A physiological-based pharmacokinetic model embedded with a target-mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments

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Abbreviations:

CYP: cytochrome P450

DDI: drug-drug interaction

TMDD: target-mediated drug disposition

PK: pharmacokinetics

PD: pharmacodynamics

CL: clearance

PBPK: physiology-based pharmacokinetic

FDA: Food and Drug Administration

AUC0-360: area-under-the-curve from time 0 to 360 hours

CV: coefficient of variations
Abstract
Warfarin, a commonly prescribed oral anticoagulant medication, is highly effective in treating deep vein thrombosis and pulmonary embolism. However, the clinical dosing of warfarin is complicated by high inter-individual variability in drug exposure and response and its narrow therapeutic index. CYP2C9 genetic polymorphism and drug-drug interactions (DDIs) are substantial contributors to this high variability of warfarin pharmacokinetics (PK), among numerous factors. Building a physiological-based pharmacokinetic (PBPK) model for warfarin is not only critical for a mechanistic characterization of warfarin PK, but also useful for investigating the complicated dose-exposure relationship of warfarin. Thus, the objective of this study was to develop a PBPK model for warfarin which integrates information regarding CYP2C9 genetic polymorphisms and their impact on DDIs. Generic PBPK models for both S- and R-warfarin, the two enantiomers of warfarin, were constructed in R with the mrgsolve package. As expected, a generic PBPK model structure did not adequately characterize the warfarin PK profile collected up to 15 days following the administration of single oral dose of warfarin, especially for S-warfarin. However, following the integration of an empirical target-mediated drug disposition (TMDD) component, the PBPK-TMDD model well characterized the PK profiles collected for both S- and R-warfarin in subjects with different CYP2C9 genotypes. Following the integration of enzyme inhibition and induction effects, the PBPK-TMDD model also characterized the PK profiles of both S- and R-warfarin in various DDI settings. The developed mathematic framework may be useful in building algorithms to better inform the clinical dosing of warfarin.
Significance Statement

The present study found a traditional physiology-based pharmacokinetic (PBPK) model cannot sufficiently characterize the pharmacokinetic profiles of warfarin enantiomers when warfarin is administered as a single dose, but a PBPK model with a target-mediated drug disposition mechanism can. After incorporating *CYP2C9* genotypes and drug-drug interaction information, the developed model is anticipated to facilitate the understanding of warfarin disposition in subjects with different *CYP2C9* genotypes in the absence and presence of both cytochrome P450 inhibitors and cytochrome P450 inducers.
Introduction
Warfarin is one of the most widely used oral anti-coagulants worldwide (Barnes et al., 2015). Warfarin exhibits its pharmacological anti-coagulation effects by inhibiting the vitamin K epoxide reductase to prevent the conversion of vitamin K epoxide to reduced vitamin K, which disrupts the vitamin K dependent blood coagulation cascade (Goodman et al., 2011; Matalqah, 2019). Although warfarin is highly efficacious in reducing the risk of stroke in arterial fibrillation patients, the narrow therapeutic index and high inter-individual variability in both drug exposure and response complicates its dosing (Jaffer and Bragg, 2003; Ufer, 2005; Flora et al., 2017). An inappropriate maintenance dose of warfarin resulting in drug exposure beyond the therapeutic window has been found to either compromise the therapeutic effects or introduce life-threatening bleeding risk (Kawai et al., 2014; Trusler, 2019).

Warfarin is administered as a racemic mixture. Although both S- and R-warfarin exhibit pharmacological activity, S-warfarin is suggested to be 3-7 fold more active than R-warfarin (Flora et al., 2017; Udoamaka Ezuruike, 2019). The elimination of warfarin is primarily via cytochrome P450 (CYP) mediated metabolism with negligible urinary excretion of the parent enantiomers (Ufer, 2005). Each warfarin enantiomer form five mono-hydroxylated metabolites, namely 4’, 6, 7, 8, 10 hydroxylated (OH) S- or R-warfarin, mediated by various CYPs. S-warfarin is metabolized primarily by CYP2C9, whereas R-warfarin is metabolized by several CYP enzymes including CYP1A2, CYP2C19 and CYP3A4 that have comparable contributions (Ufer, 2005; Flora et al., 2017; Pouncey et al., 2018).

CYP2C9 is subject to genetic polymorphism, which significantly influences warfarin exposure, particularly with respect to the S-7-OH metabolite, which is the primary elimination route for S-warfarin (Xue et al., 2017). CYP2C9 *2 (Arg144Cys) and *3 (Ile359Leu) variant alleles are associated with reduced metabolic activity and thus a higher exposure of the more pharmacologically active S-warfarin and an increase in the risk of dose-dependent adverse effects (Hamberg et al., 2007; Hamberg et al., 2010; Xue et al., 2017). More importantly, the frequency of the CYP2C9 *2 and *3 alleles can be as high as 15% in certain populations, such as Caucasians (Flora et al., 2017). Although the effect of these variants on warfarin exposure have been known for a long time, the impact of CYP2C9 *2 and *3 on the drug-drug interactions (DDIs) of warfarin has only recently been investigated. In addition, CYP2C9 *1B (-3089G>A
and -2663delTG), a regulatory genetic polymorphism, may further complicate the dosing of warfarin in a DDI setting (Chaudhry et al., 2010).

Leveraging physiological characteristics and the drug-related properties, physiological-based pharmacokinetic (PBPK) modeling is a valuable tool in model-informed drug development (Zhuang and Lu, 2016; Zhang et al., 2020). Importantly, the value of PBPK modeling in various drug development applications is gaining increasing acceptance by regulatory agency such as the US Food and Drug Administration (FDA) in recent years (Grimstein et al., 2019). An important aspect of PBPK modeling in drug development applications is predicting clinical DDIs of drugs (Grimstein et al., 2019). A successful implementation of PBPK modeling is useful not only in gaining more mechanistic insights for the investigated products, but also in supporting clinical decision-making and regulatory submission (Alhadab and Brundage, 2020).

Although the clinical use of warfarin can be traced back to the 1950s, the impact of the CYP2C9 genotypes on the clinical DDIs of warfarin is poorly understood (Flora et al., 2017). Taking advantage of a single dose warfarin clinical DDI study in healthy volunteers with various CYP2C9 genotypes and a target-mediated drug disposition (TMDD) model, our previous population PK analysis found subjects with CYP2C9 *2 and *3 variants experience less reduction in S-warfarin clearance (CL) when warfarin is administered together with the CYP inhibitor fluconazole. In contrast, this population experienced a greater increase in S-warfarin CL when warfarin is administered together with the CYP inducer rifampin as compared to individuals possessing the wild-type genotype (CYP2C9*1/*1) (Cheng et al., 2022a). However, a more physiologically relevant PBPK model has not been developed to explain the CYP2C9 genotype dependent DDIs of warfarin. In addition, it is unclear whether the TMDD mechanism utilized in our population PK analysis is needed in a PBPK model structure to explain the single dose warfarin PK profiles collected up to 15 days following the drug administration. Thus, the objective of this study was to use a PBPK modeling approach to investigate the DDIs of warfarin in the presence of various CYP2C9 genotypes using the known CYP inhibitor fluconazole and CYP inducer rifampin.
Methods

Warfarin PBPK Model Structure

A diagram of the PBPK model is shown in Figure 1 comprising 19 compartments in total. The PBPK model was compiled and implemented in R (version 3.6.3) using mrgsolve package (version 0.11.1) with mass balance differential equations (Elmokadem et al., 2019). The areas-under-the-curve (AUCs) were calculated using R package PKPDmisc (version 3.0.0).

The full PBPK model structures of S- and R-warfarin were adapted from initial literature models with physiological parameter values as shown in Table 1 (Peters, 2008). Standard weight-based allometric scaling coefficients of 0.75 and 1 were added on flow- and volume-based physiological parameters, respectively (West et al., 1999; Anderson and Holford, 2009). The structure of the initial PBPK model incorporates 14 compartments representing various physiological organs connected via arterial and venous blood flow components. In general, blood flows from the venous blood compartment and through the lungs into the arterial blood compartment, which further distributes blood into different organs. The physicochemical properties and blood and plasma binding related parameters were assumed to be the same between S- and R-warfarin, with values taken from the Sim-S-Warfarin compound file in Simcyp version 19 (Table 2) (Simcyp, 2020). Considering the relatively rapid and almost complete absorption of warfarin (Ufer, 2005), the advanced compartmental absorption and transit (ACAT) components of the original PBPK model (Peters, 2008) were not incorporated to reduce the model complexity. A simplified first-order absorption model was used instead, with drug administered into a gut lumen (GL) compartment. The organ distribution of S- and R-warfarin was assumed to follow a perfusion-rate limited manner into well-stirred physiological organs. The partition coefficients of S- and R-warfarin were assumed to be the same and were predicted using the Sim-S-Warfarin compound file with method 2 in Simcyp version 19 (Table 3) (Peters, 2008; Simcyp, 2020). The general form of the differential equation for a typical organ without elimination (brain (BR), spleen (SP), pancreas (PA), stomach (ST), heart (HT), muscle (MU), adipose (AD), skin (SK), bone (BO) and thymus (TH)) can be expressed using equation (1):
\[
\frac{dC_{\text{organ}} \times V_{\text{organ}}}{dt} = Q_{\text{organ}} \times \left( \frac{C_{\text{arterial}} - \frac{C_{\text{organ}}}{Kp_{\text{organ}}}}{BP} \right)
\] (1)

\(C_{\text{organ}}\) is the concentration of drug in each organ, \(V_{\text{organ}}\) is the organ volume, \(Q_{\text{organ}}\) is the tissue blood flow, \(C_{\text{arterial}}\) is the drug concentration in arterial blood, \(C_{\text{organ}}\) is the drug concentration in each organ, \(Kp_{\text{organ}}\) is the tissue partition coefficient defined as tissue to plasma drug concentration ratio and \(BP\) is the blood to plasma concentration ratio of the drug. The equation for gut (GU) is also expressed as equation (1) in general except for an additional first-order absorption input from the gut lumen (GL) compartment.

The equation for lung (LU) is expressed as equation (2) as shown below:

\[
\frac{dC_{\text{lung}} \times V_{\text{lung}}}{dt} = Q_{LU} \times \left( \frac{C_{\text{venous}} - \frac{C_{LU}}{Kp_{LU}/BP}}{BP} \right)
\] (2)

Elimination of S- and R-warfarin was incorporated for both liver and kidney. The clearance (CL) parameter values were taken from our previous warfarin population PK study (Table 3) (Cheng et al., 2022a). The differential equation for liver (LI) is shown as equation (3) assuming liver is receiving blood flow from the gut (GU), spleen (SP), hepatic artery (HA), pancreas (PA) and stomach (ST):

\[
\frac{dC_{\text{liver}} \times V_{\text{liver}}}{dt} = Q_{GU} \times \left( \frac{C_{GU}}{Kp_{GU}/BP} \right) + Q_{SP} \times \left( \frac{C_{SP}}{Kp_{SP}/BP} \right) + Q_{HA} \times C_{\text{arterial}}
\]

\[
+ Q_{PA} \times \left( \frac{C_{PA}}{Kp_{PA}/BP} \right) + Q_{ST} \times \left( \frac{C_{ST}}{Kp_{ST}/BP} \right) - Q_{LI} \times \left( \frac{C_{LI}}{Kp_{LI}/BP} \right)
\]

\[
- C_{\text{L}_{\text{int}}} \times \frac{C_{\text{up}}}{Kp_{LI}} \quad (3)
\]
CL\text{int} represents the hepatic intrinsic CL and f_{up} represents the free fraction in plasma.

Similarly, the differential equation for the other elimination organ kidney (KI) is expressed as equation (4):

$$\frac{dC_{\text{kidney}} \times V_{\text{kidney}}}{dt} = Q_{KI} \times \left(C_{\text{arterial}} \times \frac{C_{KI}}{Kp_{KI}}\right) - CL_{\text{int}KI} \times \frac{C_{KI} \times f_{up}}{Kp_{KI}}$$

(4)

The hepatic CL\text{int} was calculated in a retrograde fashion from the CL terms using equation (5) (Yang et al., 2007; Alhadab and Brundage, 2020):

$$CL_{\text{int}} = \frac{Q_{LI} \times CL_{LI}}{f_{up} \times (Q_{LI} - \frac{CL_{LI}}{BP})}$$

(5)

CL\text{LI} represents the hepatic CL calculated as the difference between overall CL and renal CL (CLR) as shown in Table 3. Similarly, renal CL was used to derive the intrinsic clearance by the kidney (CL\text{intKI}) using the same method (equation (6)).

$$CL_{\text{int}KI} = \frac{Q_{KI} \times CL_{KI}}{f_{up} \times (Q_{KI} - \frac{CL_{KR}}{BP})}$$

(6)

An empirical TMDD mechanism assuming constant total receptor levels was further included in the venous blood compartment to account for saturable tissue binding of warfarin. The TMDD-related parameters were taken from our warfarin population PK study (Table 3) (Cheng et al., 2022a). The differential equations for the receptor compartment (R) and the drug-receptor complex compartment (DR) are shown as equations (7) and (8):

$$\frac{dR}{dt} = -K_{on} \times \left(\frac{C_{\text{venous}}}{BP}\right) \times R + K_{off} \times DR$$

(7)
\[
\frac{dDR}{dt} = K_{on} \times \left( \frac{C_{\text{venous}}}{BP} \right) \times R - K_{off} \times DR \quad (8)
\]

R is the receptor concentration and DR is the drug-receptor complex concentration. \( K_{on} \) and \( K_{off} \) are the association and dissociation rate constants. The initial condition for R was set as \( R_{max} \) and the initial condition for DR was set as 0.

The differential equations for venous and arterial blood compartments are shown as equations (9) and (10).

\[
\frac{dC_{\text{venous}}}{dt} = \sum Q_{\text{organ}} \times \left( \frac{C_{\text{organ}}}{K_{\text{Forgan}}/BP} \right) - Q_{LU} \times C_{\text{venous}} \times K_{on} \times \left( \frac{C_{\text{venous}}}{BP} \times V \right) \times R + K_{off} \times (DR \times V) \quad (9)
\]

\[
\frac{dC_{\text{arterial}}}{dt} = Q_{LU} \times \left( \frac{C_{LU}/K_{\text{PLU}}/BP}{BP} - C_{\text{arterial}} \right) \quad (10)
\]

In equation (9), the blood flows from brain, kidney, liver, heart, muscle, adipose, skin, bone and thymus are summed and are assumed as flowing to the venous blood compartment. \( V \) is an arbitrary volume term fixed at 1 L to convert a concentration into an amount. The plasma drug concentrations are predicted as \( C_{\text{venous}}/BP \) for further analysis.

Multiplication factors were added on the absorption rate constants (MF\text{ka}), tissue partition coefficients (MF\text{kp}), blood to plasma ratios (MF\text{BP}), free drug fractions in plasma (MF\text{fup}), association rate constant (MF\text{kon}), dissociation rate constant (MF\text{koff}) and total receptor levels (MF\text{Rmax}) for further parameter optimization, with initial values set at 1 (Peters, 2008; Alhadab and Brundage, 2020).

**Clinical PK Data**

The S- and R-warfarin plasma PK data used for developing our previous warfarin population PK model were utilized in this study for visualizing the PBPK model predictions (Cheng et al., 2022a).
The warfarin PK data was collected in a clinical drug-drug interaction (DDI) study conducted with 29 healthy subjects with various CYP2C9 genotypes (CYP2C9 *1/*1, *1B/*1B, *1/*3, *2/*3 and *3/*3). Briefly, after enrollment, each subject went through three treatment periods. During treatment period one, subjects were treated with a single 10 mg oral dose of racemic warfarin. Blood samples were collected up to 15 days post-dose based on the subject’s CYP2C9 genotype, followed by a 7-day washout phase before entering the next treatment period. During treatment period two, subjects were randomized to be treated with either 400 mg fluconazole or 300 mg rifampin once daily for 7 days consecutively, to allow the concentration of each interacting drug reach steady state. On day 8, a single 10 mg oral dose of warfarin was administered in each subject with blood samples collected following the same sampling scheme as the treatment period one, followed by another 7 day washout phase. During the sampling phase of period two, interacting drugs were continuously administered with the same dosing regimens to maintain a steady state concentration. The design of treatment period three was the same as treatment period two, with subjects treated with the alternative interacting drug.

Model Parameter Optimizations

The S- and R-warfarin PK profiles in CYP2C9 *1/*1 subjects treated with warfarin only were used for initial model optimization. The multiplication factors (MFka, MFkp, MFbp and MFfup) in the PBPK model without TMDD and the multiplication factors (MFka, MFkp, MFbp, MFfup, MFkon, MFkoff and MFRmax) in the PBPK model with TMDD were adjusted 0.1, 0.25, 0.5, 1, 2, 4, 10-fold for the simulations. The resulting PBPK model predictions were overlaid with the S- and R-warfarin PK profiles in subjects with CYP2C9 *1/*1 treated with warfarin only to visualize the sensitivity of these multiplication factors on model predictions.

For the S-warfarin PK profiles in CYP2C9 *1/*1 subjects treated with warfarin only, MFkp and MFRmax were considered to be sensitive on model predictions and were selected to be further optimized. For R-warfarin PK profiles in CYP2C9 *1/*1 subjects treated with warfarin only, MFkp, MFRmax and MFkon were considered to be sensitive on model predictions and were selected to be further optimized. Optimization was performed in R (version 3.6.3) using the Nelder-Mead method with the weighted least squared objective function (Baron, 2019).
Following parameter optimization, the median predictions of the S- and R-warfarin PK profiles, in subjects with various \( CYP2C9 \) genotypes (*1/*1, *1B/*1B, *1/*3, *2/*3 and *3/*3) when warfarin is administered alone, were simulated and overlaid with the observations to visualize the model predictions.

**PK Models for Interacting Drugs**

Empirical PK models for fluconazole and rifampin were extracted from the literature and translated in R (version 3.6.3) using mrgsolve package (version 0.11.1) (Roos et al., 2008; Svensson et al., 2018). Briefly, the extracted fluconazole PK model is a one-compartment model with linear elimination, linear absorption, and the absorption lag time. The extracted PK model for rifampin is a one-compartment PK model with a nonlinear (mechaelis-menten) elimination, a transit-compartment absorption process, a dose-dependent bioavailability component and an enzyme turnover model to account for the auto-induction of rifampin. Both the fluconazole and the rifampin models were extracted with fixed and random effects. Fluconazole and rifampin PK profiles extracted from the literature were used for validating model predictions (Gross et al., 2001; Kumar et al., 2008; Wilkins et al., 2008; Seng et al., 2015).

**Incorporating Drug-Drug Interactions into Warfarin PBPK Models**

The hepatic intrinsic CL values for S- and R-warfarin were separated into five metabolic pathways (4’-, 6-, 7-, 8-, 10-monohydroxylated (OH)) pathways. The proportion of each metabolite as a function of the overall clearance was based on the results of our previous warfarin metabolites population PK modeling study (Cheng et al., 2022b). The metabolic elimination of S- and R-warfarin was assumed to be completely mediated by these five metabolic pathways. Thus, the metabolite proportions presented in the original study for each parent compound were summed and rescaled to 100% to calculate the new proportions of hepatic intrinsic CL mediated by the various metabolic pathways for use in this modeling analysis (Table 4).

The intrinsic hepatic CL of each metabolic pathway under the inhibitory effect of fluconazole was calculated using equation (11):
\[ CL_{int,\text{meta}i}^{inh} = \frac{CL_{int,\text{meta}i}}{1 + \frac{C_{fluc}}{K_i}} \quad (11) \]

\( CL_{int,\text{meta}i}^{inh} \) is the intrinsic hepatic CL of a particular metabolite pathway in the presence of the inhibitor fluconazole. \( C_{fluc} \) is the fluconazole plasma concentration predicted using an empirical PK model. \( K_i \) is the fluconazole inhibition constant.

The intrinsic hepatic CL of each metabolic pathway under the induction effect of rifampin was calculated using equation (12).

\[ CL_{int,\text{meta}i}^{ind} = CL_{int,\text{meta}i} \times \left( 1 + \frac{(ind_{max} - 1) \times C_{rifa}}{ind_{C50} + C_{rifa}} \right) \quad (12) \]

\( CL_{int,\text{meta}i}^{ind} \) is the intrinsic hepatic CL of a particular metabolite pathway in the presence of the inducer rifampin. \( C_{rifa} \) is the rifampin plasma concentration predicted using an empirical PK model. \( ind_{max} \) and \( ind_{C50} \) are the maximum fold increase in CL\textsubscript{int} that can occur following rifampin induction and the concentration of rifampin producing 50% of maximum induction of a particular metabolic pathway.

The overall hepatic intrinsic CL of each parent compound in the presence of fluconazole or rifampin was calculated as the summation of the hepatic intrinsic CL values of each metabolite pathway, under inhibition or induction conditions.

The fluconazole and rifampin effects on \( CL_R \) were included as multiplication factors based on a warfarin parent compound population PK analysis (Cheng et al., 2022a).

**Population Simulations**

Following the development of the S- and R- warfarin PBPK models and the validation of the fluconazole and rifampin empirical PK models, 30% inter-individual variability was assumed as being log-normally distributed for the absorption rate constants, CL terms, TMDD-related
parameters and partition coefficients (Kp) for performing the population simulations (Einolf et al., 2017). A virtual population with 500 subjects was simulated, with 100 subjects in each CYP2C9 genotype group (*1/*1, *1B/*1B, *1/*3, *2/*3 and *3/*3). The mean body weight of each genotype group was simulated based on the demographic information of the original study (Cheng et al., 2022a). Population-level simulations were performed using the dosing regimens of warfarin, fluconazole and rifampin in the original study (Cheng et al., 2022a). To visualize the predictions, the medians, 5th and 95th percentiles of the simulated PK profiles at each time point were calculated and overlaid with the observations of either S- or R-warfarin PK profiles in subjects with different CYP2C9 genotypes under different co-treatments. The model codes for final S- and R-warfarin PBPK models, as well as the S- and R-warfarin PBPK models with the interacting drug components, are provided in supplementary materials.
Results

PBPK Model Structure

The PBPK model structure for S- and R-warfarin is shown in Figure 1, with 14 physiological organ compartments (lungs (LU), heart (HT), brain (BR), muscle (MU), adipose (AD), skin (SK), spleen (SP), pancreas (PA), liver (LI), stomach (ST), gut (GU), bone (BO), kidney (KI) and thymus (TH)), venous and arterial blood compartments, a gut lumen (GL) compartment for drug administration, an empirical receptor compartment (R) and an empirical drug-receptor complex compartment (DR). Following the administration of drug in GL, drug is assumed to follow a first-order absorption (abs) into GU with a complete bioavailability and no delay (Table 2). LI and KI are assumed to be the organs of elimination. The empirical TMDD mechanism is arbitrarily embedded in the venous blood compartment.

To incorporate a drug-drug interaction mechanism, the hepatic CL_int of S- and R-warfarin is separated into five metabolic pathways (4’-OH, 6-OH, 7-OH, 8-OH and 10-OH). Fluconazole inhibition and rifampin induction effects were included in each metabolite pathway using the approach describe in the methods section. The fluconazole and rifampin effects were also included as multiplication factors on the CL_R. The inhibitory and induction parameters values used for simulations are displayed in Table 5 and Table 6, respectively.

Model Parameter Optimizations

The model predictions of the S- and R-warfarin PK profiles, with and without a TMDD mechanism, in CYP2C9 *1/*1 subjects when warfarin is administered alone were overlaid with the observed values (Figure 2). Inclusion of the TMDD mechanism substantially improved the model predictions for S-warfarin, but only slightly improved the model predictions for R-warfarin.

Further sensitivity analyses were conducted on the multiplication factors, for both S- and R-warfarin PBPK models with and without the TMDD mechanism, to visualize the influence of each factor on the model predictions (Figure S1-S4). MFka and MFfup had minimal influence on the model predictions for both the S- and R-warfarin PBPK models, with and without TMDD. For S-
warfarin, MFkp, MFBP and MFRmax substantially influenced the model predictions, whereas MFkon and MFkoff influenced the model predictions, but to a lesser extent. For R-warfarin, MFkp and MFBP substantially influenced the model predictions, whereas MFRmax, MFkon and MFkoff only slightly influenced the R-warfarin PK model predictions.

Sensitive parameters MFkp, MFRmax and MFkon were selected for optimizations. Both optimizations converged successfully with the optimized values of the multiplication factors displayed in the table insert of Figure 2. Optimization of the multiplication factors further improved the model predictions for both S- and R-warfarin PK profiles (Figure 2).

The PBPK models including a TMDD mechanism that were achieved following the optimizations were expanded to incorporate subjects with various CYP2C9 genotypes when warfarin is administered alone. The predicted S-and R-warfarin PK profiles adequately characterized the observations (Figure 3).

Validation of the Fluconazole and Rifampin Model Predictions

Fluconazole and rifampin PK profiles were extracted from the literature. The simulations conducted with the empirical PK models were able to capture the literature extracted PK profiles of fluconazole and rifampin (Figure S5-S6). These models were incorporated into the optimized S- and R-warfarin PBPK models that included a TMDD mechanism and utilized for predicting S- and R-warfarin PK profiles in both inhibition and induction DDI settings.

Population Simulations

Population simulations for the S- and R-warfarin PK profiles when warfarin is administered alone were conducted following the incorporation of inter-individual variation. The optimized PBPK models that include a TMDD mechanism were able to adequately characterize the S- and R-warfarin PK profiles when warfarin was administered alone (Figure 4). Following the incorporation of the fluconazole inhibition and the rifampin induction, the optimized PBPK models that included a TMDD mechanism were also able to characterize the S- and R-warfarin PK profiles in respective inhibition and induction DDI scenarios. (Figure 5 and 6).
The areas-under-the-curve from time 0 to 360 hours (AUC\textsubscript{0-360}) were calculated based on the population simulation for both S- and R- warfarin across various CYP2C9 genotypes, when warfarin is administered alone or together with fluconazole or rifampin (Figures 4-6 table insets). The AUC ratios for S- and R-warfarin when warfarin is administered together with fluconazole are 1.67 to 2.68 and 1.55 to 1.83, respectively (Figure 5 table inset). The AUC ratios for S- and R-warfarin when warfarin is administered together with rifampin are 0.423 to 0.488 and 0.297 to 0.324, respectively (Figure 6 table inset).
Discussion
Leveraging information from the literature and available clinical PK data from our previous studies, the present study develops a PBPK model framework for each warfarin enantiomer. The developed PBPK model was able to capture the plasma PK profiles of each warfarin enantiomer collected up to 15 days following the administration of a single oral dose of warfarin in subjects with various CYP2C9 genotypes under different co-medications. The developed PBPK models were able to characterize warfarin disposition in a more mechanistic manner and will be valuable for investigating the complicated dose-response relationship of warfarin.

Initially, a traditional PBPK model schematic was adapted from literature to predict warfarin PK profiles (Peters, 2008). However, we found a traditional PBPK schematic fails to explain the warfarin enantiomer PK profiles (especially S-warfarin) when collected up to 11 days in CYP2C9 *1/*1 subjects following a single dose of warfarin administration, no matter how the model parameters were adjusted (Figure 2, S1 and S3). Interestingly, dose-disproportionality of warfarin has been reported preclinically due to the presence of high-affinity and low-capacity binding sites of warfarin, which introduces the possibility of saturable tissue binding (Takada and Levy, 1979; Takada and Levy, 1980). Clinically, the saturable tissue binding of warfarin is observed as dose-dependent changes in the apparent volume of distributions (King et al., 1995). In fact, the term target-mediated drug disposition (TMDD) was first proposed by Dr. Gerhard Levy in 1994 on the basis of extensive preclinical PK research with small molecule compounds like warfarin (Levy, 1994). Dr. Levy also proposed a TMDD model for warfarin to account for the observed PK nonlinearity in apparent volume of distribution observed clinically (Levy et al., 2003). Although the TMDD model is used frequently for modeling biologics, this model is gaining more attention recently to account for the saturable tissue or plasma binding observed in the PK profiles of small molecule compounds (Mager and Jusko, 2001; An et al., 2015; An, 2017; Bach et al., 2019). Our previous population PK analysis also suggested a TMDD model was needed to characterize the warfarin PK profiles when collected up to 15 days following a single dose of warfarin after the administration of both a CYP inhibitor or a CYP inducer (Cheng et al., 2022a). In the current study, after including an empirical TMDD mechanism, we obtained a significant improvement in the PBPK model predictions of the S-warfarin PK profile. Further optimization of the PBPK model with a TMDD mechanism (PBPK-TMDD) enabled the
characterization of both the S- and R-warfarin PK profiles adequately in subjects with various CYP2C9 genotypes when warfarin was administered alone (Figure 3 and 4).

CYP2C9 *2 and *3 variants are highly associated with the reduced metabolic activity of CYP2C9. Subjects possessing the CYP2C9 *2 and *3 variants experience higher S-warfarin exposure following warfarin administration and require lower warfarin maintenance doses (Dean, 2012). In subjects with the CYP2C9 *2 and *3 variants, non-CYP2C9 mediated elimination pathways occupy a higher proportion of overall S-warfarin elimination (Cheng et al., 2022b). A differential effect of fluconazole inhibition and rifampin induction on different metabolic pathways of S-warfarin was also noted, potentially explaining our observation of CYP2C9 genotype-dependent DDIs on S-warfarin PK in our previous population PK analysis (Cheng et al., 2022a). CYP2C9 mediated metabolic pathways constitute the largest proportion of S-warfarin elimination, yet elimination by CYP2C9 is reduced in subjects with *2 and *3 variants. Consequently, our findings suggest that the degree to which these individuals experience inhibition by fluconazole is lessened resulting in a lower degree of drug inhibition interaction (genotype-dependent drug interactions). In contrast, because CYP2C9 mediated metabolic pathways are less inducible, the overall S-warfarin elimination in subjects with a lower proportion of CYP2C9 mediated elimination, such as subjects with *2 and *3 variants, are more susceptible to rifampin induction. Indeed, the K_i values (Table 5) reported in the literature suggest that CYP2C9 mediated S-warfarin metabolic pathways (6-OH-S and 7-OH-S) are inhibited to a greater extent compared with some of the other S-warfarin metabolic pathways such as 10-OH-S. Furthermore, the ind_max values we identified suggest that CYP2C9 mediated S-warfarin metabolic pathways are less inducible compared with other S-warfarin metabolic pathways mediated by other CYP enzymes (Table 6). More importantly, incorporating these inhibition and induction related parameters, our PBPK-TMDD model reflected the S-warfarin PK profiles when warfarin was administered with either fluconazole or rifampin (Figure 5 and 6). Interestingly, a previous clinical DDI study conducted with flurbiprofen as the probe drug and fluconazole as the interacting drug showed differential inhibition of CYP2C9 and non-CYP2C9 mediated pathways also resulted in CYP2C9 genotype-dependent DDIs (Kumar et al., 2008). The results of the present PBPK modeling study using S-warfarin as a probe drug are consistent with these previous study findings with flurbiprofen and fluconazole.
Additionally, the PBPK-TMDD model may be useful in informing the clinical use of warfarin. For instance, to reduce the risk of bleeding during surgery, warfarin treatment is typically discontinued about 5 days prior to surgery (Douketis et al., 2012). Following the inclusion of a TMDD mechanism, the model simulations based on the long half-life observed in our extended plasma sampling, suggest that the pharmacologically more active S-warfarin may not be eliminated as fast as earlier literature would predict (Figure 2A). Taking advantage of warfarin pharmacodynamic (PD) models published in the literature, it will be interesting to conduct simulations linking our PBPK-TMDD model together with a PD model, to investigate the impact of this observed slower elimination of S-warfarin on the International Normalized Ratio and treatment outcomes following warfarin discontinuation.

Despite the potential uses of the warfarin PBPK-TMDD models, limitations exist in the current model structure. Firstly, it is relatively empirical and arbitrary to embed the TMDD mechanism inside the venous blood compartment of a PBPK model structure to account for saturable tissue binding. A physiologically more relevant approach might be to incorporate the saturable tissue binding of warfarin into relevant organs, such as liver (Levy et al., 2003). However, lacking explicit clinical evidence about which organs exhibit saturable warfarin tissue binding, it was arbitrarily decided to embed the TMDD mechanism in the venous blood compartment of our PBPK model. Collecting additional information to inform an organ specific TMDD mechanism clinically would be beneficial for future development of a more mechanistic PBPK model schematic for warfarin. In this regard, the PBPK model constructed in the present study can be easily adapted to incorporate organ specific TMDD mechanism considering our model is developed using an open-source tool. Secondly, a significant assumption of the current PBPK model is that the hepatic CL of S- or R-warfarin is mediated completely by the five mono-hydroxylation pathways. Incorporating additional metabolic pathways of warfarin such as ketone reduction and glucuronidation might provide additional mechanistic insights to warfarin disposition but would require an even more extensive dataset (Ufer, 2005).

In summary, the present study found a traditional PBPK model structure was inadequate to describe the PK profiles of warfarin enantiomers when collected up to 15 days following a single dose of warfarin. Instead, a PBPK model embedded with an empirical TMDD mechanism
(PBPK-TMDD) was able to characterize the single dose warfarin PK profiles in subjects with clinically important *CYP2C9* genotypes. Following the integration of fluconazole inhibition and rifampin induction, the developed PBPK-TMDD models were able to describe the S- and R-warfarin PK profiles under different co-treatments in subjects with various *CYP2C9* genotypes. The developed PBPK models provide mechanistic insights regarding warfarin disposition and may also serve as a valuable tool to inform the clinical dosing of warfarin.
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Participated in research design: Shen Cheng, Darcy R. Flora, Allan E. Rettie, Richard C. Brundage, Timothy S. Tracy
Participated in data collection: Darcy R. Flora, Allan E. Rettie, Richard C. Brundage, Timothy S. Tracy
Performed data analysis: Shen Cheng, Richard C. Brundage
Wrote or contributed to the writing of the manuscript: Shen Cheng, Darcy R. Flora, Allan E. Rettie, Richard C. Brundage, Timothy S. Tracy
Reference


Cheng S, Flora DR, Tracy TS, Rettie AE and Brundage RC (2022b) Pharmacokinetic Modeling of Warfarin II – Model-based Analysis of Warfarin Metabolites following Warfarin Administered either Alone or Together with Fluconazole or Rifampin. Drug Metab Dispos 50:1302-1311.


Dean L (2012) Warfarin Therapy and VKORC1 and CYP Genotype, in Medical Genetics Summaries (Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kane MS, Kattman BL and Malheiro AJ eds), Bethesda (MD).


PUBCHEM Fluconazole compound summary, in, National Library of Medicine; National Center for Biotechnology Information, Pubchem.

PUBCHEM Rifampicin compound summary, in, National Library of Medicine; National Center for Biotechnology Information, Pubchem.


Footnotes:

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Figure Legends

Figure 1. S- and R-warfarin PBPK model diagram. Notes: Cp (plasma concentration of drug); C_venous (venous blood concentration of drugs and BP stands for blood to plasma ratio); GL (gut lumen); GU (gut); LU (lung); LI (liver); KI (kidney); BR (brain); SP (spleen); PA (pancreas); ST (stomach); HT (heart); MU (muscle); AD (adipose); SK (skin); BO (bone); TH (thymus); R: receptor; DR: drug-receptor complex.

Figure 2. S-warfarin (A) and R-warfarin (B) PBPK model predictions in subjects with CYP2C9 *1/*1 when warfarin is administrated alone. Colors represent model predictions using a PBPK model without TMDD mechanism, with TMDD mechanism and with TMDD mechanism following optimization. Table displays the multiplication factors for S- and R-warfarin following optimization. The multiplication factors are estimated based on the assumption that the volume of saturable binding target of warfarin is 1 L (arbitrarily fixed due to lack of relevant clinical information). RSE: relative standard errors.

Figure 3. Optimized S-warfarin (A) and R-warfarin (B) PBPK model with TMDD mechanism predictions overlayed with observations in subjects with various CYP2C9 genotypes when warfarin is administrated alone. Dots represent observations. Red lines represent median predictions.

Figure 4. Optimized S-warfarin (A) and R-warfarin (B) PBPK model with TMDD mechanism population predictions overlayed with observations in subjects with various CYP2C9 genotypes when warfarin is administrated alone. Dots represent observations. Red lines represent median predictions. Gray shaded areas represent the area between 5th and 95th percentiles of the model predictions. Table shows the AUC0-360 hours of S- and R-warfarin by CYP2C9 genotypes. Values in table expressed as geometric means (coefficient of variations (CV)).

Figure 5. Optimized S-warfarin (A) and R-warfarin (B) PBPK model with TMDD mechanism population predictions overlayed with observations in subjects with various CYP2C9 genotypes when warfarin is administrated together with fluconazole. Dots represent observations. Red lines represent median predictions. Gray shaded areas represent the area between 5th and 95th percentiles of the model predictions. Table inset shows the AUC0-360 hours and AUC ratios of S- and R-warfarin by CYP2C9 genotypes when warfarin is co-administered with fluconazole. Values in table expressed as geometric means (coefficient of variations (CV)).

Figure 6. Optimized S-warfarin (A) and R-warfarin (B) PBPK model with TMDD mechanism population predictions overlayed with observations in subjects with various CYP2C9 genotypes when warfarin is administrated together with rifampin. Dots represent observations. Red lines represent median predictions. Gray shaded areas represent the area between 5th and 95th percentiles of the model predictions. Table inset shows the AUC0-360 hours and AUC ratios of S- and R-warfarin by CYP2C9 genotypes when warfarin is co-administered with rifampin. Values in table expressed as geometric means (coefficient of variations (CV)).

Tables

Table 1. Physiology parameter table. Values are extracted from literature (Peters, 2008).
<table>
<thead>
<tr>
<th>Tissue</th>
<th>Volume (mL, 70kg human)</th>
<th>Flow (mL/min, 70kg human)</th>
</tr>
</thead>
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<td>Brain</td>
<td>1450</td>
<td>700</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>302</td>
<td></td>
</tr>
<tr>
<td>Gut</td>
<td>1650</td>
<td>1100</td>
</tr>
<tr>
<td>Spleen</td>
<td>192</td>
<td>77</td>
</tr>
<tr>
<td>Pancreas</td>
<td>77</td>
<td>133</td>
</tr>
<tr>
<td>Stomach</td>
<td>154</td>
<td>38</td>
</tr>
<tr>
<td>Liver</td>
<td>1690</td>
<td>1650</td>
</tr>
<tr>
<td>Kidney</td>
<td>280</td>
<td>1100</td>
</tr>
<tr>
<td>Heart</td>
<td>310</td>
<td>150</td>
</tr>
<tr>
<td>Lung</td>
<td>1172</td>
<td>5240</td>
</tr>
<tr>
<td>Muscle</td>
<td>35000</td>
<td>750</td>
</tr>
<tr>
<td>Adipose</td>
<td>10000</td>
<td>260</td>
</tr>
<tr>
<td>Skin</td>
<td>7800</td>
<td>300</td>
</tr>
<tr>
<td>Bone</td>
<td>4579</td>
<td>250</td>
</tr>
<tr>
<td>Thymus</td>
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<td>80</td>
</tr>
<tr>
<td>Arterial blood</td>
<td>1698</td>
<td></td>
</tr>
<tr>
<td>Venous blood</td>
<td>3396</td>
<td></td>
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Table 2. Warfarin drug-property specific parameters

<table>
<thead>
<tr>
<th></th>
<th>S-warfarin</th>
<th>R-warfarin</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW</td>
<td>Molecular weight</td>
<td>Molecular weight</td>
<td></td>
</tr>
<tr>
<td>Compound type</td>
<td>Monoprotic acid (Simcyp, 2020)</td>
<td>Monoprotic acid (Simcyp, 2020)</td>
<td></td>
</tr>
<tr>
<td>Log P&lt;sub&gt;o/w&lt;/sub&gt;</td>
<td>0.27 (Simcyp, 2020)</td>
<td>0.27 (Simcyp, 2020)</td>
<td>Logarithmic neutral species octanol:buffer partition coefficient</td>
</tr>
<tr>
<td>pKa</td>
<td>5.1 (Simcyp, 2020)</td>
<td>5.1 (Simcyp, 2020)</td>
<td>Acid dissociation constant</td>
</tr>
<tr>
<td>CL (L/hour)</td>
<td>0.260 (Cheng et al., 2022a)</td>
<td>0.119 (Cheng et al., 2022a)</td>
<td>Total clearance</td>
</tr>
<tr>
<td>if *1B/*1B</td>
<td>× 0.885 (Cheng et al., 2022a)</td>
<td>× 0.607 (Cheng et al., 2022a)</td>
<td>Fractional multipliers of CL if other CYP2C9 genotypes</td>
</tr>
<tr>
<td>if *1/*3</td>
<td>× 0.607 (Cheng et al., 2022a)</td>
<td>× 0.277 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>if *2/*3</td>
<td>× 0.277 (Cheng et al., 2022a)</td>
<td>× 0.215 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>if *3/*3</td>
<td>× 0.215 (Cheng et al., 2022a)</td>
<td>× 0.215 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>CLR (L/hour)</td>
<td>0.00369 (Cheng et al., 2022a)</td>
<td>0.00436 (Cheng et al., 2022a)</td>
<td>Renal clearance</td>
</tr>
<tr>
<td>K&lt;sub&gt;on&lt;/sub&gt; (L/(µg*hour))</td>
<td>0.00494 (Cheng et al., 2022a)</td>
<td>0.00137 (Cheng et al., 2022a)</td>
<td>Association rate constant</td>
</tr>
<tr>
<td>if *2/*3</td>
<td>× 0.837 (Cheng et al., 2022a)</td>
<td>× 0.518 (Cheng et al., 2022a)</td>
<td>Fractional multipliers of K&lt;sub&gt;on&lt;/sub&gt; if other CYP2C9 genotypes</td>
</tr>
<tr>
<td>if *3/*3</td>
<td>× 0.518 (Cheng et al., 2022a)</td>
<td>× 0.518 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>K&lt;sub&gt;off&lt;/sub&gt; (/hour)</td>
<td>0.0405 (Cheng et al., 2022a)</td>
<td>0.0405 (Cheng et al., 2022a)</td>
<td>Dissociation rate constant</td>
</tr>
<tr>
<td>R&lt;sub&gt;max&lt;/sub&gt; (µg/L)</td>
<td>182 (Cheng et al., 2022a)</td>
<td>188 (Cheng et al., 2022a)</td>
<td>Total receptor levels</td>
</tr>
<tr>
<td>if *1/*3</td>
<td>× 0.479 (Cheng et al., 2022a)</td>
<td>× 0.479 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>if *2/*3</td>
<td>× 2.51 (Cheng et al., 2022a)</td>
<td>× 0.506 (Cheng et al., 2022a)</td>
<td>Fractional multipliers of R&lt;sub&gt;max&lt;/sub&gt; if other CYP2C9 genotypes</td>
</tr>
<tr>
<td>if *3/*3</td>
<td>× 1.89 (Cheng et al., 2022a)</td>
<td>× 0.21 (Cheng et al., 2022a)</td>
<td></td>
</tr>
<tr>
<td>Fa (%)</td>
<td>100 (Simcyp, 2020)</td>
<td>100 (Simcyp, 2020)</td>
<td>Bioavailability</td>
</tr>
<tr>
<td>K&lt;sub&gt;a&lt;/sub&gt; (/hour)</td>
<td>1.85 (Simcyp, 2020)</td>
<td>1.85 (Simcyp, 2020)</td>
<td>Absorption rate constant</td>
</tr>
<tr>
<td>Lag time (hour)</td>
<td>0 (Simcyp, 2020)</td>
<td>0 (Simcyp, 2020)</td>
<td>Absorption lag time</td>
</tr>
<tr>
<td>BP</td>
<td>0.59 (Simcyp, 2020)</td>
<td>0.59 (Simcyp, 2020)</td>
<td>Blood to plasma ratio</td>
</tr>
<tr>
<td>f&lt;sub&gt;up&lt;/sub&gt;</td>
<td>0.009 (Simcyp, 2020)</td>
<td>0.009 (Simcyp, 2020)</td>
<td>Fraction of unbound drug in plasma</td>
</tr>
</tbody>
</table>
Table 3. Predicted S- and R-warfarin partition coefficients ($K_{ps}$) using method 2 (Rodgers et al.) in Simcyp version 19 (Simcyp, 2020).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$K_{ps}$</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.052</td>
<td>Predicted</td>
</tr>
<tr>
<td>Gut</td>
<td>0.162</td>
<td>Predicted</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.101</td>
<td>Predicted</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.064</td>
<td>Predicted</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.127</td>
<td>Calculated as the average of non-adipose tissues</td>
</tr>
<tr>
<td>Liver</td>
<td>0.090</td>
<td>Predicted</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.134</td>
<td>Predicted</td>
</tr>
<tr>
<td>Heart</td>
<td>0.160</td>
<td>Predicted</td>
</tr>
<tr>
<td>Lung</td>
<td>0.215</td>
<td>Predicted</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.038</td>
<td>Predicted</td>
</tr>
<tr>
<td>Adipose</td>
<td>0.040</td>
<td>Predicted</td>
</tr>
<tr>
<td>Skin</td>
<td>0.281</td>
<td>Predicted</td>
</tr>
<tr>
<td>Bone</td>
<td>0.103</td>
<td>Predicted</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.127</td>
<td>Calculated as the average of non-adipose tissues</td>
</tr>
</tbody>
</table>

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Table 4. The fractions of warfarin metabolic clearance by each metabolic pathway. Fraction values are calculated based on literature (Cheng et al., 2022b). Notes: The metabolic fractions presented in the original study for each parent compound were summed and rescaled to 100% to calculate the new fractions of hepatic intrinsic CL mediated by the various metabolic pathways. The key assumption of this approach is to assume the metabolism of S- or R-warfarin is totally mediated by the respective five metabolic pathways.

