# Use of a Physiologically based Pharmacokinetic – Pharmacodynamic Model to Account for Adjustments to dosing of S-warfarin in Different Populations

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## Introduction

The Physiologically-based pharmacokinetic (PBPK) approach aims to predict the exposure of drug in the body, by integrating compound specific data with the physiology of the population of interest, e.g. healthy volunteer Caucasian. Once a model prediction has been verified in a population, it can be used to predict the exposure in other populations by accounting for physiological differences, including demographic and genetic differences[1]. Linking the predicted exposure to a pharmacodynamic (PD) model can then be used to aid dose adjustments.

Warfarin is an anti-coagulant, which acts as an antagonist of the vitamin K dependent clotting pathway. It has a narrow therapeutic index, wherein too low doses can result in loss of efficacy, while too high doses or over-anticoagulation can result in severe bleeding episodes. Although available as a racemic, the S-warfarin is 3- to 5-times more potent than its R-isomer. S-Warfarin is predominantly metabolised by the polymorphic CYP2C9 enzyme, whereas R-warfarin is metabolized by CYP 1A2 and 3A4. Dosage adjustments based on the international normalised ratio (INR) monitoring are often recommended for individuals with CYP2C9*2 and *3 variant alleles due to reduced metabolic activity of these[2].

## Objective

To use PBPK-PD to predict the required dose of S-warfarin needed to maintain the INR within the therapeutic range of between 2 and 3 in different ethnic populations.

## Methods

The default S-warfarin compound within the Simcyp® Simulator V18R1 library was linked to a published PD model[2] (Figure 1). In brief, a minimal PBPK model with first order absorption and elimination via the different CYP2C9 allelic forms described the PK of S-warfarin. Predicted total S-warfarin plasma concentrations ($C_{sys}$) were used as an input to a turnover model wherein the synthesis of prothrombin (NPT) in plasma ($K_{in}$) was assumed to be inhibited in a nonlinear way by $C_{sys}$. The estimated $IC_{50}$ for individuals with a variant for the vitamin K receptor gene (VKORC1) was lower to account for the increased warfarin sensitivity observed in those individuals. A non-linear model based on the percentage inhibition of baseline NPT and defined by the exponent 'λ' described the time course of INR in response to the decrease in NPT concentration[2].

