Prediction of Prothrombin Time after Oral Administration of S-Warfarin in Different CYP2C9 Phenotypes in Asian and Caucasian populations using the Simcyp Simulator

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Introduction Physiologically based pharmacokinetic (PBPK) models have a unique advantage in integrating both the drug characteristics and the underlying physiology, along with its variability within a population to describe drugs pharmacokinetics (PK) which can then be fed into pharmacodynamics (PD) response models. Another important advantage of the PBPK approach is its extrapolation capability. Once the model performance is verified for a particular drug in one situation, it can be assessed with increased confidence for another scenario, such as higher doses, drug interactions or in a population with different characteristics.

Objectives The objective of this study is to use the PBPK approach to predict prothrombin time (PT) and prothrombin complex activity (PCA) as PD responses of S-warfarin in adult healthy Caucasian and Asian populations using scripting features in the Simcyp Simulator.

Materials and Methods Default PK settings for the compound file S-warfarin in Simcyp simulator V15R1 was coupled with a published PCA-PT PD response model for S-warfarin [1]. The PK was predicted using a first order absorption model linked to the minimal PBPK distribution model and elimination was represented by enzyme kinetics for CYP2C9. Using the Sim-Healthy volunteer (Caucasian) and also the Sim-Healthy Chinese population files, 6 trials of 10 male individuals aged between 20 – 40 years were used in the simulations. The PD response model in Caucasians was PT linked to PCA (%) as reported by Chan et al 1994 [1]. The PD model received free S-warfarin plasma concentration as the driving input to the model. The PCA and PT models were coded in Lua scripting language available as a PD Custom feature within the Simcyp Simulator. Simulated PKPD profiles in Caucasians were compared to the clinical observations. The model was also used to predict the PKPD profiles in an Asian (8 Chinese + 5 Indian) population [2]. Finally simulations were performed to compare concentration and response time profiles between Caucasian and Asian populations using two doses of 12.5mg/day for 9 days for CYP2C9 poor and extensive metabolizer sub-populations.

Results and Discussion Simulated profiles for the plasma S-warfarin concentration and prothrombin time were in agreement with the reported concentration time and response profiles in Caucasian population (Figure 1). The concentration-time profile was under-predicted in Asian population, therefore an additional clearance of 5µL/min/mg protein was added to the drug clearance to describe the plasma concentration adequately. This additional clearance was sufficient to describe the concentration profile, while the PD model remained the same. Performance of the PD model for Asian individuals is shown in Figure 2.

Predicted profiles for Asian and Caucasian populations with different CYP2C9 phenotypes are given in Figure 3. These predictions highlighted that population-specific dose calibration is needed for PM subgroups, while the differences in response is marginal in Asian and Caucasian EM subpopulation for both PCA and PT. While the developed model can help in dose adjustment, more accurate individualized dose adjustment can be achieved by incorporating CYP2C9 and VKORC1 genotypes.

