"Pharmacometric Modeling and Simulation in Special Populations"

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Abstract: Pharmacometrics modeling encompasses both pharmacokinetics (PK) and pharmacodynamics (PD) data to quantitatively describe the dose-exposure-response relationship. Pharmacometrics is widely utilized to facilitate drug development and optimize pharmacotherapy regimens in the clinic. Pharmacometrics approaches include the “top-down” population PK/PD modeling and “bottom-up” physiologically based pharmacokinetic (PBPK) modeling. Moreover, artificial intelligence (i.e., machine learning) has proven a powerful tool for pharmacometrics modeling. Pharmacometrics modeling and simulation are particularly useful in studying PK/PD in special populations, such as pediatrics and newborns, because it is practically and ethically challenging to perform conventional clinical trials in these special patient populations.

The first project of this dissertation research is to develop PBPK models to evaluate how altered carboxylesterase 1 (CES1) function could affect the exposure of methylphenidate (MPH). Various clinical scenarios that affect CES1 function, including different CES1 genotypes, drug-alcohol interactions, and different sex, were simulated regarding their impact on MPH PK. The models successfully predicted the exposure alteration of MPH caused by the G143E genetic variant, ethanol-MPH DDI, and sex. The study suggests that male G143E carriers who are alcohol consumers are at a higher risk of MPH overexposure.

Another commonly used pharmacometric method is population PK/PD modeling. The second project is to build a population PK/PD model to describe the PK and PD of midazolam (MDZ) in neonates treated at the Neonatal Intensive Care Unit (NICU). To describe MDZ PK/PD profiles, we developed a two-compartment population PK model for MDZ and its two metabolites, 1-hydroxymidazolam(1-OH-MDZ) and 4-hydroxymidazolam(4-OH-MDZ). Bodyweight, creatinine, and alanine transaminase (ALT) levels were finally incorporated into the population PK model as covariates to explain the interindividual variability. The prediction of MDZ, 1-OH-MDZ, and 4-OH-MDZ PK profiles by our model matched well with the observed clinical data via the visual prediction check of goodness-of-fit plots. A binary probability model was used as the PD model. No significant correlation was observed between MDZ PK and PD profiles.

Since the classic population PK/PD model had difficulty describing MDZ PD response in neonates, we further developed machine learning-based models to reveal the exposure-response relationship. We assessed six machine learning models (K Nearest Neighbor, Support Vector Machine, Decision Tree, Random Forest, Naïve Bayes, and Neural Network). Models were trained with a training dataset, and the final prediction performance of each model was evaluated using a testing dataset. The random forest classifier had the best prediction performance of the PD response for our current dataset, with the accuracy = 0.83, precision = 0.98, and area under the receiver operating characteristic curve = 0.81. Postmenstrual age, birth weight, and dosing weight were the top three most important features for the random forest classifier.