

Objectives : With increasing incidence of infections caused by multi drug resistance (MDR) Gram negative pathogen and paucity of new agents to confront to these infection, the old drug colistin is reemerged as a last line treatment. It is administrated intravenously in the form of prodrug, colistin methanesulfonate (CMS), which is less toxic and hydrolyzed to colistin within the body. However accurate pharmacokinetic (PK) and pharmacodynamics (PD) properties of colistin are still poorly understood. The aim of this study is to develop a Population PK (PopPK) model and improve the optimal dosing strategy based on model derived simulated concentration data.

Methods : Previous 3 literatures(1, 2, 3) were considered to obtain PopPK models and parameters. Based on these models, we generated virtual concentration data. The structural model consists of 2-compartment model for CMS and 1-compartment model for colistin. Model parameters were estimated using Bayesian inference. Stan version 2.18 (Stan Development Team) with the R package Rstan (Stan Development Team) was used. To estimate parameters of two-compartment PK models of CMS and 1-compartment PK model of colistin, we utilized popular priors. we used Gaussian priors for creatinine clearance, (CL) and central compartment volume (Vc) of CMS of individual, set inverse gamma priors for random effects and error. And choose uniform priors for first-order transfer rate constants k_{12} , k_{21} of CMS.

We obtain 5,000 posterior samples from the Markov chain Monte Carlo (MCMC) posterior simulation after a burn-in period of 5,000 samples. The MCMC algorithm was simulated with the RStan. And the predictability of developed model was tested with real concentration data of colistin.

Result : In the current study, the PK parameters for the population model were estimated and then individual drug concentrations were predicted by the developed PopPK model of colistin. The model provided reasonable estimates for population PK parameters and its individual drug concentration prediction performance was also comparable with the other alternative colistin PopPK models.

Conclusion : This study developed PopPK model of colistin based on RStan, which can be comparable predictability to the previous PopPK models and this model is the first model that considers characteristics of Korean population demographic characters. We expect that this result will contribute to elucidate pharmacokinetic properties of colistin and to build therapeutic drug monitoring support tool for the colistin in Korean population.