Population-Based Pharmacokinetic Model for Intravenous Polymyxin B: A Quantitative Framework to Predict Pharmacokinetic Estimates in Patients with Gram-Negative Infections

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Objectives: Polymyxin B (PMB) is used as a treatment of last resort for multidrug-resistant Gram-negative infections. There is a paucity of contemporary pharmacokinetic (PK) data guiding optimal dosing in patients. The objectives of this study were to examine PMB pharmacokinetics and investigate factor(s) influencing pharmacokinetic variability in patient sub-population.

Methods: This prospective, multicenter, open-labeled study was conducted at 4 clinical sites. Adult patients (≥ 18 years) prescribed PMB were included; 4 serial blood samples were collected from each patient at steady state. A total of 139 data points were analyzed. A maximum likelihood expectation maximization approach (using 1- and 2-compartment models with log-normal distributions) was used to fit data. Structural models were discriminated using log-likelihood ratio test, adjusted for the degrees of freedom. Various demographic variables were investigated as potential covariates for clearance (CL) and volume of distribution (Vd) by linear regression.

Results: 35 subjects (23 males) with mean ± SD age, actual body weight (ABW), and creatinine clearance (CLCR) of 58.8 ± 14.9 years, 57.7 ± 15.4 kg, and 67 ± 42 mL/min, respectively were included. 1-compartment model was the best-fit model (r² = 0.85). Population means ± SD for CL and Vd were 2.9 ± 0.9 L/h and 36.9 ± 7.7 L, respectively. Age and CLCR were statistically significant covariates of CL, but the magnitudes were deemed clinically insignificant. The gender had no significant impact on PK estimates. Vd was poorly predicted by ABW.

Conclusion: This population model could be used as a robust quantitative tool to assess PK estimates of the patients in clinical settings. Further model validation to estimate interindividual pharmacokinetic variability is ongoing.