TOWARDS INDIVIDUALIZED DOSAGE ADJUSTMENT OF ANTIMICROBIAL DRUGS USING POPULATION PHARMACOKINETIC MODELING AND SIMULATION

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論　文　名	TOWARDS INDIVIDUALIZED DOSAGE ADJUSTMENT OF ANTIMICROBIAL DRUGS USING POPULATION PHARMACOKINETIC MODELING AND SIMULATION (母集団薬物動態モデリング＆シミュレーションによる抗微生物薬の個別化投与設計に関する研究)
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論 文 審 査 の 結 果 の 要 旨

The World Health Organization has identified antimicrobial resistance (AMR) as one of the top 10 global public health threats facing humanity. It was estimated that 4.95 million deaths were associated with bacterial AMR in 2019, including 1.27 million deaths attributable to antibiotic. This number is predicted to increase to 10 million deaths per year by 2050 if no action is taken. The overuse and misuse of antibiotics is believed to be the main factor leading to the emergence of AMR.

Pharmacometrics is a science that uses mathematical models such as modeling and simulation to understand and predict the pharmacokinetics and pharmacodynamics (PK/PD) relationships of drugs both in individuals and in populations. In the context of AMR, pharmacometrics can be used to optimize dosing regimen, maximize efficacy and minimize the risk of therapeutic failure associated with inappropriate use of antimicrobial drugs, through population pharmacokinetics modeling and simulation (PPK).

Thus, the aim of this study was to apply PPK Modeling & Simulation, as well as extensive statistics to hematologic malignancies population to: (1) evaluate the PK and safety of antibiotic drugs, and (2) simulate optimal dosing regimen to maximize efficacy and minimize the risk of therapeutic failure associated with inappropriate use of antimicrobial drugs. The first chapter was dedicated to the development of a PPK model for vancomycin (VCM), a glycopeptide antibiotic frequently used in treating severe bacterial infections caused by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). While the second chapter focused on the development of a PPK model for posaconazole (PCZ), a systemic triazole antifungal indicated in the prophylaxis of invasive fungal infections (IFI) in highly immunocompromised patients.

First, the author successfully developed a PPK model of VCM and proposed for the first time an optimized dosing regimen in the adult population with hematologic malignancies, based on a target AUCss = 400–600 mg·h/L at an MIC of 1 mg/L. The VCM PK data were best described with a one-compartment model. The typical values of CL and Vd were 3.09 L/h (normalized to Ccr value of 90 mL/min) and 122 L/70 kg, respectively. Creatinine clearance (Ccr), diagnosis of acute myeloid leukemia (AML), and neutropenia were identified as significant covariates on VCM clearance (CL). The final estimates for the effect of Ccr and AML were 0.973 and 1.15, respectively. Additionally, the influence of neutropenia on VCM CL was

found to be greater in patients with augmented renal clearance (ARC) than in those without ARC, with 1.13 and 1.09, respectively. Concerning the effect on VCM dosing, AML patients required 15% higher doses than non-AML patients, independently of renal function. In contrast, for neutropenic patients, only those with augmented renal clearance (ARC, Ccr value ≥130 mL/min) required a 10% dose increase compared to non-neutropenic patients.

Next, PCZ data were adequately described by a one-compartment PPK model with first-order absorption. Diarrhea and total proteins were identified as significant covariates on PCZ apparent clearance CL/F, with effects of 1.26, and -1.40, respectively. The typical values of CL/F and Vd/F were 7.54 L/h and 296 L, respectively. Additionally, the simulation results suggested that both covariates could be clinically relevant on PCZ exposure. The incidence of hepatotoxicity following PCZ therapy was 38.5% (10/26). For all patients, the levels of liver function tests (LFTs) were reversible and moderately elevated (grade 2 or less). Multivariate cox regression analysis revealed that hepatotoxicity was independently associated with older age (Hazard-ratio 5.8, $p < 0.05$), and PCZ average trough concentration at steady-state (Hazard-ratio 4.7, $p < 0.05$).

In addition to PPK modeling, a rapid, simple, and sensitive bioanalytical method for the quantification of letermovir in human plasma was developed and validated in accordance with FDA guidelines. The method was validated over a linear range of 10–1000 ng/mL with a coefficient of determination (R^2) > 0.99 with the weighting factor: $1/x^2$. The total run time was 6.1 min, including 2 min of re-equilibration. The intra- and inter-assay accuracy (nominal%) and precision (relative standard deviation%) were within ± 15% and ≤ 15%, respectively. Letermovir was stable in neat solvent and plasma for at least 1 year and 30 days, respectively. The specificity, recovery, matrix effect, and dilution integrity of this method were also within acceptable limits. This work could be useful to perform not only clinical PK/PD studies but also to investigate drug–drug interactions and letermovir side effects, which will be instructive in the creation of a dosage regimen and optimization of letermovir safety and efficacy.

In the present thesis, pharmacometrics approaches were successfully applied to characterize the PK and safety of VCM and PCZ. Through this work, the author has demonstrated the importance of mathematical modeling and simulations in the optimization of antibiotics dosing to maximize efficacy and minimize the risk of toxicity. Using PPK modeling and simulation, we found out that AML patients with neutropenia and ARC represent a critical population with a higher risk of VCM underexposure. In addition, the identified novel AUC-based dose regimen could be applied in clinical practice to improve the efficacy of VCM while reducing the incidence of nephrotoxicity.

Furthermore, a PPK model was established for PCZ delayed-release tablet formulation in Japanese population with underlying hematologic malignancies, and provided a better understanding of the PK of PCZ.
PCZ exposure was further shown to be associated with a higher probability of occurrence of hepatotoxicity. To our knowledge, this is the first study to investigate the relationship between PCZ trough concentration and elevation of LFTs, using a cox regression model. While PCZ delayed-release tablets has been shown to be relatively safe, its safety profile with respect to hepatotoxicity remains a concern. LFTs should be monitored closely during PCZ therapy, and further investigations are warranted in a large population. The present findings have the potential to be used to better understand the incidence, mechanism, and management of PCZ-induced hepatotoxicity.

本論文は博士（臨床薬学）の学位に値すると認める。