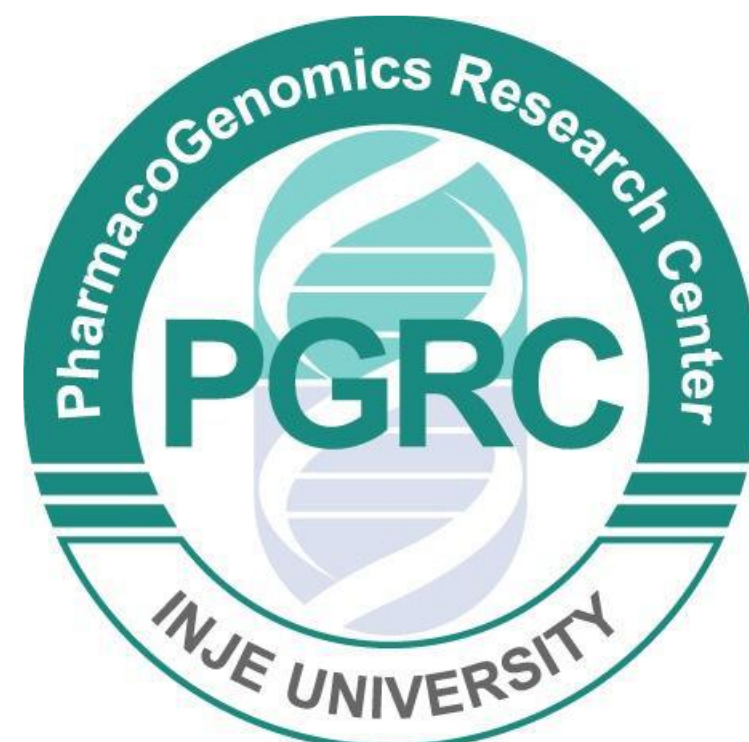




Population pharmacokinetic analysis of Doripenem in Korean patients with acute infections

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OBJECTIVE

The aim of this study is to investigate the population pharmacokinetic (PK) profiles of doripenem in Korean patients with acute infections.

METHODS

Four consecutive 250-mg or 500-mg doses of doripenem were intravenously infused over 1 hour every 8 hour for patients with creatinine clearance of ≤ 50 ml/min or > 50 ml/min, respectively. Blood samples from 38 patients at steady-state were taken pre-dose and at 0 min, 30 min and 4-6 hours after the 4th infusion. The population PK analysis was conducted using a nonlinear mixed effect modeling software, NONMEM. Covariate screening was conducted applying general additive models for PK parameters. Likelihood ratio test was used to select significant covariates, with the significance levels of $p < 0.05$ for selection and $p < 0.01$ for elimination. The final model was evaluated by the visual predictive check. The probability of patients with %T>MIC (the percentage of a dosing interval during which the concentration of drug exceeds the minimal inhibitory concentration) of $\geq 40\%$ (1, 2) for MIC of 1, 2, 3, 4, 6 and 8 $\mu\text{g/mL}$ was calculated in each dataset with 38 patients for 100 simulation datasets.

RESULTS

The doripenem PK was well described by a one-compartment model. The typical values (relative standard error) were 6.921 L/h (7.940%) and 16.71 L (8.320%) for clearance and volume of distribution, respectively. The coefficient of variations of the inter-individual variability (relative standard error) for these parameters were 45.64% (10.45%) and 37.89% (15.72%), respectively. The correlation coefficient between clearance and volume of distribution was 0.2819. Residual variability was best explained by a combined error model with 23.62% proportional and 0.1767 $\mu\text{g/mL}$ additive error. Doripenem clearance increased by 1.102% with creatinine clearance increasing by 1 ml/min and the inter-individual variability for clearance decreased from 60% to 45% with the covariate. (**Table 1**) Some lack of fits by under-predictions were observed at higher concentrations. (**Figure 1&2**) Most of the observed data were within the 90% prediction interval in the visual predictive check. (**Figure 3**) The simulated probability of patients with %T>MIC of $\geq 40\%$ were calculated from the final model. (**Figure 4**) The median (range) probability of patients with T>MIC of 40% were 97% (84-100%), 92% (74-100%), 87% (76-97%), 79% (61-92%), 61% (39-84%) and 42% (18-71%) for MIC of 1, 2, 3, 4, 6 and 8 $\mu\text{g/mL}$. When 10%, 20%, or 30% of standard deviation (SD) for MICs were assumed, %T>MICs were hardly different from %T>MIC with 0% SD.

CONCLUSIONS

The PK profiles of doripenem at steady-state in Korean patients with acute infections were well described by a one-compartment model. Doripenem clearance was significantly influenced by the creatinine clearance. The dose of doripenem is recommended to be adjusted according to MIC.

Table 1. The final parameter estimates

OFV	532.7499		Inter-individual Variability in Parameters $\theta_i = \theta \times \exp(\eta_i)$
Parameter	Estimate	RSE(%)	
θ_{CL} (L/h)	6.921	7.94%	Intra-individual Variability in Observations $y_{ij} = \hat{y}_{ij} \times (1 + \varepsilon_{\text{Proportional}}) + \varepsilon_{\text{Additive}}$
θ_{Vc} (L)	16.71	8.32%	
θ_{Rinf} (mg/h)	9.56	17.04%	Covariate Model $CL = 6.921 \times (1 + 0.01102 \times (GFR_{CG} - 68.20))$ *GFR _{CG} = glomerular filtration rate by Cockcroft-Gault equation
θ_{CL_GFR}	0.01102	22.77%	
ω_{CL}	45.64%	10.45%	
ω_{CL_Vc}	0.2819	45.85%	
ω_{Vc}	37.89%	15.72%	
ω_{Rinf}	81.44%	16.55%	
σ_{Additive}	0.1767	43.05%	
$\sigma_{\text{Proportional}}$	23.62%	12.34%	

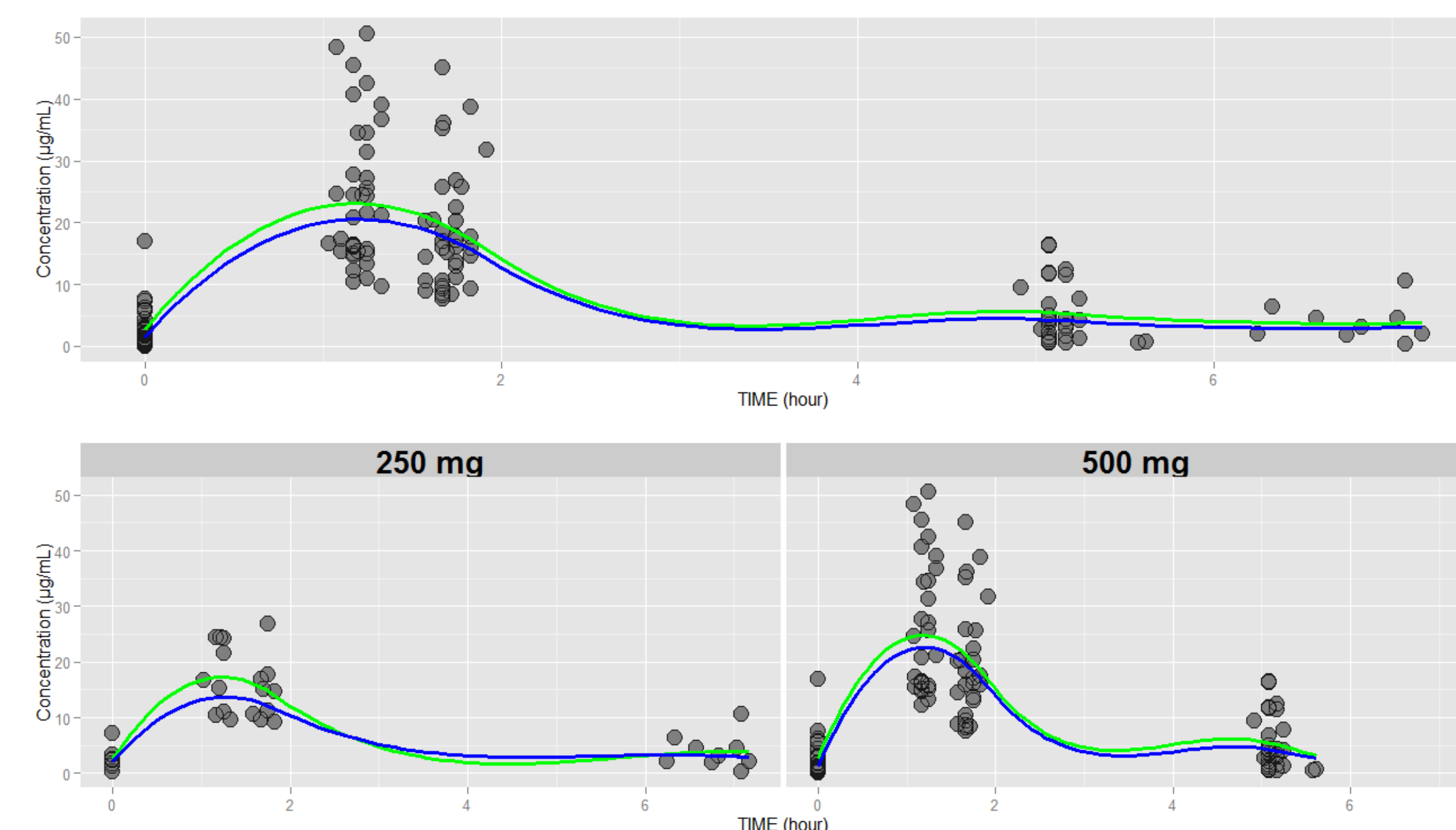


Figure 1. Concentrations versus time plots (upper: all doses, lower left: 250 mg, lower right: 500 mg). Green and blue lines are loess for the observed and predicted concentrations, respectively.

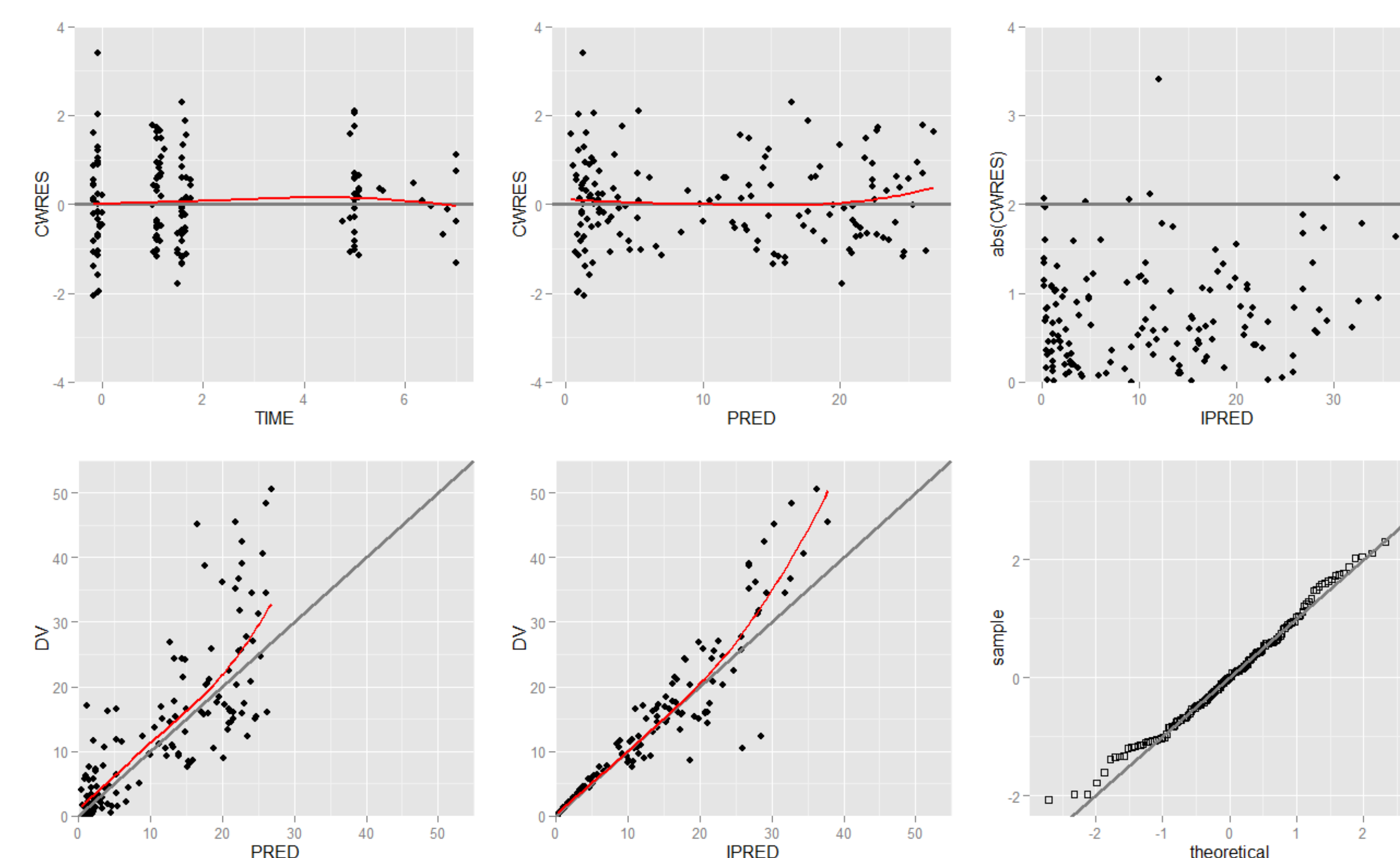


Figure 2. Goodness of fit plots for final model.

