

A meta-analysis methodology to estimate population pharmacokinetic parameters from reported non-compartmental values with sparse sampling

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Objectives

To develop and assess the performance of a meta-analysis method to estimate the population pharmacokinetic parameters with the respective inter-individual variabilities (IIV) from reported non-compartmental parameter values (NCPs), taking into account the sampling schedule that was used to calculate the latter.

Simulation study

To evaluate the performance of the method, simulations were carried out. 100 datasets were generated and estimated. Each dataset was consisting of the GMs, means and CVs of the NCPs for 10 groups, each of which was derived from 10 individuals, and was generated as graphically presented:

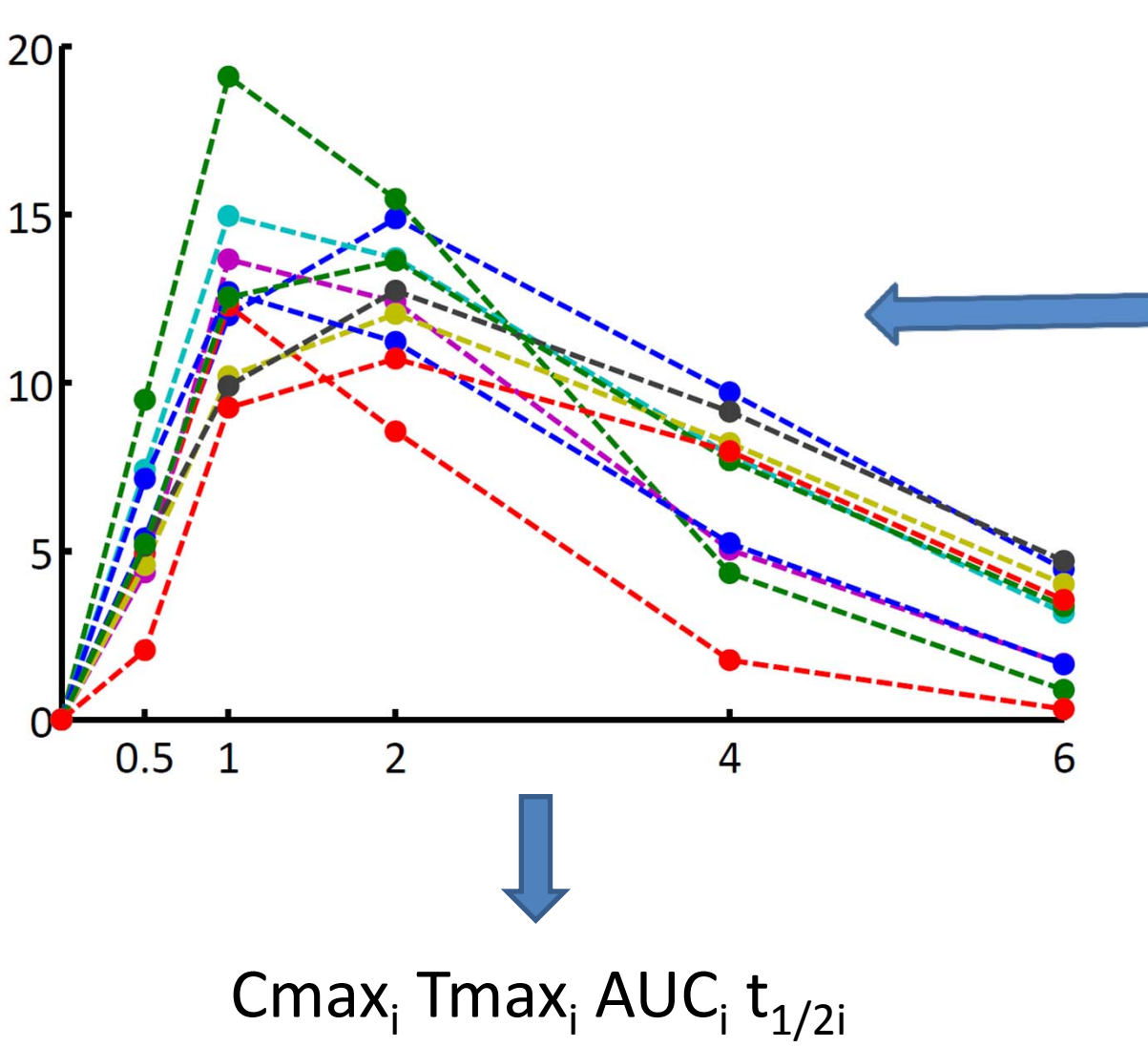


Table 1. Parameters values used for the simulation study

Parameters	Mean values	IIV (%cv)
CL (L/h)	20	30
V (L)	60	30
ka (1/h)	1.5	30
tlag (h)	0.3	20
Residual variability (cv)	0.05	

Using the procedure described in methods the datasets were estimated and percent mean relative bias (%RBIAS), percent relative root mean squared error (%RMSE) and percent absolute relative bias (%RABSB) were calculated. Results are presented in Table 2 for mean population values (upper) and for IIV (lower).

Table 2. Parameters estimate accuracy and imprecision metrics

	CL	V	ka	tlag
%RBIAS	-1	-3	-14	-0.2
%RMSE	4	6	17	13
%RABSB	3	4	14	10

	IIV _{CL}	IIV _V	IIV _{ka}	IIV _{tlag}
%RBIAS	-13	-20	57	-
%RMSE	22	28	62	-
%RABSB	18	24	58	-

Application to valaciclovir : Methods

The method was applied to develop a PopPK model for valaciclovir administered to paediatric population. NCPs reported as means, GMs and CVs from three studies (Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No 1901/2006, as amended for Valtrex: HS210914, HS210915 and HS210916) were stratified according to age groups (Table 3) and analysed with the presented model.

Table 3. Data from valaciclovir oral administration to children aged 1 month (mo) to 12 years

Group	Group age	N	Dose (mg/kg)	AUC (µg*h/ml)			Cmax (µg/ml)			t _{1/2} (h)			Tmax (h)	
				GM	mean	CV	GM	mean	CV	GM	mean	CV	mean	CV
1	1 to 2 mo	9	25	26.90	27.6	0.25	6.88	7.02	0.22	1.99	2.03	0.23	1.87	0.22
2	3 to 5 mo	9	25	16.00	17.7	0.37	4.67	5.17	0.43	1.69	1.79	0.41	1.58	0.34
3	6 to 11 mo	7	25	13.70	14.1	0.25	4.86	4.94	0.21	1.24	1.25	0.12	1.81	0.27
4	12 to 23 mo	6	10	6.44	6.63	0.27	2.35	2.49	0.37	1.37	1.39	0.22	1.19	0.57
5	12 to 23 mo	6	20	13.29	14.41	0.43	3.82	4.03	0.34	1.97	2.13	0.41	1.25	0.33
6	12 to 23 mo	9	25	14.50	15.3	0.34	4.14	4.67	0.44	1.33	1.33	0.07	1.93	0.48
7	2 to 5 years	12	10	5.48	5.72	0.3	2.00	2.05	0.23	1.53	1.65	0.45	1.15	0.47
8	2 to 5 years	12	20	9.59	10.09	0.33	3.59	3.75	0.3	1.51	1.54	0.23	1.30	0.35
9	2 to 5 years	12	25	19.80	19.9	0.13	6.40	6.52	0.19	1.44	1.45	0.14	1.21	0.41
10	6 to 11 years	8	10	8.72	8.84	0.17	3.05	3.08	0.15	1.56	1.58	0.19	1.19	0.45
11	6 to 11 years	8	20	12.75	13.08	0.26	4.59	4.71	0.25	1.42	1.43	0.11	1.14	0.31

The model

A structural model was constructed to calculate the NCPs, namely Cmax, AUC, Tmax and t_{1/2}. Unlike other methods in which the NCPs are calculated according to theoretical formulas, here they are calculated exactly as reported, taking into account the sampling scheme. A schematic example for Cmax is given in Figure 1, where a difference between the theoretical Cmax and the one calculated from the model is observed.

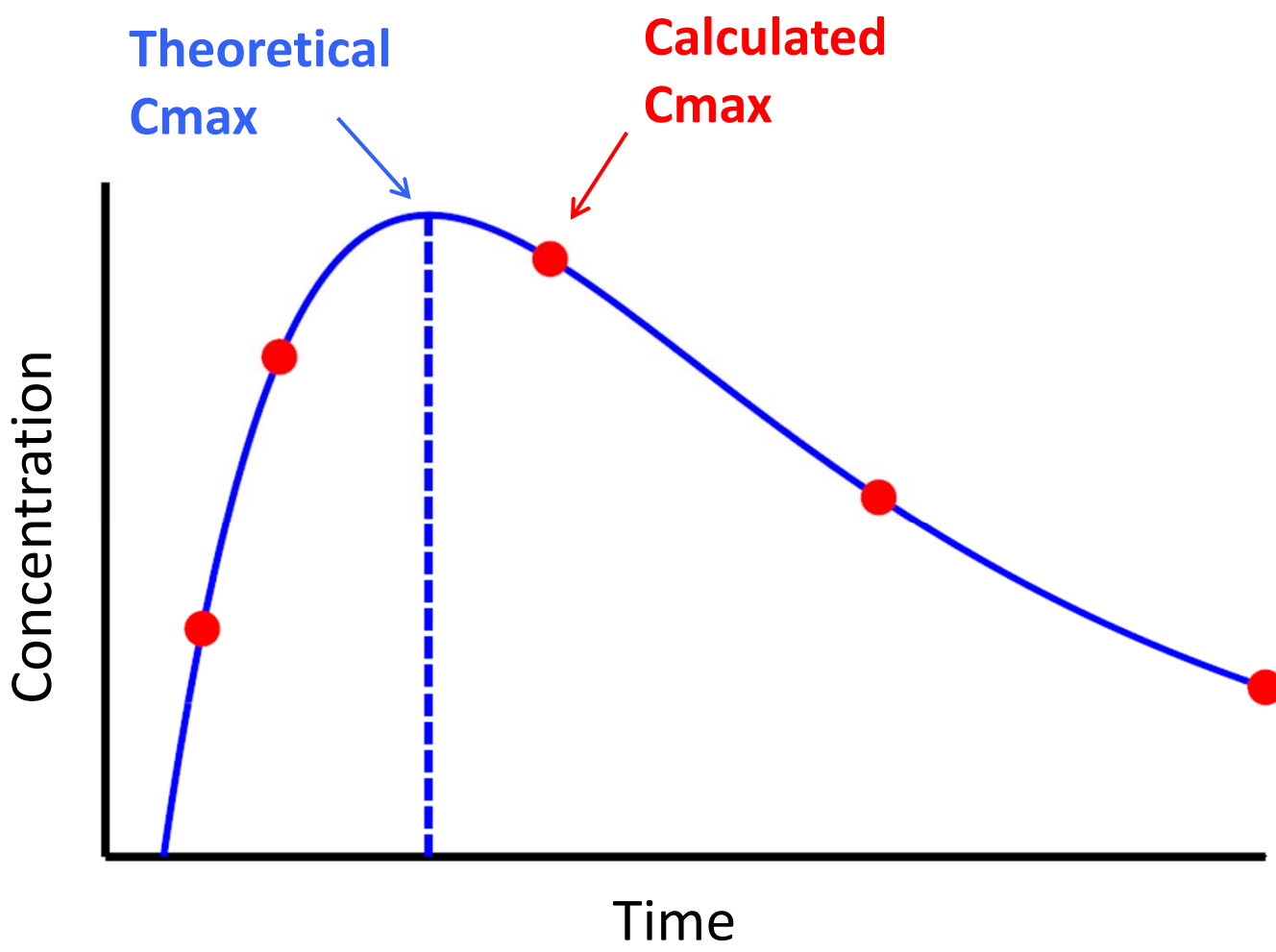


Figure 1. Difference between theoretical and calculated Cmax.

Using a one-compartment model with first order absorption and lag time (tlag), the concentrations at specific sampling time points are simulated. Cmax

and Tmax are the maximum of these concentrations and the respective time, t_{1/2} is calculated from the slope of the log transformed three last points and AUC by the trapezoidal rule and extrapolation to infinity.

A two stage approach is applied to estimate the compartmental parameters (CP), CL, V, ka and tlag. Initially, geometric means (GM) of the NCPs, namely Cmax, Tmax, AUC and t_{1/2}, are used to estimate population means of the CP. In this case, Tmax is calculated according to the theoretical formula, to avoid discrete values of Tmax. Inter-study variability is also included as random effects to account for random variability of the different reported NCPs from which covariates can be determined.

At a second stage, the IIV of the CP, except for tlag, is estimated by the means and the coefficients of variation (CVs) of the NCPs, namely Cmax, AUC, tmax and t_{1/2}. A custom written Fortran subroutine was used to calculate the CVs by Monte Carlo sampling. Estimation was performed using FOCE method in NONMEM V7.2.0 compiled with gfortran.

Application to valaciclovir: Results

Analyzing the GMs, mean population PK parameters were obtained (Table 4). CL/F and V/F were found to be related with age, defined as post-conceptual age (PCA), with the power law: $CL = \theta_1 \left(\frac{PCA}{50} \right)^{\theta_2}$ and $V = \theta_3 \left(\frac{PCA}{50} \right)^{\theta_4}$. IIV was estimated using the means and the CVs of the NCPs. Goodness of fit plots are presented in Figure2 and 3.

Table 4. Valaciclovir population pharmacokinetic model parameter estimates.

	NONMEM	Bootstrap	
	Estimate	Median (RSE%)	95% CI
θ ₁ (L/h)	14.7	15.3 (9.8)	(13, 18.5)
θ ₂	0.78	0.76 (25)	(0.42, 0.99)
θ ₃ (L)	28.8	30.9 (12)	(22.9, 37.9)
θ ₄	0.65	0.63 (21)	(0.38, 0.81)
θ ₅ (ka h ⁻¹)	2.2	2.6 (43)	(1.2, 5.8)
θ ₆ (tlag h)	0.5	0.5 (35)	(0.19, 0.94)
σ _{mean} (%)	22	19 (21)	(12, 25)
CV _{CL} (%)	20	-	-
CV _V (%)	27	-	-
CV _{ka} (%)	18	-	-
σ _{cv} (%)	42	-	-

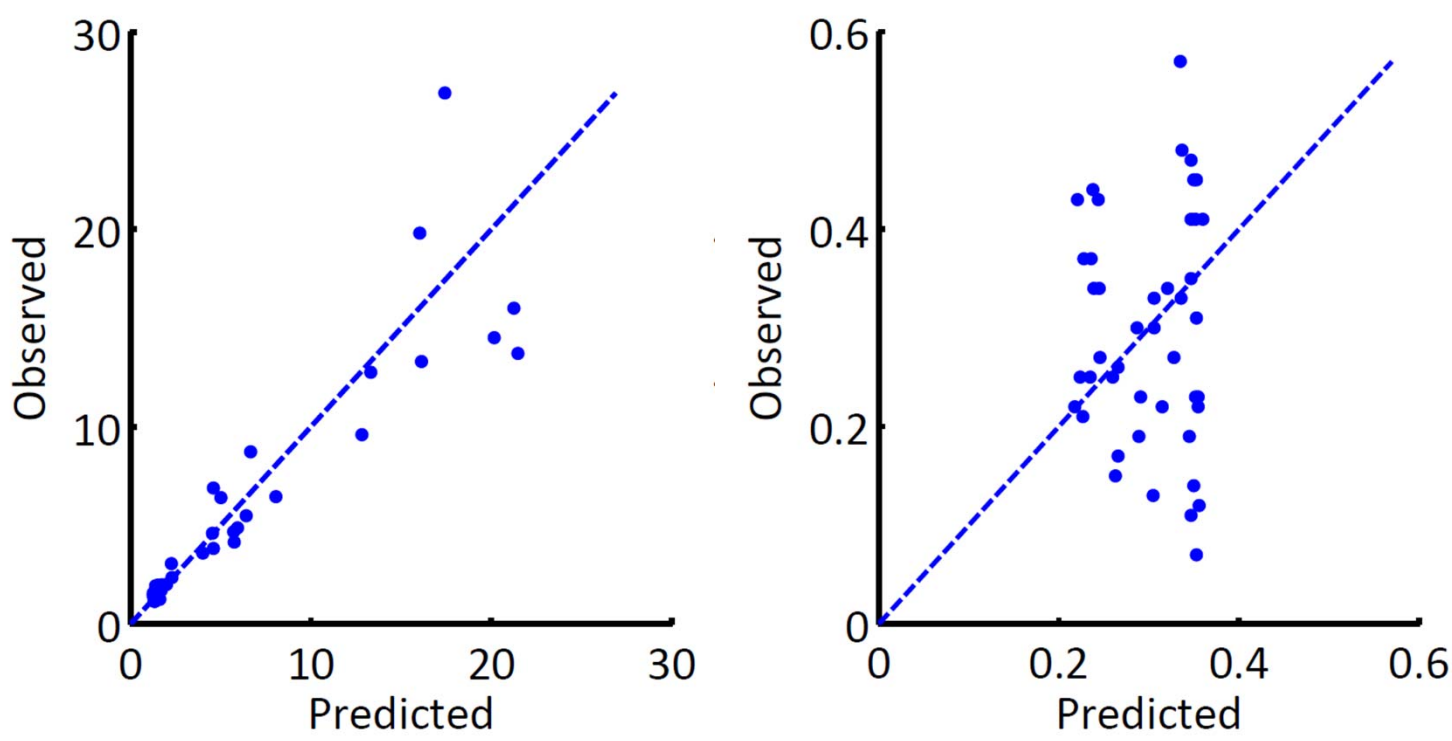


Figure 2. Observed vs predicted of geometric means (left), and CVs(right).

