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

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（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　内　容　の　要　旨

**Background**

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.

**Method and Results**

**Chapter 1 Population pharmacokinetic model and dosing optimization of vancomycin in hematologic malignancies with neutropenia and augmented renal clearance.**

A retrospective study was conducted in patients with underlying hematologic malignancies treated with vancomycin (VCM). A total of 148 patients were enrolled for PPK modeling. Simulation analyses were performed to identify dosing regimens achieving a target exposure of $AUC_{0\text{-}24}$ of 400–600 mg·h/L at the steady-state.

The VCM PK data were best described with a one-compartment model. Significant covariates included creatinine clearance (Ccr), diagnosis of acute myeloid leukemia (AML) and neutropenia on VCM clearance (CL), and body weight (WT) on the volume of distribution (Vd). 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. 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.

**Chapter 2 Evaluation of the pharmacokinetics and safety of Posaconazole delayed-release tablet in Japanese population with hematologic malignancies.**

A retrospective study was conducted in patients with underlying hematologic malignancies who received

Posaconazole (PCZ) delayed-release tablets (DRT). A total of 26 patients were enrolled in the PPK study, and simulations were performed to evaluate the clinical effects of the covariates. In addition, cox regression analysis was used to investigate the association between PCZ average trough concentration at steady-state ($C_{avr}$) and the occurrence of hepatotoxicity.

PCZ data were adequately described by a one-compartment model with first-order absorption. Diarrhea and total proteins were identified as significant covariates on PCZ apparent clearance CL/F. The incidence of hepatotoxicity was 38.5% (10/26). Multivariate analysis revealed that hepatotoxicity was independently associated with older age ≥65 years (Hazard-ratio 5.8, $p$ <0.05), and PCZ $C_{avr}$ (Hazard-ratio 4.7, $p$ <0.05).

**Chapter 3 Development and full falidation of a bioanalytical method for quantifying letermovir in human plasma using ultra-performance liquid chromatography coupled with mass spectrometry.**

A rapid and simple UPLC/MS method was developed and validated for the quantification of letermovir in human plasma. Separation was performed in reverse phase mode using an ACQUITY UPLC BEH C18 column (130 Å, 1.7 μm, 2.1 mm × 50 mm) at a flow rate of 0.3 mL/min, 10 mM ammonium acetate-0.1% formic acid solution as mobile phase A, and acetonitrile as mobile phase B with a gradient elution. The method was validated over a linear range of 10–1000 ng/mL with a coefficient of determination ($R^2$) >0.99). The intra- and inter-assay accuracy and precision were within ± 15% and ≤15%, respectively. The specificity, recovery, matrix effect, stability, and dilution integrity of this method were also within acceptable limits.

**Discussion**

In chapter 1, we successfully developed a PPK model for VCM and proposed an optimized dosing regimen for the adult population with hematologic malignancies, which can be applied in clinical practice to improve the efficacy of VCM while reducing the incidence of nephrotoxicity. We also identified neutropenia and underlying AML as potential risk factors for increased VCM clearance. Our findings provide a better understanding of the PK of VCM and an optimal dosing strategy for managing “high-risk” patients in routine clinical practice.

In chapter 2, we established a PPK model to characterize the PK and safety profile of DRT formulation in Japanese population with underlying hematologic malignancies. 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 analysis. The presents findings have the potential to be used to better understand the incidence and management of PCZ-induced hepatotoxicity.

In chapter 3, the developed method constitutes the first described LC/MS method for the quantification of letermovir in human plasma. The advantage of this method lies in its short analysis time of 6.1 min, a simple sample preparation method, and a high sensitivity following the use of a MS detector through a single ion recording. 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.