Population Pharmacokinetic Analysis of Multiple Peaking Phenomena in Sumatriptan

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Background/Aims

- Sumatriptan is a selective agonist at vascular 5-hydroxytryptamin (5-HT) 1B/1D receptor subtype, which has proved to be effective and safe for the treatment of migraine attacks.
- It frequently shows an atypical absorption profile with multiple peaks of plasma concentration.
- Few reports on population pharmacokinetic (PK) properties of sumatriptan have been published.
- In this study, we developed a population PK model for sumatriptan with multiple peaks phenomenon in healthy Korean male subjects.

Study Design and Methods

Subjects
- Healthy Korean male volunteers (n=26).
- Informed written consent.

Study Design
- All subjects were received sumatriptan as a single 50mg oral dose.
- Blood sampling: 0 (pre-dose), 0.25, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after dosing.

Concentration assay
- Ultra performance liquid chromatography-tandem mass spectrometry (UPLC/MS/MS).

Population PK dataset
- The model building dataset contained a total of 312 sumatriptan concentrations.

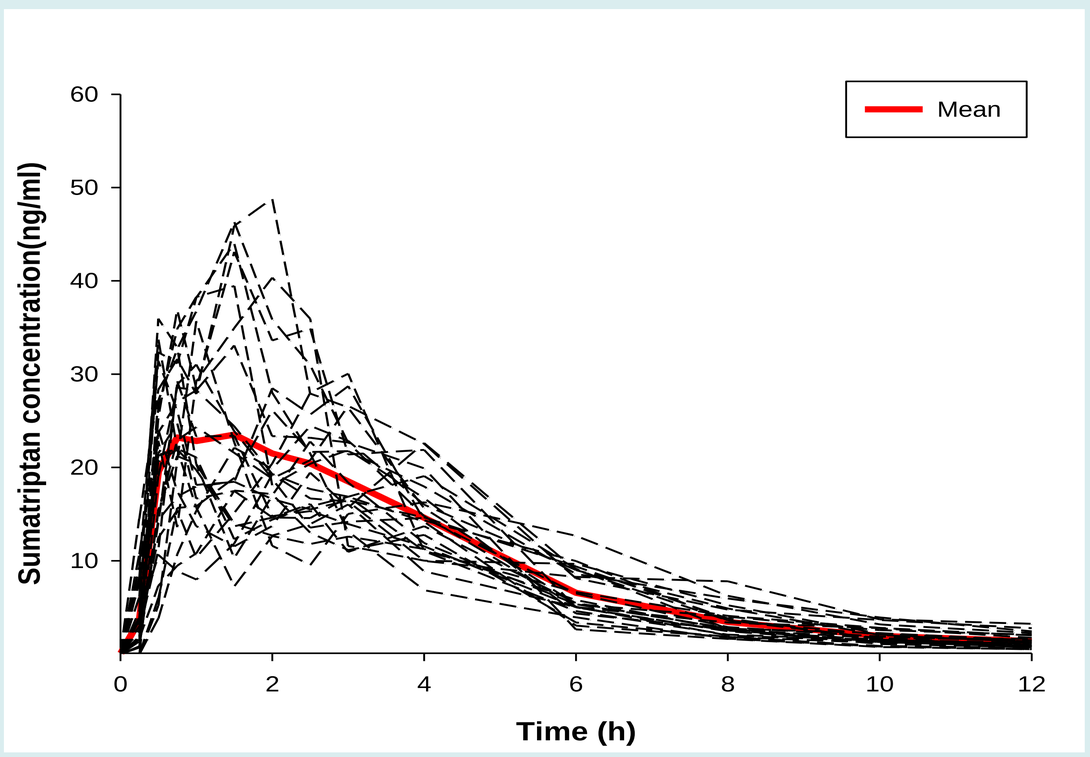

Figure 1. Individual plasma concentration versus time plots of sumatriptan

Modeling Approach
- A population PK analysis was performed using NONMEM (Version 7.2, Icon Development Solution, Ellicott City, MD, USA)
- The model parameters were estimated using the first-order conditional estimation (FOCE) method with η-ε interaction for all the applicable estimation.
- Both single- and multi-compartmental models were tested to describe sumatriptan distribution.
- First-order kinetics was assumed for all the PK processes, except for the absorption process.
- To find the best PK model for description of the absorption profile, which showed "multiple peaking" in many people, first- and zero-order absorption models and their combined form, with or without lag time, were tested.

Covariate analysis
- Every covariate was explored graphically as well as numerically using the generalized additive model (GAM) with X-pose ver. 4.0.4.
- Screened covariates: Demographic variables, clinical variables.

Model evaluation
- The standard basic model diagnosis plots, including individual fitting plots, goodness-of-fit plots, visual predictive check (VPC) plots and nonparametric bootstrap analysis were examined to access model fitting and predictive performance.

