Population pharmacokinetic model and external validation of meropenem in severe pulmonary infected patients

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Introduction

Patients diagnosed as severe pulmonary infection are characterized by high mortality. The increased usage of β-lactam antibiotics has attracted extensive attention. In this study, we aimed to describe the population pharmacokinetic (popPK) model of meropenem in patients with severe pulmonary infection and to evaluate prospectively the predictive performance of this new model.

Methods

64 patients (211 samples) with severe pulmonary infection treated with meropenem were composed of modeling dataset used for the model building.The population pharmacokinetic models were developed by NONMEM software.Validation dataset made up of additional 38 patients (150 samples) was used for external model evaluation.The predictive performance of the pharmacokinetic model was assessed for bias and precision using the Bland-Altman method. Using Phoenix 8.0 software, population pharmacokinetics analysis and external model evaluation were performed.

Results

A one-compartment linear model with first-order elimination was most appropriate with modeling dataset where the values of pharmacokinetic parameter estimates for CL and V were 7.8 L/h and 22.8 L. The CL_{CR} was observed as a significant covariate affecting meropenem clearance.The model exhibited a mean value (95%CI) of prediction error (MPE), relative mean prediction error (MPE%), mean absolute prediction error (MAPE) and relative mean absolute prediction error (MAPE%) were 1.56 μg/mL (0.53-2.59 μg/mL), 24.21% (15.61%-32.80%), 4.24 μg/mL (3.44-5.05 μg/mL) and 36.00% (28.56%-43.43%). Our model evaluated overpredicted meropenem plasma concentrations.

FIGURE 1. Two-dimensional liquid chromatography with ultraviolet detection (2D-LC-UV)

Table 1. Population pharmacokinetic parameter estimates from the final model and bootstrap validation

PPK parameter	Final model			
	Original estimates		1000 times bootstrap	
	Estimate	%RSE	Estimate	95%CI
CL (L/h)	7.8	7.1	7.8	6.6-9.2
Vd (L)	22.7	7.9	22.6	19.7-26.0
CLcr -CL	0.697	10.1	0.698	0.563-0.857
Interindividual variability				
ω^2CL	23.9	48.9	23.2	-
ω^2V	18.8	43.4	17.1	-
Shrinkage(CL)	7.0		7.0	-
Shrinkage(V),%	28.5		28.5	-
Residual variability				
σ(additive, mg/L)	29.2	11.3	28.8	0.226-0.351

The final model is:
CL（L/h）= 7.8×[（CLcr/78）]^0.697 ×exp^(ηCL)
Vd（L）=22.7
Cobs_ij=（Cpred_(ij)+1）* ε

