Exploration of Factors Affecting the Activated Partial Thromboplastin Time and Prothrombin Time-International Normalized Ratio Using a Quantitative Systems Pharmacology Model

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Objectives: To evaluate the identifiability of factors affecting the activated partial thromboplastin time (APTT) and prothrombin time-international normalized ratio (PT-INR) using a quantitative systems pharmacology (QSP) approach.

Methods: The equations used in a previously reported QSP model of the coagulation network [1] were implemented in the MONOLIX software. The impacts of several coagulation and anticoagulation factors, including fibrinogen, factors II, V, VII, VIII, IX, X and XI, and proteins C and S, on APTT and PT-INR were evaluated using model-based simulations of the coagulation tests in which the initial concentration of a factor was varied from 0.01- to 100-fold the normal levels. In addition, the initial levels of vitamin K-dependent factors were simultaneously varied to mimic the anticoagulant effect of warfarin.

Results: The QSP model-based simulations indicated that factors affecting APTT include fibrinogen and factors II, VIII, IX, X and XI, whereas the impacts of factors V and VII, and proteins C and S on APTT were negligible. PT-INR was markedly changed by fibrinogen and factors II, VII and X; no substantial effects of factors V, VIII, IX and XI, and proteins C and S on PT-INR were suggested. A reduction of approximately 80% in the levels of vitamin K-dependent factors from normal was predicted to result in a PT-INR value within a range of 2.0 to 3.0, which is the target of anticoagulant therapy with warfarin.

Conclusions: The QSP approach appears useful for exploring the factors affecting APTT and PT-INR by quantifying their impacts, and for characterizing in a quantitative manner the biological mechanisms underlying the values of therapeutically targeted biomarkers. The simulation-derived findings need to be validated by actual observations to understand how accurately (or inaccurately) the model captures the reality of each component of the system.

References: