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ORIGINAL ARTICLE

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Population pharmacokinetic modeling and model validation of a spicamycin derivative, KRN5500, in phase 1 study

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Abstract *Purpose:* KRN5500, a novel spicamycin derivative, shows the greatest activity against a human tumor xenograft model and the highest therapeutic index among spicamycin derivatives. KRN5500 is currently under clinical development in Japan and the United States. The objective of this study was to develop a population pharmacokinetic model that describes the KRN5500 plasma concentration versus time data. *Methods:* Data were collected from 18 patients entered in a phase 1 study. These patients received KRN5500 3–21 mg/m^2 as a 2-h infusion. A total of 219 concentration measurements were available. The data were analyzed using the nonlinear mixed effect model (NONMEM) program. In addition, the basic and final population pharmacokinetic models were evaluated using bootstrapping resampling. *Results:* The basic model selected was a two-compartment model with a combination of additive and constant coefficient of variation error models. The basic model fitted well not only the original data, but also 100 bootstrap replicates generated from the original data set. With regard to the effect of covariates selected by generalized additive modeling analysis, gender (SEX) and performance status were found to be possible determinants of the volume of central compartment by NONMEM analysis. The final regression model for V1 was $V1 = \theta_{V1}(1 - SEX \times \theta_{SEX})$, where V1 is the typical population value of the volume of central compartment, and SEX = 0 if the patient is male, otherwise SEX = 1. The final model was fitted to the 200 bootstrapped samples. The mean parameter estimates were within 15% of those obtained with the original data set. *Conclusions:* The KRN5500 plasma concentration versus time data obtained from the phase 1 study were well described by the population pharmacokinetic model. Further evaluation by bootstrapping showed that the population pharmacokinetic model was stable.

Key words KRN5500 · Population pharmacokinetics · NONMEM · Model building · Model validation

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Introduction

Spicamycin, a nucleoside antibiotic containing fatty acids with various chain lengths, induces potent differentiation in HL-60 and M1 myeloid leukemic cells [1, 2]. Several semisynthetic spicamycin analogues differing in the chain length of the fatty acid moiety, have been examined for their structure-antitumor activity relationships [3, 4]. KRN5500 (6-[4-deoxy-4-(2*E*,4*E*)-tetradecadienoylglycyl] amino-L-glycero-β-L-mannoheptopyranosyl]amino-9*H*-purin), a novel spicamycin derivative, shows the greatest activity against a human tumor xenograft model and the highest therapeutic index among spicamycin derivatives [5, 6]. KRN5500 is currently under clinical development in Japan and the United States.

A population pharmacokinetic approach is useful for modeling phase 1 pharmacokinetic data and is helpful in identifying covariates that affect drug behavior in early drug development [7]. We report here for the first time a population pharmacokinetic modeling and model validation of KRN5500. A pharmacokinetic analysis using a standard two-stage approach could not give precise parameter estimates among lower dosage groups due to the issue of lower limit of quantification. The data from a phase 1 study were analyzed using the nonlinear mixed

effect model (NONMEM) program (version 5.0; NONMEM Project Group, University of California at San Francisco, San Francisco, Calif.). As the population pharmacokinetic model is used for prediction, it is important to develop a model that is validated in population modeling [8]. There are two types of methods to evaluate the stability of the model. The first, external validation, is the application of the developed model to a data set (validation data set) from another study. Internal validation, the second type of validation, refers to the use of data splitting [9] and resampling techniques (cross-validation and bootstrapping) [8, 10]. Bootstrapping is a useful internal validation technique and has the advantage of using the entire data set for model development. Because of the limited number of patients in this study, evaluation of the model validation was performed by bootstrapping.

Materials and methods

Patient population and data collection

Data were collected from 18 patients entered in a phase 1 study. Ten of the patients had large intestine cancer, the others had stomach cancer (four), lung cancer (three), or bladder cancer (one). Written informed consent was obtained from all patients. These patients received KRN5500 at 3–21 mg/m^2 as a 2-h infusion. A total of 16 blood samples were drawn from the vein of each patient immediately before the infusion (0 h) and then 0.5, 1, 1.5, 2, 2.083, 2.25, 2.5, 3, 4, 6, 8, 10, 14, 26, and 50 h after the start of administration. KRN5500 was assayed by a validated reversed-phase high performance liquid chromatographic technique according to a previously published method [11]. The calibration curves were linear over concentrations ranging from 2.0 (quantification limit) to 500 ng/ml. Samples with a concentration higher than 500 ng/ml were diluted so that the concentration fell within the range of the calibration curve.

Acceptance criteria for validating the analytical results of each run were as follows [12]. Quality control (QC) samples in duplicate at three concentrations (5, 100 and 400 ng/ml) were incorporated into each run. The results of the QC samples provided the basis for accepting or rejecting the run. At least four of the six QC samples had to be within 20% of their respective nominal values, and two of the six QC samples (not both at the same concentration) had to be outside the $\pm 20\%$ respective nominal value. A total of 219 concentration measurements were available. The following demographic and physiopathological parameters were recorded and considered in the analysis: gender (SEX), male (10), female (8); age, 34–73 years; weight, 39–71.5 kg; body surface area, 1.252–1.797 m^2; performance status (PS), 0 (5), 1 (13); the presence of liver metastasis, no (9), yes (9); GPT, 5–36 IU/l; serum albumin (ALB), 3.6–4.5 g/dl; blood urea nitrogen, 9–26 mg/dl; creatinine clearance, 64.5–167 ml/min.

Population model building

A stepwise approach was used in the analysis of the data [13]: (1) exploratory data analysis to examine the distribution and correlations between covariates, (2) a basic pharmacokinetic modeling using the NONMEM program and obtaining Bayesian individual parameter estimates, (3) validation of a basic model using a bootstrap resampling technique, (4) generalized additive modeling (GAM) for the selection of covariate candidates, (5) final NONMEM modeling to determine the population pharmacokinetic model, and (6) validation of the final model. The NONMEM program and PREDPP package were used throughout the analysis. The first-order conditional estimation method was used in all of the analysis process because of extensive sampling design in the study. Initial parameter estimates for NONMEM modeling were calculated using the data obtained from the patients in the highest dosing group by WinNonlin (version 1.1; Pharsight Corporation, Mountain View, Calif.).

Step 1: examination of distribution and correlations. The sampling distribution of each covariate was examined graphically by means of histograms. To reduce the dimensionality of the covariate vector, graphic inspection of bivariate scatterplots and pairwise analysis based on the calculation of correlation coefficients were used.

Step 2: basic pharmacokinetic modeling without bootstrapping. A one-, two-, or three-compartment model with constant rate infusion was fitted to the KRN5500 concentration-time data. Interindividual variability in clearance (CL) was modeled using an exponential error model as follows:

$$\mathrm{CL_j} = \mathrm{CL}\exp(\eta_{\mathrm{jCL}}); \eta_{\mathrm{jCL}} = \text{i.i.d.}\tilde{\mathrm{N}}(0, \omega^2_{\mathrm{CL}}),$$

where $\mathrm{CL_j}$ is the hypothetical true clearance for the jth individual as predicted by the regression model. CL is the typical population value of clearance, and η_{jCL} represents the persistent difference between the jth individual's CL value and that predicted by the regression model; η_{jCL}s are independent, identically distributed random variables with mean zero and variance ω^2. Interindividual variabilities in other parameters were similarly modeled.

Residual intraindividual variability was identically distributed and was modeled using the additive error, the constant coefficient of variation (CCV) error or the combination of the additive and CCV error models. The combination of the additive and CCV error models is described by the following equation:

$$\mathrm{Cp_{ij}} = \mathrm{Cp_{mij}} + \mathrm{Cp_{mij}} \times \epsilon_{1\mathrm{ij}} + \epsilon_{2\mathrm{ij}}$$

where $\mathrm{Cp_{ij}}$ is the ith observed concentration for the jth individual and $\mathrm{Cp_{mij}}$ is the ith concentration predicted by the model at the ith observation time for the jth individual. ϵ_1 and ϵ_2 are independent, statistical errors with mean zero and variance σ^2. The magnitude of residual intraindividual variability usually depends on measurement, dosing, sampling and model misspecification errors, but also on the presence of interoccasion variability [14].

With the fixed and random effects chosen, empirical Bayes estimates of pharmacokinetic parameters were subsequently obtained using the POSTHOC option within the NONMEM program. The choice of a basic population model was based on monitoring the Akaike's information criterion (AIC). The reliability of the model selection was checked by the analysis of residuals and by visual inspection of plots of predicted versus measured concentrations.

Step 3: validation of a basic model using the bootstrap resampling technique. Resampling the original data with replacement generated 100 bootstrap samples. The resampling unit comprised the samples obtained from each patient. The appropriate structural model that best describes the data from each sample was determined. This was done to ensure that the model that best described the bootstrap data was not different from the basic model used for developing the population pharmacokinetic model in the subsequent step. In addition, the density plots of each pharmacokinetic parameter estimate were used to examine the adequacy of the basic model.

Step 4: selection of covariate candidates. Exploratory data analysis was performed on the empirical Bayesian parameter estimates from step 3 treated as data to examine distributions, shapes, and relationships between covariates and individual pharmacokinetic parameter estimates.

The data were subjected to a stepwise (single term addition/deletion) procedure using the GAM procedure in the Xpose program (version 2.0) [15] running on the S-PLUS statistical software package (version 4.5J; MathSoft, Cambridge, Mass.). Each covariate was allowed to enter the model in any of several functional representations. AIC was used for model selection [16]. At each

step, the model was changed by addition or deletion of the covariate that resulted in the largest decrease in AIC. The search was stopped when AIC reached a minimum value.

Step 5: population model building using NONMEM. For each NONMEM analysis, the improvement in fit obtained upon addition of a covariate selected from step 4 to the regression model was assessed by change in the NONMEM objective function. Minimization of NONMEM objective function, equal to twice the negative log-likelihood of the data, is equivalent to maximizing the probability of the data. The change in objective function of the NONMEM value showed approximately a χ^2 distribution. A difference in the NONMEM objective function value of 3.84, associated with a *P*-value of less than 0.05, was considered statistically significant.

The construction of the regression model for each structural model parameter was performed in three steps using the original data set. The covariates were first screened one by one. Next the full model was defined as incorporating all (screening step) significant covariates. Lastly, the final model was elaborated by backward elimination from the full model.

Step 6: validation of the final population pharmacokinetic model. Resampling with replacement generated 200 bootstrap samples used for the evaluation of stability of the final model built in step 5. The final population pharmacokinetic model was fitted repeatedly to the 200 additional bootstrap samples. The mean parameter estimates obtained from the 200 bootstrap replications were compared with those obtained from the original data set.

Results

Exploratory data analysis

A histogram of the demographic and physiopathological covariates revealed a normality in the distribution (data not shown). With the relationships between covariates, weight and body surface area were found to be highly correlated, but other covariates showed no marked correlation (data not shown).

Determination of a basic pharmacokinetic model

The average plasma concentration versus time curve is shown in Fig. 1. The parameter estimates of various structural models are given in Table 1. The combination of the additive and CCV error models (the combination error model) was found to describe intraindividual error better than the CCV error model or the additive error model. Two- and three-compartment with the combination error models gave similar low AIC values. The analysis of residuals and plots of observed versus predicted concentration were performed to check the reliability of the basic model selection. The residuals calculated in the two-compartment with the combination error model were not obviously different from those obtained in the three-compartment with the combination error model (data not shown). The stability of these two models was examined in a subsequent step.

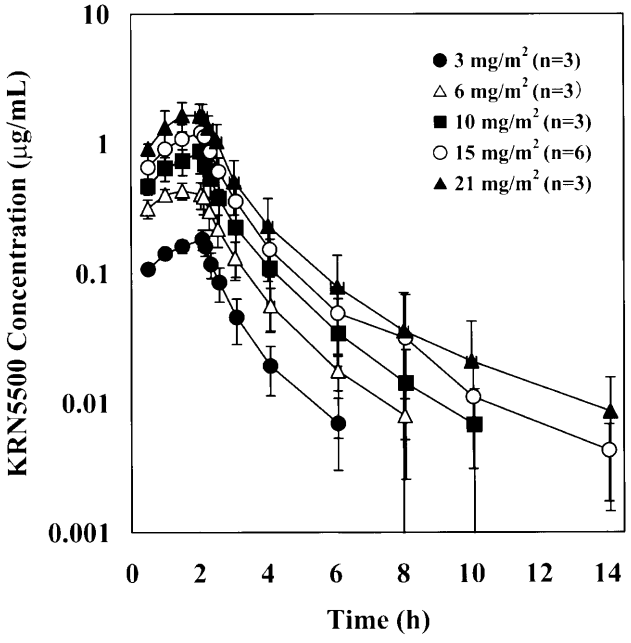

Fig. 1 Plasma concentration of KRN5500 during and after intravenous infusion. Each point is the mean with SD indicated by bars

