Poster

[P25-4] P25-4: Anti-infective drugs (4): Vancomycin

Chair: Noboru Okamura, Japan

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[P25-4-1] Vancomycin PBPK modeling in special populations to elucidate case-based clinical PK observations

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Background

Vancomycin is the cornerstone treatment for serious infections caused by Gram-positive bacteria resistant to β-lactam antibiotics in various disease populations and across ages. Its pharmacokinetics (PK) have been widely studied to control variability in various populations including critically ill adult and pediatric patients, and patients with renal or hepatic impairment. Despite many years of effort, the large variability in vancomycin PK is not fully explained by the PK predictive covariates identified. Our hypothesis is that the large variability is due to changes in multiple physiological parameters observed in patients. The aim of this study was to develop a flexible simulation platform using physiologically-based PK (PBPK) modeling to elucidate case-based clinical observations in a mechanistic fashion.

Methods

Vancomycin specific information, such as physicochemical parameters and *in-vivo* renal clearance estimates were collected from the literature. A vancomycin PBPK model was developed using the Simcyp Simulator (version 14 and version 16, Certara). The developed model was evaluated by a visual predictive check using vancomycin PK profiles observed in healthy volunteers. Additionally, the PK simulations with other system models (*e.g.* organ dysfunction, pediatric populations) were performed and compared with clinical PK profiles observed in each patient population, as well as sensitivity analyses changing cardiac output.

Results

The vancomycin PBPK model simulations with physiological parameters in healthy Caucasian and Japanese volunteers accurately predicted the vancomycin concentration-time profiles and the clinical data were within the 5^{th}- and 95^{th} percentiles. The predicted PK parameters, C_{max} and AUC, were also within a 2-fold range of the observed data. After the model evaluation, the developed PBPK model, combined with changes in age- and disease-dependent physiological parameters, captured clinical PK profiles of vancomycin observed in children and patients with organ dysfunction. Sensitivity analyses focusing on cardiac output provided a *posteriori* justification on changes in vancomycin PK profiles for patients before cardiac surgery.

Conclusions

We developed a vancomycin PBPK model to predict the concentration-time profiles among different populations. This study demonstrates that PBPK modeling has great potential to provide mechanistic insights into altered PK profiles often observed in patients who have changes in renal and hemodynamic functions, and their maturation.