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}$$

The base model, which includes key parameters and does not incorporate covariates, was selected based on goodness-of-fit plots, precision of estimates, and the log likelihood-ratio test (LRT) within NONMEM. The results were considered statistically significant if the decreases in the objective function value (OFV) of the two nested models were 3.84 units ($P < 0.05$, $df = 1$)

Table 2. PK model development process

Model	Model tested	Objective function value
M1	Two-compartment model with first-order absorption followed by zero-order absorption with lag time	1169.47
M2	Two-compartment model with zero-order absorption followed by first-order absorption with lag time	1175.19
M3	M1 with nonlinear elimination by the Michaelis-Menten equation	1144.67
M4	M2 with nonlinear elimination by the Michaelis-Menten equation	1172.26
M5	One-compartment model with a combined transit compartment model and first-order absorption	1078.99
M6	M5 with CrCL as a covariate for f	1071.57
M7	M5 with nonlinear elimination by the Michaelis-Menten equation	1068.82

and 5.99 units ($P < 0.05$, $df = 2$). In the case of non-nested models, the value of the Akaike information criteria (AIC) was used. [10] Each parameter was sequentially tested to determine if it should remain in the base model. We have attached the NONMEM code as supplemental material.

Covariate selection

All demographic variables included in the dataset were screened as potential covariates for PK parameters. Each covariate was screened using both visual and numerical methods. For visual screening, a parameter versus covariate scatter plot was used for continuous variables and a box plot was used for categorical variables. Generalized additive modeling (GAM), implemented in the Xpose library of 'R' (ver. 2.11.1; R Foundation for Statistical Computing, Vienna, Austria[10]), was used for numerical screening. Only the variables showing a positive result in this screening and having physiological relevance to PK parameters were included in the model and evaluated using LRT. The significance level was $P < 0.05$ during forward inclusion and $P < 0.01$ during backward deletion.

Model evaluation

Graphical diagnostics (basic goodness-of-fit plot and other accessory plots) were used for single run-based diagnostics during model development. For the final model, the robustness and the predictive performance were evaluated using multiple run-based diagnostics, such as bootstrapping and the visual predictive check (VPC).

A bootstrap procedure was conducted with a total of 1,000 bootstrap-resampled datasets from the original dataset. The median and 90% confidence intervals (CIs, 5th and 95th percentiles) of parameters obtained from this step were compared with the final parameter estimates. Results from the VPC with 1,000 simulations were assessed by graphical comparison of the 90% prediction interval from the simulated data with an overlay of the raw data. Systematic patterns or an excess of data falling outside the prediction interval suggested that the parameter estimates were not robust.

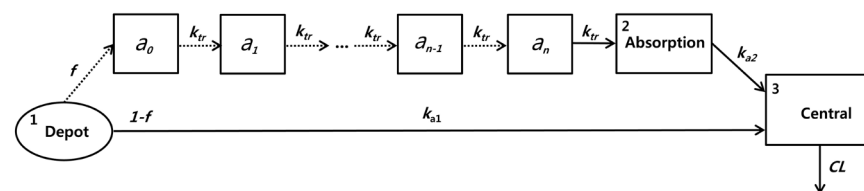


Figure 2. The scheme of the final PK model of sumatriptan. k_{a1} , absorption rate constant from the depot; k_{a2} , absorption rate constant from the final transit compartment to the central compartment; k_{tr} , identical transfer rate constant of the transit compartment model; f , fraction of the dose absorbed through the absorption compartment; n , number of transit compartments placed before the central compartment; a_n , the drug amount in the n^{th} compartment; CL , clearance.

Results

The present study developed population PK models for the multiple peaks phenomenon after oral administration of sumatriptan in healthy male subjects. The structural model included one- and two-compartment models with first-order elimination, and the following approaches were tested for the absorption process, which showed the multiple peaks phenomenon in many subjects: first-order absorption followed by zero-order absorption with lag time (M1), and zero-order absorption followed by first-order absorption with lag time (M2). Also, nonlinear elimination was joined to M1 and M2 by the Michaelis-Menten equation, which considered potential saturable elimination (M3 and M4).

The structure of M1 is similar to a model described by Cosson et al.[6] However, the estimated PK parameter values have considerable differences between our model and that of Cosson et al. The clearance and the lag time for first-order absorption estimated here were similar to that of Cosson et al., but the absorption constant (4.05 h^{-1} vs. 0.667 h^{-1}), the lag-time (1.71 h vs. 0.48 h) and the duration (1.59 h vs. 3.97 h) for zero-order absorption were distinct between the models.

We also evaluated a model that included zero-order absorption followed by first absorption (M2). The absorption structure of M2 corresponded to that reported by Christensen et al.[11], except for the distribution structure, which used a two-compartment model in our study versus a one-compartment model in the Christensen et al. study. The volume of distribution in the steady state was higher in our study than the values reported from Christensen et al. Clearance was estimated to be lower than the value estimated by Christensen et al. The value (1.91 h^{-1}) of the absorption constant here was lower than that (7.03 h^{-1}) described in Christensen et al. There were also significant differences between the two models in lag time (0.21 h vs. 0.41 h) and duration (0.42 h vs. 1.29 h) for zero-order absorption. The estimated fraction of the dose absorbed via first-order absorption was higher (0.75) than the value reported by Christensen et al. (0.33). These differences in results may be related substantially to the structural PK model and the characteristics (including populations) of the subjects. The M1 model decreased the objective function value (OFV) significantly ($P < 0.05$) and yielded a lower AIC value when compared with the M2 model.

Sumatriptan is metabolized primarily (80%) by the MAO-A isozyme. [6,12] Furthermore, sumatriptan and its metabolites are predominantly renally excreted. Modeling was performed under the assumption that saturation may occur in the metabolism or elimination phases. [12,13] Consequently, elimination was expressed by parallel linear and nonlinear pathways. Nonlinear elimi-

nation was incorporated using the Michaelis-Menten equation described by the maximal elimination rate of the saturable pathway in terms of amount per unit time denoted as V_{max} (mg/

h) and K_m (mg/L), the concentration at which the elimination rate is half the maximal rate. Therefore, nonlinear elimination was incorporated into M1 and M2 using the Michaelis-Menten

Table 3. Final parameter estimates and bootstrap results

Parameter (unit)	Definition	Estimate (%RSE)		BSV (CV%) (%RSE)	Bootstrap 95% CI	Shrinkage of BSV (%)
CL/F (L/h)	Apparent oral clearance	418	(4)	18.5 (25.9)	383 - 455	6.41
V/F (L)	Apparent volume of distribution	56.9	(35.4)	70.9 (28.9)	17.2 - 93.7	2.16
k_{a1} (h^{-1})	Absorption rate constant of first-order absorption	0.62	(9.13)	-	0.53 - 0.75	-
k_{a2} (h^{-1})	Absorption rate constant from the final transit compartment to the central compartment	0.29	(6.89)	24.6 (39.3)	0.25 - 0.33	14.2
MTT (h)	Mean transit time	1.94	(9.89)	35.6 (29.6)	1.54 - 2.30	7.1
n	Number of transit compartments	11	(23.2)	-	6.47 - 25.4	-
$ALAG1$ (h)	Lag time for k_{a1}	0.24	(1.32)	-	0.23 - 0.25	-
f	Fraction of the dose absorbed by transit compartment model	0.56	(6.18)	14.4 (40.7)	0.49 - 0.67	18.6
f_{CrCL}	CrCL as a covariate for f	-0.985	(34.6)	-	-	-
Proportional error		0.21	(7.3)	-	0.17 - 0.24	-
Additive error		0.3	(15.2)	-	0.17 - 0.37	-

BSV, Between-Subject Variability; -, Not estimated.

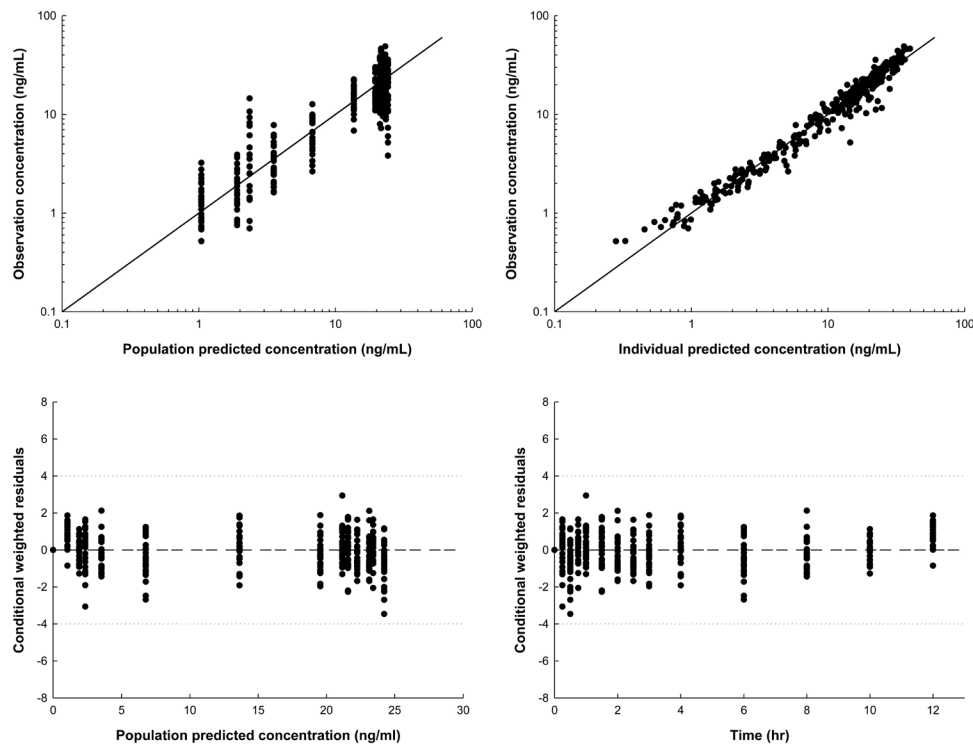


Figure 3. Final model diagnosis plot produced using the final pharmacokinetic model. (A) Observations (DV) vs. population predictions (PRED) (B) DV vs. individual predictions (IPRED) (C) Conditional weighted residuals (CWRES) vs. PRED and (D) CWRES vs. time (TIME).

equation (M3 and M4). With this model (M3), a marked decrease in OFV was obtained as compared to that in M1 ($\Delta = -24.801$, $P < 0.001$, $df = 2$), indicating improved fit of the model to the data. However, M4 did not improve the model to a greater extent than did M3. Among the four models (M1-M4), the data were best described using a two-compartment model with first-order absorption followed by zero-order absorption, and parallel elimination of the linear and nonlinear pathway (M3).

The best structure of the PK model available to explain the time-concentration profiles of sumatriptan is the one-compartment model with an atypical absorption process, characterized by multiple peaks, described by the combined transit compartment model and first-order absorption (M5). A schematic overview of the proposed PK model is shown in Figure 2.

The final structural model was parameterized using the identical transfer rate constant for transit compartment absorption (k_{tr}), the rate constant of first-order absorption (k_{a1}), the absorption rate constant from the final transit compartment to the central compartment (k_{a2}), the fraction of the dose absorbed by the transit (f) and the first-order input ($1-f$) processes, mean transit time (MTT), the number of transit compartments placed before the central compartment (n), the lag time of first-order absorption ($ALAG1$), the apparent clearance (CL/F) and the apparent central volume of distribution (V/F), where F is the bio-availability. The BSV for CL/F , V/F , k_{a2} and MTT were estimated successfully. Combined residual errors were estimated in the final model. In addition, screening for the effects of covariates on the PK parameters suggested that the inclusion of creatinine clearance ($CrCL$) had a significant effect ($\Delta OFV = 7.42$, $P < 0.01$)

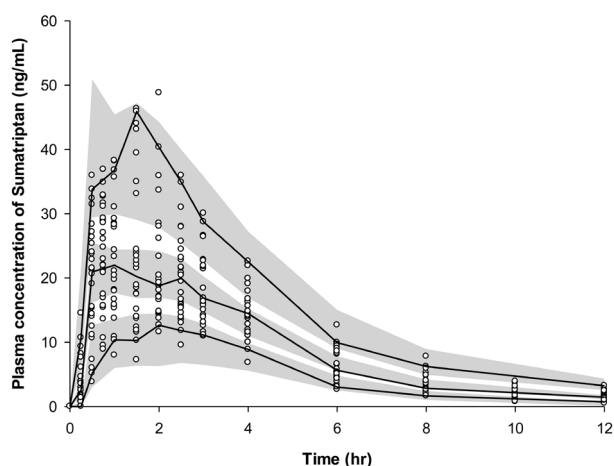


Figure 4. Visual predictive check plot of the final model 0 and 12 h after a single oral administration of 50 mg sumatriptan. A total of 1,000 datasets were simulated using the final PK parameter estimates. Circles represent the observed sumatriptan plasma concentrations: the 90% confidence interval of the simulated concentrations (gray area), and observed concentration (solid line) of the 5th, median, and 95th percentiles.

on the absorption fraction (f) (M6). Other covariates including age, weight and BMI did not appear to affect any of the PK parameters. Final parameter estimates with corresponding coefficients of variation (CV) and bootstrap results are summarized in Table 3. The basic goodness-of-fit plots for the final model are presented in Figure 3.

The model and parameter estimates were adequately robust in the bootstrap procedure. All parameter estimates from the final model were within the 95% bootstrap confidence interval (CI). The predictive performance was also sufficient, according to the VPC result (Fig. 4). The trend of the predicted time-concentration profile accorded well with the raw data.

Discussion

In this study, we presented the results of PK modeling of the time-concentration profiles of sumatriptan after oral administration in healthy subjects. The population PK of sumatriptan is well described by a one-compartment with combined transit compartment model and first-order absorption. This combined absorption model successfully fits the multiple peaks observed in the absorption phase of sumatriptan (Fig. 5).

We do occasionally encounter the multiple peaks phenomenon in pharmacokinetics. The multiple peaks phenomenon can occur due to a number of different mechanisms, including those related to physicochemical and formulation factors (solubility-limited absorption, complexation: formation of poorly absorbable bile salt micelles and modified-release formulation) and physiological factors (enterohepatic recycling, gastric emptying and intestinal transit time, site-specific absorption, gastric secretion-enteral reabsorption, anesthesia and surgery).[14] Davies et al. and Aurora et al. have reported that gastric motor activity and gastric emptying play important roles in the multiple peaks phenomenon following oral administration of sumatriptan. [14,15] A non-linear mixed effect modeling analysis with a two-process absorption model was described for the observed multiple peaks phenomenon of sumatriptan concentration-time data. [6,11] Although the two-process absorption model resulted in an improved model compared with typical absorption models, the multiple peaks of individual subjects were well not captured visually by these models. Thus, we developed a model using a transit compartment model to pursue more mechanistic PK modeling approaches.

The use of a transit compartment model to describe a delay in the onset of absorption was developed by Radojka Savic et al.[8] They reported that a transit compartment model describes drug absorption delay as a multi-step process, represented by a chain of identical pre-systemic compartments that are linked to the central compartment by a first-order absorption process, without assigning a physical correlate to each transit compartment. [8] They suggested that one of the complexities of the absorption process is incomplete gastric emptying. The combined transit compartment model and first-order absorption had a reduced AIC value compared with the previous conventional

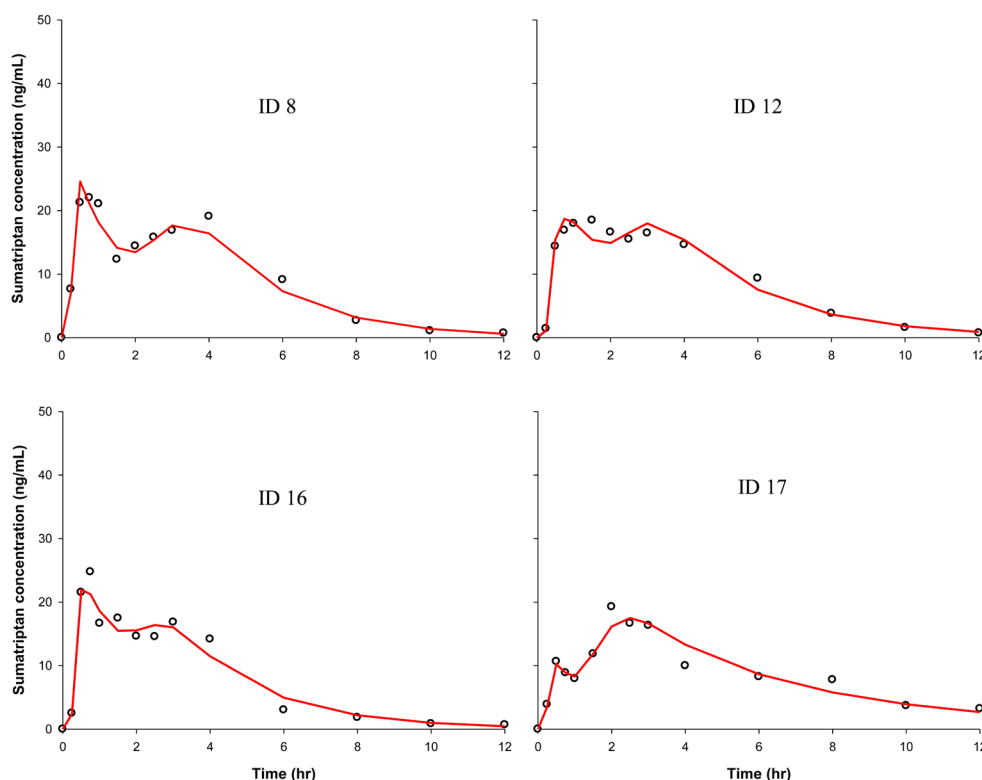


Figure 5. PK curves from representative individuals showing multiple peaks. Circle, observed value; solid red line, individual predicted value.

models (Table 2), and captured the multiple peaks in the absorption phase of sumatriptan well.

We also explored the incorporation of significant covariates in the base model. Although we included only healthy adult male volunteers, who were evaluated under well-controlled experimental conditions, CrCL as covariate had a significant effect on the absorption fraction (f) ($P < 0.01$) (M6 in Table 2). One possible explanation for this is that as the elimination of sumatriptan is increased, sumatriptan is relatively well absorbed by first-order absorption. Studies from a more diverse population may allow for more meaningful results and accurate PK modeling of sumatriptan. There was good agreement between the observed and predicted concentrations, and no obvious trends in the weighted residuals vs. time (Fig. 3). The PK parameters were generally well-estimated, with the standard error for the estimation being under 40% of the estimated population parameter values. Additionally, when nonlinear elimination was incorporated into the base model (M5) using the Michaelis-Menten equation, the OFV of M7 decreased significantly compared to that of M5 ($\Delta = -10.17$, $P < 0.01$, $df = 2$). These results indicate that saturation may have occurred in the metabolism or elimination processes. The saturation of the MAO-A isozyme in sumatriptan was not assessed in this study, but would be a reasonable factor to assess in future studies.

In this study, a population PK model for multiple peaks was

developed and reasonable parameters were obtained from the data of healthy Korean male subjects. We could find that the estimated parameters were altered by the adjusted models in the PK showing multiple peaks. This is the first study to model the PK of sumatriptan, which frequently exhibits an atypical absorption profile with multiple peaks, using a combined transit compartment model and first-order absorption using NONMEM. This model may facilitate the determination of basic sumatriptan PK characteristics. Furthermore, our absorption model may facilitate PK modeling of multiple peaks during the absorption phase.

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Conflict of interest

The authors have no conflicts of interest to declare.

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[Supplements: NONMEM code]

```

$SUBROUTINE ADVAN6 TOL=6
$MODEL
  COMP=(DEPOT1)
  COMP=(DEPOT2)
  COMP=(CENTRAL, DEFOBS)
$PK
  CL      = THETA(1) * EXP(ETA(1)) ; Drug elimination clearance
  V3      = THETA(2) * EXP(ETA(2)) ; Volume of the central compartment
  KA1     = THETA(3) * EXP(ETA(3)) ; Absorption rate constant of first-order absorption
  KA2     = THETA(4) * EXP(ETA(4)) ; Absorption rate constant from the final transit compartment
                                           ; to the central compartment
  MTT     = THETA(5) * EXP(ETA(5)) ; Mean transit time
  NN      = THETA(6) * EXP(ETA(6)) ; Number of transit compartments
  ALAG1   = THETA(7) * EXP(ETA(7)) ; Lag time for KA1
  FR      = THETA(8) * EXP(ETA(8)) ; Fraction of the dose absorbed by the transit compartment model
  S3 = V3/1000
  K30 = CL/V3
  F1 = 1-FR
  F2=0 ; Transit compartment
  KTR = (NN+1)/MTT ; Transit rate constant
  LNFAC = LOG(2.5066)+(NN+0.5)*LOG(NN)-NN
$DES
  DADT(1) = -KA1*A(1)
  DADT(2) = EXP(LOG(FR*DOS+0.00001)+LOG(KTR)+NN*LOG(KTR*TIME+0.00001)
  -KTR*TIME-LNFAC) - KA2*A(2)
  DADT(3) = KA1*A(1) + KA2*A(2) - K30*A(3)
$ERROR
  W=SQRT(THETA(9)**2 + THETA(10)**2 * IPRED**2)
  IRES=DV-IPRED
  IWRES=IRES/W
  Y=IPRED + W*ERR(1)

```