<table>
<thead>
<tr>
<th>S-warfarin</th>
<th>CYP2C9 *1/*1</th>
<th>CYP2C9 *1B/*1B</th>
<th>CYP2C9 *1/*3</th>
<th>CYP2C9 *2/*3</th>
<th>CYP2C9 *3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4'-OH (%)</td>
<td>2.8</td>
<td>2.9</td>
<td>4.7</td>
<td>10.4</td>
<td>28.2</td>
</tr>
<tr>
<td>6-OH (%)</td>
<td>19.8</td>
<td>16.8</td>
<td>20.1</td>
<td>17.6</td>
<td>20.6</td>
</tr>
<tr>
<td>7-OH (%)</td>
<td>75.3</td>
<td>78.4</td>
<td>72.6</td>
<td>68.5</td>
<td>42.5</td>
</tr>
<tr>
<td>8-OH (%)</td>
<td>1.5</td>
<td>1.2</td>
<td>1.7</td>
<td>1.9</td>
<td>4.8</td>
</tr>
<tr>
<td>10-OH (%)</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
<td>1.5</td>
<td>4.0</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>R-warfarin</th>
<th>CYP2C9 *1/*1</th>
<th>CYP2C9 *1B/*1B</th>
<th>CYP2C9 *1/*3</th>
<th>CYP2C9 *2/*3</th>
<th>CYP2C9 *3/*3</th>
</tr>
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<tr>
<td>4'-OH (%)</td>
<td>2.8</td>
<td>3.3</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>6-OH (%)</td>
<td>61.1</td>
<td>72.5</td>
<td>61.7</td>
<td>61.7</td>
<td>61.7</td>
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<tr>
<td>7-OH (%)</td>
<td>9.8</td>
<td>11.7</td>
<td>9.9</td>
<td>9.9</td>
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<tr>
<td>8-OH (%)</td>
<td>23.5</td>
<td>9.2</td>
<td>23.8</td>
<td>23.8</td>
<td>23.8</td>
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<tr>
<td>10-OH (%)</td>
<td>2.8</td>
<td>3.3</td>
<td>2.8</td>
<td>2.8</td>
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Table 5. Fluconazole inhibitory parameters

<table>
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<tr>
<th>MW (g/mol)</th>
<th>306.271 (PUBCHEM)</th>
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<td>Ki (mg/L)</td>
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<tr>
<td>4’-OH-S</td>
<td>8.88 (Brown et al., 2006; Damle et al., 2011)</td>
</tr>
<tr>
<td>6-OH-S</td>
<td>6.74 (Brown et al., 2006)</td>
</tr>
<tr>
<td>7-OH-S</td>
<td>6.74 (Brown et al., 2006)</td>
</tr>
<tr>
<td>8-OH-S</td>
<td>0.64 (Damle et al., 2011)</td>
</tr>
<tr>
<td>10-OH-S</td>
<td>19.3 (Brown et al., 2006; Damle et al., 2011)</td>
</tr>
<tr>
<td>4’-OH-R</td>
<td>8.88 (Brown et al., 2006; Damle et al., 2011)</td>
</tr>
<tr>
<td>6-OH-R</td>
<td>30.63 (Kunze et al., 1996)</td>
</tr>
<tr>
<td>7-OH-R</td>
<td>12.67</td>
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<tr>
<td>8-OH-R</td>
<td>0.64 (Brown et al., 2006)</td>
</tr>
<tr>
<td>10-OH-R</td>
<td>19.3 (Brown et al., 2006; Damle et al., 2011)</td>
</tr>
</tbody>
</table>

Fluconazole effects on CLR (multiplication factor)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S-warfarin</td>
<td>0.847 (Cheng et al., 2022a)</td>
</tr>
<tr>
<td>R-warfarin</td>
<td>0.752 (Cheng et al., 2022a)</td>
</tr>
</tbody>
</table>
Table 6. Rifampin induction parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MW (g/mol)</th>
<th>( \text{ind}_{\text{max}} )</th>
<th>( \text{indC}_{50} ) (mg/L)</th>
<th>Rifampin effects on CLR (multiplication factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW (g/mol)</td>
<td>822.94 (PUBCHEM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{ind}_{\text{max}} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4'-OH-S</td>
<td>8.4 (Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
<td>0.239 (Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>6-OH-S</td>
<td>3.6 (Krishna Machavaram, 2017)</td>
<td></td>
<td>1.234 (Krishna Machavaram, 2017)</td>
<td></td>
</tr>
<tr>
<td>7-OH-S</td>
<td>3.6 (Krishna Machavaram, 2017)</td>
<td></td>
<td>1.234 (Krishna Machavaram, 2017)</td>
<td></td>
</tr>
<tr>
<td>8-OH-S</td>
<td>5.5 (Yamazaki et al., 2019)</td>
<td></td>
<td>0.370 (Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>10-OH-S</td>
<td>16.0 (Yamazaki et al., 2019)</td>
<td></td>
<td>0.263 (Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>4'-OH-R</td>
<td>8.4 (Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
<td>0.239 (Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>6-OH-R</td>
<td>3.8 (Pelletier et al., 2013)</td>
<td></td>
<td>0.181 (Pelletier et al., 2013)</td>
<td></td>
</tr>
<tr>
<td>7-OH-R</td>
<td>7.8 (Pelletier et al., 2013; Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
<td>0.214 (Pelletier et al., 2013; Krishna Machavaram, 2017; Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>8-OH-R</td>
<td>5.5 (Yamazaki et al., 2019)</td>
<td></td>
<td>0.370 (Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>10-OH-R</td>
<td>16.0 (Yamazaki et al., 2019)</td>
<td></td>
<td>0.263 (Yamazaki et al., 2019)</td>
<td></td>
</tr>
<tr>
<td>( \text{indC}_{50} ) (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-warfarin</td>
<td>1.30 (Cheng et al., 2022a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-warfarin</td>
<td>1.43 (Cheng et al., 2022a)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Fluconazole and rifampin effects**

**TMDD**

\[ Cp = \frac{C_{\text{venous}}}{BP} \]

**Cp** + **R** → **DR**
Multiplication factors

<table>
<thead>
<tr>
<th>Multiplication factors</th>
<th>S-warfarin (Estimates (RSE))</th>
<th>R-warfarin (Estimates (RSE))</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFkp</td>
<td>0.924 (17.3%)</td>
<td>0.665 (23.5%)</td>
</tr>
<tr>
<td>MFRmax</td>
<td>3.74 (28.9%)</td>
<td>7.64 (24.7%)</td>
</tr>
<tr>
<td>MFkon</td>
<td>13.9 (95.8%)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3
### CYP2C9 genotypes and AUC<sub>0-360</sub> hours (ng\(\times\)hour/mL)

<table>
<thead>
<tr>
<th>CYP2C9 genotypes</th>
<th>AUC&lt;sub&gt;0-360&lt;/sub&gt; hours (ng(\times)hour/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1 (N=100)</td>
<td>19797 (34.8 %)</td>
</tr>
<tr>
<td>*1B/*1B (N=100)</td>
<td>22645 (32.1%)</td>
</tr>
<tr>
<td>*1/*3 (N=100)</td>
<td>27580 (30.6%)</td>
</tr>
<tr>
<td>*2/*3 (N=100)</td>
<td>53342 (30.4%)</td>
</tr>
<tr>
<td>*3/*3 (N=100)</td>
<td>53561 (27.7%)</td>
</tr>
</tbody>
</table>

**Figure 4**
Table 1: AUC of S- and R-warfarin in CYP2C9 genotypes

<table>
<thead>
<tr>
<th>CYP2C9 genotypes</th>
<th>AUC(_{0-360}) hours (ng*hour/mL)</th>
<th>AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-warfarin</td>
<td>R-warfarin</td>
</tr>
<tr>
<td>*1/*1 (N=100)</td>
<td>53061 (32.8%)</td>
<td>59579 (37.7%)</td>
</tr>
<tr>
<td>*1B/*1B (N=100)</td>
<td>59090 (31.2%)</td>
<td>52576 (32.7%)</td>
</tr>
<tr>
<td>*1/*3 (N=100)</td>
<td>69466 (26.9%)</td>
<td>63620 (28.8%)</td>
</tr>
<tr>
<td>*2/*3 (N=100)</td>
<td>102331 (26.6%)</td>
<td>77007 (31.2%)</td>
</tr>
<tr>
<td>*3/*3 (N=100)</td>
<td>89672 (21.1%)</td>
<td>60985 (31.0%)</td>
</tr>
</tbody>
</table>

Figure 5
<table>
<thead>
<tr>
<th>CYP2C9 genotypes</th>
<th>AUC_{0-360} hours (ng*hour/mL)</th>
<th>AUC Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S-warfarin</td>
<td>R-warfarin</td>
</tr>
<tr>
<td>*1/*1 (N=100)</td>
<td>9017 (42.0%)</td>
<td>10960 (42.7%)</td>
</tr>
<tr>
<td>*1B/*1B (N=100)</td>
<td>10074 (34.9%)</td>
<td>10702 (35.5%)</td>
</tr>
<tr>
<td>*1/*3 (N=100)</td>
<td>12673 (36.3%)</td>
<td>10611 (38.2%)</td>
</tr>
<tr>
<td>*2/*3 (N=100)</td>
<td>26016 (35.2%)</td>
<td>12513 (40.1%)</td>
</tr>
<tr>
<td>*3/*3 (N=100)</td>
<td>22648 (36.9%)</td>
<td>10328 (41.6%)</td>
</tr>
</tbody>
</table>

Figure 6
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments

Shen Cheng, Darcy R. Flora, Allan E. Rettie, Richard, C. Brundage, Timothy S. Tracy

Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Twin Cities (S.C., D.R.F., R.C.B.), Tracy Consultants (T.S.T.), Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle (A.E.R.), Present Affiliation: Metrum Research Group, Tariffville, Connecticut (S.C.), Present Affiliation: GRYT Health Inc., Rochester (D.R.F)
Supplementary materials

Contents:

Figure S1. Sensitivity analysis on multiplication factors of S-warfarin PBPK model without TMDD mechanism in subjects with CYP2C9 *1/*1 when warfarin is administered alone.

Figure S2. Sensitivity analysis on multiplication factors of S-warfarin PBPK model with TMDD mechanism in subjects with CYP2C9 *1/*1 when warfarin is administered alone.

Figure S3. Sensitivity analysis on multiplication factors of R-warfarin PBPK model without TMDD mechanism in subjects with CYP2C9 *1/*1 when warfarin is administered alone.

Figure S4. Sensitivity analysis on multiplication factors of R-warfarin PBPK model with TMDD mechanism in subjects with CYP2C9 *1/*1 when warfarin is administered alone.

Figure S5. Validation of fluconazole model predictions. Dots represent literature extracted observations. Gray shaded areas represent 2.5th and 97.5th percentiles of fluconazole empirical PK model predictions.

Figure S6. Validation of rifampin model predictions. Dots represent literature extracted observations. Gray shaded areas represent 2.5th and 97.5th percentiles of rifampin empirical PK model predictions.
Figure S2

- MFKₐ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFKₚ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFBP:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFKₚ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFRₘₐₓ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFkₜₜ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10

- MFkₜ₂ₙ:
  - Concentration (µg/mL)
  - Time (h)
  - Lines for different concentrations: 0.1, 0.25, 0.5, 1, 2, 4, 10
Figure S3
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments.
S-warfarin PBPK model mrgsolve model file

Shen Cheng

2021-09-13

[set] delta = 0.1 ,end=360 //360 hours/15 Days

[PARAM]
//Tissue volumes (L); for 70kg human
TVVbr = 1450/1000 //brain mL to L
TVVgu = 1650/1000 //Gut
TVVsp = 192/1000 //spleen
TVVpa = 77/1000 //pancreas
TVVst = 154/1000 //stomach (not in simcyp)
TVVli = 1690/1000 //liver
TVVki = 280/1000 //kidneys
TVVhe = 310/1000 //heart
TVVlu = 1172/1000 //lungs
TVVmu = 35000/1000 //muscle
TVVad = 10000/1000 //adipose
TVVsk = 7800/1000 //skin
TVVbo = 4579/1000 //bone
TVVth = 29/1000 //thymus (not in simcyp)

TVVab = 1698/1000 //arterial blood
TVVvb = 3396/1000 //venous blood

//Tissue blood flows (L/h); for 70kg human
TVQbr = (700*60)/1000 //brain mL/min to L/hr
TVQha = (302*60)/1000 //hepatic artery
TVQgu = (1100*60)/1000 //gut
TVQsp = (77*60)/1000 //spleen
TVQpa = (133*60)/1000 //pancreas
TVQst = (38*60)/1000 //stomach
TVQli = (1650*60)/1000 //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 //kidney
TVQhe = (150*60)/1000 //heart
TVQlu = (5240*60)/1000 //lung,
//should be same as cardiac output(adjusted to 5240, 5233 original)
//to match the total Q
TVQmu = (750*60)/1000 //muscle
TVQad = (260*60)/1000 //adipose
TVQsk = (300*60)/1000 //skin
TVQbo = (250*60)/1000 //bone
TVQth = (80*60)/1000 //thymus

<table>
<thead>
<tr>
<th>Partition Coefficient</th>
<th>Description</th>
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<tbody>
<tr>
<td>TVKpbr = 0.0523693</td>
<td>brain:plasma</td>
</tr>
<tr>
<td>TVKpgu = 0.1618</td>
<td>gut:plasma</td>
</tr>
<tr>
<td>TVKpsp = 0.100666</td>
<td>spleen:plasma</td>
</tr>
<tr>
<td>TVKpaa = 0.0639167</td>
<td>pancreas:plasma</td>
</tr>
<tr>
<td>TVKpab = 0.1271972</td>
<td>stomach:plasma (not in simcyp) calculated as average of non adipose Kps</td>
</tr>
<tr>
<td>TVKpli = 0.089772</td>
<td>liver:plasma</td>
</tr>
<tr>
<td>TVKpki = 0.133745</td>
<td>kidney:plasma</td>
</tr>
<tr>
<td>TVKple = 0.105004</td>
<td>heart:plasma</td>
</tr>
<tr>
<td>TVKplu = 0.215004</td>
<td>lungs:plasma</td>
</tr>
<tr>
<td>TVKpmu = 0.037509</td>
<td>muscle:plasma</td>
</tr>
<tr>
<td>TVKpad = 0.0396971</td>
<td>adipose:plasma</td>
</tr>
<tr>
<td>TVKpbo = 0.281144</td>
<td>skin:plasma</td>
</tr>
<tr>
<td>TVKpmbo = 0.102876</td>
<td>bone:plasma</td>
</tr>
<tr>
<td>TVKpbo = 0.1271972</td>
<td>thymus:plasma (not in simcyp) calculated as average of non adipose Kps</td>
</tr>
</tbody>
</table>

//in vivo clearance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVCL</td>
<td>0.26</td>
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</tbody>
</table>

//renal clearance

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVCL_Ki</td>
<td>0.00369</td>
</tr>
</tbody>
</table>

//TMDD param (unpublished warfarin manuscript)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVkon</td>
<td>0.00494</td>
</tr>
<tr>
<td>TVkoff</td>
<td>0.0405</td>
</tr>
<tr>
<td>TVRmax</td>
<td>182</td>
</tr>
</tbody>
</table>

//other parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVka</td>
<td>1.85</td>
</tr>
<tr>
<td>TVBP</td>
<td>0.59</td>
</tr>
<tr>
<td>TVFup</td>
<td>0.009</td>
</tr>
</tbody>
</table>

//scalars

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENO</td>
<td>1</td>
</tr>
<tr>
<td>weight</td>
<td>68.7</td>
</tr>
<tr>
<td>MFka</td>
<td>1</td>
</tr>
<tr>
<td>MFp</td>
<td>1</td>
</tr>
<tr>
<td>MFBP</td>
<td>1</td>
</tr>
<tr>
<td>MFfup</td>
<td>1</td>
</tr>
<tr>
<td>MFkon</td>
<td>1</td>
</tr>
<tr>
<td>MFkoff</td>
<td>1</td>
</tr>
<tr>
<td>MFRmax</td>
<td>1</td>
</tr>
</tbody>
</table>

//GENO effect on CL
CL_GENO2 = 0.885
CL_GENO3 = 0.607
CL_GENO4 = 0.277
CL_GENO5 = 0.215

//GENO on kon and Rmax
kon_GENO4 = 0.837
kon_GENO5 = 0.518
Rmax_GENO4 = 2.51
Rmax_GENO5 = 1.89

[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2

[MAIN]
//allometric scaling of volume
  double Vbr = TVVbr*pow(weight/70, 1); //brain
  double Vgu = TVVgu*pow(weight/70, 1); //Gut
  double Vsp = TVVsp*pow(weight/70, 1); //spleen
  double Vpa = TVVpa*pow(weight/70, 1); //pancreas
  double Vst = TVVst*pow(weight/70, 1); //stomach
  double Vli = TVVli*pow(weight/70, 1); //liver
  double Vki = TVVki*pow(weight/70, 1); //kidneys
  double Vhe = TVVhe*pow(weight/70, 1); //heart
  double Vlu = TVVlu*pow(weight/70, 1); //lungs
  double Vmu = TVVmu*pow(weight/70, 1); //muscle
  double Vad = TVVad*pow(weight/70, 1); //adipose
  double Vsk = TVVsk*pow(weight/70, 1); //skin
  double Vbo = TVVbo*pow(weight/70, 1); //bone
  double Vth = TVVth*pow(weight/70, 1); //thymus
  double Vab = TVVab*pow(weight/70, 1); //arterial blood
  double Vvb = TVVvb*pow(weight/70, 1); //venous blood

//allometric scaling of flow
  double Qbr = TVQbr*pow(weight/70, 0.75); //brain
  double Qha = TVQha*pow(weight/70, 0.75); //hepatic artery
  double Qgu = TVQgu*pow(weight/70, 0.75); //gut
  double Qsp = TVQsp*pow(weight/70, 0.75); //spleen
  double Qpa = TVQpa*pow(weight/70, 0.75); //pancreas
  double Qst = TVQst*pow(weight/70, 0.75); //stomach
  double Qli = TVQli*pow(weight/70, 0.75); //liver (total) (= Qha +
Qgu + Qsp + Qpa + Qst)
double Qki = TVQki*pow(weight/70, 0.75); //kidney
double Qhe = TVQhe*pow(weight/70, 0.75); //heart
double Qlu = TVQlu*pow(weight/70, 0.75); //lung
double Qmu = TVQmu*pow(weight/70, 0.75); //muscle
double Qad = TVQad*pow(weight/70, 0.75); //adipose
double Qsk = TVQsk*pow(weight/70, 0.75); //skin
double Qbo = TVQbo*pow(weight/70, 0.75); //bone
double Qth = TVQth*pow(weight/70, 0.75); //thymus

double Kpbr = TVKpbr*MFkp*exp(ETA(1)); //brain:plasma
double Kpgu = TVKpgu*MFkp*exp(ETA(2)); //gut:plasma
double Kpsp = TVKpsp*MFkp*exp(ETA(3)); //spleen:plasma
double Kppa = TVKppa*MFkp*exp(ETA(4)); //pancreas:plasma
double Kpst = TVKpst*MFkp*exp(ETA(5)); //stomach:plasma
double Kpki = TVKpki*MFkp*exp(ETA(7)); //kidney:plasma
double Kphe = TVKphe*MFkp*exp(ETA(8)); //heart:plasma
double Kplu = TVKplu*MFkp*exp(ETA(9)); //lungs:plasma
double Kpmu = TVKpmu*MFkp*exp(ETA(10)); //muscle:plasma
double Kpad = TVKpad*MFkp*exp(ETA(11)); //adipose:plasma
double Kpsk = TVKpsk*MFkp*exp(ETA(12)); //skin:plasma
double Kpbo = TVKpbo*MFkp*exp(ETA(13)); //bone:plasma
double Kpth = TVKpth*MFkp*exp(ETA(14)); //thymus:plasma

double CL_GENO = 1;
if (GENO==2) CL_GENO = CL_GENO2;
if (GENO==3) CL_GENO = CL_GENO3;
if (GENO==4) CL_GENO = CL_GENO4;
if (GENO==5) CL_GENO = CL_GENO5;

double CL = TVCL*CL_GENO*exp(ETA(15))*pow(weight/70, 0.75); //total in vivo clearance

double CL_Ki = TVCL_Ki*exp(ETA(16))*pow(weight/70, 0.75); //renal clearance

double CLint = Qli*(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP)); //CLint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
double CLint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

//TMDD param
double kon = TVkon*MFkon*exp(ETA(17));
if (GENO == 4) kon = TVkon*MFkon*kon_GENO4*exp(ETA(17));
if (GENO == 5) kon = TVkon*MFkon*kon_GENO5*exp(ETA(17));

double koff = TVkoff*MFkoff;

double Rmax = TVRmax*MFRmax*exp(ETA(18));
if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));

//other parameters
double ka = TVka*MFka*exp(ETA(19));
double BP = TVBP*MFBP;
double fup = TVfup*MFfup;

//receptor(R) baseline
R_0 = Rmax;

[ODE]
//Calculation of tissue drug concentrations (ug/L)

double Cbrain = BRAIN/Vbr;
double Cgut = GUT/Vgu;
double Cspleen = SPLEEN/Vsp;
double Cpancreas = PANCREAS/Vpa;
double Cstomach = STOMACH/Vst;
double Cliver = LIVER/Vli;
double Ckidney = KIDNEY/Vki;
double Cheart = HEART/Vhe;
double Clung = LUNG/Vlu;
double Cmuscle = MUSCLE/Vmu;
double Cadipose = ADIPOSE/Vad;
double Cskin = SKIN/Vsk;
double Cbone = BONE/Vbo;
double Cthymus = THYMUS/Vth;
double Carterial = ART/Vab;
double Cvenous = VEN/Vvb;

//ODEs

dxdt_GUTLUMEN = -ka*GUTLUMEN; \(\text{///(1) absorption}\)
dxdt_BRAIN = Qbr*(Carterial - Cbrain/(Kpbr/BP)); \(\text{///(2)}\)
dxdt_GUT = ka*GUTLUMEN + Qgu*(Carterial - Cgut/(Kpgu/BP)); \(\text{///(3) to liver}\)
dxdt_SPLEEN = Qsp*(Carterial - Cspleen/(Kpsp/BP)); \(\text{///(4) to liver}\)
dxdt_PANCREAS = Qpa*(Carterial - Cpancreas/(Kppa/BP)); \(\text{///(5) to liver}\)
dxdt_STOMACH = Qst*(CArticular - Cstomach/(Kpst/BP)) ;/(6) to liver

dxdt_LIVER = Qgu*(Cgut/(Kgu/BP)) //from gut
+ Qsp*(Cspleen/(Ksp/BP)) //from spleen
+ Qpa*(Cpancreas/(Kappa/BP)) //from pancreas
+ Qst*(Cstomach/(Kpst/BP)) //from stomach
+ Qha*(Carterial) //from hepatic arterial
- Qli*(Cliver/(Kpli/BP))
- CLint*(Cliver*fup/Kpli) ;/(7)

dxdt_KIDNEY = Qki*(Carterial - Ckidney/(Kpki/BP))
- CLint_Ki*(Ckidney*fup/Kpki) ;/(8)

dxdt_HEART = Qhe*(Carterial - Cheart/(Kphe/BP)) ;/(9)

dxdt_LUNG = Qlu*(Cvenous - Clung/(Kplu/BP)) ;/(10)

dxdt_MUSCLE = Qmu*(Carterial - Cmuscle/(Kpmu/BP)) ;/(11)

dxdt_ADIPOSE = Qad*(Carterial - Cadipose/(Kpad/BP)) ;/(12)

dxdt_SKIN = Qsk*(Carterial - Cskin/(Kpsk/BP)) ;/(13)

dxdt_BONE = Qbo*(Carterial - Cbone/(Kpbo/BP)) ;/(14)

dxdt_THYMUS = Qth*(Carterial - Cthymus/(Kpth/BP)) ;/(15)

dxdt_VEN = Qbr*(Cbrain/(Kbr/BP)) //from brain
+ Qli*(Cliver/(Kpli/BP)) //from liver
+ Qki*(Ckidney/(Kpli/BP)) //from kidney
+ Qhe*(Cheart/(Kphe/BP)) //from heart
+ Qmu*(Cmuscle/(Kpmu/BP)) //from muscle
+ Qad*(Cadipose/(Kpad/BP)) //from adipose
+ Qsk*(Cskin/(Kpsk/BP)) //from skin
+ Qbo*(Cbone/(Kpbo/BP)) //from bone
+ Qth*(Cthymus/(Kpth/BP)) //from thymus
- Qlu*Cvenous
- kon*(Cvenous/BP)*R
+ koff*DR ;/(16)

dxdt_ART = Qlu*(Clung/(Kplu/BP) - Carterial) ;/(17)

dxdt_R = - kon*(Cvenous/BP)*R + koff*DR ;/(18)

dxdt_DR = kon*(Cvenous/BP)*R - koff*DR ;/(19)

[OMEGA]
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 //Kps
0.09 //CL
0.09 //CL_Ki
0.09 //kon
0.09 //Rmax
0.09 //Ka
[TABLE]
capture CP = Cvenous/BP;
capture GENO = GENO;
capture WEIGHT = weight;
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments.

Shen Cheng, Darcy R. Flora, Allan E. Rettie, Richard, C. Brundage, Timothy S. Tracy

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S-warfarin PBPK model with fluconazole inhibition mrgsolve model file

Shen Cheng
2021-09-13

[set] delta = 0.1 , end = 720 // 720 hours / 30 Days

[PARAM]
// Tissue volumes (L); for 70kg human
TVVbr = 1450/1000 // brain mL to L
TVVgu = 1650/1000 // Gut
TVVsp = 192/1000 // spleen
TVVpa = 77/1000 // pancreas
TVVst = 154/1000 // stomach (not in simcyp)
TVVli = 1690/1000 // liver
TVVki = 280/1000 // kidneys
TVVhe = 310/1000 // heart
TVVlu = 1172/1000 // lungs
TVVmu = 35000/1000 // muscle
TVVad = 10000/1000 // adipose
TVVsk = 7800/1000 // skin
TVVbo = 4579/1000 // bone
TVVth = 29/1000 // thymus (not in simcyp)

TVVab = 1698/1000 // arterial blood
TVVvb = 3396/1000 // venous blood

// Tissue blood flows (L/h); for 70kg human
TVQbr = (700*60)/1000 // brain mL/min to L/hr
TVQha = (302*60)/1000 // hepatic artery
TVQgu = (1100*60)/1000 // gut
TVQsp = (77*60)/1000 // spleen
TVQpa = (133*60)/1000 // pancreas
TVQst = (38*60)/1000 // stomach
TVQli = (1650*60)/1000 // liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 // kidney
TVQhe = (150*60)/1000 // heart
TVQlu = (5240*60)/1000 // lung,
// should be same as cardiac output (adjusted to 5240, 5233 original)
// to match the total Q
TVQmu = (750*60)/1000 // muscle
TVQad = (260*60)/1000 // adipose
TVQsk = (300*60)/1000 // skin
TVQbo = (250*60)/1000 // bone
\[ TVQ_{th} = \frac{(80\times60)}{1000} \quad \text{//thymus} \]


\[ TVK_{pbr} = 0.0523693 \quad \text{//brain:plasma} \]
\[ TVK_{pgu} = 0.1618 \quad \text{//gut:plasma} \]
\[ TVK_{psp} = 0.100666 \quad \text{//spleen:plasma} \]
\[ TVK_{ppa} = 0.0639167 \quad \text{//pancreas:plasma} \]
\[ TVK_{pst} = 0.1271972 \quad \text{//stomach:plasma (not in simcyp) calculated as average of non adipose Kps} \]
\[ TVK_{pli} = 0.089772 \quad \text{//liver:plasma} \]
\[ TVK_{pki} = 0.133745 \quad \text{//kidney:plasma} \]
\[ TVK_{phe} = 0.160367 \quad \text{//heart:plasma} \]
\[ TVK_{plu} = 0.215004 \quad \text{//lungs:plasma} \]
\[ TVK_{pmu} = 0.037509 \quad \text{//muscle:plasma} \]
\[ TVK_{pad} = 0.0396971 \quad \text{//adipose:plasma} \]
\[ TVK_{psk} = 0.281144 \quad \text{//skin:plasma} \]
\[ TVK_{pbo} = 0.102876 \quad \text{//bone:plasma} \]
\[ TVK_{pth} = 0.1271972 \quad \text{//thymus:plasma (not in simcyp) calculated as average of non adipose Kps} \]

//in vivo clearance
\[ TVCL = 0.26 \quad \text{//(L/hr) in vivo clearance (unpublished warfarin manuscript, simcyp sim-warfarin)} \]

//renal clearance
\[ TVCL_{K_{i}} = 0.00369\times0.847 \quad \text{//(L/hr) renal clearance (unpublished warfarin manuscript)} \]
\[ //0.847: fluconzole effect on S-warfarin renal clearance(unpublished manuscript) \]

//TMDD param (unpublished warfarin manuscript)
\[ TVKon = 0.00494 \quad \text{// L/(µg*hour)} \]
\[ TVKoff = 0.0405 \quad \text{// /hour} \]
\[ TVR_{max} = 182 \quad \text{// ug/L} \]

//other parameters
\[ TVka = 1.85 \quad \text{//absorption rate constant (/hr) assumed (simcyp sim-warfarin)} \]
\[ TVBP = 0.59 \quad \text{//blood:plasma ratio (simcyp sim-warfarin)} \]
\[ TVfup = 0.009 \quad \text{//fraction of unbound drug in plasma (simcyp sim-warfarin)} \]

//scalars
\[ GENO = 1 \quad \text{//1:*1/*1; 2:*1B/*1B; 3:*1*/3; 4: *2*/3; 5: *3*/3} \]
\[ weight = 68.7 \quad \text{//(kg)} \]
\[ MFka = 1 \quad \text{//scalar for Ka} \]
\[ MFkp = 1 \quad \text{//scalar for Kps} \]
\[ MFBP = 1 \quad \text{//scalar for BP} \]
\[MF_{\text{fup}} = 1 \quad \text{// scalar for fup}\]
\[MF_{\text{kon}} = 1 \quad \text{// scalar for kon}\]
\[MF_{\text{koff}} = 1 \quad \text{// scalar for koff}\]
\[MF_{\text{Rmax}} = 1 \quad \text{// scalar for Rmax}\]

// GENO effect on CL
\[CL_{\text{GENO2}} = 0.885\]
\[CL_{\text{GENO3}} = 0.607\]
\[CL_{\text{GENO4}} = 0.277\]
\[CL_{\text{GENO5}} = 0.215\]

// GENO on kon and Rmax
\[kon_{\text{GENO4}} = 0.837\]
\[kon_{\text{GENO5}} = 0.518\]
\[Rmax_{\text{GENO4}} = 2.51\]
\[Rmax_{\text{GENO5}} = 1.89\]

// fluconzole empirical model
// A one-compartment model with lagged first-order input and first-order elimination
// Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2561119/
\[tv_{\text{cl-fluc}} = 1.18 \quad \text{// fluconzole clearance L/hr}\]
\[tv_{\text{v-fluc}} = 55.7 \quad \text{// fluconzole volume of distribution L}\]
\[tv_{\text{ka-fluc}} = 3.38 \quad \text{// fluconzole absorption rate constant /hr}\]

// fluc inhibition parameters (\(k_i\): concentration of fluconazole that supports half maximal 2c9 inhibition)
// check calculation: https://www.graphpad.com/quickcalcs/Molarityform.cfm
// fluconazole mw: 306.271 g/mol
// fluconazole is a strong inhibitor for 2C19, but moderate for 2C9 and 3A4

\[tv_{\text{ki-4oh}} = 8.88 \quad \text{// mg/L 29uM assumed to be eliminated by a mix effect of 2C9, 2C19 and 3A4 (}{(Ki_{2C9} + Ki_{2C19} + Ki_{3A4})/3}{)}\]
\[tv_{\text{ki-6oh}} = 6.74 \quad \text{// mg/L 22uM assumed to be eliminated through 2C9}\]
\[tv_{\text{ki-7oh}} = 6.74 \quad \text{// mg/L 22uM assumed to be eliminated through 2C9}\]
\[tv_{\text{ki-8oh}} = 0.64 \quad \text{// mg/L 2.1uM assumed to be eliminated through 2C19}\]
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195022/parity:~:text=The%20inhibition%20constant%20(Ki,was%2020.1%20%CE%BCM%20(31) 2.1uM)
\[tv_{\text{ki-10oh}} = 19.30 \quad \text{// mg/L 63uM assumed to be eliminated through 3A4}\]

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195022/parity:~:text=The%20inhibition%20constant%20(Ki,was%2020.1%20%CE%BCM%20(31) range 1.9 -63uM)
[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other
tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2

flucdepot //fluconazole depot compartment
fluccent //fluconazole central compartment

[MAIN]
//allometric scaling of volume
double Vbr = TVVbr*pow(weight/70, 1); //brain
double Vgu = TVVgu*pow(weight/70, 1); //Gut
double Vsp = TVVsp*pow(weight/70, 1); //spleen
double Vpa = TVVpa*pow(weight/70, 1); //pancreas
double Vst = TVVst*pow(weight/70, 1); //stomach
double Vli = TVVli*pow(weight/70, 1); //liver
double Vki = TVVki*pow(weight/70, 1); //kidneys
double Vhe = TVVhe*pow(weight/70, 1); //heart
double Vlu = TVVlu*pow(weight/70, 1); //lungs
double Vmu = TVVmum*pow(weight/70, 1); //muscle
double Vad = TVVad*pow(weight/70, 1); //adipose
double Vsk = TVVsk*pow(weight/70, 1); //skin
double Vbo = TVVbo*pow(weight/70, 1); //bone
double Vth = TVVth*pow(weight/70, 1); //thymus
double Vab = TVVab*pow(weight/70, 1); //arterial blood
double Vvb = TVVvb*pow(weight/70, 1); //venous blood

//allometric scaling of flow
double Qbr = TVQbr*pow(weight/70, 0.75); //brain
double Qha = TVQha*pow(weight/70, 0.75); //hepatic artery
double Qgu = TVQgu*pow(weight/70, 0.75); //gut
double Qsp = TVQsp*pow(weight/70, 0.75); //spleen
double Qpa = TVQpa*pow(weight/70, 0.75); //pancreas
double Qst = TVQst*pow(weight/70, 0.75); //stomach
double Qli = TVQli*pow(weight/70, 0.75); //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
double Qki = TVQki*pow(weight/70, 0.75); //kidney
double Qhe = TVQhe*pow(weight/70, 0.75); //heart
double Qlu = TVQlu*pow(weight/70, 0.75); //lung
double Qmu = TVQmu*pow(weight/70, 0.75); //muscle
double Qad = TVQad*pow(weight/70, 0.75); //adipose
double Qsk = TVQsk*pow(weight/70, 0.75); //skin
double Qbo = TVQbo*pow(weight/70, 0.75); //bone
double Qth = TVQth*pow(weight/70, 0.75); //thymus
double Kpbr  = TVKpbr*MFkp*exp(ETA(1))   ;  //brain:plasma
double Kpgu  = TVKpgu*MFkp*exp(ETA(2))   ;  //gut:plasma
double Kpsp  = TVKpsp*MFkp*exp(ETA(3))   ;  //spleen:plasma
double Kppa  = TVKppa*MFkp*exp(ETA(4))   ;  //pancreas:plasma
double Kpst  = TVKpst*MFkp*exp(ETA(5))   ;  //stomach:plasma
double Kppli = TVKppli*MFkp*exp(ETA(6))  ;  //liver:plasma
double Kpki  = TVKpki*MFkp*exp(ETA(7))   ;  //kidney:plasma
double Kphe  = TVKphe*MFkp*exp(ETA(8))   ;  //heart:plasma
double Kpplu = TVKpplu*MFkp*exp(ETA(9))  ;  //lungs:plasma
double Kpmu  = TVKpmu*MFkp*exp(ETA(10))  ;  //muscle:plasma
double Kpad  = TVKpad*MFkp*exp(ETA(11))  ;  //adipose:plasma
double Kpsk  = TVKpsk*MFkp*exp(ETA(12))  ;  //skin:plasma
double Kpbo  = TVKpbo*MFkp*exp(ETA(13))  ;  //bone:plasma
double Kpth  = TVKpth*MFkp*exp(ETA(14))  ;  //thymus:plasma

//allometric scaling of clearance (hepatic and renal)
double CL_GENO = 1;
    if (GENO==2)  CL_GENO = CL_GENO2;
    if (GENO==3)  CL_GENO = CL_GENO3;
    if (GENO==4)  CL_GENO = CL_GENO4;
    if (GENO==5)  CL_GENO = CL_GENO5;

double CL     = TVCL   *CL_GENO*exp(ETA(15))*pow(weight/70, 0.75) ;  //total in vivo clearance
    double CL_Ki  = TVCL_Ki *exp(ETA(16))*pow(weight/70, 0.75) ;  //renal clearance

    //Clint (liver intrinsic clearance: back calculated from liver clearance: CL-CL_Ki)
    //reference: Ali A. Alhadab et.al., CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 1 | July 2020
    double Clint   = Qli*(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP));

    //Clint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
    double Clint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

    //TMDD param
    double kon     = TVkon*MFkon*exp(ETA(17));
        if (GENO == 4) kon = TVkon*MFkon*kon_GENO4*exp(ETA(17));
        if (GENO == 5) kon = TVkon*MFkon*kon_GENO5*exp(ETA(17));
    double koff    = TVkoff*MFkoff;

double Rmax     = TVRmax*MFRmax*exp(ETA(18));
        if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));

//other parameters
double ka   = TVka*MFka*exp(ETA(19));
double BP   = TVBP*MFBP;
double fup  = TVfup*MFfup;

//receptor(R) baseline
R_0 = Rmax;

//fluconazole
ALAG_flucdepot = 0.23 ; //absorption lag time h
double cl_fluc  = tvcl_fluc*exp(ETA(20)) ; //clearance L/hr
double v_fluc   = tvv_fluc *exp(ETA(21)) ; //volume of distribution L
double ka_fluc  = tvka_fluc*exp(ETA(22)) ; //absorption rate constant /hr

//fluconazole inhibitory effects
double ki_4oh   = tvki_4oh ;
double ki_6oh   = tvki_6oh ;
double ki_7oh   = tvki_7oh ;
double ki_8oh   = tvki_8oh ;
double ki_10oh  = tvki_10oh ;

//parse intrinsic clearance (Clint)
//based on figure 5 of warfarin metabolite manuscript (unpublish till 3/23/2021)
  //6-S, 7-S assumed to be eliminated through 2C9
  //4-S is assumed to be eliminated by a mix effect of 2C9, 3A4 and 2C19
  //8-S is assumed to be eliminated through 2C19
  //10-S assumed to be eliminated through 3A4

double Clint_4oh  = (1.5  / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * Clint;
  if (GENO == 2) Clint_4oh  = (1.7  / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * Clint;
  if (GENO == 3) Clint_4oh  = (2.5  / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * Clint;
  if (GENO == 4) Clint_4oh  = (5.5  / (5.5 + 9.3  + 36.1 + 1.0 + 0.8)) * Clint;
  if (GENO == 5) Clint_4oh  = (7.1  / (7.1 + 5.2  + 10.7 + 1.2 + 1.0)) * Clint;

double Clint_6oh  = (10.5 / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * Clint;
  if (GENO == 2) Clint_6oh  = (10.0 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * Clint;
  if (GENO == 3) Clint_6oh  = (10.7 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * Clint;
  if (GENO == 4) Clint_6oh  = (9.3  / (5.5 + 9.3  + 36.1 + 1.0 + 0.8)) * Clint;
  if (GENO == 5) Clint_6oh  = (5.2  / (7.1 + 5.2  + 10.7 + 1.2 + 1.0)) * Clint;
double CLint_7oh = (40.0 / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * CLint;
    if (GENO == 2) CLint_7oh = (46.5 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
    if (GENO == 3) CLint_7oh = (38.6 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
    if (GENO == 4) CLint_7oh = (36.1 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
    if (GENO == 5) CLint_7oh = (10.7 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

double CLint_8oh = (0.8 / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * CLint;
    if (GENO == 2) CLint_8oh = (0.7 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
    if (GENO == 3) CLint_8oh = (0.9 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
    if (GENO == 4) CLint_8oh = (1.0 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
    if (GENO == 5) CLint_8oh = (1.2 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

double CLint_10oh = (0.3 / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * CLint;
    if (GENO == 2) CLint_10oh = (0.4 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
    if (GENO == 3) CLint_10oh = (0.5 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
    if (GENO == 4) CLint_10oh = (0.8 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
    if (GENO == 5) CLint_10oh = (1.0 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

[ODE]
    // Calculation of tissue drug concentrations (ug/L)
    double Cbrain     = BRAIN/Vbr   ;
    double Cgut       = GUT/Vgu     ;
    double Cspleen    = SPLEEN/Vsp  ;
    double Cpancreas  = PANCREAS/Vpa;
    double Cstomach   = STOMACH/Vst ;
    double Cliver     = LIVER/Vli   ;
    double Ckidney    = KIDNEY/Vki  ;
    double Cheart     = HEART/Vhe   ;
    double Clung      = LUNG/Vlu    ;
    double Cmuscle    = MUSCLE/Vmu  ;
    double Cadipose   = ADIPOSE/Vad ;
    double Cskin      = SKIN/Vsk    ;
    double Cbone      = BONE/Vbo    ;
    double Cthymus    = THYMUS/Vth  ;
    double Carterial  = ART/Vab     ;
    double Cvenous    = VEN/Vvb     ;

    // fluc inhibitory effect on CLint
/\text{Clint,} i = \text{Clint} / (1 + [I] / k_i) \\
\text{equation reference: https://pubmed.ncbi.nlm.nih.gov/16984215/ equation(1)} \\
\text{equation reference: https://pubmed.ncbi.nlm.nih.gov/18378563/ equation(2)} \\
\text{double cp_fluc = flucents/v_fluc; //flucosazole central compartment concentration}

double Clint_4oh_inh = Clint_4oh / (1 + cp_fluc / ki_4oh ); \\
double Clint_6oh_inh = Clint_6oh / (1 + cp_fluc / ki_6oh ); \\
double Clint_7oh_inh = Clint_7oh / (1 + cp_fluc / ki_7oh ); \\
double Clint_8oh_inh = Clint_8oh / (1 + cp_fluc / ki_8oh ); \\
double Clint_10oh_inh = Clint_10oh / (1 + cp_fluc / ki_10oh );

double Clint_inh = Clint_4oh_inh + Clint_6oh_inh + Clint_7oh_inh + Clint_8oh_inh + Clint_10oh_inh;

//ODEs  
\text{dxdt\_GUTLUMEN} = - ka\*GUTLUMEN \quad ;/(1) \text{ absorption}  
\text{dxdt\_BRAIN} = Qbr\*(\text{Carterial} - \text{Cbrain}/(Kpbr/BP)) \quad ;/(2)  
\text{dxdt\_GUT} = ka\*GUTLUMEN  
+ Qgu\*(\text{Carterial} - \text{Cgut}/(Kpgu/BP)) \quad ;/(3) \text{ to liver}  
\text{dxdt\_SPLEEN} = Qsp\*(\text{Carterial} - \text{Cspleen}/(Kpsp/BP)) \quad ;/(4) \text{ to liver}  
\text{dxdt\_PANCREAS} = Qpa\*(\text{Carterial} - \text{Cpancreas}/(Kppa/BP)) \quad ;/(5) \text{ to liver}  
\text{dxdt\_STOMACH} = Qst\*(\text{Carterial} - \text{Cstomach}/(Kpst/BP)) \quad ;/(6) \text{ to liver}  
\text{dxdt\_LIVER} = Qgu\*(\text{Cgut}/(Kpgu/BP)) \quad \text{ from gut}  
+ Qsp\*(\text{Cspleen}/(Kpsp/BP)) \quad \text{ from spleen}  
+ Qpa\*(\text{Cpancreas}/(Kppa/BP)) \quad \text{ from pancreas}  
+ Qst\*(\text{Cstomach}/(Kpst/BP)) \quad \text{ from stomach}  
+ Qha\*(\text{Carterial}) \quad \text{ from hepatic arterial}  
- Qli\*(\text{Cliver}/(Kpli/BP))  
- \text{Clint\_inh}\*(\text{Cliver}\_fup/Kpli) \quad ;/(7)  
\text{dxdt\_KIDNEY} = Qki\*(\text{Carterial} - \text{Ckidney}/(Kpki/BP)) \quad ;/(8)  
\text{dxdt\_HEART} = Qhe\*(\text{Carterial} - \text{Cheart}/(Kphe/BP)) \quad ;/(9)  
\text{dxdt\_LUNG} = Qlu\*(\text{Cvenous} - \text{Clung}/(Kpul/BP)) \quad ;/(10)  
\text{dxdt\_MUSCLE} = Qmu\*(\text{Carterial} - \text{Cmuscle}/(Kpmu/BP)) \quad ;/(11)  
\text{dxdt\_ADIPPOSE} = Qad\*(\text{Carterial} - \text{Cadipose}/(Kpad/BP)) \quad ;/(12)  
\text{dxdt\_SKIN} = Qsk\*(\text{Carterial} - \text{Cskin}/(Kpsk/BP)) \quad ;/(13) 
\text{dxdt\_BONE} = Qbo\*(\text{Carterial} - \text{Cbone}/(Kpbo/BP)) \quad ;/(14) 
\text{dxdt\_THYMUS} = Qth\*(\text{Carterial} - \text{Cthymus}/(Kpth/BP)) \quad ;/(15)  
\text{dxdt\_VEN} = Qbr\*(\text{Cbrain}/(Kpbr/BP)) \quad \text{ from brain}  
+ Qli\*(\text{Cliver}/(Kpli/BP)) \quad \text{ from liver}  
+ Qki\*(\text{Ckidney}/(Kpki/BP)) \quad \text{ from kidney}  
+ Qhe\*(\text{Cheart}/(Kphe/BP)) \quad \text{ from heart}
+ Qmu*(Cmuscle/(Kpmu/BP))                 //from muscle
+ Qad*(Cadipose/(Kpad/BP))               //from adipose
+ Qsk*(Cskin/(Kpsk/BP))                  //from skin
+ Qbo*(Cbone/(Kpbo/BP))                 //from bone
+ Qth*(Cthymus/(Kpth/BP))               //from thymus
- Qlu*Cvenous
- kon*(Cvenous/BP)*R
+ koff*DR ;///(16)

dxdt_ART = Qlu*(Clung/(Kplu/BP) - Carterial) ;///(17)

dxdt_R = - kon*(Cvenous/BP)*R + koff*DR ;///(18)
dxdt_DR = kon*(Cvenous/BP)*R - koff*DR ;///(19)

dxdt_flucdepot = - ka_fluc*flucdepot ;///(20) fluc depot compartment (mass)
dxdt_fluccent = ka_fluc*flucdepot - cl_fluc*cp_fluc ;///(21) fluc central compartment (mass)