Results

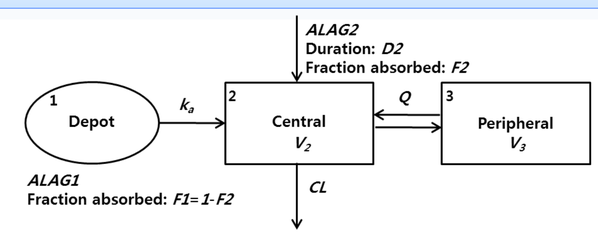

Figure 2. Final PK model scheme

Table 1. Final Parameter Estimates and Bootstrap Results

Parameter	Description (units)	Estimate (%RSE)	Bootstrap Results 95% CI
Fixed Effects			
θ_1	*CL/F*, apparent oral clearance (L/hr)	394 (6.12)	274-460
θ_2	V_2/F, apparent volume of distribution (L)	1210 (5.30)	982-1446
θ_3	*Q/F*, intercompartment clearance (Q/F)	53.40 (38.50)	50.86-198.17
θ_4	V_3/F, apparent volume of distribution (L)	849 (76.68)	618-13662
θ_5	k_a, absorption rate constant of first-order absorption (h^{-1})	1.43 (56.01)	0.96-2.57
θ_6	*D2*, duration of zero-order absorption (hr)	0.65 (16.54)	0.29-0.66
θ_7	*ALAG1*, lag time of first-order absorption (hr)	1.66 (4.36)	1.51-2.10
θ_8	F_2, fraction of the dose absorbed by zero-order absorption	0.77 (3.19)	0.61-0.80
θ_9	*ALAG2*, lag time of zero-order absorption (hr)	0.17 (8.31)	0.15-0.23
Random Effects (Estimates presented in CV%)			
ω_1^2	BSV of *CL/F*	0.02 (77.50)	0.01-0.07
ω_2^2	BSV of V_2/F	0.03 (24.09)	0.03-0.21
ω_3^2	BSV of *Q/F*	NE	NE
ω_4^2	BSV of V_3/F	NE	NE
ω_5^2	BSV of k_a	NE	NE
ω_6^2	BSV of *D2*	0.30 (45.96)	0.10-0.79
ω_7^2	BSV of *ALAG1*	0.03 (70.60)	0.01-0.10
ω_8^2	BSV of F_2	NE	NE
ω_9^2	BSV of *ALAG2*	NE	NE
Residual Error			
σ_1^2	Residual error (proportional)	0.33	0.27-0.36

BSV: Between Subject Variability, NE: Not estimated

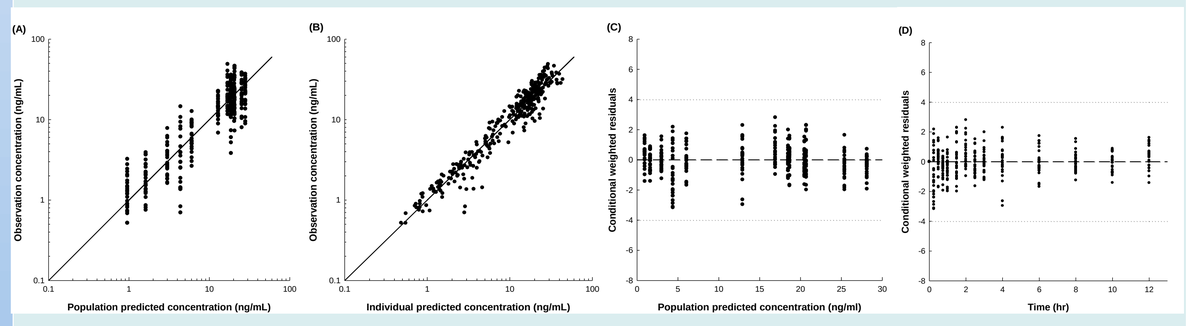

Figure 3. Basic model diagnosis plot produced using the final pharmacokinetic model. (A) Observations (DV) vs. population predictions (PRED) (B) DV vs. individual predictions (IPRED) (C) Conditional weighted residuals (CWRES) vs. PRED and (D) CWRES vs. time (TIME)

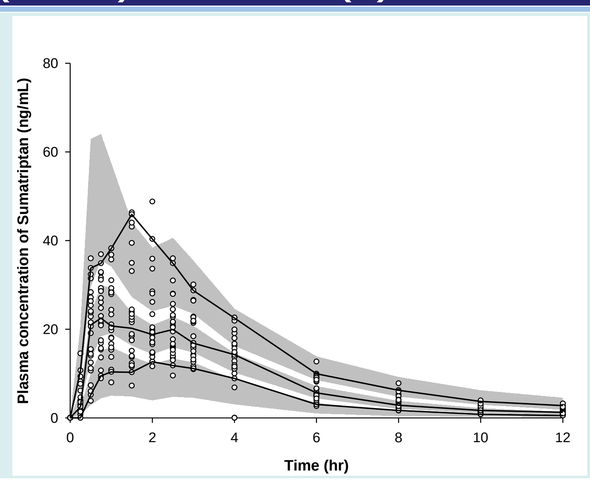

Figure 4. Visual predictive check plot of the final model between 0 and 12h after a single oral administration of 50 mg sumatriptan. A total of 2,000 datasets were simulated using the final PK parameter estimates. *Circles* represent the observed sumatriptan plasma concentrations: the 95% confidence interval of the simulated concentrations (*gray area*), and observed concentration (*solid line*) of the 2.5th, median, and 97.5th percentile.

Conclusion

- A population PK model was developed and reasonable parameters were obtained from the data of healthy Korean male subjects.
- Two-compartment model with first-order elimination and a mixture of zero- and first-order absorption with lag time was successful to describe the PK with multiple peaks in absorption process of sumatriptan.
- There were no significant covariates affecting PK parameters.

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