A Quantitative Systems Pharmacology Model to Predict the Effects of Warfarin, Rivaroxaban and Enoxaparin on the Human Coagulation Network

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Objectives: To develop a quantitative systems pharmacology (QSP) model describing the coagulation network to monitor anti-coagulation factor levels under warfarin, enoxaparin, and rivaroxaban treatment and to aid in optimization of anti-thrombotic therapy in light of optimal time-to-clot dissolution.

Methods: Individual steady-state coagulation factor level data from therapeutic drug monitoring of 312 subjects on enoxaparin, rivaroxaban, and warfarin/phenprocoumon (Vitamin K antagonists (VKA)) treatment were used to develop a QSP model of the coagulation network in MATLAB®, based on Wajima et al.1 Parameter values for all factor rate constants (V_{max}, K_m) and production rates were estimated and the model was adjusted given the available data. Sobol sensitivity analysis was performed to identify key parameters having the greatest impact on clot dissolution.

Results: Predictions of individual coagulation factor time courses under steady-state VKA, enoxaparin, and rivaroxaban treatment reflected the suppression of the endogenous clot dissolution components PC and PS under VKA compared to rivaroxaban and enoxaparin. The model was used to simulate treatment switch from VKA to enoxaparin or rivaroxaban, and was able to describe the observed 50% increase within 9 and 11 days in PC and PS factor levels, respectively. Treatment switch from enoxaparin to VKA lead to a 50% decrease in PC and PS factor levels within 8 and 10 days, respectively. Sobol sensitivity analysis identified production rates for vitamin K being the most influential parameters to stimulate clot-dissolution.

Conclusion: A QSP model was developed to describe the human coagulation network and time courses of several clotting factors under different treatment regimens. The model may be used as a tool during clinical practice to predict the effects of different anti-coagulant therapies on individual clotting factor time-courses and to optimize anti-thrombotic therapy regimens.

References: