

Population pharmacokinetics of imatinib mesylate in healthy Korean subjects

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Imatinib (GleevecTM; Novartis Pharmaceuticals) is an orally administered protein-tyrosine kinase inhibitor. The goal of this study was to investigate the population pharmacokinetics (PK) of imatinib (as imatinib mesylate) in healthy male Koreans. A total of 1,773 plasma samples from 112 healthy male volunteers enrolled in three phase I clinical studies were used. Among the subjects, 76 received 400 mg and 36 received 100 mg as single oral doses. Peripheral blood sampling for PK analysis was done at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 60 and 72 (at 400 mg group) h after dosing. The first-order conditional estimation with interaction method of NONMEM[®] (ver. 7.3) was used to build the population PK model. A two-compartment model with Weibull absorption and elimination gave the best fit to the data. The estimates of clearance (CL/F), volume of central compartment (V_c/F), inter-compartmental clearance (Q/F), peripheral volume (V_p/F) and their interindividual variability (%CV) were 13.6 L/h (23.4%), 153 L (29.2%), 8.64 L/h (35.9%) and 64 L (67%), respectively.

Introduction

Targeted therapies have expanded therapeutic options against cancer with less toxicity. There are multiple types of targeted therapies available, including monoclonal antibodies, antisense inhibitors of growth factor receptors and inhibitors of tyrosine kinase.[1] Tyrosine kinases are pivotal mediators of signal transduction process leading to cell proliferation, differentiation, migration, metabolism and programmed cell death. Genetically or epigenetically altered signaling pathway of this enzyme brought to effect in several steps of neoplastic development and progression.[2] Tyrosine kinases well-defined as anticancer drug targets include BCR-ABL tyrosine kinase,[3] c-KIT tyrosine kinase,[4] PDGFR kinase for imatinib, EGFR tyrosine kinase[5] for gefitinib, erlotinib, FLT-3kinase[6] for sunitinib and B-Raf kinase[7] for sorafenib. Imatinib (GleevecTM) is a highly selective inhibitor of BCR-ABL oncogene, and also platelet-derived growth factor receptors, and c-KIT receptor tyrosine kinase.[8, 9] It was first approved for the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia (CML) and, shortly thereafter, for c-KIT-positive metastatic and unresectable gastrointestinal

stromal tumor.[10,11] It competitively inhibits the ATP binding of the enzyme, thereby restricting the phosphorylation of protein substrates involved in signal transduction and consequent CML cell growth.[12] Other cancers known to be responsive to imatinib are mast-cell tumors, neuroblastoma, germ-cell tumors, melanoma, small-cell lung cancer, breast and ovarian cancers, and AML.[4]

It has been reported that imatinib pharmacokinetics (PK) follows a one-compartment model with first-order absorption and elimination.[13,14] On the other hand, Schmidli et al have reported that its absorption is best described by a zero-order absorption model.[15] Because nothing is reported on the population PK of imatinib in Korean subjects we aimed to explore the population PK using PK data in healthy male Koreans.

Methods

Study design and data

Data from 112 healthy male subjects, providing 1,773 blood samples in three different clinical trials, were merged for population PK analysis. The three comparative PK (reference versus test formulation) studies with open-labelled, randomized, 2×2 crossover design were conducted at the clinical trial center of Seoul St. Mary's hospital. Imatinib was administered orally at a single dose of 100 mg for 36 subjects in one study and 400 mg

for 76 subjects in the other two studies. Eligibility criteria in the three studies included: healthy Korean volunteers between 20 and 55 years old, weighing within 20% of their ideal body weight (Ideal body weight=(height(cm)-100)×0.9), and no clinically-relevant conditions identified at their medical history, physical examination, and laboratory tests. A previous history of hypersensitivity to drugs was one of the important exclusion criteria. Participants abstained from drugs, foods, and any other lifestyle factors that might alter the PK characteristics of imatinib for at least 24 hours before hospitalization and throughout the participation period. The following data were recorded for each subjects: body weight, sex, age, height, vital signs, electrocardiogram, clinical laboratory test including CBC (complete blood count), clinical chemistry, urinalysis and concomitant intake of medications that might be influence the PK of imatinib. Blood samples were taken at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 60 and 72 (in case of 400 mg) h after dosing. Only PK data obtained after administration of the reference formulation (GeevecTM) were used for this modeling. The protocols were approved by the institutional review board (IRB) of Seoul St. Mary's hospital and the studies were conducted in compliance with the Declaration of Helsinki and the Guidelines

for Korean Good Clinical Practice. Written informed consents were obtained from all subjects. The demographic characteristics of subjects are summarized in Table 1.