[OMEGA]
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 ///Kps
0.09 ///CL
0.09 ///CL_Ki
0.09 ///kon
0.09 ///Rmax
0.09 ///Ka

0.0481 ///cl_fluc
0.0298 ///v_fluc
1.426 ///ka_fluc

[TABLE]
capture CP = Cvenous/BP;
capture GENO = GENO;
capture WEIGHT = weight;
capture CP_FLUC = cp_fluc;
capture CLINT = CLint_inh;
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various \textit{CYP2C9} genotypes under different co-treatments

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S-warfarin PBPK model with rifampin induction mrgsolve model file

Shen Cheng
2021-09-13

[set] delta = 0.1 ,end = 720 //720 hours/30 Days

[PARAM]
//Tissue volumes (L); for 70kg human
TVVbr = 1450/1000  //brain mL to L
TVGgu = 1650/1000  //Gut
TVVsp = 192/1000   //spleen
TVVpa = 77/1000    //pancreas
TVVst = 154/1000   //stomach (not in simcyp)
TVVli = 1690/1000  //liver
TVVki = 280/1000   //kidneys
TVVhe = 310/1000   //heart
TVVlu = 1172/1000  //lungs
TVVMu = 35000/1000 //muscle
TVVad = 10000/1000 //adipose
TVVs = 7800/1000   //skin
TVVBo = 4579/1000  //bone
TVVth = 29/1000    //thymus (not in simcyp)

TVVab = 1698/1000  //arterial blood
TVVvb = 3396/1000  //venous blood

//Tissue blood flows (L/h); for 70kg human
TVQbr = (700*60)/1000  //brain mL/min to L/hr
TVQha = (302*60)/1000  //hepatic artery
TVQgu = (1100*60)/1000 //gut
TVQsp = (77*60)/1000   //spleen
TVQpa = (133*60)/1000  //pancreas
TVQst = (38*60)/1000   //stomach
TVQli = (1650*60)/1000 //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 //kidney
TVQhe = (150*60)/1000  //heart
TVQlu = (5240*60)/1000 //lung,
//should be same as cardiac output(adjusted to 5240, 5233 original)
//to match the total Q
TVQmu = (750*60)/1000 //muscle
TVQad = (260*60)/1000 //adipose
TVQsk = (300*60)/1000 //skin
TVQbo = (250*60)/1000 //bone
\[ TVQ_{th} = \frac{(80 \times 60)}{1000} \quad \text{\(\text{thymus}\)}\]


\[ TVK_{pbr} = 0.0523693 \quad \text{\(\text{brain:plasma}\)}\]
\[ TVK_{pgu} = 0.1618 \quad \text{\(\text{gut:plasma}\)}\]
\[ TVK_{psp} = 0.100666 \quad \text{\(\text{spleen:plasma}\)}\]
\[ TVK_{ppa} = 0.0639167 \quad \text{\(\text{pancreas:plasma}\)}\]
\[ TVK_{pst} = 0.1271972 \quad \text{\(\text{stomach:plasma (not in simcyp) calculated as average of non adipose Kps}\)}\]
\[ TVK_{pli} = 0.089772 \quad \text{\(\text{liver:plasma}\)}\]
\[ TVK_{pki} = 0.133745 \quad \text{\(\text{kidney:plasma}\)}\]
\[ TVK_{phe} = 0.160367 \quad \text{\(\text{heart:plasma}\)}\]
\[ TVK_{plu} = 0.215004 \quad \text{\(\text{lungs:plasma}\)}\]
\[ TVK_{pmu} = 0.037509 \quad \text{\(\text{muscle:plasma}\)}\]
\[ TVK_{pad} = 0.0396971 \quad \text{\(\text{adipose:plasma}\)}\]
\[ TVK_{psk} = 0.281144 \quad \text{\(\text{skin:plasma}\)}\]
\[ TVK_{pbo} = 0.102876 \quad \text{\(\text{bone:plasma}\)}\]
\[ TVK_{pth} = 0.1271972 \quad \text{\(\text{thymus:plasma (not in simcyp) calculated as average of non adipose Kps}\)}\]

//in vivo clearance
\[ TVCL = 0.26 \quad \text{\(\text{(L/hr) in vivo clearance (unpublished warfarin manuscript, simcyp sim-warfarin)}\)}\]

//renal clearance
\[ TVCL_{Ki} = 0.00369 \times 1.3 \quad \text{\(\text{(L/hr) renal clearance (unpublished warfarin manuscript)}\)}\]
\[ \text{//1.3: rifampin effect on S-warfarin renal clearance(unpublished manuscript)}\]

//TMDD param (unpublished warfarin manuscript)
\[ TVkon = 0.00494 \quad \text{\(\text{L/(µg*hour)}\)}\]
\[ TVkoff = 0.0405 \quad \text{\(\text{/hour)}\}\]
\[ TVRmax = 182 \quad \text{\(\text{ug/L)}\}\]

//other parameters
\[ TVka = 1.85 \quad \text{\(\text{absorption rate constant (/hr) assumed (simcyp sim-warfarin)}\)}\]
\[ TVBP = 0.59 \quad \text{\(\text{blood:plasma ratio (simcyp sim-warfarin)}\)}\]
\[ TVfup = 0.009 \quad \text{\(\text{fraction of unbound drug in plasma (simcyp sim-warfarin)}\)}\]

//scalars
\[ GENO = 1 \quad \text{\(\text{1:*1*/1; 2:*1B*/1B; 3:*1*/3; 4: *2*/3; 5: *3*/3)}\]
\[ \text{weight} = 68.7 \quad \text{\(\text{(kg)}\)}\]
\[ MFka = 1 \quad \text{\(\text{scalar for Ka)}\}\]
\[ MFkp = 1 \quad \text{\(\text{scalar for Kps)}\}\]
\[ MFBP = 1 \quad \text{\(\text{scalar for BP)}\}\]
MFfup = 1  // scalar for fup
MFkon = 1  // scalar for kon
MFkoff = 1  // scalar for koff
MFRmax = 1  // scalar for Rmax

// GENO effect on CL
CL_GENO2 = 0.885
CL_GENO3 = 0.607
CL_GENO4 = 0.277
CL_GENO5 = 0.215

// GENO on kon and Rmax
kon_GENO4 = 0.837
kon_GENO5 = 0.518
Rmax_GENO4 = 2.51
Rmax_GENO5 = 1.89

// rifampin empirical model
// A one-compartment model with M-M elimination and transit compartments
// enzyme turnover model accounting for autoinduction
// dose dependent bioavailability (Emax equation)
tvvm_rifa = 525  // mg/h/70kg  maximal elimination rate
vk_rifa = 35.3  // mg/L   rifampicin concentration at which the elimination is half-maximal
tv_rifa = 87.2  // L/70kg   volume of distribution
tvka_rifa = 1.77  // /hr  absorption rate constant
tvmtt_rifa = 0.513  // hr   mean transit time
tvnn_rifa = 23.8  // number of transit compartments
tvemax_rifa = 1.16  // maximal increase in enzyme production rate
tvec50_rifa = 0.0699  // mg/L  rifampicin concentration at which half the emax is reached
tvkenz_rifa = 0.00603  // /hr  first-order rate constant for enzyme pool degradation
tvemax_rifa = 0.504  // maximal increase in relative bioavailability above 450mg
tvfed50_rifa = 67.0  // mg  difference in rifampicin dose from 450mg at which half the fmax is reached

ffm = 45  // kg  fat free mass
occ = 1  // occasion

// rifampin inducing parameters
// indmax: maximal induction fold over vehicle
// indc50: inducer concentration that supports half-maximal induction (µM)
// check calculation: https://www.graphpad.com/quickcalcs/Molarityform.cfm
// rifampin mw: 822.94 g/mol

tvindmax_4oh = 7.4 //fold increase, assumed to be eliminated by a mix effect of 2C9, 2C19 and 3A4 ((3.6 + 5.5 + 16)/3 = 8.4)
tvindmax_6oh = 2.6 //fold increase, assumed to be eliminated through 2C9 (3.6, https://www.certara.com/app/uploads/2017/10/Machavaram_2017_ISSX_CYP2C9.pdf)
tvindmax_7oh = 2.6 //fold increase, assumed to be eliminated through 2C9 (3.6, https://www.certara.com/app/uploads/2017/10/Machavaram_2017_ISSX_CYP2C9.pdf)
tvindmax_8oh = 4.5 //fold increase, assumed to be eliminated through 2C9 (5.5, table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)
tvindmax_10oh = 15 //fold increase, assumed to be eliminated through 3A4 (16, table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)

tvindc50_4oh = 0.239 //mg/L 0.29 uM assumed to be eliminated by a mix effect of 2C9, 2C19 and 3A4 ((0.1 + 0.45 + 0.32)/3)
tvindc50_6oh = 1.234 //mg/L 1.5 uM assumed to be eliminated through 2C9 (https://www.certara.com/app/uploads/2017/10/Machavaram_2017_ISSX_CYP2C9.pdf)
tvindc50_7oh = 1.234 //mg/L 1.5 uM assumed to be eliminated through 2C9 (https://www.certara.com/app/uploads/2017/10/Machavaram_2017_ISSX_CYP2C9.pdf)
tvindc50_8oh = 0.370 //mg/L 0.45 uM assumed to be eliminated through 2C19 (table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)
tvindc50_10oh = 0.263 //mg/L 0.32 uM assumed to be eliminated through 3A4 (table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)

[global ]
int ndose = 0;
double dosetime[300];
double dose[300];

[PREAMBLE]
double last_dose = 0;

[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other

tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2

rifadepot //rifampin depot compartment
rifacent //rifampin central compartment
rifaenz //rifampin enzyme compartment

[MAIN]
// allometric scaling of volume
double Vbr = TVVbr*pow(weight/70, 1); // brain
double Vgu = TVVgu*pow(weight/70, 1); // Gut
double Vsp = TVVsp*pow(weight/70, 1); // spleen
double Vpa = TVVpa*pow(weight/70, 1); // pancreas
double Vst = TVVst*pow(weight/70, 1); // stomach
double Vli = TVVli*pow(weight/70, 1); // liver
double Vki = TVVki*pow(weight/70, 1); // kidneys
double Vhe = TVVhe*pow(weight/70, 1); // heart
double Vlu = TVVlu*pow(weight/70, 1); // lungs
double Vmu = TVVmu*pow(weight/70, 1); // muscle
double Vad = TVVad*pow(weight/70, 1); // adipose
double Vsk = TVVsk*pow(weight/70, 1); // skin
double Vbo = TVVbo*pow(weight/70, 1); // bone
double Vth = TVVth*pow(weight/70, 1); // thymus

double Vab = TVVab*pow(weight/70, 1); // arterial blood
double Vvb = TVVvb*pow(weight/70, 1); // venous blood

// allometric scaling of flow
double Qbr = TVQbr*pow(weight/70, 0.75); // brain
double Qha = TVQha*pow(weight/70, 0.75); // hepatic artery
double Qgu = TVQgu*pow(weight/70, 0.75); // gut
double Qsp = TVQsp*pow(weight/70, 0.75); // spleen
double Qpa = TVQpa*pow(weight/70, 0.75); // pancreas
double Qst = TVQst*pow(weight/70, 0.75); // stomach
double Qli = TVQli*pow(weight/70, 0.75); // liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)

double Qki = TVQki*pow(weight/70, 0.75); // kidney
double Qhe = TVQhe*pow(weight/70, 0.75); // heart
double Qlu = TVQlu*pow(weight/70, 0.75); // lung
double Qmu = TVQmu*pow(weight/70, 0.75); // muscle
double Qad = TVQad*pow(weight/70, 0.75); // adipose
double Qsk = TVQsk*pow(weight/70, 0.75); // skin
double Qbo = TVQbo*pow(weight/70, 0.75); // bone
double Qth = TVQth*pow(weight/70, 0.75); // thymus

// scaled Kps
double Kpbr = TVKpbr*MFkp*exp(ETA(1)); // brain:plasma
double Kpgu = TVKpgu*MFkp*exp(ETA(2)); // gut:plasma
double Kpap = TVKpsp*MFkp*exp(ETA(3)); // spleen:plasma
double Kppa = TVKpap*MFkp*exp(ETA(4)); // pancreas:plasma
double Kpst = TVKpap*MFkp*exp(ETA(5)); // stomach:plasma
double Kpil = TVKpil*MFkp*exp(ETA(6)); // liver:plasma
double Kpki = TVKpki*MFkp*exp(ETA(7)); // kidney:plasma
double Kphe = TVKphe*MFkp*exp(ETA(8)); // heart:plasma
double Kplu = TVKplu*MFkp*exp(ETA(9)); // lungs:plasma
double Kpmu = TVKpmu*MFkp*exp(ETA(10)); // muscle:plasma
double Kpad = TVKpad*MFkp*exp(ETA(11)); // adipose:plasma
double Kpsk = TVKpsk*MFkp*exp(ETA(12)); // skin:plasma
double Kpbo = TVKpbo*MFkp*exp(ETA(13)); //bone:plasma
double Kpth = TVKpth*MFkp*exp(ETA(14)); //thymus:plasma

// allometric scaling of clearance (hepatic and renal)
double CL_GENO = 1;
if (GENO==2) CL_GENO = CL_GENO2;
if (GENO==3) CL_GENO = CL_GENO3;
if (GENO==4) CL_GENO = CL_GENO4;
if (GENO==5) CL_GENO = CL_GENO5;

double CL = TVCL *CL_GENO*exp(ETA(15))*pow(weight/70, 0.75) ;
// total in vivo clearance
double CL_Ki = TVCL_Ki *exp(ETA(16))*pow(weight/70, 0.75) ;
// renal clearance

// CLint (liver intrinsic clearance: back calculated from liver clearance: CL-CL_Ki)
// reference: Ali A. Alhadab et.al., CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 1 | July 2020
double CLint = Qli*(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP));

// CLint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
double CLint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

// TMDD param
double kon = TVkon*MFkon*exp(ETA(17));
if (GENO == 4) kon = TVkon*MFkon*kon_GENO4*exp(ETA(17));
if (GENO == 5) kon = TVkon*MFkon*kon_GENO5*exp(ETA(17));

double koff = TVkoff*MFkoff;

double Rmax = TVRmax*MFRmax*exp(ETA(18));
if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));

// other parameters
double ka = TVka*MFka*exp(ETA(19));
double BP = TVBP*MFBP;
double fup = TVfup*MFfup;

// receptor(R) baseline
R_0 = Rmax;

// rifampin empirical pk model start----------------------------------------
// rifampin empirical pk model parameters
double vmax_rifa = tvvmax_rifa * exp(ETA(20));  //maximal elimination rate L/hr
double km_rifa = tvkm_rifa * exp(ETA(21)) * exp(iovkm_rifa);  //rifampicin concentration at which the elimination is half-maximal
double v_rifa = tvv_rifa *(ffm / 70) * exp(ETA(22)) * exp(iovv_rifa);  //volume of distribution L
double ka_rifa = tvka_rifa * exp(ETA(23)) * exp(iovka_rifa);  //absorption rate constant /hr
double ec50_rifa = tvec50_rifa;  //rifampicin concentration at which half the emax is reached
double emax_rifa = tvemax_rifa;  //maximal increase in enzyme production rate
double kenz_rifa = tvkenz_rifa;  //first-order rate constant for enzyme pool degradation
double femax_rifa = tvfemax_rifa;  //maximal increase in relative bioavailability above 450mg
double fed50_rifa = tvfed50_rifa;  //difference in rifampicin dose from 450mg at which half the fmax is reached
double mtt_rifa = tvmtt_rifa * exp(ETA(24));  //mean transit time hr
double nn_rifa = tvnn_rifa * exp(ETA(25));  //number of transit compartments

//calculate dose*****
if(EVID == 1 && self.cmt == 20){
  last_dose = self.amt; //reference: https://mrgsolve.github.io/user_guide/model-specification.html#self.amt
}

double f450 = 1;  //assuming bioavailability for 450mg dose is 1
double f_rifa = f450*(1 + femax_rifa*(last_dose-450) / (fed50_rifa + (last_dose - 450))) * exp(iovf_rifa);  //Emax on bioavailability

declare ktr
double ktr_rifa = (nn_rifa + 1) / mtt_rifa;  //rate constant for transit compartments

//logarithm of the approximation to the gamma function
double l = 0.9189385 + (nn_rifa + 0.5) * log(nn_rifa) - nn_rifa + log(1 + 1/(12 * nn_rifa));  //logarithm of gamma_n
double lbpd = log(f_rifa * last_dose);  //logarithm of f*dose
double lktr = log(ktr_rifa);  //logarithm of ktr
double cumul = lbpd + lktr - 1;  //logarithm of f*dose*ktr/gamma_n
//interoccasion vaibility(IOV)

double iovkm_rifa = ETA(26);
if (occ != 1) iovkm_rifa = ETA(27);

double iovv_rifa = ETA(28);
if (occ != 1) iovv_rifa = ETA(29);

double iovka_rifa = ETA(30);
if (occ != 1) iovka_rifa = ETA(31);

double iovf_rifa = ETA(32);
if (occ != 1) iovf_rifa = ETA(33);

//Initialize compartments
F_rifadepot = 0 ; //transit absorption compartment
rifacent_0 = 0.0001 ; //central compartment
rifaenz_0 = 1 ; //enzyme compartment

//compute ndose (the index of dose)
//dosetime: time after dose
//dose: dosage

if(NEWIND < 2) ndose = 0; //index of dose

if(self.amt > 0 && self.cmt == 20) {
    ndose = ndose + 1;
    dosetime[ndose] = self.time;
}

//rifampin empirical pk model end------------------------------------------

//rifampin inducing effects
double indmax_4oh = tvindmax_4oh ;
double indmax_6oh = tvindmax_6oh ;
double indmax_7oh = tvindmax_7oh ;
double indmax_8oh = tvindmax_8oh ;
double indmax_10oh = tvindmax_10oh ;

double indc50_4oh = tvindc50_4oh ;
double indc50_6oh = tvindc50_6oh ;
double indc50_7oh = tvindc50_7oh ;
double indc50_8oh = tvindc50_8oh ;
double indc50_10oh = tvindc50_10oh ;

//parse intrinsic clearance (Clint)
//based on figure 5 of warfarin metabolite manuscript (unpublish till 3/23/2021)
//6-S, 7-S assumed to be eliminated through 2C9
//4S is assumed to be eliminated by a mix effect of 2C9, 3A4 and 2C19
//8-S is assumed to be eliminated through 2C19
//10-S assumed to be eliminated through 3A4

double CLint_4oh = (1.5 / (1.5 + 10.5 + 40.0 + 0.8 + 0.3)) * CLint;
if (GENO == 2) CLint_4oh = (1.7 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
if (GENO == 3) CLint_4oh = (2.5 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
if (GENO == 4) CLint_4oh = (5.5 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
if (GENO == 5) CLint_4oh = (7.1 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

if (GENO == 2) CLint_6oh = (10.0 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
if (GENO == 3) CLint_6oh = (10.7 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
if (GENO == 4) CLint_6oh = (9.3 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
if (GENO == 5) CLint_6oh = (5.2 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

if (GENO == 2) CLint_7oh = (46.5 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
if (GENO == 3) CLint_7oh = (38.6 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
if (GENO == 4) CLint_7oh = (36.1 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
if (GENO == 5) CLint_7oh = (10.7 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

if (GENO == 2) CLint_8oh = (0.7 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
if (GENO == 3) CLint_8oh = (0.9 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
if (GENO == 4) CLint_8oh = (1.0 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
if (GENO == 5) CLint_8oh = (1.2 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

if (GENO == 2) CLint_10oh = (0.4 / (1.7 + 10.0 + 46.5 + 0.7 + 0.4)) * CLint;
if (GENO == 3) CLint_10oh = (0.5 / (2.5 + 10.7 + 38.6 + 0.9 + 0.5)) * CLint;
if (GENO == 4) CLint_10oh = (0.8 / (5.5 + 9.3 + 36.1 + 1.0 + 0.8)) * CLint;
if (GENO == 5) CLint_10oh = (1.0 / (7.1 + 5.2 + 10.7 + 1.2 + 1.0)) * CLint;

[ODE]
// Calculation of tissue drug concentrations (ug/L)
double Cbrain = BRAIN/Vbr ;
double Cgut = GUT/Vgu ;
double Cspleen = SPLEEN/Vsp ;
double Cpancreas = PANCREAS/Vpa;
double Cstomach = STOMACH/Vst ;
double Cliver = LIVER/Vli ;
double Ckidney = KIDNEY/Vki ;
double Cheart = HEART/Vhe ;
double Clung = LUNG/Vlu ;
double Cmuscle = MUSCLE/Vmu ;
double Cadipose = ADIPOSE/Vad ;
double Cskin = SKIN/Vsk ;
double Cbone = BONE/Vbo ;
double Cthymus = THYMUS/Vth ;
double Carterial = ART/Vab ;
double Cvenous = VEN/Vvb ;