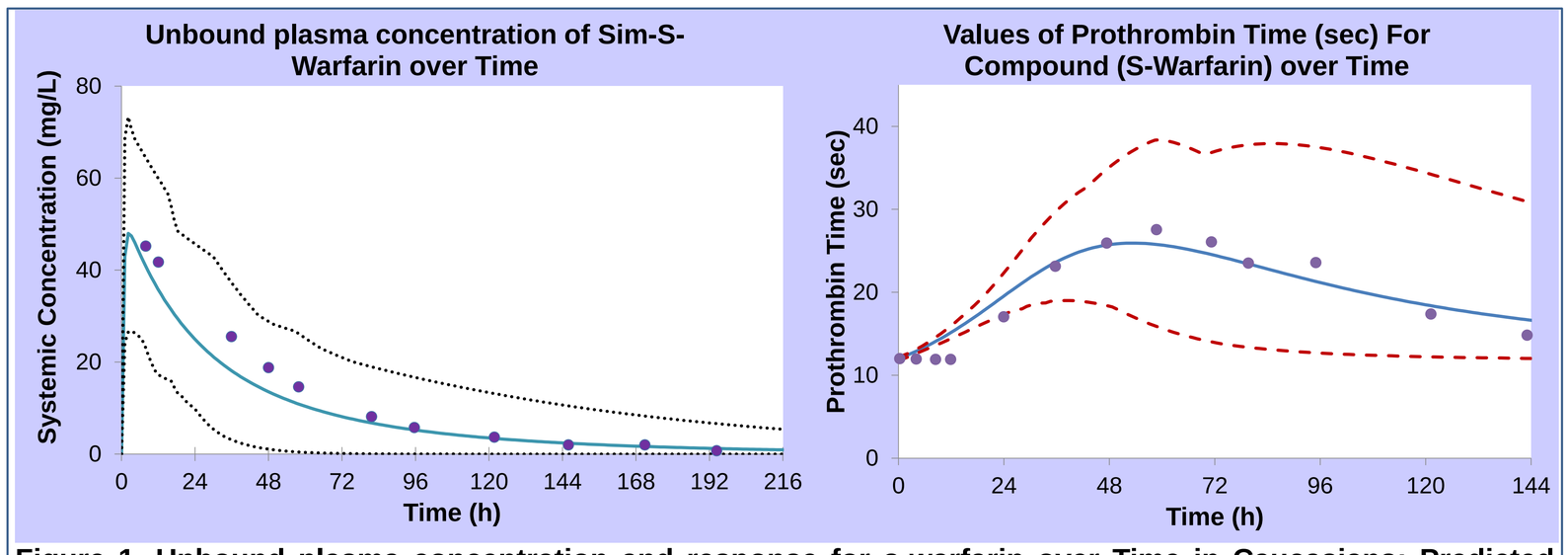

Figure 1. Unbound plasma concentration and response for s-warfarin over Time in Caucasians; Predicted (lines) and reported (dots) [1].