Table 1 Parameter estimates of various structural models (*CL* clearance, *Q1* intercompartmental CL between central and peripheral 1, *Q2* intercompartmental CL between central and peripheral 2, *V1* volume of central compartment, *V2* volume of peripheral compartment 1, *V3* volume of peripheral compartment 2, *AIC* Akaike's information criterion)

Model	Intraindividual error model[a]	CL (l/h/m^2)	Q1 (l/h/m^2)	Q2 (l/h/m^2)	V1 (l/m^2)	V2 (l/m^2)	V3 (l/m^2)	AIC
One-compartment	CCV	5.68			22.4			−1010.7
	Additive	5.92			4.33			−936.4
	Combination	5.85			4.46			−1017.8
Two-compartment	CCV	2.51	1.29		3.88	2.33		−1215.7
	Additive	5.43	0.958		3.98	1.91		−968.9
	Combination	5.41	1.27		3.78	1.98		−1239.1
Three-compartment	CCV	4.49	0.337	0.937	8.14	0.514	1.79	−1201.8
	Additive	5.43	201	0.850	1.76	2.23	1.88	−962.9
	Combination	5.29	1.18	0.201	3.78	1.65	4.49	−1239.3

[a] *CCV* constant coefficient of variation model, *Additive* additive error model, *Combination* combination of the additive and CCV models

Stability of the basic model as assessed by the bootstrap resampling technique

From the original data, 100 bootstrap replicates were generated and used for the evaluation of stability of the basic pharmacokinetic model selected in the previous step. The density plots of each pharmacokinetic parameter estimate for the two-compartment with the combination error model are shown in Fig. 2. The estimates were obtained from each bootstrap data set. Each parameter distribution of this model is in a narrow range and unimodal. Figure 3 shows the density plots of each pharmacokinetic parameter estimate for the three-compartment with the combination error model. Each parameter distribution in Fig. 3 is in a markedly broad range. Therefore, it was found that the two-compartment model with the combination error model was adequate and this model was used as the basic population model in subsequent steps. The correlation matrix of parameter estimates of this model calculated by the POSTHOC option did not show any marked relationships.

Selection of covariate candidates

The GAM analysis indicated that CL is a function of performance status, V1 is a function of gender and performance status, and V2 is a linear function of albumin (data not shown).

Population model building and stability of the population models

The population model was built using the NONMEM program on the basis of the result of the GAM analysis. Testing for the significance of each covariate, SEX and PS were found to be predictors of V1 with a log likelihood difference (LLD) of more than 3.84 ($P < 0.05$) between the V1 model in which each covariate was introduced singly and the basic model of V1 modeled without any covariates (Table 2). No other covariates reached statistical significance. Gender (SEX) and performance status (PS) were then combined in the following full regression model:

$$V1 = \theta_{V1} \times (1 - SEX \times \theta_{SEX} + PS \times \theta_{PS})$$

where V1 is the typical population value of volume of the central compartment, and SEX = 0 if the patient is male, otherwise SEX = 1. The full model was tested against reduced models (Table 3). SEX and PS are possible determinants of V1 and were kept in the subsequent population structural model. The parameter estimates of the full model are given in Table 4.

The population pharmacokinetic model obtained from the previous step was fitted repeatedly to the 200 bootstrapped samples. A summary of the average parameter values from the 200 bootstrap replicates is provided in Table 4. It is worth noting that the regression coefficient on PS status is imprecise. The 95% confidence interval on this coefficient, –0.048–0.458, includes zero, indicating no statistical significance. The final population model for V1 is described by the following equation:

$$V1 = \theta_{V1} \times (1 - SEX \times \theta_{SEX})$$

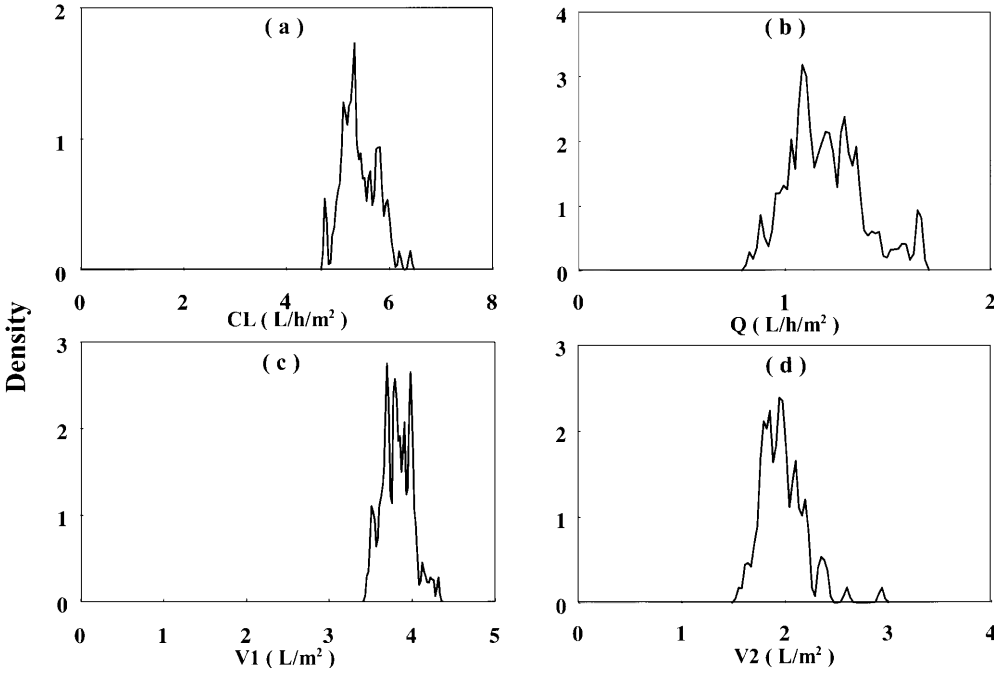

Fig. 2a–d Density plots of population pharmacokinetic parameter estimates of the two-compartment with the combination of the additive and CCV error models (**a** CL, **b** Q, **c** V1, **d** V2)

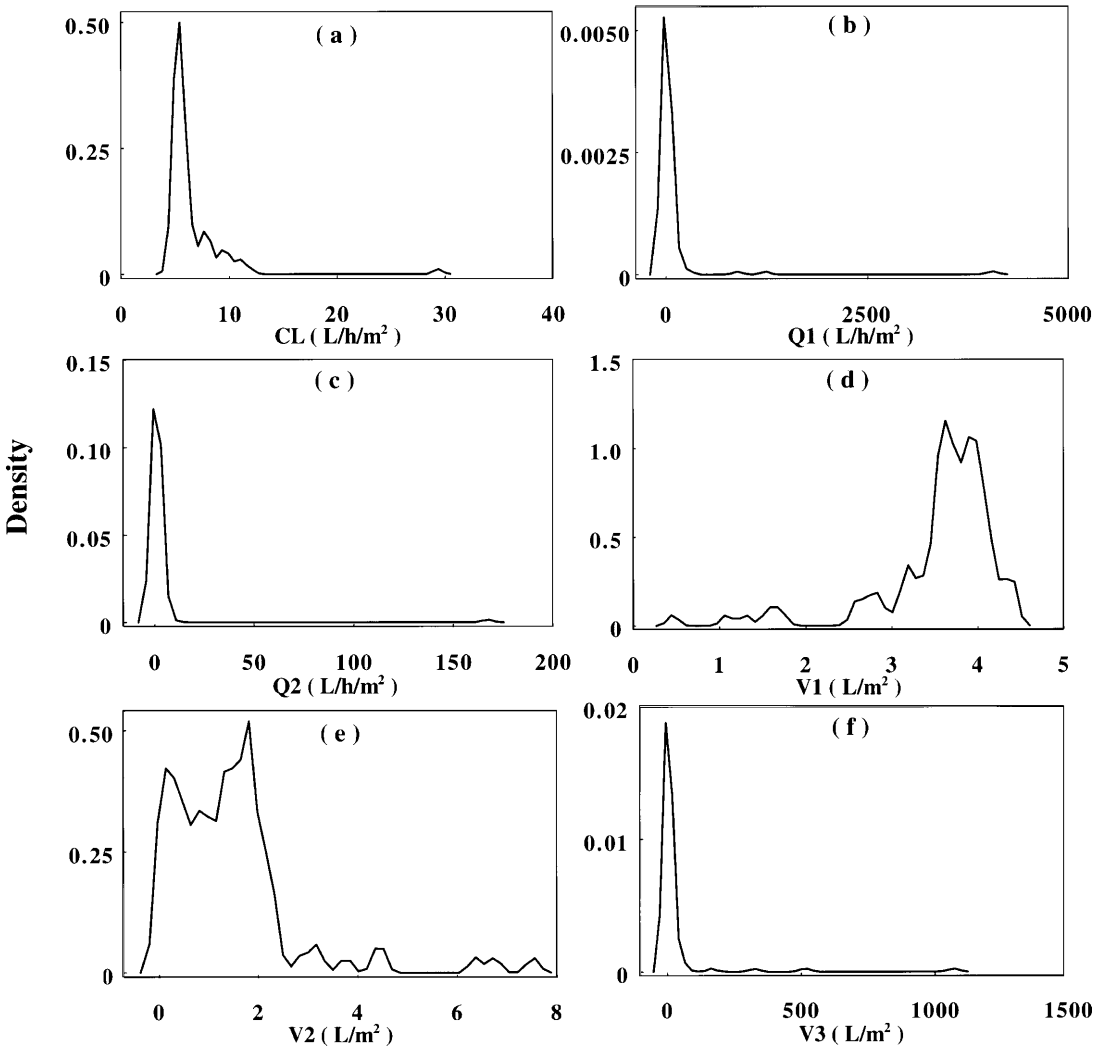

Fig. 3a–f Density plots of population pharmacokinetic parameter estimates of the three-compartment with the combination of the additive and CCV error models (**a** CL, **b** Q1, **c** Q2, **d** V1, **e** V2, **f** V3)

Table 2 Effect of performance status (PS), gender (SEX) and serum albumin (ALB) on structural model parameters. Each θ represents a population parameter estimate (*CL* clearance, *V1* volume of central compartment, *V2* volume of peripheral compartment, *LLD* log likelihood difference; SEX = 0 if the patient is male, otherwise, SEX = 1)

Regression model	LLD (vs $\theta_{covariant} = 0$)
$CL = \theta_{CL} \times (1 - PS \times \theta_{PS})$	0.724
$V1 = \theta_{V1} \times (1 - SEX \times \theta_{SEX})$	7.39*
$V1 = \theta_{V1} \times (1 + PS \times \theta_{PS})$	4.84*
$V2 = \theta_{V2} \times (1 + ALB \times \theta_{ALB})$	1.37

*$P < 0.05$

The parameter estimates of the final model using the original data and the mean parameter estimates obtained from the additional 200 bootstrap replicates are provided in Table 5. These mean parameter estimates were within 15% of those obtained with the original data set. Figure 4 shows the individual weighted residual plots for the final structural model. The distribution of individual weighted residuals at each time-point was relatively symmetric and not distorted, and changed little along the time course.

Table 3 Comparison of the full model and reduced model. Each θ represents a population parameter estimate (*V1* volume of central compartment, *LLD* log likelihood difference, *PS* performance status; SEX = 0 if the patient is male, otherwise SEX = 1)

Regression model	LLD (vs full model)
Full model	
$V1 = \theta_{V1} \times (1 - SEX \times \theta_{SEX} + PS \times \theta_{PS})$	0
Reduced model	
$\theta_{SEX} = 0$	–6.90*
$\theta_{PS} = 0$	–4.35*

*$P < 0.05$

Discussion

The population pharmacokinetic approach is useful for understanding the quantitative relationships between each pharmacokinetic parameter and important cova-

Table 4 Typical population parameter estimates and stability of the full population model (*SEX* gender, *PS* performance status, *OBJ* objective function value)

Parameter	Typical population parameter estimates (SE)[a]	Mean population pharmacokinetic parameter estimates (SE)[b]
θ_{CL} (l/h/m^2)	5.39 (0.33)	5.39 (0.34)
θ_{Q} (l/h/m^2)	1.27 (0.17)	1.22 (0.22)
θ_{V1} (l/m^2)	3.73 (0.38)	3.80 (0.45)
θ_{V2} (l/m^2)	1.99 (0.24)	2.01 (0.25)
θ_{SEX}	0.241 (0.079)	0.235 (0.082)
θ_{PS}	0.196 (0.103)	0.205 (0.129)
ω_{CL} (%)	25.7	24.7 (3.3)
ω_{Q} (%)	36.2	31.7 (10.1)
ω_{V1} (%)	16.0	13.9 (7.3)
ω_{V2} (%)	41.5	37.3 (12.5)
σ_1 (%)	7.99	8.06 (0.76)
σ_2 (ng/ml)	6.63	5.63 (3.39)
OBJ	–1270.9	

[a]Obtained from the original data set
[b]Calculated from 200 bootstrap replicates

Table 5 Typical population parameter estimates and stability of the final population model (*SEX* gender, *OBJ* objective function value)

Parameter	Typical population parameter estimates (SE)[a]	Mean population pharmacokinetic parameter estimates (SE)[b]
θ_{CL} (l/h/m^2)	5.39 (0.34)	5.38 (0.34)
θ_{Q} (l/h/m^2)	1.27 (0.17)	1.23 (0.22)
θ_{V1} (l/m^2)	4.29 (0.31)	4.34 (0.30)
θ_{V2} (l/m^2)	1.99 (0.24)	2.01 (0.25)
θ_{SEX}	0.241 (0.079)	0.233 (0.080)
ω_{CL} (%)	25.7	24.6 (3.3)
ω_{Q} (%)	37.0	31.8 (10.5)
ω_{V1} (%)	18.6	16.7 (4.9)
ω_{V2} (%)	41.6	37.4 (12.7)
σ_1 (%)	7.93	8.00 (0.77)
σ_2 (ng/ml)	6.69	5.70 (3.42)
OBJ	–1266.5	

[a]Obtained from the original data set
[b]Calculated from 200 bootstrap replicates

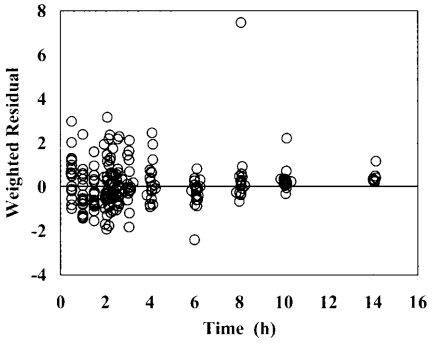

Fig. 4 The individual weighted residual plots for the final population pharmacokinetic model

riates and can be influential in the design of subsequent clinical trials during the development of a new drug [7]. The reliability of the results obtained from population pharmacokinetic analyses depends on the modeling procedure. Providing evidence for the quality of these results is important in the subsequent phases of the drug development up to registration. Therefore, validation of the population pharmacokinetic model is crucial. There are two types of validation: external validation, which is the application of the built model to a new data set, and internal validation [8, 10]. The choice of the two depends on the objective of the analysis. In the absence of a new data set, bootstrapping, one of the internal validation methods, can be especially useful for evaluating the reliability of the population model [8].

The objective of this study was to develop a population pharmacokinetic model which describes the KRN5500 plasma concentration versus time data for design and implementation of a limited sampling schedule in subsequent clinical trials. A stepwise approach was used in building the model [13]. In addition, evaluation of the basic and the final population pharmacokinetic models was performed using bootstrapping resampling because of the limited number of patients in this study.

The basic population model selected during model development was a two-compartment with combination error model. The basic model fitted not only the original data, but also 100 bootstrap replicates generated from the original data. Further, the distribution of each parameter obtained from the basic model was in a narrow range and unimodal (Fig. 2). This indicates that the basic model is not changed according to the data set of a particular patient.

With regard to the effect of covariates selected by the GAM analysis on the KRN5500 pharmacokinetic parameters, SEX and PS were found to be possible determinants of V1 by NONMEM analysis (Table 3). Although the full model was fitted well to 200 bootstrapped samples, PS was found to be a statistically insignificant covariate. Therefore, PS was not kept in the final model. Since the physiological function was relatively well controlled in this limited population, the variation of covariates was in a narrow range or within the normal limits. The limitation of developing a population model based on such a small, relatively uniform patient population has been reported [17]. Therefore, the relationships between covariates and KRN5500 pharmacokinetic parameters need further investigation in a larger population. The V1 values were small, considering that KRN5500 is a small molecule (Table 5). This shows that blood plasma occupies about 50–60% of the V1. The ratio of adipose tissue to body weight in females is generally higher than that in males. Therefore, the ratio of total blood volume to body weight is lower in females (about 7%) than in males (about 8%). This indicates that the difference in total blood may be relevant to the sex differences in V1.

The final population pharmacokinetic model built in this study was fitted well to the 200 bootstrapped sam-

ples. The mean parameter estimates obtained with the 200 bootstrap replicates of the data were within 15% of those obtained from the original data. This indicates that the final model is stable.

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