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

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Abstract

Background: 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: The prospective and observational study was conducted on patients with severe pulmonary infection. The data of 64 patients treated with meropenem were composed of modeling dataset used for the model building. Validation dataset made up of additional 38 patients was used for external model evaluation. Meropenem was administered as 0.5-3h intravenous (i.v.) infusions at doses of 0.5-1 g every 8 or 12h. Meropenem plasma concentrations were measured by automatic two-dimensional high-performance liquid chromatography (2D-HPLC) method. **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: 211 plasma concentrations of 64 patients were analyzed in model building. 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} (calculated by Cockcroft-Gault formulation) was observed as a significant covariate affecting meropenem clearance. Parameter formulation showed as CL（L/h）=7.8×[（CLcr/78）]$^{\wedge 0.697}$ ×exp$^{\wedge(\eta CL)}$. Validation dataset contained 150 plasma concentrations from 38 patients. 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**.

Conclusions: The CL_{CR} 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.

Key Words: Meropenem; population pharmacokinetic; severe pulmonary infection; external model evaluation.