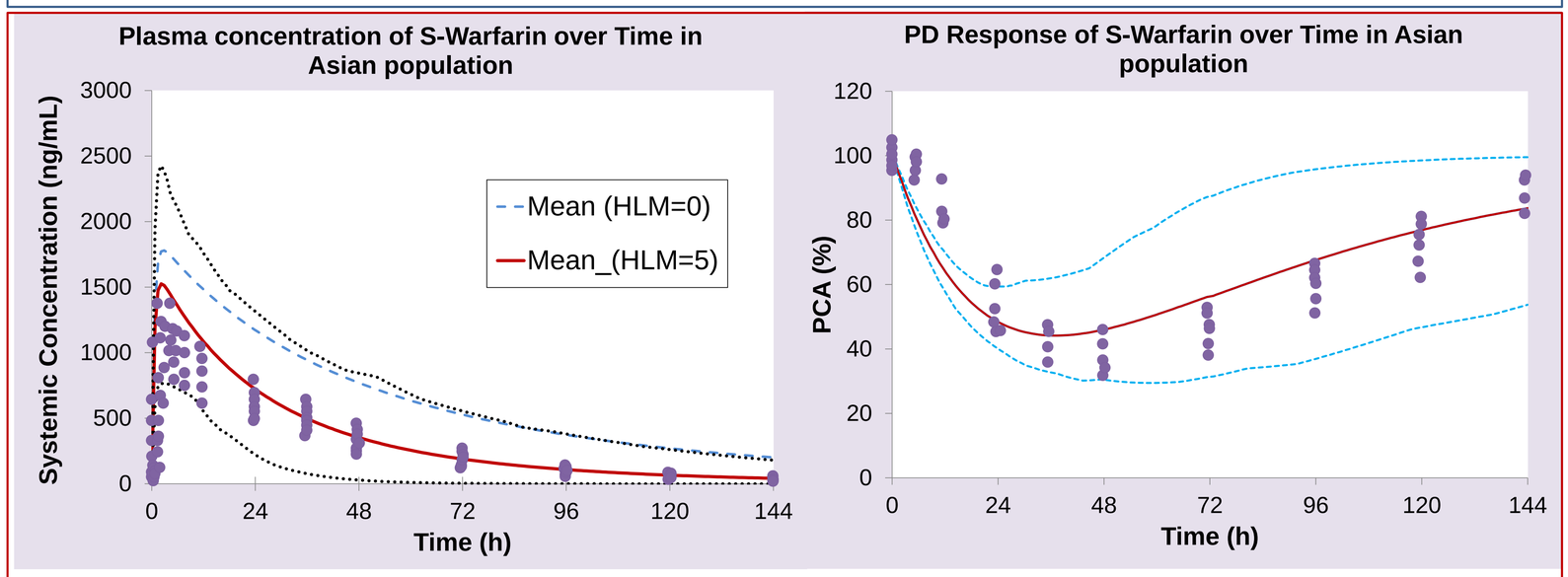

Figure 2. Plasma concentration and response for S-warfarin over Time in an Asian population; Predicted (lines) and reported (dots) [2].

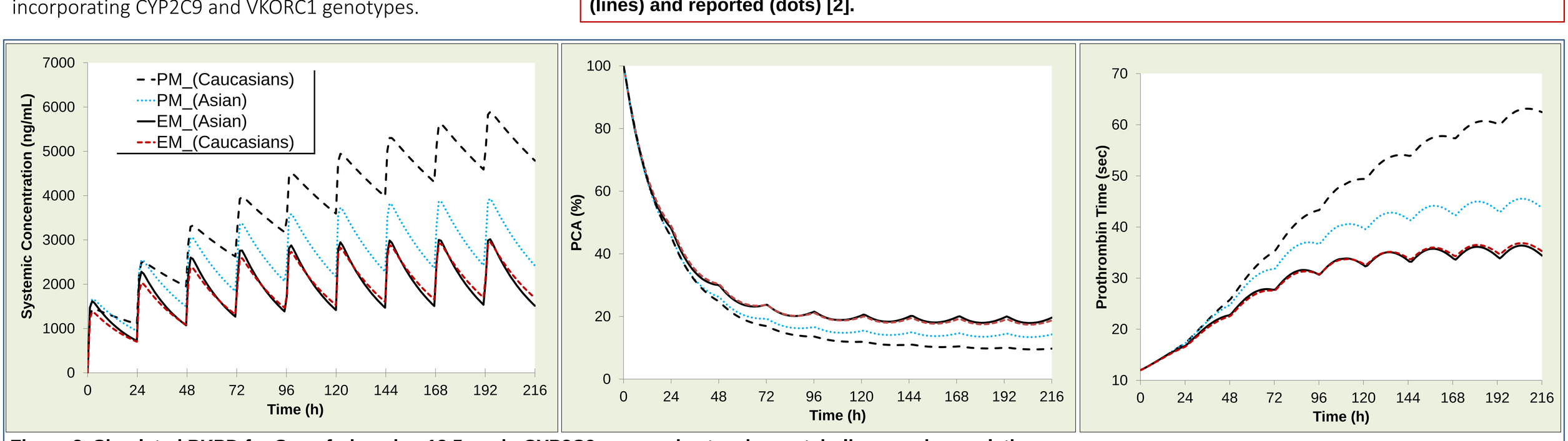

Figure 3. Simulated PKPD for S-warfarin using 12.5 mg in CYP2C9 poor and extensive metabolisers sub-populations

References

[1] Chan E, McLachlan A, O'Reilly R, Rowland M. Stereochemical aspects of warfarin drug interactions: use of a combined pharmacokinetic–pharmacodynamic model. Clin Pharmacol Ther 1994; 56: 286–94.

[2] Yuen E1, Gueorguieva I, Wise S, Soon D, Aarons L. Ethnic differences in the population pharmacokinetics and pharmacodynamics of warfarin. J Pharmacokinet Pharmacodyn. 2010 Feb;37(1):3-24.