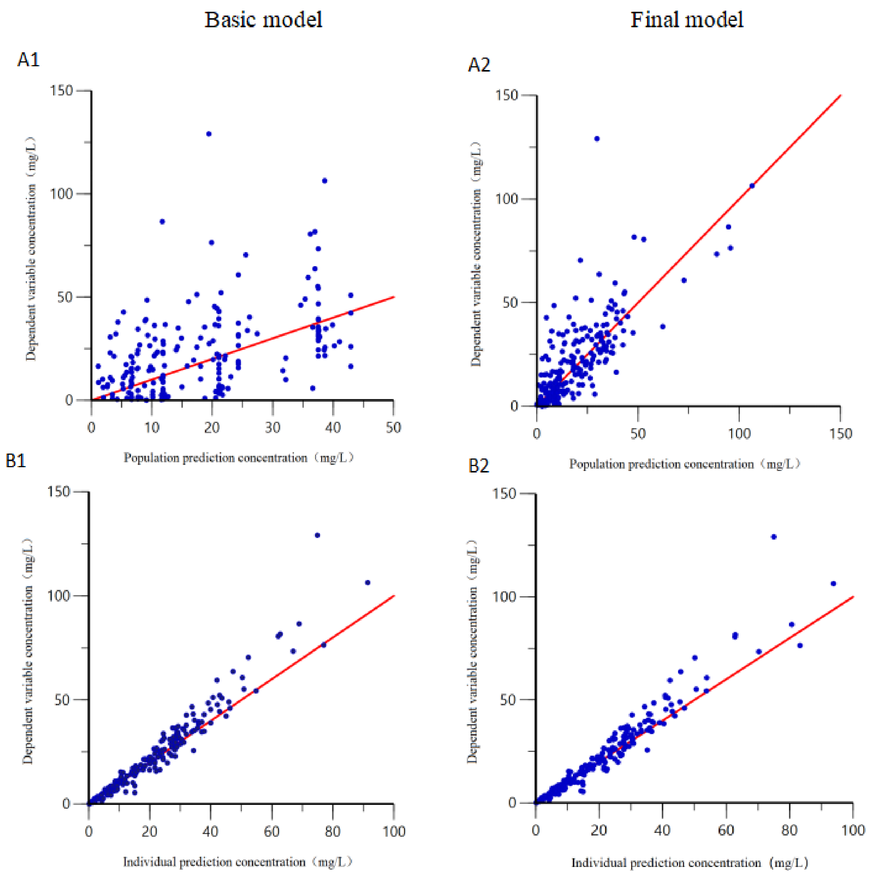

FIGURE 2. Diagnostic goodness-of-fit plots for basic model (A1, B1) and final model (A2, B2). A1and A2, Observed concentrations versus population-predicted concentrations; B1 and B2, Observed voriconazole plasma concentrations versus individual-predicted concentrations; the lines are the lines of unity y=x

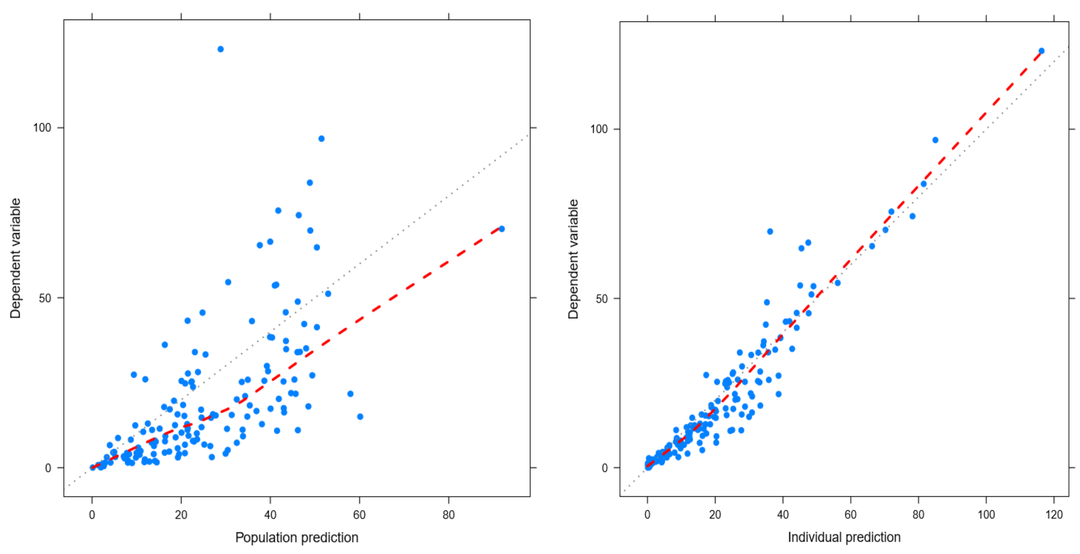

FIGURE 3. The scatter plots between dependent variables of external validation dataset and population prediction, dependent variables and individual prediction of the model

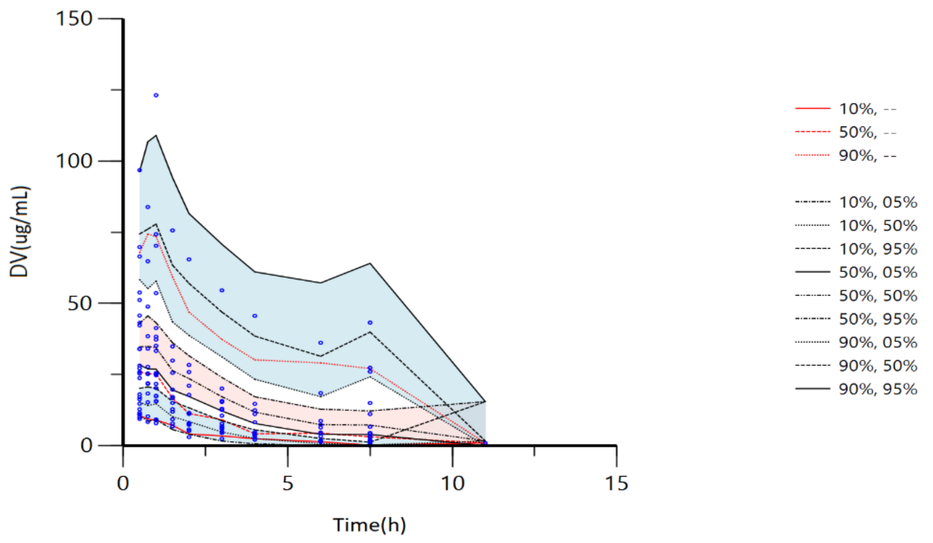

FIGURE 4. Visual predictive verification for external validation dataset

Conclusions

The CLCR had significant influence on meropenem clearance in severe pulmonary infected patients. Meropenem popPK model showed a good precision and performance and slightly tended to overestimate meropenem concentrations.

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