Plasma concentration analysis

Plasma imatinib concentrations were determined using the HPLC-MS/MS method.[16,17] Quantitative analyses of imatinib of the three studies were done at the same organization. For higher sensitivity at 100 mg dose groups, the MS/MS instruments used were different by dose groups (Table 2).

Blood samples collected into the heparin tubes were shaken lightly to mix and were kept in the ice box temporarily. After centrifugation for 10 minutes at 3,000 rpm, 1.5 mL of plasma was put into the microcentrifuge tube to be stored at -70°C until analysis. Linear calibration curves were analyzed in the range of 5 to 5,000 ng/mL imatinib (400 mg) or 3 to 1,000 ng/mL (100 mg) (correlation coefficient, $r \geq 0.9950$). The lower limits of quantification for imatinib were 5 ng/mL (400 mg) or 3 ng/mL (100 mg). Both the intra-day and inter-day precision %CVs for imatinib were less than 15% (but 20% at LLOQ) levels for both doses. The intra-day and inter-day accuracies (%nominal) were between 80% and 120% at LLOQ level for both doses, too.

Table 1. Study-subjects demographic characteristics

Study	Subjects N (%)	Samples N (%)	Sampling points (h)	Age (years) mean (range)	Weight (kg) mean (range)	Dose N (%)	
						100 mg	400 mg
1	38 (33.9)	606 (34.2)	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72	25.21 (20–44)	66.17 (53.4–76.4)	–	38
2	38 (33.9)	593 (33.4)	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 72	27.11 (20–45)	66.79 (54–83.8)	–	38
3	36 (32.2)	574 (32.4)	Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 60	24.33 (20–32)	68.49 (52.8–85.9)	36 (32.1)	–
Total	112 (100)	1773 (100)	–	25.57 (20–45)	67.12 (52.8–85.9)	36 (32.1)	76 (67.9)

Table 2. Quantitative concentration analysis of imatinib for each dose

	100 mg dose study	400 mg dose study
HPLC	Nanospace SI-2, Shiseido, Japan	Nanospace SI-2, Shiseido, Japan
MS/MS	API 4000, AB SCIEX, USA	4000 QTRAP, AB SCIEX, USA
Linear calibration curve	3–1,500 ng/mL	5–5,000 ng/mL
LLOQ	3 ng/mL	5 ng/mL
Precision (CV%)	<15, <20 at LLOQ	<15, <20 at LLOQ
Accuracy (%)	85–115, 80–120 at LLOQ	85–115, 80–120 at LLOQ

HPLC, High-performance liquid chromatography; MS, mass spectrometry; LLOQ, lower limit of quantification.

Population pharmacokinetic analysis

NONMEM (Ver. 7.3.0, Icon development solutions, Ellicott City, MD) was used with R (version 3.2.3)[18] and Xpose4 (version 4.5.3)[19] for the population PK analysis of imatinib. The first-order conditional estimation with interaction (FOCE-I) method was used throughout the modeling process. Because data from 100 mg and 400 mg studies were merged for PK modeling, VPCs (visual predictive check) were performed separately to explore dose-related differences if any.

A two-compartment model was selected for imatinib distribution after comparison of one- and two-compartment models. To select the best absorption model, models such as first-order absorption with or without a lag-time, zero-order absorption with or without a lag-time (previously reported for imatinib, [13-15]) and Weibull absorption using the following equation was tested:

$$k_a(t) = 1 - e^{-(k_1 t)^\gamma}$$

where $k_a(t)$ is time dependent absorption rate constant, k is apparent absorption rate constant, [20] and γ is shape factor.

PK parameters of the j th subjects (P_j) were described as following:

$$P_j = \text{TVP} \times \exp(\eta_j)$$

where TVP represents the typical population value of PK parameters, such as clearance (CL/F), central volume of distribution (Vc/F) etc. The inter-individual variability (η_j) for each parameter was assumed to follow a normal distribution with the mean of 0 and variance of ω^2 . The combined residual error form was used, as follows:

$$DV_{ij} = DV_{ipred,ij} \times (1 + \varepsilon_{prop,ij}) + \varepsilon_{add,ij}$$

where DV_{ij} is the j th measured concentration in the i th individual, $DV_{ipred,ij}$ is the j th predicted value in the i th individual, and $\varepsilon_{prop,ij}$ and $\varepsilon_{add,ij}$ are the residual variability with means of 0 and the variance of σ_{prop}^2 and σ_{add}^2 , respectively. Possible correlation between the interindividual variability was explored using the correlation coefficient as follows:

$$\rho_{x,y} = \frac{\omega_{x,y}}{\sqrt{\omega_{x,x}^2} \times \sqrt{\omega_{y,y}^2}}$$

Models were selected based on decrease in the objective function value (OFV) > 3.84 ($P=0.05$, $df=1$) and visual exploration of the diagnostic scatterplots. The residual-based model diagnosis was performed using conditional weighted residuals. Considering the covariance between the corresponding variance terms, The OMEGA block structure was applied to ETAs which showed higher correlation coefficients ($r>0.7$) between

two elements of OMEGA after covariate selection. The covariate screening process was performed using visual exploration (parameter versus variable scatter plots) and numerical GAM (generalized additive modeling, version 1.12)[21] implemented by Xpose4 approaches. Influences of the covariates that passed the screening (study, age and body weight) on PK parameters were examined using linear, power, or exponential equations. During the covariate model-building process, stepwise forward selection and backward elimination were performed. Variables that decreased the OFV by >3.84 ($p<0.05$) and decreased the inter-individual variabilities were selected at forward selection and those failed to increase the OFV by >6.63 ($p<0.01$) at backward elimination were removed from the model.

The final model was then evaluated using visual predictive checks (VPCs) by overlaying observed data points with 5th, 50th, and 95th percentile curves of 1,000 simulated data from the final model for 100 mg and 400 mg dose, respectively. The bootstrap resampling method (Wings for NONMEM, version 740)[22] was utilized to assess the solidity and robustness of the final PK model. Resampling generated 1,000 bootstrap data sets, and the final population PK model structure was repeatedly run using each of the resampled dataset. Medians and ninety-five percent confidence intervals (CI) were acquired from the bootstrap replications.

Results

Development of the basic model and covariate model was based on the OFV and basic goodness-of-fit plots as well as individual plots. A two-compartment model with Weibull absorption and first-order elimination best described the observed data of imatinib (Fig. 1). The process of base model selection is summarized in Table 3. The PK variables used in the model were CL/F, Vc/F, Vp/F (peripheral volume), Q/F (inter-compartmental clearance), KA1 (scale parameter of Weibull function; apparent absorption rate constant[20]) and GAMMA (shape parameter of Weibull function). Details of the final structural model and parameter estimates are shown in Table 5.

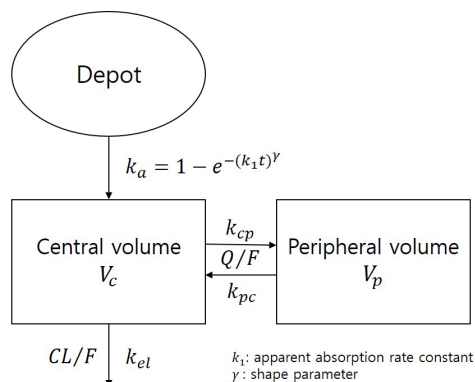


Figure 1. Pharmacokinetic model for imatinib.

Table 3. Summary of basic model building steps

Model steps	OFV	Parameters estimated
<u>first-order absorption, 1-compartment distribution</u>		
ADVAN2 TRANS2	15732.266	$\theta_{CL}, \theta_V, \theta_{ka}$ $\omega_{CL}, \omega_V, \omega_{ka}$
<u>first-order absorption, 2-compartment distribution</u>		
ADVAN4 TRANS4	15279.718	$\theta_{CL}, \theta_V, \theta_{Vp}, \theta_Q, \theta_{ka}$ $\omega_{CL}, \omega_{Vc}, \omega_{Vp}, \omega_Q, \omega_{ka}$
<u>zero-order absorption, 2-compartment distribution</u>		
ADVAN3 TRANS4	15851.349	$\theta_{CL}, \theta_{Vc}, \theta_{Vp}, \theta_Q, \theta_D$ $\omega_{CL}, \omega_{Vc}, \omega_{Vp}, \omega_Q, \omega_D$
<u>Weibull absorption, 2-compartment distribution</u>		
ADVAN6	14234.527	$\theta_{CL}, \theta_{Vc}, \theta_{Vp}, \theta_Q, \theta_{KA1}, \theta_{GA}$ $\omega_{CL}, \omega_{Vc}, \omega_{Vp}, \omega_Q, \omega_{KA1}, \omega_{GA}$

OFV, objective function value; θ_{CL} , THETA for clearance; θ_V , THETA for volume of distribution; θ_{Vc} , THETA for central volume of distribution; θ_{Vp} , THETA for peripheral volume of distribution; θ_Q , THETA for inter-compartmental clearance; θ_D , THETA for absorption duration; θ_{ka} , THETA for absorption rate constant; θ_{KA1} , THETA for apparent absorption rate constant of Weibull function; θ_{GA} , THETA for shape factor of Weibull function; ω_{CL} , ETA for clearance; ω_V , ETA for volume of distribution; ω_{Vc} , ETA for central volume of distribution; ω_{Vp} , ETA for peripheral volume of distribution; ω_Q , ETA for inter-compartmental clearance; ω_D , ETA for absorption duration; ω_{ka} , ETA for absorption rate constant; ω_{KA1} , ETA for apparent absorption rate constant of Weibull function; ω_{GA} , ETA for shape factor of Weibull function.

The age was significantly (a decrease of OFV at least 3.84, $p < 0.05$) correlated with central volume of distribution, inter-compartmental clearance, and body weight was related to peripheral volume of distribution, GAMMA. After applying further stepwise backward elimination with significance of an increase of OFV at least 6.63 ($p < 0.01$), the age was the only covariate survived in the final model (Table 4). The correlation between ETAs (Fig. 2) was incorporated as the OMEGA block structure.

The basic goodness-of-fit plots from the final PK model are given in Figure 3. The medians of 1000 bootstrap estimates were within $\pm 15\%$ of the point estimates of the final model, suggesting that the final model was stable and adequately described the data (Table 5). VPCs stratified by doses (100 mg and 400 mg) of

Table 4. Summary of covariate model building steps

Model step	OFV	Δ OFV to base model	Variables screened by GAM	Significant
<u>Base model</u>				
1	14234.527	NA		
<u>Covariate screening</u>				
2	14232.466	-2.061	Bwt on CL	Not significant
3	14226.851	-7.676	Age on Vc	Significant
5	14223.151	-11.376	Age, Bwt on Vc	Not significant
6	14228.543	-5.984	Bwt on Vp	Significant
7	14224.34	-10.187	Bwt, age on Vp	Not significant
8	14224.741	-9.786	age on Q	Significant
10	14230.548	-3.979	Bwt on GAMMA	Significant
11	14226.861	-7.666	Bwt, age on GAMMA	Not significant
<u>Full model</u>				
12	14209.911	-24.616		
<u>Final model: Simultaneous inclusion of significant covariates</u>				
13	14219.532	-14.995	Age on Vc and Q	

OFV, objective function value; GAM, generalized additive model; NA, not available; Bwt, body weight; CL, clearance; Vc, central volume of distribution; Vp, peripheral volume of distribution; Q, inter-compartmental clearance; GAMMA, shape factor of Weibull function.

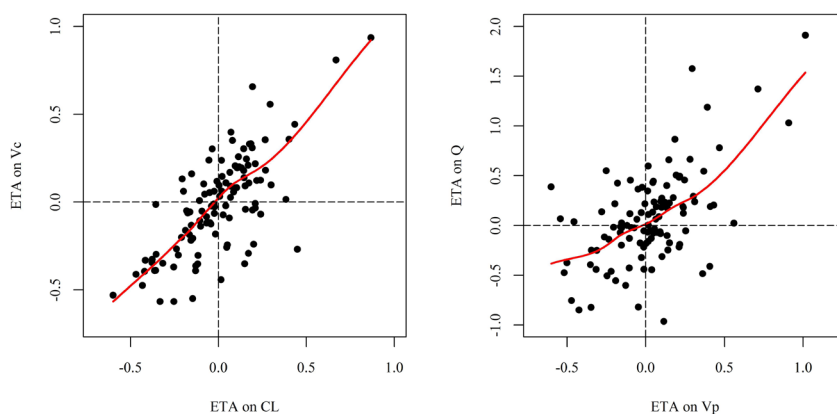


Figure 2. Scatterplots representing correlation between ETAs.

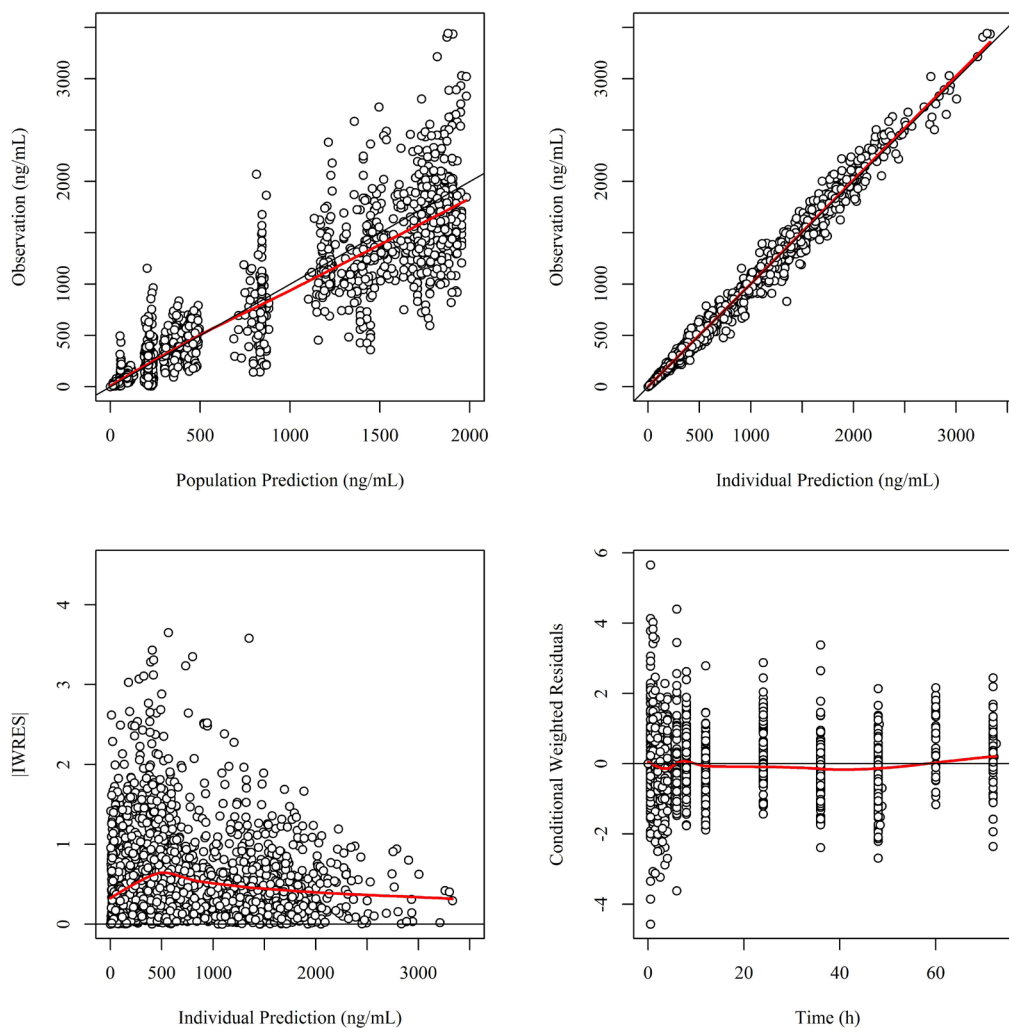


Figure 3. Basic goodness-of-fit plot for the PK model. Open circles are observations. Solid lines are line of identity. Red lines are LOESS (locally weighted regression) smoothed lines.