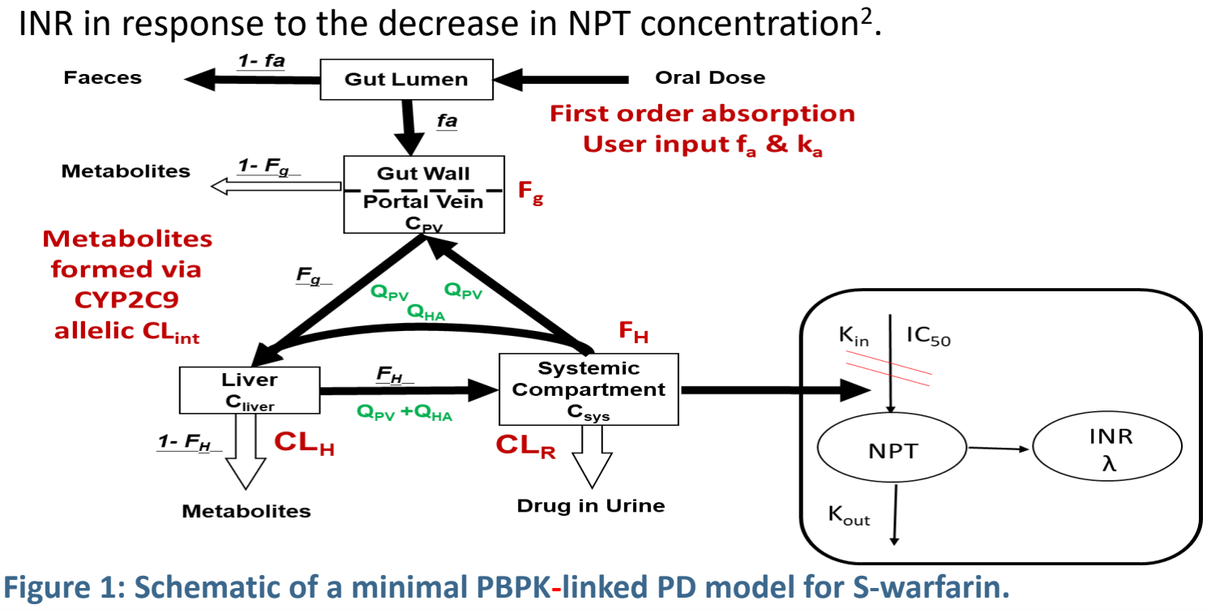


**Figure 1: Schematic of a minimal PBPK-linked PD model for S-warfarin.**

## Results

**Table 1: Predicted (10 trials x 'N' individuals in each study group, same proportion of females) and observed arithmetic mean (± SD) oral clearance of S-warfarin in healthy volunteer Caucasian adults with different CYP2C9 allelic variants.**

| | Mean (± SD) S-Warfarin CLpo (mL/h) | | | |
|---|---|---|---|---|
| | CYP2C9*1*1 (N=69) | CYP2C9*1*2 (N=41) | CYP2C9*1*3 (N=26) | CYP2C9*2*2 (N=8), *2*3 (N=5), *3*3 (N=1) |
| **Predicted** | 435 ± 321 | 339 ± 264 | 241 ± 288 | 198 ± 185 |
| **Observed**[3] | 255 ± 88 | 180 ± 49 | 156 ± 59 | 136 ± 38 |

The results of the predictions of S-warfarin clearance in individuals with different CYP2C9 allelic forms compared with clinical data[3] are shown in Table 1. The PBPK model showed a decrease in S-warfarin clearance in individuals with variant alleles compared to wild type similar to the observed data; with the predicted clearances all within 2 fold of the observed data.

## Results

The predicted INR response levels for a 20-year old male Caucasian administered a 5 mg loading dose of S-warfarin for 5 days followed by a maintenance dose of 2.5 mg assumed to have the CYP2C9*1*1 and VKORC1*2/*2 were compared to predicted INR response in a 20-year old Japanese and Chinese individual with the same genotypes.

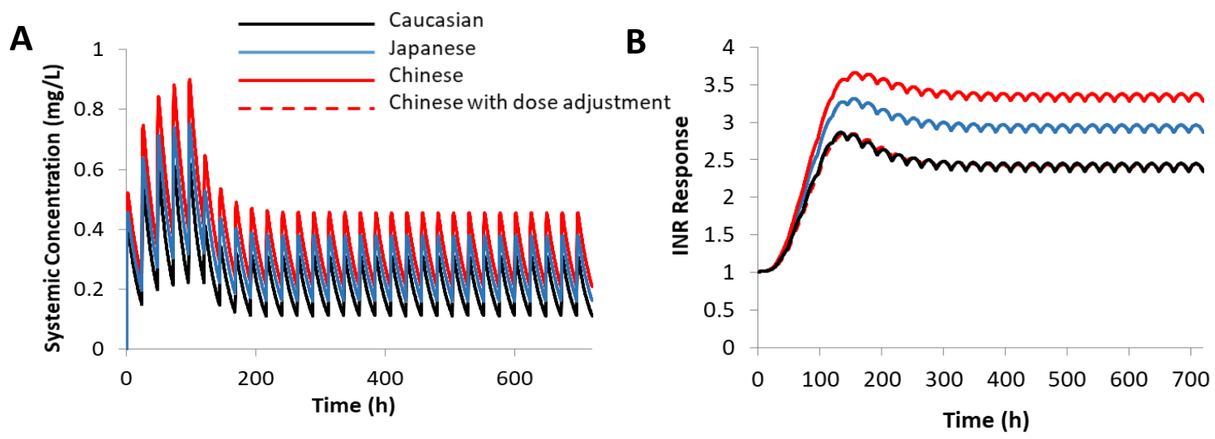


**Figure 2: (A) Simulated plasma concentration time profile of S-warfarin after a 5 mg loading dose for 5 days followed by a 2.5 mg maintenance dose for 25 days in a Caucasian, Japanese and Chinese 20-year old male and (B) corresponding INR response levels.**

As shown in Figure 2A, the steady state S-warfarin plasma concentration was highest in the Chinese followed by the Japanese and then the Caucasian population representative due to physiological differences such as CYP2C9 enzyme abundances and liver volume in the three ethnic populations, already considered in the PBPK model[1]. Given that the INR response level for the Chinese was outside the therapeutic range of between 2 and 3, a dose adjustment of 3 mg loading dose followed by 1.5 mg maintenance dose estimated to give a similar steady state concentration of S-warfarin as the Caucasian was made resulting in INR response levels within the recommended therapeutic range (Figure 2B).

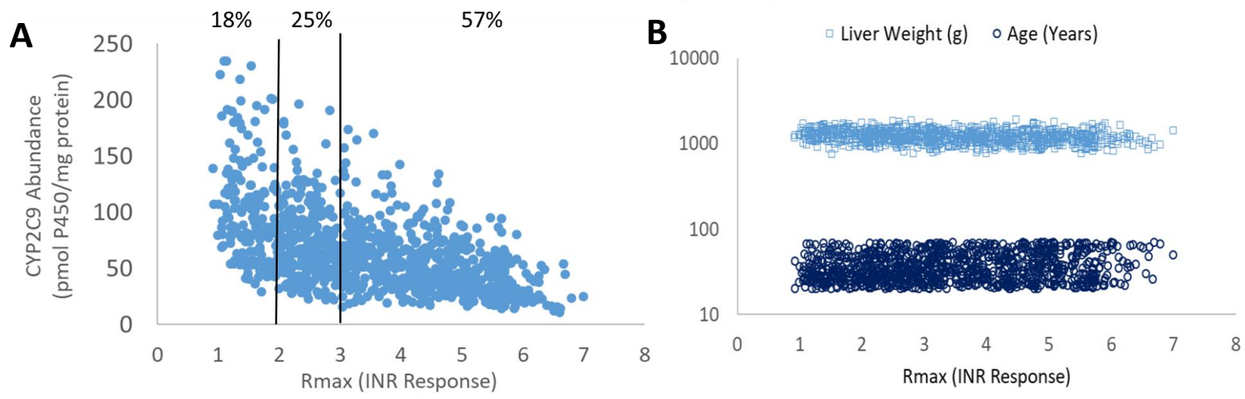


**Figure 3: (A) Plot of individual CYP2C9 liver abundance (B) age and liver weight of 1000 simulated Chinese healthy volunteers against their predicted steady state INR response after a loading dose of S-warfarin of 3 mg for 5 days followed by a maintenance dose of 1.5 mg for 25 days.**

Although a loading dose of 3 mg S-warfarin followed by a maintenance dose of 1.5 mg was suitable for a 20-year old male, that same dose administered to a population of Chinese volunteers (20 x 50 individuals, 20 – 70 years, 0.5 females) was only appropriate for 25% of the population, while 18% would be at a risk of under-coagulation, and 57% at a risk of over-coagulation and both groups would therefore require dose adjustments. A number of physiological parameters such as age, liver weight, CYP2C9 abundance and genotype can affect the clearance of S-warfarin and hence the INR response of an individual. However in this study, CYP2C9 abundance was the parameter with the strongest correlation with the INR response (Figure 3). Individuals with higher INR response levels had lower CYP2C9 abundance levels, thereby having a lower drug clearance.

## Conclusions

This study demonstrates the utility of a PBPK-PD model in exploring the impact of inter-ethnic physiological differences on the therapeutic response of S-warfarin; and how prior knowledge of these can inform necessary dosage adjustments, thereby preventing unwanted effects.

## References

1. Barter *et al.* 2013 Clin Pharmacokinet 52(12): 1085-1100
2. Ohara *et al.* 2014 PLOS ONE Vol 9(8)
3. Shaul *et al.* 2017 Mol Diagn Ther 21: 75-83

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