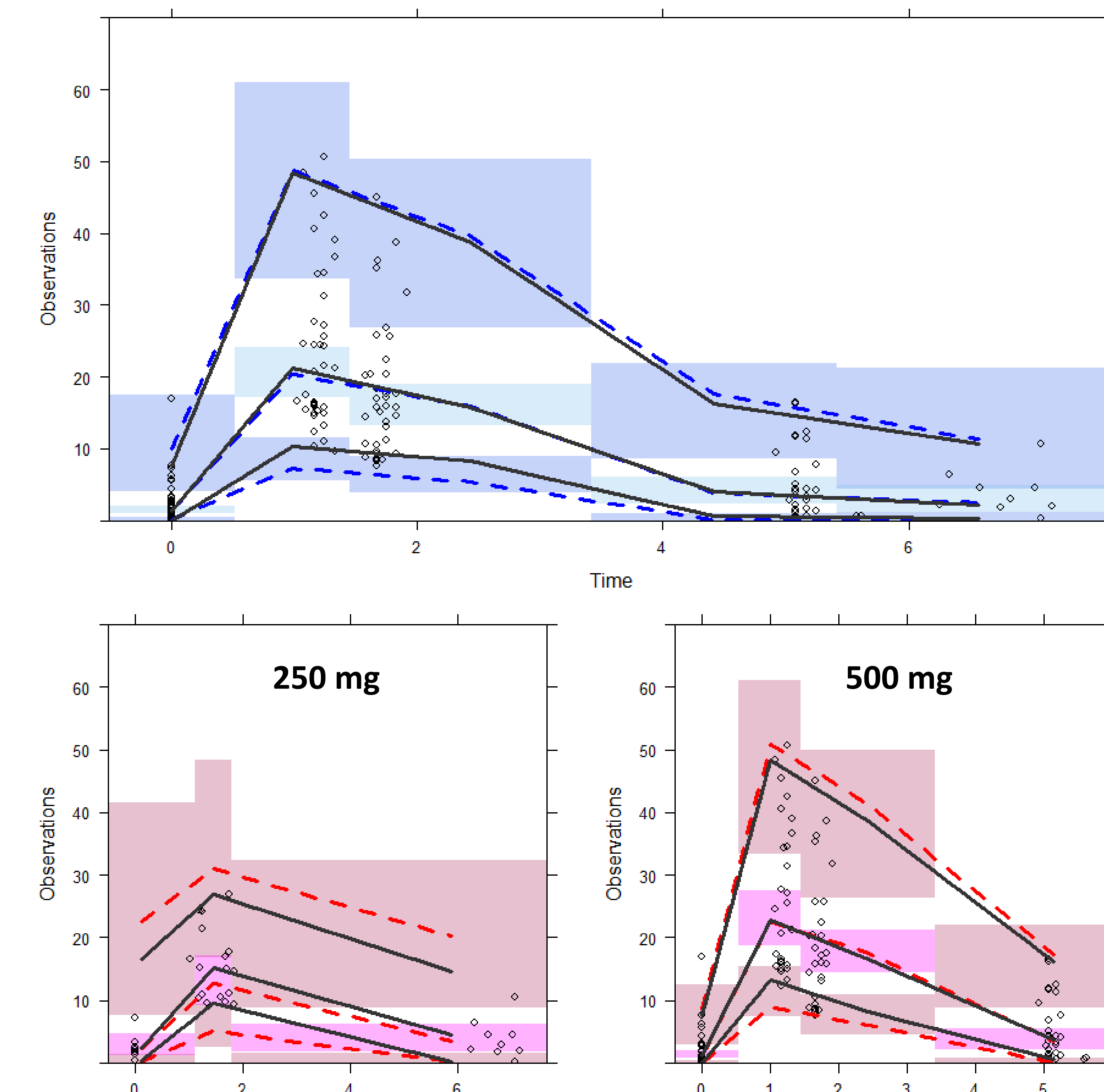


Figure 3. Visual predictive check (upper: all doses, lower left: 250 mg, lower right: 500 mg) Solid lines and dotted lines represent 5th, 50th and 90th percentile lines for observation and simulated concentrations, respectively. The areas are 95% confidence intervals for each percentile line.

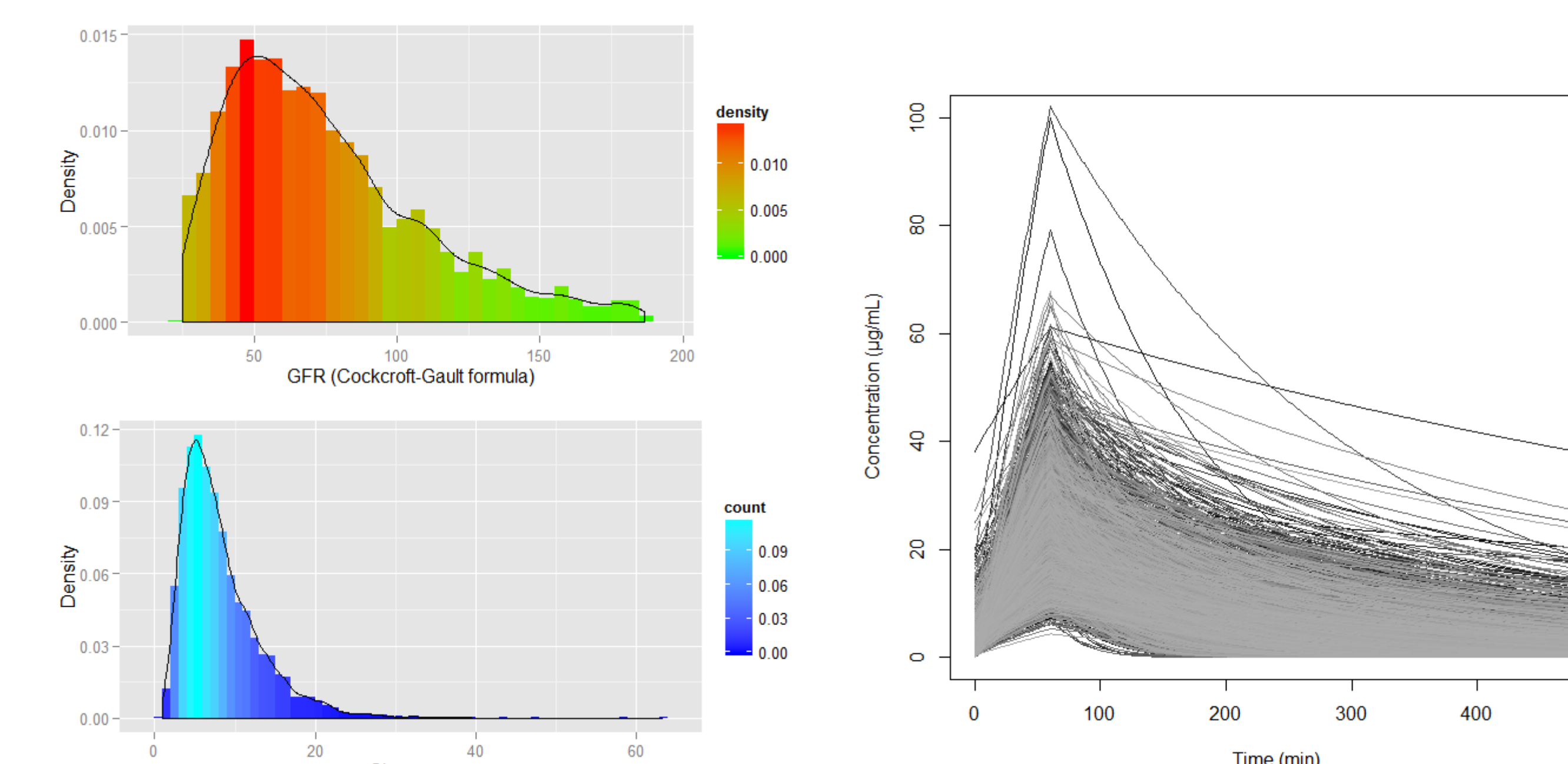


Figure 4. Simulated glomerular filtration ratio (GFR), clearance and concentrations for doripenem applying the final model.

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