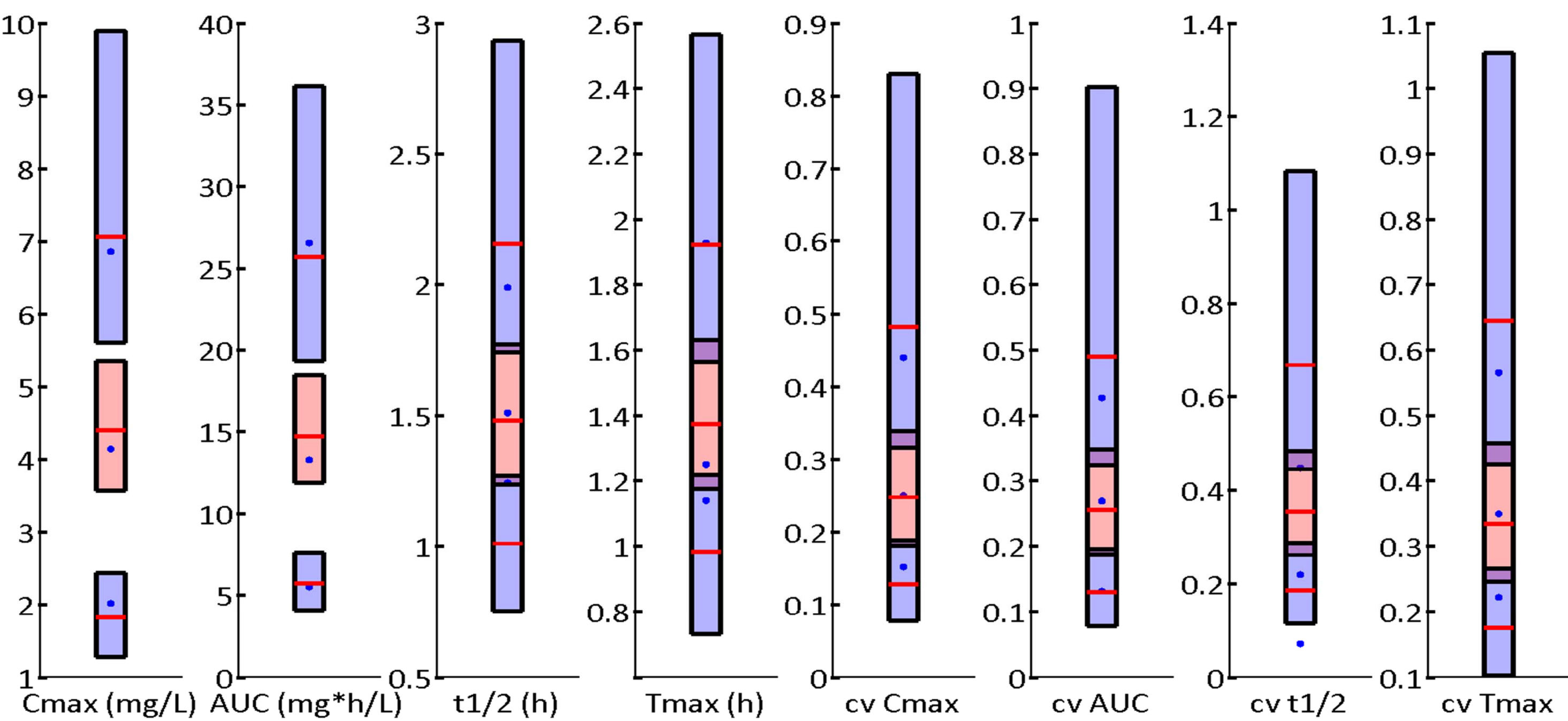


Figure 3. Visual predictive check for the geometric means and CVs of the NCP of valaciclovir. Blue dots are the 5th, 50th and 95th percentiles of the data. Boxes represent the 95% CI for the 5th, 50th and 95th percentiles of the prediction interval, where red lines are the medians.

Conclusions

The method can cancel out the bias of the NCP values introduced by the relatively sparse sampling, by taking into account the exact way these were calculated in the first place. Mean population PK parameters can be estimated with satisfactory accuracy and precision. The imprecision is larger for the IIV parameters, but still in an acceptable level, except for ka. IIV estimate for ka is not reliable. Applying the method to a real dataset, a pop-PK model was developed for valaciclovir orally administered to children.