

Use of a physiologically based pharmacokinetic – pharmacodynamic (PBPK-PD) model to guide dose adjustments to S-warfarin in different populations

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Introduction

The 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. Once a model has been verified in one population, it can be used to predict the exposure in other populations by accounting for demographic and genetic differences. Linking the predicted exposure to a pharmacodynamic (PD) response model can aid dose adjustments.

Warfarin is an anti-coagulant, which acts as an antagonist of the vitamin K dependent clotting pathway. It is a drug with a narrow therapeutic index, wherein too low doses or under-anticoagulation can result in thrombosis, 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 and is primarily metabolised by the polymorphic CYP2C9 enzyme. Dosage adjustments based on INR monitoring are often recommended for individuals with *2 and *3 variant alleles due to reduced metabolic activity.

Objective

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

Methods

The default Simcyp® Simulator V18 library S-warfarin PBPK model was linked to a published PD model¹ (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. Total S-warfarin plasma concentrations were input into the PD model. The PD model was an indirect model wherein the synthesis of prothrombin (NPT) in plasma was assumed to be inhibited by the Emax model. The estimated IC₅₀ 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 concentration¹.

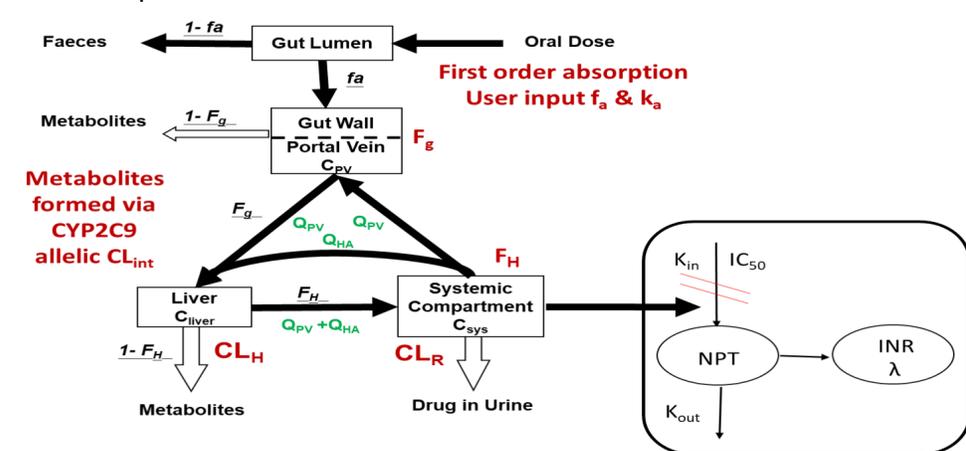


Figure 1: Schematic of a minimal PBPK linked PD model for S-warfarin, wherein plasma concentrations of S-warfarin mediates the inhibition of prothrombin synthesis and hence the INR response.

Results

Table 1: Predicted and observed mean clearance of S-warfarin in healthy volunteer Caucasian adults with different CYP2C9 allelic variants.

	Mean (± SD) S-Warfarin CLpo (mL/h)			
	CYP2C9*1*1	CYP2C9*1*3	CYP2C9*2*3	CYP2C9*3*3
Predicted	375 ± 292	209 ± 143	165 ± 118	36 ± 15
Observed	282 ± 62	180 ± 49	84 ± 7	71 ± 5

The results of the predictions of S-warfarin clearance in individuals with different CYP2C9 allelic forms, based on the clinical study by Flora *et al.*, 2017² are shown in Table 1 below. The PBPK model showed reasonable recovery of the observed data with the predicted clearances all within 2 fold of the observed data. In addition, clearance in individuals with *2 and *3 variant alleles of CYP2C9 were significantly lower than those with the wild type.

Results

In addition to the reduced metabolic effect in CYP2C9 variant alleles, physiological differences between ethnic populations have been shown to bring about changes in the clearance of drugs. We therefore explored what the INR response levels would be for a 20 year old male Caucasian administered a 5mg loading dose of S-warfarin for 5 days followed by a maintenance dose of 2.5mg assumed to have the CYP2C9*1*1 and VKORC1*2. We then compared the INR response in a similar Japanese and Chinese individual.

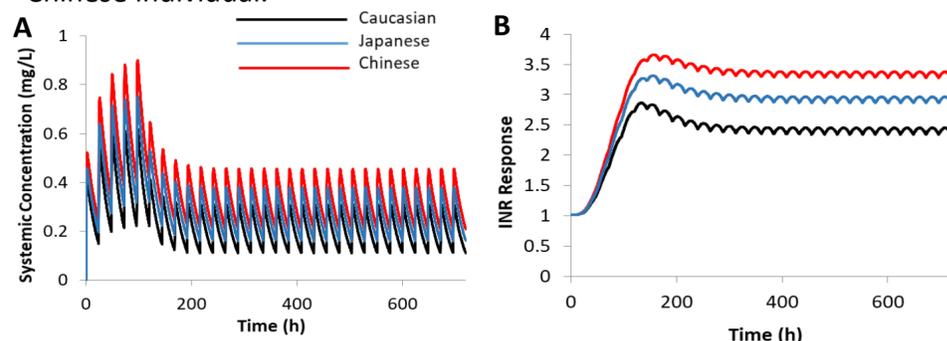


Figure 2: Simulated plasma concentration time profile of S-warfarin after a 5mg loading dose for 5 days followed by a 2.5mg maintenance dose for 25 days (A); and the corresponding INR response levels (B) in a Caucasian, Japanese and Chinese 20 year old male.

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 due to physiological differences in the three ethnic populations, already considered in the PBPK model. Given that the INR response level for the Chinese was outside the therapeutic range of between 2 and 3 (Figure 2B), a dose adjustment of 3mg loading dose followed by 1.5mg maintenance dose was estimated to give a similar steady state concentration of S-warfarin as the Caucasian (graph not shown).

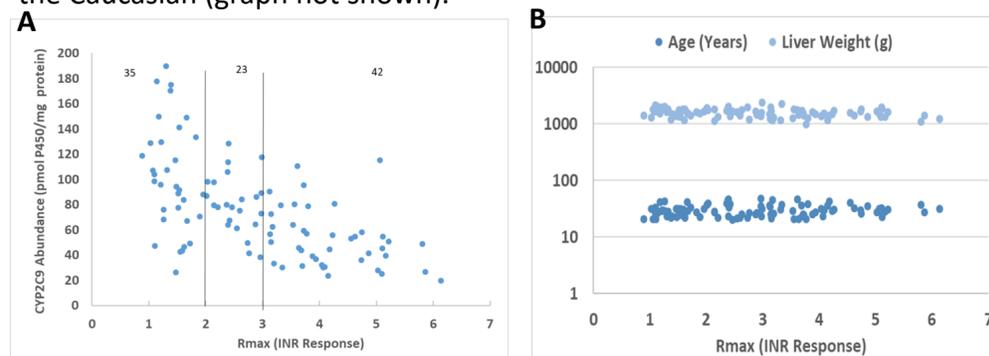


Figure 3: Plot of individual CYP2C9 liver abundance (A), age and liver weight (B) of 100 simulated Chinese volunteers against their predicted steady state INR response after a loading dose of S-warfarin of 3mg for 5 days followed by a maintenance dose of 1.5 mg for 25 days.

Although a loading dose of 3mg S-warfarin followed by a maintenance dose of 1.5mg was suitable for a 20 year old male, that same dose administered to a mixed population of Chinese volunteers (10 x 10 individuals, 20 – 50 years, 0.5 females) was only appropriate for 23% of the population. 35% would be at a risk of under-coagulation, and 42% at a risk of over-coagulation and would therefore require dose adjustments. CYP2C9 abundance was the physiological parameter shown to have the highest correlation with the INR response. Individuals with a low abundance had higher INR response levels due to lower drug clearance, while those with a high abundance have a lower INR response due to higher drug clearance.

Conclusions

This study demonstrates the utility of a PBPK-PD model in identifying individuals on S-warfarin at a risk of under-coagulation or over-coagulation; as well as estimating the required dosage adjustments needed to maintain the INR response within the recommended therapeutic range.

References

- Ohara *et al* 2014 PLOS ONE Vol 9(8)
- Flora *et al* 2017 J Clin Pharmacol 57(3): 382-393