Table 5. Population pharmacokinetic parameters of imatinib

Parameter (unit)	Estimate	SE (% RSE)	Bootstrap median (95% CI)
Fixed effects			
<u>Apparent clearance model (CL/F)</u>			
$CL = \theta_1$			
θ_1 CL/F (L/h)	13.6	0.379 (2.79)	13.6 (13.572–13.611)
<u>Apparent central volume model (Vc/F)</u>			
$Vc = \theta_2 \times (Age/24)\theta_9$			
θ_2 Vc/F (L)	153	5.55 (3.63)	153 (152.750–153.366)
θ_9 Age on Vc	0.312	0.147 (47.12)	0.309 (0.297–0.312)
<u>Apparent peripheral volume model (Vp/F)</u>			
$Vp = \theta_3$			
θ_3 Vp (L)	64	3.58 (5.59)	63.5 (63.356–63.811)
<u>Inter-compartmental clearance (Q/F)</u>			
$Q = \theta_4 \times (Age/24)\theta_{10}$			
θ_4 Q (L/h)	8.64	0.898 (10.39)	8.455 (8.443–8.567)
θ_{10} Age on Q	0.531	0.342 (64.41)	0.539 (0.554–0.593)
<u>Scale parameter</u>			
$KA1 = \theta_5$			
θ_5 Scale parameter	0.998	0.0751 (7.53)	1.01 (1.007–1.014)
<u>Shape parameter</u>			
$GAMMA = \theta_6$			
θ_6 Shape parameter	2.24	0.212 (9.46)	2.26 (2.249–2.270)
Random effects			
<u>Interindividual variability (Exponential model)</u>			
ω_{11}^2 IIV on CL	0.0548	0.0067 (12.3)	0.0538 (0.0536–0.0547)
ω_{22}^2 IIV on Vc	0.0852	0.0141 (16.55)	0.0835 (0.0824–0.0841)
ω_{12}^2 Cov (CL, Vc)	0.0519	0.0075 (14.45)	0.5837 (0.5631–0.5765)
ω_{33}^2 IIV on Vp	0.129	0.0284 (22.02)	0.1253 (0.1237–0.1282)
ω_{44}^2 IIV on Q	0.448	0.0884 (19.73)	0.4238 (0.4093–0.4292)
ω_{34}^2 Cov (Vp, Q)	0.212	0.0485 (22.88)	0.8028 (0.7924–0.8045)
ω_{55}^2 IIV on scale parameter	0.362	0.0576 (15.91)	0.3624 (0.3620–0.3706)
ω_{66}^2 IIV on shape parameter	0.483	0.102 (21.12)	0.4624 (0.4573–0.4693)
<u>Residual error (Combined model)</u>			
σ_1^2 Additive part, fixed	0.0001	–	–
σ_2^2 Proportional part	0.108	0.00175 (1.64)	0.108 (0.1074–0.1079)

SE, standard error; RSE, relative standard error; CI, confidence interval.

Table 6. Summary of PPK studies reviewed

References	Absorption model	Distribution model	Subject number	Subjects characteristics	PK sampling	Dose (mg/m ²)	Administration route	CL/F estimate (SE) (L/h)	V/F estimates (SE) (L)
[23]	Zero-order	One-	34	GIST	Pre-dose, 1–3 h, 6–9 h, 24 h (day 1), day 30, day 60	400–600	PO	7.97	168
[27]	Zero-order	One-	73	GIST	Pre-dose, 1–3 h, 6–9 h, 24 h (day 1), day 29	400–600	IM	8.18	168 + 58.5 (day 28)
[24] (Model1)	Zero-order	One-	43	GIST Soft tissue sarcoma	Pre-dose, 1, 2, 3, 4, 8, 12, 14, 24 h (day 1)	300, 400, 500	–	9.33 (0.98)	184 (14)
[24] (Model2)	Zero-order	One-	42	GIST Soft tissue sarcoma	Pre-dose, 2, 8, 24h (day29) Pre-dose, 2, 4h (extension phase)	300, 400, 500	–	10.6 (1.16)	183 (16)
[25]	Zero-order	One-	31	CML	Pre-dose, 1–3 h, 6–9 h, 12 h, 24 h over 24–48 h (day1, 8, 18)	260–570	PO	10.3	251
				Osteosarcoma					
				Ewing sarcoma Desmoplastic small round cell tumor Synovial cell sarcoma GIST of young adult and children					
[13]	First-order	One-	67	GIST of adult and children	Adult: Pre-dose, 1–3 h, 6–9 h, 24 h (day 1), day 30, day 60 Children: Pre-dose, 1, 3, 5, 7, 13, 24 h (day 1) Pre-dose, 2–4 h (day 30, 60)	400, 600	PO	7.29	202
[15]	Zero-order	One-	553	CML	Pre-dose, 1–3 h, 6–9 h, 24 h (day 1, 29)	400	PO	13.8	252
[14]	First-order	One-	59	GIST CML ALL	Pre-dose, 2, 4, 6, 8 h	150–800	–	14.3	347
[26]	First-order	One-	34	CML	0–1 h, 0–8 h, 8–16 h, 16–30.5 h	100–600	–	8.7(5.3)	430 (9.9)
Our results	Weibull function	Two-	112	Healthy volunteers	Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, 60 and 72 h (at 400 mg group only)	100, 400	PO	13.6 (0.379)	153 (5.55)* 64 (3.58) [†]

*Central compartment volume, [†]Peripheral compartment volume. One-, one-compartment; Two-, two-compartment; GIST, gastrointestinal stromal tumor; CML, chronic myeloid leukemia; AML; acute myeloid leukemia.

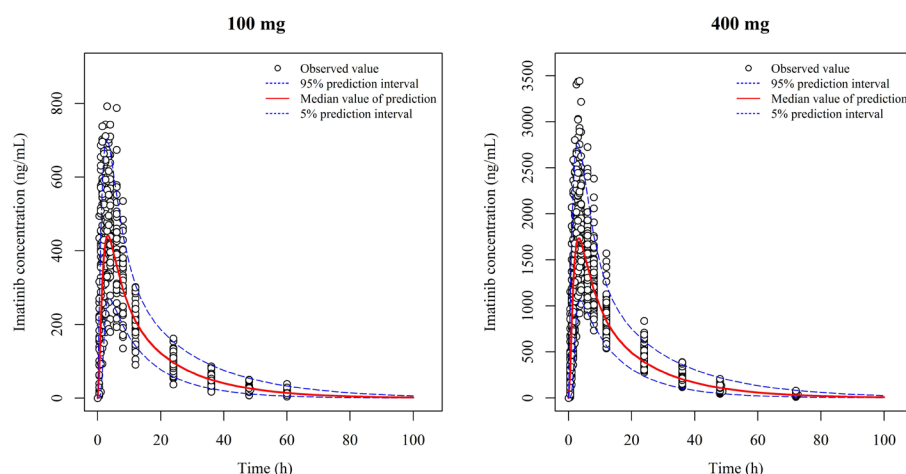


Figure 4. Visual predictive checks of the final PK model classified by dose of 100 mg and 400 mg.

the final population PK model are shown in Figure 4.

Discussion

The objective of this study was to characterize the population PK of imatinib in healthy Koreans. A two-compartment model with Weibull absorption successfully described the data from three studies conducted in healthy Koreans while most of previous modeling reports[13-15,23-26] supported a single compartment with zero-order or first-order absorption (Table 6). The estimated parameters in this study were comparable to those reported elsewhere.

From pathophysiological changes by disease, patients with CML or GIST may show imatinib PK characteristics substantially different from those of healthy volunteers. Except one study,[15] the population PK analysis was conducted at steady state, while our study was done with single dose data. The present study suggested a two-compartment model for disposition in contrast to one-compartment models in their reports. Such a difference in the distribution model structure may have been caused by rather sparse and/or short (i.e., less than 24 h) sampling schemes at daily dosing situation in patients. Although many other reports employed zero-order absorption[15,23-25, 27] or first-order absorption models,[13,14,26] we tried Weibull function[28] to describe the absorption pattern more precisely. Because of the flexibilities of the Weibull function, it may be applied in cases where the absorption model involves the first-order, zero-order absorption, or a combination of both.[29]

Laboratory markers such as α 1-acid glycoprotein (AAG) albumin, hemoglobin, WBC count, as well as body weight, were identified as significant covariates for CL, V in previous reports. [13-15,24,25,27] Age was correlated with central volume (Vc), inter-compartmental clearance (Q) in this study, but its implication is not clear because the number of subjects or the range of age was not large enough. Although the PK data used were from

healthy subjects only, this is the first report on the population PK of imatinib in Koreans.

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Conflict of interest

The authors declared no conflict of interest.

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