Extensive Simulation for Dosage Optimization of Factor Xa Inhibitors Considering the Difference in Pharmacokinetic and Pharmacodynamic Profiles: A Model-Based Meta-Analysis of Large Clinical Studies of Rivaroxaban, Apixaban, and Edoxaban

Hideki Yoshioka, Hisaka Akihiro
Department of Clinical Pharmacology and Pharmacometrics, Graduate School of Pharmaceutical Sciences, Chiba University

Objectives: The objective of this study is to estimate the optimal regimens of three factor Xa Inhibitors (FXaIs: rivaroxaban, apixaban, and edoxaban) by extensive simulation using model-based meta-analysis assuming that the therapeutic and adverse event responses relative to their blood anticoagulant activities are the same.

Methods: Based on the data from five randomized controlled trials which evaluate efficacy or safety of FXaIs in patients with atrial fibrillation, the mixed-effect logistic models were developed for the frequency of ischemic stroke or systemic embolism and major bleeding. Prothrombin time international normalized ratios (PT-INRs) at the steady state minimum, average and maximum drug concentrations were calculated from patient characteristics using the population pharmacokinetic/pharmacodynamic model and compared as variable in the developing models based on the goodness of fit of predictions to observations. The optimal fixed-dosages for each FXaI were calculated by minimization of model-predicting overall risk of event with testing of three different dosing-times; once, twice and three times a day (QD, BID and TID, respectively), and compared with the current regimens in simulated patient population. Modeling analysis in this study was performed using NONMEM 7.3.

Results: The frequencies of ischemic stroke or systemic embolism and major bleeding were modeled using estimated PT-INRs at the average and maximum plasma concentrations, respectively (Figure 1). The result of simulation showed that the overall event risks of rivaroxaban and edoxaban were reduced notably by modification of dosage and increasing dosing times to BID from current QD, while that of apixaban, currently dosed BID, was consistently lower than them in any dosing time due to its stable profile of PT-INR.

Conclusions: Although the prediction accuracy of the present simulation would be restricted because the information of dose-response for individual drug is unavailable, this study suggested that the therapeutic dose of anticoagulants should be determined very carefully considering clinical problems such as medication adherence and may need to be reexamined.