// rifampin inducing effect on CLint
// CLint,i = CLint*(1 + (indmax*cp_rifa)/(indc50 + cp_rifa))
double cp_rifa = rifacent/v_rifa               ; // central compartment concentration mg/L
  double cl_rifa = vmax_rifa/(km_rifa + cp_rifa) ; // nonlinear clearance L/hr
  double k_rifa = cl_rifa/v_rifa                ; // elimination rate constant mg/hr
  double CLint_4oh_ind = CLint_4oh * (1 + (indmax_4oh*cp_rifa) / (indc50_4oh + cp_rifa));
  double CLint_6oh_ind = CLint_6oh * (1 + (indmax_6oh*cp_rifa) / (indc50_6oh + cp_rifa));
  double CLint_7oh_ind = CLint_7oh * (1 + (indmax_7oh*cp_rifa) / (indc50_7oh + cp_rifa));
  double CLint_8oh_ind = CLint_8oh * (1 + (indmax_8oh*cp_rifa) / (indc50_8oh + cp_rifa));
  double CLint_10oh_ind = CLint_10oh * (1 + (indmax_10oh*cp_rifa) / (indc50_10oh + cp_rifa));
  double CLint_ind = CLint_4oh_ind + CLint_6oh_ind + CLint_7oh_ind + CLint_8oh_ind + CLint_10oh_ind;

//ODEs
dxdt_GUTLUMEN = - ka*GUTLUMEN ;//(1) absorption
\[ \text{dxdt\_BRAIN} = Qbr*(\text{Carterial} - \text{C\text{brain}}/(Kpbr/BP)) \quad // (2) \]

\[ \text{dxdt\_GUT} = ka*\text{GUTLUMEN} \]
\[ + Qgu*(\text{Carterial} - \text{C\text{gut}}/(Kpgu/BP)) \quad // (3) \text{ to liver} \]

\[ \text{dxdt\_SPLEEN} = Qsp*(\text{Carterial} - \text{C\text{spleen}}/(Kpsp/BP)) \quad // (4) \text{ to liver} \]

\[ \text{dxdt\_PANCREAS} = Qpa*(\text{Carterial} - \text{C\text{pancreas}}/(Kppa/BP)) \quad // (5) \text{ to liver} \]

\[ \text{dxdt\_STOMACH} = Qst*(\text{Carterial} - \text{C\text{stomach}}/(Kpst/BP)) \quad // (6) \text{ to liver} \]

\[ \text{dxdt\_LIVER} = Qgu*(\text{C\text{gut}}/(Kpgu/BP)) //\text{from gut} \]
\[ + Qsp*(\text{C\text{spleen}}/(Kpsp/BP)) //\text{from spleen} \]
\[ + Qpa*(\text{C\text{pancreas}}/(Kppa/BP)) //\text{from pancreas} \]
\[ + Qst*(\text{C\text{stomach}}/(Kpst/BP)) //\text{from stomach} \]
\[ + Qha*(\text{Carterial}) //\text{from hepatic arterial} \]
\[ - Qli*(\text{Cliver}/(Kpli/BP)) \]
\[ - CLint\_\text{ind}*(\text{Cliver}*\text{fup}/Kpli) \quad // (7) \]

\[ \text{dxdt\_KIDNEY} = Qki*(\text{Carterial} - \text{C\text{kidney}}/(Kpki/BP)) \quad // (8) \]
\[ - CLint\_\text{Ki}*(\text{C\text{kidney}}*\text{fup}/Kpki) \]

\[ \text{dxdt\_HEART} = Qhe*(\text{Carterial} - \text{C\text{heart}}/(Kphe/BP)) \quad // (9) \]

\[ \text{dxdt\_LUNG} = Qlu*(\text{C\text{venous}} - \text{C\text{lungs}}/(Kplu/BP)) \quad // (10) \]

\[ \text{dxdt\_MUSCLE} = Qmu*(\text{Carterial} - \text{C\text{muscle}}/(Kpmu/BP)) \quad // (11) \]

\[ \text{dxdt\_ADIPOSE} = Qad*(\text{Carterial} - \text{C\text{adipose}}/(Kpad/BP)) \quad // (12) \]

\[ \text{dxdt\_SKIN} = Qsk*(\text{Carterial} - \text{C\text{skin}}/(Kpsk/BP)) \quad // (13) \]

\[ \text{dxdt\_BONE} = Qbo*(\text{Carterial} - \text{C\text{bone}}/(Kpbo/BP)) \quad // (14) \]

\[ \text{dxdt\_THYMUS} = Qth*(\text{Carterial} - \text{C\text{thymus}}/(Kpth/BP)) \quad // (15) \]

\[ \text{dxdt\_VEN} = Qbr*(\text{C\text{brain}}/(Kpbr/BP)) //\text{from brain} \]
\[ + Qli*(\text{Cliver}/(Kpli/BP)) //\text{from liver} \]
\[ + Qki*(\text{C\text{kidney}}/(Kpki/BP)) //\text{from kidney} \]
\[ + Qhe*(\text{C\text{heart}}/(Kphe/BP)) //\text{from heart} \]
\[ + Qmu*(\text{C\text{muscle}}/(Kpmu/BP)) //\text{from muscle} \]
\[ + Qad*(\text{C\text{adipose}}/(Kpad/BP)) //\text{from adipose} \]
\[ + Qsk*(\text{C\text{skin}}/(Kpsk/BP)) //\text{from skin} \]
\[ + Qbo*(\text{C\text{bone}}/(Kpbo/BP)) //\text{from bone} \]
\[ + Qth*(\text{C\text{thymus}}/(Kpth/BP)) //\text{from thymus} \]
\[ - Qlu*\text{C\text{venous}} \]
\[ - k\text{on}*(\text{C\text{venous}})*R \]
\[ + k\text{off}*\text{DR} \quad // (16) \]

\[ \text{dxdt\_ART} = Qlu*(\text{Clung}/(Kplu/BP) - \text{Carterial}) \quad // (17) \]

\[ \text{dxdt\_R} = - k\text{on}*(\text{C\text{venous}})*R + k\text{off}*\text{DR} \quad // (18) \]

\[ \text{dxdt\_DR} = k\text{on}*(\text{C\text{venous}})*R - k\text{off}*\text{DR} \quad // (19) \]

//des for rifampin model
int i = 0;
while(i <= ndose) {
    double delta = SOLVERTIME - dosetime[i];
    if(SOLVERTIME > dosetime[i]) {
        double ktt_rifa = ktr_rifa*delta;
        dxdt_rifadepot = exp(cumul + nn_rifa*log(ktt_rifa) - ktt_rifa) -
                      ka_rifa*rifadepot; // (20) rifampin depot compartment (mass)
    } else{
        ktt_rifa = 0;
        dxdt_rifadepot = 0;
    }
    ++i;
}

double eff_rifa = (emax_rifa * cp_rifa) / (ec50_rifa + cp_rifa) ; // rifampin induction effect on enzyme

dxdt_rifacent = ka_rifa * rifadepot - (cl_rifa *pow(ffm / 70, 0.75) / v_rifa) * rifacent * rifaenz; // (21) rifampin central compartment (mass)
dxdt_rifaenz = kenz_rifa * (1 + eff_rifa) - kenz_rifa*rifaenz; // (22) rifampin compartment (mass)

[OMEGA]
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 // Kps
0.09 // CL
0.09 // CL_Ki
0.09 // kon
0.09 // Rmax
0.09 // Ka

[OMEGA] @correlation
0.0862 // vmax_rifa
0.389 0.121 // km_rifa

[OMEGA]
0.00616 // v_rifa
0.108 // ka_rifa
0.136 // mtt_rifa
0.474 // n_rifa

[OMEGA]
0.0351 // iovkm_rifa occ1
0.0351 // iovkm_rifa occ other than 1
0.0940 // iovv_rifa occ1
0.0940 // iovv_rifa occ other than 1
0.276 // iovka_rifa occ1
0.276 // iovka_rifa occ other than 1
0.0244 // iovf_rifa occ1
```plaintext
 capture CP       = Cvenous/BP;
capture GENO     = GENO;
capture WEIGHT   = weight;
capture CP_RIFA  = cp_rifa;
capture CLINT    = Clint_ind;
capture dos     = last_dose;
capture DELTA    = delta;
capture CL_RIFA  = cl_rifa;
capture BIO_RIFA = f_rifa;
```
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various \textit{CYP2C9} genotypes under different co-treatments

Shen Cheng, Darcy R. Flora, Allan E. Rettie, Richard, C. Brundage, Timothy S. Tracy

Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Twin Cities (S.C., D.R.F., R.C.B.), Tracy Consultants (T.S.T.), Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle (A.E.R.), Present Affiliation: Metrum Research Group, Tariffville, Connecticut (S.C.), Present Affiliation: GRYT Health Inc., Rochester (D.R.F)
R-warfarin PBPK model mrgsolve model file

Shen Cheng
2021-09-13

[set] delta = 0.1 ,end=360 //360 hours/15 Days

[PARAM]
//Tissue volumes (L); for 70kg human
TVbr = 1450/1000 //brain mL to L
TVgu = 1650/1000 //Gut
TVsp = 192/1000 //spleen
TVpa = 77/1000 //pancreas
TVst = 154/1000 //stomach (not in simcyp)
TVli = 1690/1000 //liver
TVki = 280/1000 //kidneys
TVhe = 310/1000 //heart
TVlu = 1172/1000 //lungs
TVmu = 35000/1000 //muscle
TVad = 10000/1000 //adipose
TVsk = 7800/1000 //skin
TVbo = 4579/1000 //bone
TVVth = 29/1000 //thymus (not in simcyp)

TVVab = 1698/1000 //arterial blood
TVVvb = 3396/1000 //venous blood

//Tissue blood flows (L/h); for 70kg human
TVbbr = (700*60)/1000 //brain mL/min to L/hr
TVQha = (302*60)/1000 //hepatic artery
TVQgu = (1100*60)/1000 //gut
TVQsp = (77*60)/1000 //spleen
TVQpa = (133*60)/1000 //pancreas
TVQst = (38*60)/1000 //stomach
TVQli = (1650*60)/1000 //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 //kidney
TVQhe = (150*60)/1000 //heart
TVQlu = (5240*60)/1000 //lung,
//should be same as cardiac output(adjusted to 5240, 5233 original)
//to match the total Q
TVQmu = (750*60)/1000 //muscle
TVQad = (260*60)/1000 //adipose
TVQsk = (300*60)/1000 //skin
TVQbo = (250*60)/1000 //bone
TVQth = (80*60)/1000 //thymus

\[
\begin{align*}
TVK_{pbr} &= 0.0523693 \quad \text{brain:plasma} \\
TVK_{pgu} &= 0.1618 \quad \text{gut:plasma} \\
TVK_{psp} &= 0.100666 \quad \text{spleen:plasma} \\
TVK_{paa} &= 0.0639167 \quad \text{pancreas:plasma} \\
TVK_{pst} &= 0.1271972 \quad \text{stomach:plasma} \text{ (not in simcyp) calculated as average of non adipose Kps} \\
TVK_{pli} &= 0.089772 \quad \text{liver:plasma} \\
TVK_{pki} &= 0.133745 \quad \text{kidney:plasma} \\
TVK_{phe} &= 0.160367 \quad \text{heart:plasma} \\
TVK_{plu} &= 0.215004 \quad \text{lungs:plasma} \\
TVK_{pmu} &= 0.037509 \quad \text{muscle:plasma} \\
TVK_{pad} &= 0.0396971 \quad \text{adipose:plasma} \\
TVK_{psk} &= 0.281144 \quad \text{skin:plasma} \\
TVK_{pbo} &= 0.102876 \quad \text{bone:plasma} \\
TVK_{pth} &= 0.1271972 \quad \text{thymus:plasma} \text{ (not in simcyp) calculated as average of non adipose Kps}
\end{align*}
\]

\[TVCL = 0.119 \quad \text{(L/hr) in vivo clearance (simcyp sim-warfarin)}\]

\[TVCL_{Ki} = 0.00436 \quad \text{(L/hr) renal clearance (simcyp sim-warfarin)}\]

\[TVkon = 0.00137 \quad \text{L/(µg*hour)}\]

\[TVkoff = 0.0405 \quad \text{/hour}\]

\[TVRmax = 188 \quad \text{ug/L}\]

\[TVka = 1.85 \quad \text{absorption rate constant (/hr) assumed}\]

\[TVBP = 0.59 \quad \text{blood:plasma ratio (simcyp sim-warfarin)}\]

\[TVfup = 0.009 \quad \text{fraction of unbound drug in plasma (simcyp sim-warfarin)}\]

\[\text{GENO} = 1 \quad \text{1:*1/1; 2:*1B/1B; 3:*1*/3; 4: *2*/3; 5: *3*/3}\]

\[\text{weight} = 68.7 \quad \text{(kg)}\]

\[\text{MFka} = 1 \quad \text{scalar for Ka}\]

\[\text{MFkp} = 1 \quad \text{scalar for Kps}\]

\[\text{MFBP} = 1 \quad \text{scalar for BP}\]

\[\text{MFfup} = 1 \quad \text{scalar for fup}\]

\[\text{MFkon} = 1 \quad \text{scalar for kon}\]

\[\text{MFkoff} = 1 \quad \text{scalar for koff}\]

\[\text{MFRmax} = 1 \quad \text{scalar for Rmax}\]

\[\text{GENO on Rmax}\]
Rmax_GENO3 = 0.479
Rmax_GENO4 = 0.506
Rmax_GENO5 = 0.21

[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2

[MAIN]
//allometric scaling of volume
double Vbr = TVVbr*pow(weight/70, 1); //brain
double Vgu = TVVgu*pow(weight/70, 1); //Gut
double Vsp = TVVsp*pow(weight/70, 1); //spleen
double Vpa = TVVpa*pow(weight/70, 1); //pancreas
double Vst = TVVst*pow(weight/70, 1); //stomach
double Vli = TVVli*pow(weight/70, 1); //liver
double Vki = TVVki*pow(weight/70, 1); //kidneys
double Vhe = TVVhe*pow(weight/70, 1); //heart
double Vlu = TVVlu*pow(weight/70, 1); //lungs
double Vmu = TVVmu*pow(weight/70, 1); //muscle
double Vad = TVVad*pow(weight/70, 1); //adipose
double Vsk = TVVsk*pow(weight/70, 1); //skin
double Vbo = TVVbo*pow(weight/70, 1); //bone
double Vth = TVVth*pow(weight/70, 1); //thymus
double Vab = TVVab*pow(weight/70, 1); //arterial blood
double Vvb = TVVvb*pow(weight/70, 1); //venous blood

//allometric scaling of flow
double Qbr = TVQbr*pow(weight/70, 0.75); //brain
double Qha = TVQha*pow(weight/70, 0.75); //hepatic artery
double Qgu = TVQgu*pow(weight/70, 0.75); //gut
double Qsp = TVQsp*pow(weight/70, 0.75); //spleen
double Qpa = TVQpa*pow(weight/70, 0.75); //pancreas
double Qst = TVQst*pow(weight/70, 0.75); //stomach
double Qli = TVQli*pow(weight/70, 0.75); //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
double Qki = TVQki*pow(weight/70, 0.75); //kidney
double Qhe = TVQhe*pow(weight/70, 0.75); //heart
double Qlu = TVQlu*pow(weight/70, 0.75); //lungs
double Qmu = TVQmu*pow(weight/70, 0.75); //muscle
double Qad = TVQad*pow(weight/70, 0.75); //adipose
double Qsk = TVQsk*pow(weight/70, 0.75); //skin
double Qbo = TVQbo*pow(weight/70, 0.75); //bone
double Qth = TVQth*pow(weight/70, 0.75); //thymus

//scaled Kps
double Kpbr = TVKpbr*MFkp*exp(ETA(1)); //brain:plasma
double Kpgu = TVKpgu*MFkp*exp(ETA(2)); //gut:plasma
double Kpsp = TVKpsp*MFkp*exp(ETA(3)); //spleen:plasma
double Kppa = TVKppa*MFkp*exp(ETA(4)); //pancreas:plasma
double Kpst = TVKpst*MFkp*exp(ETA(5)); //stomach:plasma
double Kpki = TVKpki*MFkp*exp(ETA(6)); //liver:plasma
double Kphe = TVKphe*MFkp*exp(ETA(8)); //heart:plasma
double Kplu = TVKplu*MFkp*exp(ETA(9)); //lungs:plasma
double Kpmu = TVKpmu*MFkp*exp(ETA(10)); //muscle:plasma
double Kpad = TVKpad*MFkp*exp(ETA(11)); //adipose:plasma
double Kpsk = TVKpsk*MFkp*exp(ETA(12)); //skin:plasma
double Kpbo = TVKpbo*MFkp*exp(ETA(13)); //bone:plasma
double Kpth = TVKpth*MFkp*exp(ETA(14)); //thymus:plasma

//allometric scaling of clearance (hepatic and renal)
double CL_GENO = 1;

double CL = TVCL*CL_GENO*exp(ETA(15))*pow(weight/70, 0.75); //total in vivo clearance

double CL_Ki = TVCL_Ki*exp(ETA(16))*pow(weight/70, 0.75); //renal clearance

//Clint (liver intrinsic clearance: back calculated from liver clearance: CL-CL_Ki)
//reference: Ali A. Alhadab et.al., CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 1 | July 2020

double Clint = Qli*(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP));

//Clint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
double Clint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

//TMDD param
double kon = TVkon*MFkon*exp(ETA(17));
double koff = TVkoff*MFkoff;

double Rmax = TVRmax*MFRmax*exp(ETA(18));
if (GENO == 3) Rmax = TVRmax*MFRmax*Rmax_GENO3*exp(ETA(18));
if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));
// other parameters
  double ka = TVka*MFka*exp(ETA(19)) ;
  double BP = TVBP*MFBP ;
  double fup = TVfup*MFfup ;

// receptor(R) baseline
  R_0 = Rmax;

[ODE]
// Calculation of tissue drug concentrations (ug/L)
  double Cbrain = BRAIN/Vbr   ;
  double Cgut   = GUT/Vgu     ;
  double Cspleen= SPLEEN/Vsp  ;
  double Cpancreas= PANCREAS/Vpa;
  double Cstomach= STOMACH/Vst ;
  double Cliver = LIVER/Vli   ;
  double Ckidney= KIDNEY/Vki  ;
  double Cheart = HEART/Vhe   ;
  double Clung = LUNG/Vlu     ;
  double Cmuscle= MUSCLE/Vmu  ;
  double Cadipose= ADIPOSE/Vad ;
  double Cskin = SKIN/Vsk    ;
  double Cbone = BONE/Vbo    ;
  double Cthymus= THYMUS/Vth ;

  double Carterial = ART/Vab   ;
  double Cvenous = VEN/Vvb    ;

// ODEs
  dxdt_GUTLUMEN = - ka*GUTLUMEN                ;//(1) absorption
  dxdt_BRAIN    =   Qbr*(Carterial - Cbrain/(Kpbr/BP))) ;//(2)
  dxdt_GUT      =   ka*GUTLUMEN
                  + Qgu*(Carterial - Cgut/(Kpgu/BP)) ;//(3) to liver
  dxdt_SPLEEN   =   Qsp*(Carterial - Cspleen/(Kpsp/BP))) ;//(4) to liver
  dxdt_PANCREAS =   Qpa*(Carterial - Cpancreas/(Kppa/BP)) ;//(5) to liver
  dxdt_STOMACH  =   Qst*(Carterial - Cstomach/(Kpst/BP)) ;//(6) to liver
  dxdt_LIVER    =   Qgu*(Cgut/(Kpgu/BP))
                  + Qsp*(Cspleen/(Kpsp/BP))
                  + Qpa*(Cpancreas/(Kppa/BP))
                  + Qst*(Cstomach/(Kpst/BP))
                  + Qha*(Carterial) // from hepatic
                  - Qli*(Cliver/(Kpli/BP))
                  - Clint*(Cliver*fup/Kpli) ;//(7)
  dxdt_KIDNEY   =   Qki*(Carterial - Ckidney/(Kpki/BP))
                  - Clint_Ki*(Ckidney*fup/Kpki) ;//(8)
dxdt_HEART = Qhe*(Carterial - Cheart/(Kphe/BP)) ;/(9)
dxdt_LUNG = Qlu*(Cvenous - Clung/(Kplu/BP)) ;/(10)
dxdt_MUSCLE = Qmu*(Carterial - Cmuscle/(Kpmu/BP)) ;/(11)
dxdt_ADIPOSE = Qad*(Carterial - Cadipose/(Kpad/BP)) ;/(12)
dxdt_SKIN = Qsk*(Carterial - Cskin/(Kpsk/BP)) ;/(13)
dxdt_BONE = Qbo*(Carterial - Cbone/(Kpbo/BP)) ;/(14)
dxdt_THYMUS = Qth*(Carterial - Cthymus/(Kpth/BP)) ;/(15)

dxdt_VEN = Qbr*(Cbrain/(Kpbr/BP)) //from brain + Qli*(Cliver/(Kpli/BP)) //from liver + Qki*(Ckidney/(Kpki/BP)) //from kidney + Qhe*(Cheart/(Kphe/BP)) //from heart + Qmu*(Cmuscle/(Kpmu/BP)) //from muscle + Qad*(Cadipose/(Kpad/BP)) //from adipose + Qsk*(Cskin/(Kpsk/BP)) //from skin + Qbo*(Cbone/(Kpbo/BP)) //from bone + Qth*(Cthymus/(Kpth/BP)) //from thymus - Qlu*Cvenous - kon*(Cvenous/BP)*R + koff*DR ;/(16)

dxdt_ART = Qlu*(Clung/(Kplu/BP) - Carterial) ;/(17)
dxdt_R = - kon*(Cvenous/BP)*R + koff*DR ;/(18)
dxdt_DR = kon*(Cvenous/BP)*R - koff*DR ;/(19)

[OMEGA]
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 //Kps
0.09 //CL
0.09 //CL_Ki
0.09 //kon
0.09 //Rmax
0.09 //Ka

[TABLE]
capture CP = Cvenous/BP;
capture GENO = GENO;
capture WEIGHT =weight;
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments.

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Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Twin Cities (S.C., D.R.F., R.C.B.), Tracy Consultants (T.S.T.), Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle (A.E.R.), Present Affiliation: Metrum Research Group, Tariffville, Connecticut (S.C.), Present Affiliation: GRYT Health Inc., Rochester (D.R.F)
R-warfarin PBPK model with fluconazole inhibition mrgsolve model file

Shen Cheng
2021-09-13

[set] delta = 0.1 ,end = 720 //720 hours/30 Days

[PARAM]
//Tissue volumes (L); for 70kg human
TVVbr = 1450/1000   //brain mL to L
TVVgu = 1650/1000   //Gut
TVVsp = 192/1000    //spleen
TVVpa = 77/1000     //pancreas
TVVst = 154/1000    //stomach (not in simcyp)
TVVli = 1690/1000   //liver
TVVki = 280/1000    //kidneys
TVVhe = 310/1000    //heart
TVVlu = 1172/1000   //lungs
TVVmu = 35000/1000  //muscle
TVVad = 10000/1000  //adipose
TVVsk = 7800/1000   //skin
TVVbo = 4579/1000   //bone
TVVth = 29/1000     //thymus (not in simcyp)

TVVab = 1698/1000   //arterial blood
TVVvb = 3396/1000   //venous blood

//Tissue blood flows (L/h); for 70kg human
TVQbr = (700*60)/1000 //brain mL/min to L/hr
TVQha = (302*60)/1000 //hepatic artery
TVQgu = (1100*60)/1000 //gut
TVQsp = (77*60)/1000  //spleen
TVQpa = (133*60)/1000 //pancreas
TVQst = (38*60)/1000  //stomach
TVQli = (1650*60)/1000 //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 //kidney
TVQhe = (150*60)/1000 //heart
TVQlu = (5240*60)/1000 //lung,
//should be same as cardiac output(adjusted to 5240, 5233 original)
//to match the total Q
TVQmu = (750*60)/1000 //muscle
TVQad = (260*60)/1000 //adipose
TVQsk = (300*60)/1000 //skin
TVQbo = (250*60)/1000 //bone
TVQth = (80*60)/1000 //thymus

//partition coefficients estimated by Rodgers et.al., method suggested by
TVKpbr = 0.0523693 //brain:plasma
TVKpgu = 0.1618 //gut:plasma
TVKpsp = 0.100666 //spleen:plasma
TVKppa = 0.0639167 //pancreas:plasma
TVKpst = 0.1271972 //stomach:plasma (not in simcyp) calculated as
average of non adipose Kps
TVKpli = 0.089772 //liver:plasma
TVKpki = 0.133745 //kidney:plasma
TVKphe = 0.160367 //heart:plasma
TVKplu = 0.215004 //lungs:plasma
TVKpmu = 0.037509 //muscle:plasma
TVKpad = 0.0396971 //adipose:plasma
TVKpsk = 0.281144 //skin:plasma
TVKPth = 0.1271972 //thymus:plasma (not in simcyp) calculated as
average of non adipose Kps

//in vivo clearance
TVCL = 0.119 //L/hr in vivo clearance (unpublished warfarin manuscript, simcyp sim-warfarin)

//renal clearance
TVCL_Ki = 0.00436*0.752 //L/hr renal clearance (unpublished warfarin manuscript)

//0.752: fluconzole effect on R-warfarin renal clearance(unpublished manuscript)

//TMDD param (unpublished warfarin manuscript)
TVkon = 0.00137 // L/(µg*hour)
TVkoff = 0.0405 // /hour
TVRmax = 188 // µg/L

//other parameters
TVka = 1.85 //absorption rate constant (/hr) assumed (simcyp sim-warfarin)
TVBP = 0.59 //blood:plasma ratio (simcyp sim-warfarin)
TVfup = 0.009 //fraction of unbound drug in plasma (simcyp sim-warfarin)

//scalars
GENO = 1 // 1:*1/*1; 2:*1B/*1B; 3:*1*/3; 4: *2/*3; 5: *3/*3
weight = 68.7 // (kg)
MFka = 1 //scalar for Ka
MFkp = 1 //scalar for Kps
MFBP = 1 //scalar for BP
MFfup = 1 //scalar for fup
MFkon = 1 //scalar for kon
MFkoff = 1 //scalar for koff
MFRmax = 1 //scalar for Rmax

//GENO on Rmax
Rmax_GENO3 = 0.479
Rmax_GENO4 = 0.506
Rmax_GENO5 = 0.21

//fluconazole empirical model
//A one-compartment model with lagged first-order input and first-order elimination
//Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2561119/
tvc1_fluc = 1.18 //fluconazole clearance L/hr
ttv_fluc = 55.7 //fluconazole volume of distribution L
tvka_fluc = 3.38 //fluconazole absorption rate constant /hr

//fluconazole inhibition parameters (ki: concentration of fluconazole that supports half maximal 2c9 inhibition)
//check calculation: https://www.graphpad.com/quickcalcs/Molarityform.cfm
//fluconazole mw: 306.271 g/mol
tvki_4oh = 8.88 //mg/L 29uM assumed to be eliminated by a mix effect of 2C9, 2C19 and 3A4 ((Ki,2C9 + Ki,2C19 + Ki,3A4)/3)
tvki_6oh = 30.63 //mg/L 100uM assumed to be eliminated through 1A2 (https://pubmed.ncbi.nlm.nih.gov/8801056/, very weak inhibitor, range: >800 uM)
tvki_7oh = 12.67 //mg/L 41.4uM assumed to be eliminated through 2C9, 1A2 and 2C19 ((Ki,2C9 + Ki,2C19 + Ki,1A2)/3)
tvki_8oh = 0.64 //mg/L 2.1uM assumed to be eliminated through 2C19 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195022/#:~:text=The%20inhibition%20constant%20(Ki,was%202.1%20%CE%BCM%20(31) 2.1uM)

//fluconazole inhibition parameters (ki: concentration of fluconazole that supports half maximal 2c9 inhibition)
//check calculation: https://www.graphpad.com/quickcalcs/Molarityform.cfm
//fluconazole mw: 306.271 g/mol
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tvki_8oh = 0.64 //mg/L 2.1uM assumed to be eliminated through 2C19 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195022/#:~:text=The%20inhibition%20constant%20(Ki,was%202.1%20%CE%BCM%20(31) 2.1uM)

[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2
flucdepot  fluconazole depot compartment
fluccent  fluconazolecenral compartment

[MAIN]

// allometric scaling of volume
double Vbr  = TVVbr*pow(weight/70, 1);  //brain
double Vgu  = TVVgu*pow(weight/70, 1);  //Gut
double Vsp  = TVVsp*pow(weight/70, 1);  //spleen
double Vpa  = TVVpa*pow(weight/70, 1);  //pancreas
double Vst  = TVVst*pow(weight/70, 1);  //stomach
double Vli  = TVVli*pow(weight/70, 1);  //liver
double Vki  = TVVki*pow(weight/70, 1);  //kidneys
double Vhe  = TVVhe*pow(weight/70, 1);  //heart
double Vlu  = TVVlu*pow(weight/70, 1);  //lungs
double Vmu  = TVVmu*pow(weight/70, 1);  //muscle
double Vad  = TVVad*pow(weight/70, 1);  //adipose
double Vsk  = TVVsk*pow(weight/70, 1);  //skin
double Vbo  = TVVbo*pow(weight/70, 1);  //bone
double Vth  = TVVth*pow(weight/70, 1);  //thymus

double Vab  = TVVab*pow(weight/70, 1);  //arterial blood
double Vvb  = TVVvb*pow(weight/70, 1);  //venous blood

// allometric scaling of flow
double Qbr  = TVQbr*pow(weight/70, 0.75);  //brain
double Qha  = TVQha*pow(weight/70, 0.75);  //hepatic artery
double Qgu  = TVQgu*pow(weight/70, 0.75);  //gut
double Qsp  = TVQsp*pow(weight/70, 0.75);  //spleen
double Qpa  = TVQpa*pow(weight/70, 0.75);  //pancreas
double Qst  = TVQst*pow(weight/70, 0.75);  //stomach
double Qli  = TVQli*pow(weight/70, 0.75);  //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
double Qki  = TVQki*pow(weight/70, 0.75);  //kidney
double Qhe  = TVQhe*pow(weight/70, 0.75);  //heart
double Qlu  = TVQlu*pow(weight/70, 0.75);  //lung
double Qmu  = TVQmu*pow(weight/70, 0.75);  //muscle
double Qad  = TVQad*pow(weight/70, 0.75);  //adipose
double Qsk  = TVQsk*pow(weight/70, 0.75);  //skin
double Qbo  = TVQbo*pow(weight/70, 0.75);  //bone
double Qth  = TVQth*pow(weight/70, 0.75);  //thymus

// scaled Kps
double Kpbr  = TVKpbr*MFkp*exp(ETA(1));  //brain:plasma
double Kpgu  = TVKpgu*MFkp*exp(ETA(2));  //gut:plasma
double Kpsp  = TVKpsp*MFkp*exp(ETA(3));  //spleen:plasma
double Kppa  = TVKppa*MFkp*exp(ETA(4));  //pancreas:plasma
double Kpst  = TVKpst*MFkp*exp(ETA(5));  //stomach:plasma
double Kpli = TVKpli*MFkp*exp(ETA(6)); //liver:plasma
double Kpki = TVKpki*MFkp*exp(ETA(7)); //kidney:plasma
double Kphe = TVKphe*MFkp*exp(ETA(8)); //heart:plasma
double Kplu = TVKplu*MFkp*exp(ETA(9)); //lungs:plasma
double Kpmu = TVKpmu*MFkp*exp(ETA(10)); //muscle:plasma
double Kpad = TVKpad*MFkp*exp(ETA(11)); //adipose:plasma
double Kpsk = TVKpsk*MFkp*exp(ETA(12)); //skin:plasma
double Kpbo = TVKpbo*MFkp*exp(ETA(13)); //bone:plasma
double Kpth = TVKpth*MFkp*exp(ETA(14)); //thymus:plasma

//allometric scaling of clearance (hepatic and renal)
double CL_GENO = 1;

double CL       = TVCL   *CL_GENO*exp(ETA(15))*pow(weight/70, 0.75); //total in vivo clearance
double CL_Ki    = TVCL_Ki        *exp(ETA(16))*pow(weight/70, 0.75); //renal clearance

//Clint (liver intrinsic clearance: back calculated from liver clearance: CL-CL_Ki)
//reference: Ali A. Alhadab et.al., CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 1 | July 2020
double Clint   = Qli*(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP));

//Clint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
double Clint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

//TMDD param
double kon  = TVkon*MFkon*exp(ETA(17));
double koff = TVkoff*MFkoff;

double Rmax = TVRmax*MFRmax*exp(ETA(18));
if (GENO == 3) Rmax = TVRmax*MFRmax*Rmax_GENO3*exp(ETA(18));
if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));

//other parameters
double ka   = TVka*MFka*exp(ETA(19));
double BP   = TVBP*MFBP;
double fup  = TVfup*MFfup;

//receptor(R) baseline
R_0 = Rmax;

//fluconazole
ALAG_flucdepot = 0.23; //absorption lag time h
double cl_fluc = tvcl_fluc*exp(ETA(20)) ; //clearance L/hr
double v_fluc = tvv_fluc *exp(ETA(21)) ; //volume of distribution L
double ka_fluc = tvka_fluc*exp(ETA(22)) ; //absorption rate constant /hr

//fluconazole inhibitory effects
double ki_4oh = tvki_4oh ;
double ki_6oh = tvki_6oh ;
double ki_7oh = tvki_7oh ;
double ki_8oh = tvki_8oh ;
double ki_10oh = tvki_10oh ;

//parse intrinsic clearance (CLint)
//based on figure 6 of warfarin metabolite manuscript (unpublish till 4/25/2021)
//4-R is assumed to be eliminated by a mix effect of 2C9, 3A4 and 2C19
//6-R is assumed to be eliminated by 1A2
//7-R assumed to be eliminated through 2C9, 1A2, 2C19
//8-R is assumed to be eliminated through 2C19
//10-S assumed to be eliminated through 3A4

double CLint_4oh = (0.8 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_4oh = (0.8 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_4oh = (0.5 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_4oh = (0.5 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 5) CLint_4oh = (0.5 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
double CLint_6oh = (17.4 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_6oh = (17.4 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_6oh = (17.4 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_6oh = (17.4 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 5) CLint_6oh = (17.4 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
double CLint_7oh = (2.8 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_7oh = (2.8 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_7oh = (2.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_7oh = (2.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 5) CLint_7oh = (2.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
double CLint_8oh = (6.7 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_8oh = (2.2 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) *
if (GENO == 3) CLint_8oh = (6.7 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_8oh = (6.7 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 5) CLint_8oh = (6.7 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

double CLint_10oh = (0.8 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_10oh = (0.8 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_10oh = (0.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_10oh = (0.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 5) CLint_10oh = (0.8 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

[ODE]

//Calculation of tissue drug concentrations (ug/L)
double Cbrain = BRAIN/Vbr;
double Cgut = GUT/Vgu;
double Cspleen = SPLEEN/Vsp;
double Cpancreas = PANCREAS/Vpa;
double Cstomach = STOMACH/Vst;
double Cliver = LIVER/Vli;
double Ckidney = KIDNEY/Vki;
double Cheart = HEART/Vhe;
double Clung = LUNG/Vlu;
double Cmuscle = MUSCLE/Vmu;
double Cadipose = ADIPOSE/Vad;
double Cskin = SKIN/Vsk;
double Cbone = BONE/Vbo;
double Cthymus = THYMUS/Vth;
double Carterial = ART/Vab;
double Cvenous = VEN/Vvb;

//fluc inhibitory effect on CLint
//CLint,i = CLint/(1 + [I]/ki)
double cp_fluc = fluccent/v_fluc; //fluconazole central compartment concentration

double CLint_4oh_inh = CLint_4oh / (1 + cp_fluc / ki_4oh);
double CLint_6oh_inh = CLint_6oh / (1 + cp_fluc / ki_6oh);
double CLint_7oh_inh = CLint_7oh / (1 + cp_fluc / ki_7oh);
double CLint_8oh_inh = CLint_8oh / (1 + cp_fluc / ki_8oh);
double CLint_10oh_inh = CLint_10oh / (1 + cp_fluc / ki_10oh);
double CLint_inh = CLint_4oh_inh + CLint_6oh_inh + CLint_7oh_inh + CLint_8oh_inh + CLint_10oh_inh;

//ODEs
dxdt_GUTLUMEN = - ka*GUTLUMEN ;//(1) absorption
dxdt_BRAIN    =   Qbr*(Carterial - Cbrain/(Kpbr/BP)) ;//(2)
dxdt_GUT      =   ka*GUTLUMEN
                   + Qgu*(Carterial - Cgut/(Kpgu/BP)) ;//(3) to liver
dxdt_SPLEEN   =   Qsp*(Carterial - Cspleen/(Kpsp/BP)) ;//(4) to liver
dxdt_PANCREAS = Qpa*(Carterial - Cpancreas/(KpPa/BP)) ;//(5) to liver
dxdt_STOMACH  =   Qst*(Carterial - Cstomach/(KpSt/BP)) ;//(6) to liver
dxdt_LIVER    =   Qgu*(Cgut/(Kpgu/BP))                   //from gut
                   + Qsp*(Cspleen/(Kpsp/BP))                   //from spleen
                   + Qpa*(Cpancreas/(KpPa/BP))                 //from pancreas
                   + Qst*(Cstomach/(KpSt/BP))                 //from stomach
                   + Qha*(Carterial)                         //from hepatic arterial
                   - Qli*(Cliver/(Kpli/BP))
                   - CLint_inh*(Cliver*fup/Kpli) ;//(7)
dxdt_KIDNEY   =    Qki*(Carterial - Ckidney/(KpKi/BP))
                   - CLint_Ki*(Ckidney*fup/KpKi)               ;//(8)
dxdt_HEART    =    Qhe*(Carterial - Cheart/(KpHe/BP))     ;//(9)
dxdt_LUNG     =    Qlu*(Cvenous - Clung/(KPlu/BP))        ;//(10)
dxdt_MUSCLE   =    Qmu*(Carterial - Cmuscle/(KpMu/BP))    ;//(11)
dxdt_ADIPOSE  =    Qad*(Carterial - Cadipose/(Kpad/BP))  ;//(12)
dxdt_SKIN     =    Qsk*(Carterial - Cskin/(Kpsk/BP))      ;//(13)
dxdt_BONE     =    Qbo*(Carterial - Cbone/(Kpbo/BP))      ;//(14)
dxdt_THYMUS   =    Qth*(Carterial - Cthymus/(KpTh/BP))    ;//(15)
dxdt_VEN      =    Qbr*(Cbrain/(Kpbr/BP))                 //from brain
                   + Qli*(Cliver/(Kpli/BP))                   //from liver
                   + Qki*(Ckidney/(KpKi/BP))                 //from kidney
                   + Qhe*(Cheart/(KpHe/BP))                 //from heart
                   + Qmu*(Cmuscle/(KpMu/BP))                 //from muscle
                   + Qad*(Cadipose/(Kpad/BP))                //from adipose
                   + Qsk*(Cskin/(KpSk/BP))                  //from skin
                   + Qbo*(Cbone/(Kpbo/BP))                  //from bone
                   + Qth*(Cthymus/(KpTh/BP))                //from thymus
                   - Qlu*Cvenous
                   - kon*(Cvenous/BP)*R
                   + koff*DR                                ;//(16)
dxdt_ART      =    Qlu*(Clung/(KPlu/BP) - Carterial) ;//(17)
\[ \frac{dxdt}{dt}_{R} = -kon \frac{(Cvenous/BP) \times R + koff \times DR}{ } \quad ;/(18) \]

\[ \frac{dxdt}{dt}_{DR} = kon \frac{(Cvenous/BP) \times R - koff \times DR}{ } \quad ;/(19) \]

\[ \frac{dxdt}{dt}_{flucdepot} = -ka_{fluc} \times flucdepot \quad ;/(20) \]

fluc depot compartment (mass)

\[ \frac{dxdt}{dt}_{fluc}\text{cent} = ka_{fluc} \times flucdepot - cl_{fluc} \times cp_{fluc} \quad ;/(21) \]

central compartment (mass)

[OMEGA]

0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09  //Kps
0.09  //CL
0.09  //CL_{Ki}
0.09  //kon
0.09  //Rmax
0.09  //Ka

0.0481  //cl_{fluc}
0.0298  //v_{fluc}
1.426   //ka_{fluc}

[TABLE]
capture CP = Cvenous/BP;
capture GENO = GENO;
capture WEIGHT = weight;
capture CP\_FLUC = cp\_fluc;
capture CLINT = CLint\_inh;
A physiological-based pharmacokinetic model embedded with a target mediated drug disposition mechanism can characterize single dose warfarin pharmacokinetic profiles in subjects with various CYP2C9 genotypes under different co-treatments

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R-warfarin PBPK model with rifampin induction mrgsolve model file

Shen Cheng
2021-09-13

[set] delta = 0.1 , end = 720 //720 hours/30 Days

[PARAM]
//Tissue volumes (L); for 70kg human
TVVbr = 1450/1000  //brain mL to L
TVVgu = 1650/1000  //Gut
TVVsp = 192/1000   //spleen
TVVpa = 77/1000    //pancreas
TVVst = 154/1000   //stomach (not in simcyp)
TVVli = 1690/1000  //liver
TVVki = 280/1000   //kidneys
TVVhe = 310/1000   //heart
TVVlu = 1172/1000  //lungs
TVVmu = 35000/1000 //muscle
TVVad = 10000/1000 //adipose
TVVsk = 7800/1000  //skin
TVVbo = 4579/1000  //bone
TVVth = 29/1000    //thymus (not in simcyp)

TVVab = 1698/1000  //arterial blood
TVVvb = 3396/1000  //venous blood

//Tissue blood flows (L/h); for 70kg human
TVQbr = (700*60)/1000  //brain mL/min to L/hr
TVQha = (302*60)/1000  //hepatic artery
TVQgu = (1100*60)/1000 //gut
TVQsp = (77*60)/1000   //spleen
TVQpa = (133*60)/1000  //pancreas
TVQst = (38*60)/1000   //stomach
TVQli = (1650*60)/1000 //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
TVQki = (1100*60)/1000 //kidney
TVQhe = (150*60)/1000  //heart
TVQlu = (5240*60)/1000 //lung,
//should be same as cardiac output(adjusted to 5240, 5233 original)
//to match the total Q
TVQmu = (750*60)/1000 //muscle
TVQad = (260*60)/1000 //adipose
TVQsk = (300*60)/1000 //skin
TVQbo = (250*60)/1000 //bone
TVQth = (80*60)/1000  //thymus partition coefficients estimated by Rodgers et.al., method suggested by Sheila Annie Peters, Clin Pharmacokinet 2008 47 (4): 261-275

TVKpbr = 0.0523693  //brain:plasma
TVKpgu = 0.1618  //gut:plasma
TVKpsp = 0.100666  //spleen:plasma
TVKppa = 0.0639167  //pancreas:plasma
TVKpst = 0.1271972  //stomach:plasma (not in simcyp) calculated as average of non adipose Kps

TVKpdi = 0.089772  //liver:plasma
TVKpki = 0.133745  //kidney:plasma
TVKphe = 0.160367  //heart:plasma
TVKplu = 0.215004  //lungs:plasma
TVKpmu = 0.037509  //muscle:plasma
TVKpad = 0.0396971  //adipose:plasma
TVKpsk = 0.281144  //skin:plasma
TVKpbo = 0.102876  //bone:plasma
TVKpth = 0.1271972  //thymus:plasma (not in simcyp) calculated as average of non adipose Kps

//in vivo clearance
TVCL = 0.119  //(L/hr) in vivo clearance (unpublished warfarin manuscript, simcyp sim-warfarin)

//renal clearance
TVCL_Ki = 0.00436*1.43  //(L/hr) renal clearance (unpublished warfarin manuscript)

//1.43: rifampin effect on R-warfarin renal clearance(unpublished manuscript)

//TMDD param (unpublished warfarin manuscript)
TVkon = 0.00137  //L/(µg*hour)
TVkoff = 0.0405  //hour
TVRmax = 188  //ug/L

//other parameters
TVka = 1.85  //absorption rate constant (/hr) assumed (simcyp sim-warfarin)
TVBP = 0.59  //blood:plasma ratio (simcyp sim-warfarin)
TVfup = 0.009  //fraction of unbound drug in plasma (simcyp sim-warfarin)

//scalars
GENO = 1  //1:*1/*1; 2:*1B/*1B; 3:*1*/3; 4: *2/*3; 5: *3/*3
weight = 68.7  //(kg)
MFka = 1  //scalar for Ka
MFkp = 1  //scalar for Kps
MFBP = 1  //scalar for BP
MFfup = 1 // scalar for fup
MFkon = 1 // scalar for kon
MFkoff = 1 // scalar for koff
MFRmax = 1 // scalar for Rmax

// GENO on Rmax
Rmax_GENO3 = 0.479
Rmax_GENO4 = 0.506
Rmax_GENO5 = 0.21

// rifampin empirical model
// A one-compartment model with M-M elimination and transit compartments
// enzyme turnover model accounting for autoinduction
// dose dependent bioavailability (Emax equation)
tvmax_rifa = 525 // mg/h/70kg maximal elimination rate
tvkm_rifa = 35.3 // mg/L rifampicin concentration at which the elimination is half-maximal
tv_rifa = 87.2 // L/70kg volume of distribution
tvk_a_rifa = 1.77 // /hr absorption rate constant
tvmtt_rifa = 0.513 // hr mean transit time
tvnn_rifa = 23.8 // number of transit compartments
tvemax_rifa = 1.16 // maximal increase in enzyme production rate
tvec50_rifa = 0.0699 // mg/L rifampicin concentration at which half the emax is reached
tvkenz_rifa = 0.00603 // /hr first-order rate constant for enzyme pool degradation
tvfemax_rifa = 0.504 // maximal increase in relative bioavailability above 450mg
tvfed50_rifa = 67.0 // mg difference in rifampicin dose from 450mg at which half the fmax is reached

ffm = 45 // kg fat free mass
occ = 1 // occasion

// rifa inducing parameters
// indmax: maximal induction fold over vehicle
// indc50: inducer concentration that supports half-maximal induction (µM)
// check calculation: https://www.graphpad.com/quickcalcs/Molarityform.cfm
// rifampin mw: 822.94 g/mol
// rifampin is a strong inhibitor for 2C19 and 3A4, but moderate for 2C9

// 4-R is assumed to be eliminated by a mix effect of 2C9, 3A4 and 2C19
// 6-R is assumed to be eliminated by 1A2
// 7-R assumed to be eliminated through 2C9, 1A2, 2C19
// 8-R is assumed to be eliminated through 2C19
// 10-S assumed to be eliminated through 3A4

tvindmax_4oh = 7.4  //fold increase, assumed to be eliminated by a mix
effect of 2C9, 2C19 and 3A4 ((3.6 + 5.5 + 16)/3 = 8.4)
tvindmax_6oh = 2.8  //fold increase, assumed to be eliminated through 1A2
(https://journals.sagepub.com/doi/pdf/10.1177/1087057112463732, table 6 (a))
tvindmax_7oh = 6.8  //fold increase, assumed to be eliminated through 2C9,
1A2 and 2C19 ((3.6 + 3.8 + 16)/3 = 7.8)
tvindmax_8oh = 4.5  //fold increase, assumed to be eliminated through 2C19
(5.5, table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)
tvindmax_10oh = 15   //fold increase, assumed to be eliminated through 3A4
(16, table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)

tvindc50_4oh = 0.239   //mg/L 0.29 uM assumed to be eliminated by a mix
effect of 2C9, 2C19 and 3A4 ((0.1 + 0.45 + 0.32)/3)
tvindc50_6oh = 0.181   //mg/L 0.22 uM assumed to be eliminated through
1A2 (https://journals.sagepub.com/doi/pdf/10.1177/1087057112463732, table 6
(a))
tvindc50_7oh = 0.214   //mg/L 0.26 uM assumed to be eliminated through
2C9, 1A2 and 2C19 ((0.1 + 0.22 + 0.45)/3 = 8.4)
tvindc50_8oh = 0.370   //mg/L 0.45 uM assumed to be eliminated through
2C19 (table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)
tvindc50_10oh = 0.263   //mg/L 0.32 uM assumed to be eliminated through 3A4
(table S1 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6765699/)

[ global ]
int ndose = 0;
double dosetime[300];
double dose[300];

[PREAMBLE]
double last_dose = 0;

[CMT]
GUTLUMEN //dosing compartment X1
GUT STOMACH SPLEEN PANCREAS //tissue comp connected with liver X4
ADIPOSE BRAIN HEART BONE KIDNEY LIVER LUNG MUSCLE SKIN THYMUS //other
tissue comp X10
ART VEN //circulation X2
R DR //TMDD comp x2

rifadepot //rifampin depot compartment
rifacent //rifampin central compartment
rifaenz //rifampin enzyme compartment

[MAIN]
//allometric scaling of volume
double Vbr = TVVbr*pow(weight/70, 1) ; //brain
double Vgu = TVVgu*pow(weight/70, 1); //Gut
double Vsp = TVVsp*pow(weight/70, 1); //spleen
double Vpa = TVVpa*pow(weight/70, 1); //pancreas
double Vst = TVVst*pow(weight/70, 1); //stomach
double Vli = TVVli*pow(weight/70, 1); //liver
double Vki = TVVki*pow(weight/70, 1); //kidneys
double Vhe = TVVhe*pow(weight/70, 1); //heart
double Vlu = TVVlu*pow(weight/70, 1); //lungs
double Vmu = TVVmu*pow(weight/70, 1); //muscle
double Vad = TVVad*pow(weight/70, 1); //adipose
double Vsk = TVVsk*pow(weight/70, 1); //skin
double Vbo = TVVbo*pow(weight/70, 1); //bone
double Vth = TVVth*pow(weight/70, 1); //thymus

double Vab = TVVab*pow(weight/70, 1); //arterial blood
double Vvb = TVVvb*pow(weight/70, 1); //venous blood

//allometric scaling of flow
double Qbr = TVQbr*pow(weight/70, 0.75); //brain
double Qha = TVQha*pow(weight/70, 0.75); //hepatic artery
double Qgu = TVQgu*pow(weight/70, 0.75); //gut
double Qsp = TVQsp*pow(weight/70, 0.75); //spleen
double Qpa = TVQpa*pow(weight/70, 0.75); //pancreas
double Qst = TVQst*pow(weight/70, 0.75); //stomach
double Qli = TVQli*pow(weight/70, 0.75); //liver (total) (= Qha + Qgu + Qsp + Qpa + Qst)
double Qki = TVQki*pow(weight/70, 0.75); //kidney
double Qhe = TVQhe*pow(weight/70, 0.75); //heart
double Qlu = TVQlu*pow(weight/70, 0.75); //lung
double Qmu = TVQmu*pow(weight/70, 0.75); //muscle
double Qad = TVQad*pow(weight/70, 0.75); //adipose
double Qsk = TVQsk*pow(weight/70, 0.75); //skin
double Qbo = TVQbo*pow(weight/70, 0.75); //bone
double Qth = TVQth*pow(weight/70, 0.75); //thymus

//scaled Kps
double Kpbr = TVKpbr*MFkp*exp(ETA(1)); //brain:plasma
double Kpku = TVKpku*MFkp*exp(ETA(2)); //gut:plasma
double Kpsp = TVKpsp*MFkp*exp(ETA(3)); //spleen:plasma
double Kppa = TVKppa*MFkp*exp(ETA(4)); //pancreas:plasma
double Kpst = TVKpst*MFkp*exp(ETA(5)); //stomach:plasma
double Kpil = TVKpil*MFkp*exp(ETA(6)); //liver:plasma
double Kpki = TVKpki*MFkp*exp(ETA(7)); //kidney:plasma
double Kphe = TVKphe*MFkp*exp(ETA(8)); //heart:plasma
double Kplu = TVKplu*MFkp*exp(ETA(9)); //lung:plasma
double Kpmu = TVKpmu*MFkp*exp(ETA(10)); //muscle:plasma
double Kpad = TVKpad*MFkp*exp(ETA(11)); //adipose:plasma
double Kpsk = TVKpsk*MFkp*exp(ETA(12)); //skin:plasma
double Kpbo = TVKpbo*MFkp*exp(ETA(13)); //bone:plasma
double Kpth = TVKpth*MFkp*exp(ETA(14)); //thymus:plasma
// allometric scaling of clearance (hepatic and renal)
double CL_GENO = 1;

double CL = TVCL * CL_GENO * exp(ETA(15)) * pow(weight/70, 0.75);

// total in vivo clearance
double CL_Ki = TVCL_Ki * exp(ETA(16)) * pow(weight/70, 0.75);

// renal clearance

// CLint (liver intrinsic clearance: back calculated from liver clearance: CL-CL_Ki)
// reference: Ali A. Alhadab et.al., CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 108 NUMBER 1 | July 2020
double CLint = Qli *(CL-CL_Ki)/(fup*(Qli-(CL-CL_Ki)/BP));

// CLint_Ki (kidney intrinsic clearance: back calculated from renal clearance: CL_Ki)
double CLint_Ki = Qki*CL_Ki/(fup*(Qki-CL_Ki/BP));

// TMDD param
double kon = TVkon*MFkon*exp(ETA(17));
double koff = TVkoff*MFkoff;

double Rmax = TVRmax*MFRmax*exp(ETA(18));
    if (GENO == 3) Rmax = TVRmax*MFRmax*Rmax_GENO3*exp(ETA(18));
    if (GENO == 4) Rmax = TVRmax*MFRmax*Rmax_GENO4*exp(ETA(18));
    if (GENO == 5) Rmax = TVRmax*MFRmax*Rmax_GENO5*exp(ETA(18));

// other parameters
double ka = TVka*MFka*exp(ETA(19));
double BP = TVBP*MFBP;
double fup = TVfup*MFfup;

// receptor(R) baseline
R_0 = Rmax;

// rifampin empirical pk model start----------------------------------------
// rifampin empirical pk model parameters
double vmax_rifa = tvvmax_rifa * exp(ETA(20));
    // maximal elimination rate L/hr
double km_rifa = tvkm_rifa * exp(ETA(21)) * exp(iovkm_rifa); // rifampicin concentration at which the elimination is half-maximal
double v_rifa = tvv_rifa *(ffm / 70) * exp(ETA(22)) * exp(iovv_rifa); // volume of distribution L
double ka_rifa = tvka_rifa * exp(ETA(23));
exp iovka_rifa ;  //absorption rate constant /hr
  double ec50_rifa   = tvec50_rifa
;  //rifampicin concentration at which half the emax is reached
  double emax_rifa   = tvemax_rifa
;  //maximal increase in enzyme production rate
  double kenz_rifa   = tvkenz_rifa
;  //first-order rate constant for enzyme pool degradation
  double femax_rifa   = tvfemax_rifa
;  //maximal increase in relative bioavailability above 450mg
  double fed50_rifa   = tvfed50_rifa
;  //difference in rifampicin dose from 450mg at which half the fmax is reached
  double mtt_rifa     = tvmtt_rifa * exp(ETA(24))  //mean transit time hr
  double nn_rifa      = tvnn_rifa * exp(ETA(25))  //number of transit compartments

//calculate dose****
  if(EVID == 1 && self.cmt == 20){
    last_dose = self.amt;  //reference: https://mrgsolve.github.io/user_guide/model-specification.html#self.amt
  }

//dose dependent relative bioavailability
  double f450 = 1;  //assuming bioavailability for 450mg dose is 1
  double f_rifa = f450*(1 + femax_rifa*(last_dose-450) / (fed50_rifa + (last_dose - 450))) * exp(iovf_rifa);  //Emax on bioavailability

//define ktr
  double ktr_rifa   = (nn_rifa + 1) / mtt_rifa;  //rate constant for transit compartments

//logarithm of the approximation to the gamma function
  double l       = 0.9189385 + (nn_rifa + 0.5) * log(nn_rifa) - nn_rifa + log(1 + 1/(12 * nn_rifa));  //logarithm of gamma_n
  double lbpd    = log(f_rifa * last_dose)  //logarithm of f*dose
;  //logarithm of ktr
  double lktr    = log(ktr_rifa)  //logarithm of ktr
;  //logarithm of f*dose*ktr/gamma_n

//interoccasion vaibility(VOV)
  double iovkm_rifa         = ETA(26);
  if (occ != 1) iovkm_rifa  = ETA(27);
  double iovv_rifa          = ETA(28);
  if (occ != 1) iovv_rifa   = ETA(29);
double iovka_rifa = ETA(30);
if (occ != 1) iovka_rifa = ETA(31);

double iovf_rifa = ETA(32);
if (occ != 1) iovf_rifa = ETA(33);

//Initialize compartments
F_rifadepot = 0; //transit absorption compartment
rifacent_0 = 0.0001; //central compartment
rifaenz_0 = 1; //enzyme compartment

//compute ndose (the index of dose)
//dosetime: time after dose
//dose: dosage

if (NEWIND < 2) ndose = 0; //index of dose
if (self.amt > 0 && self.cmt == 20) {
    ndose = ndose + 1;
    dosetime[ndose] = self.time;
    dose[ndose] = self.amt; //reference:
    https://mrgsolve.github.io/user_guide/model-specification.html#self.amt
}

//rifampin empirical pk model end------------------------------------------

//rifampin inducing effects
double indmax_4oh = tvindmax_4oh;
double indmax_6oh = tvindmax_6oh;
double indmax_7oh = tvindmax_7oh;
double indmax_8oh = tvindmax_8oh;
double indmax_10oh = tvindmax_10oh;

double indc50_4oh = tvindc50_4oh;
double indc50_6oh = tvindc50_6oh;
double indc50_7oh = tvindc50_7oh;
double indc50_8oh = tvindc50_8oh;
double indc50_10oh = tvindc50_10oh;

//parse intrinsic clearance (CLint)
//based on figure 6 of warfarin metabolite manuscript (unpublish till 4/25/2021)
//4-R is assumed to be eliminated by a mix effect of 2C9, 3A4 and 2C19
//6-R is assumed to be eliminated by 1A2
//7-R assumed to be eliminated through 2C9, 1A2, 2C19
//8-R is assumed to be eliminated through 2C19
//10-S assumed to be eliminated through 3A4
double CLint_4oh  = (0.8  / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_4oh  = (0.8  / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_4oh  = (0.5  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_4oh  = (0.5  / (0.5 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 5) CLint_4oh  = (0.5  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

double CLint_6oh  = (17.4 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_6oh  = (17.4 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_6oh  = (17.4 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_6oh  = (17.4 / (0.5 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 5) CLint_6oh  = (17.4 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

double CLint_7oh  = (2.8  / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_7oh  = (2.8  / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_7oh  = (2.8  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_7oh  = (2.8  / (0.5 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 5) CLint_7oh  = (2.8  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

double CLint_8oh  = (6.7 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_8oh  = (6.7 / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_8oh  = (6.7 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_8oh  = (6.7 / (0.5 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 5) CLint_8oh  = (6.7 / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

double CLint_10oh = (0.8 / (0.8 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 2) CLint_10oh = (0.8  / (0.8 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 3) CLint_10oh = (0.8  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;
if (GENO == 4) CLint_10oh = (0.8  / (0.5 + 17.4 + 2.8 + 2.2 + 0.8)) * CLint;
if (GENO == 5) CLint_10oh = (0.8  / (0.5 + 17.4 + 2.8 + 6.7 + 0.8)) * CLint;

[ODE]
  // Calculation of tissue drug concentrations (ug/L)
  double Cbrain     = BRAIN/Vbr   ;
  double Cgut       = GUT/Vgu     ;
double Cspleen = SPLEEN/Vsp;
double Cpancreas = PANCREAS/Vpa;
double Cstomach = STOMACH/Vst;
double Cliver = LIVER/Vli;
double Ckidney = KIDNEY/Vki;
double Cheart = HEART/Vhe;
double Clung = LUNG/Vlu;
double Cmuscle = MUSCLE/Vmu;
double Cadipose = ADIPOSE/Vad;
double Cskin = SKIN/Vsk;
double Cbone = BONE/Vbo;
double Cthymus = THYMUS/Vth;
double Carterial = ART/Vab;
double Cvenous = VEN/Vvb;

//rifampin inducing effect on CLint
//CLint,i = CLint*(1 + (indmax*cp_rifa)/(indc50 + cp_rifa))
double cp_rifa = rifacent/v_rifa;  //central compartment concentration mg/L
double cl_rifa = vmax_rifa/(km_rifa + cp_rifa);  //nonlinear clearance L/hr
double k_rifa = cl_rifa/v_rifa;  //elimination rate constant mg/hr

double CLint_4oh_ind = CLint_4oh *(1 + (indmax_4oh*cp_rifa) / (indc50_4oh + cp_rifa));
double CLint_6oh_ind = CLint_6oh *(1 + (indmax_6oh*cp_rifa) / (indc50_6oh + cp_rifa));
double CLint_7oh_ind = CLint_7oh *(1 + (indmax_7oh*cp_rifa) / (indc50_7oh + cp_rifa));
double CLint_8oh_ind = CLint_8oh *(1 + (indmax_8oh*cp_rifa) / (indc50_8oh + cp_rifa));
double CLint_10oh_ind = CLint_10oh *(1 + (indmax_10oh*cp_rifa) / (indc50_10oh + cp_rifa));

double CLint_ind = CLint_4oh_ind + CLint_6oh_ind + CLint_7oh_ind + CLint_8oh_ind + CLint_10oh_ind;

//ODEs
dx/dt_GUTLUMEN = - ka*GUTLUMEN;  ///(1) absorption
dx/dt_BRAIN = Q_br*(Carterial - Cbrain/(Kp_br/BP));  ///(2)

dx/dt_GUT = ka*GUTLUMEN + Q_gut*(Carterial - C_gut/(Kp_gut/BP));  ///(3) to liver
dx/dt_SPLEEN = Q_sp*(Carterial - C_spleen/(Kp_sp/BP));  ///(4) to liver
dx/dt_PANCREAS = Q_p_a*(Carterial - C_pancreas/(K_p_a/BP));  ///(5) to liver
dx/dt_STOMACH = Q_s_t*(Carterial - C_stomach/(Kp_st/BP));  ///(6) to liver
\[
\frac{dx_{\text{LIVER}}}{dt} = \frac{Q_{\text{gu}}(C_{\text{gut}}/(K_{\text{pgu}}/BP))}{\text{from gut}} + \frac{Q_{\text{sp}}(C_{\text{spleen}}/(K_{\text{psp}}/BP))}{\text{from spleen}} + \frac{Q_{\text{pa}}(C_{\text{pancreas}}/(K_{\text{ppa}}/BP))}{\text{from pancreas}} + \frac{Q_{\text{st}}(C_{\text{stomach}}/(K_{\text{pst}}/BP))}{\text{from stomach}} + \frac{Q_{\text{ha}}(C_{\text{arterial}})}{\text{from hepatic arterial}} - \frac{Q_{\text{li}}(C_{\text{liver}}/(K_{\text{pli}}/BP))}{\text{from liver}} - CL_{\text{int\_ind}}(C_{\text{liver}}*f_{\text{up}}/K_{\text{pli}}) \quad ;/(7)
\]

\[
\frac{dx_{\text{KIDNEY}}}{dt} = \frac{Q_{\text{ki}}(C_{\text{arterial}} - C_{\text{kidney}}/(K_{\text{pki}}/BP))}{\text{from kidney}} - CL_{\text{int\_Ki}}(C_{\text{kidney}}*f_{\text{up}}/K_{\text{pki}}) \quad ;/(8)
\]

\[
\frac{dx_{\text{HEART}}}{dt} = \frac{Q_{\text{he}}(C_{\text{arterial}} - C_{\text{heart}}/(K_{\text{phe}}/BP))}{\text{from heart}} \quad ;/(9)
\]

\[
\frac{dx_{\text{LUNG}}}{dt} = \frac{Q_{\text{lu}}(C_{\text{venous}} - C_{\text{lung}}/(K_{\text{plu}}/BP))}{\text{from lung}} \quad ;/(10)
\]

\[
\frac{dx_{\text{MUSCLE}}}{dt} = \frac{Q_{\text{mu}}(C_{\text{arterial}} - C_{\text{muscle}}/(K_{\text{pmu}}/BP))}{\text{from muscle}} \quad ;/(11)
\]

\[
\frac{dx_{\text{ADIPOSE}}}{dt} = \frac{Q_{\text{ad}}(C_{\text{arterial}} - C_{\text{adipose}}/(K_{\text{pad}}/BP))}{\text{from adipose}} \quad ;/(12)
\]

\[
\frac{dx_{\text{SKIN}}}{dt} = \frac{Q_{\text{sk}}(C_{\text{arterial}} - C_{\text{skin}}/(K_{\text{psk}}/BP))}{\text{from skin}} \quad ;/(13)
\]

\[
\frac{dx_{\text{BONE}}}{dt} = \frac{Q_{\text{bo}}(C_{\text{arterial}} - C_{\text{bone}}/(K_{\text{pbo}}/BP))}{\text{from bone}} \quad ;/(14)
\]

\[
\frac{dx_{\text{THYMUS}}}{dt} = \frac{Q_{\text{th}}(C_{\text{arterial}} - C_{\text{thymus}}/(K_{\text{pth}}/BP))}{\text{from thymus}} \quad ;/(15)
\]

\[
\frac{dx_{\text{VEN}}}{dt} = \frac{Q_{\text{br}}(C_{\text{brain}}/(K_{\text{pbr}}/BP))}{\text{from brain}} + \frac{Q_{\text{li}}(C_{\text{liver}}/(K_{\text{pli}}/BP))}{\text{from liver}} + \frac{Q_{\text{ki}}(C_{\text{kidney}}/(K_{\text{pki}}/BP))}{\text{from kidney}} + \frac{Q_{\text{he}}(C_{\text{heart}}/(K_{\text{phe}}/BP))}{\text{from heart}} + \frac{Q_{\text{mu}}(C_{\text{muscle}}/(K_{\text{pmu}}/BP))}{\text{from muscle}} + \frac{Q_{\text{ad}}(C_{\text{adipose}}/(K_{\text{pad}}/BP))}{\text{from adipose}} + \frac{Q_{\text{sk}}(C_{\text{skin}}/(K_{\text{psk}}/BP))}{\text{from skin}} + \frac{Q_{\text{bo}}(C_{\text{bone}}/(K_{\text{pbo}}/BP))}{\text{from bone}} + \frac{Q_{\text{th}}(C_{\text{thymus}}/(K_{\text{pth}}/BP))}{\text{from thymus}} - \frac{Q_{\text{lu}}(C_{\text{venous}})}{\text{from venous}} - k_{\text{on}}(C_{\text{venous}}/BP)*R + k_{\text{off}}*DR \quad ;/(16)
\]

\[
\frac{dx_{\text{ART}}}{dt} = \frac{Q_{\text{lu}}(C_{\text{venous}}/(K_{\text{plu}}/BP) - C_{\text{arterial}})}{\text{from arterial}} \quad ;/(17)
\]

\[
\frac{dx_{\text{R}}}{dt} = - k_{\text{on}}(C_{\text{venous}}/BP)*R + k_{\text{off}}*DR \quad ;/(18)
\]

\[
\frac{dx_{\text{DR}}}{dt} = k_{\text{on}}(C_{\text{venous}}/BP)*R - k_{\text{off}}*DR \quad ;/(19)
\]

//des for rifampin model

```c
int i = 0;
while (i <= ndose) {
    double delta = SOLVERTIME - dosetime[i];
    if (SOLVERTIME > dosetime[i]) {
        double ktt_rifa = ktr_rifa*delta;
        dxdt_rifadepot = exp(cumul + nn_rifa*log(ktt_rifa) - ktt_rifa) - ka_rifa*rifadepot ;/(20) rifampin depot compartment (mass)
    }
} else{
```
ktt_rifa = 0;
dxdt_rifadepot = 0;
}
++i;
}

double eff_rifa = (emax_rifa * cp_rifa) / (ec50_rifa + cp_rifa);
//rifampin induction effect on enzyme

dxdt_rifacent = ka_rifa * rifadepot - (cl_rifa * pow(ffm / 70, 0.75) / v_rifa) * rifacent * rifaenz ; //(21)rifampin central compartment (mass)
dxdt_rifaenz = kenz_rifa * (1 + eff_rifa) - kenz_rifa*rifaenz ; //(22)rifampin compartment (mass)

[OMEGA]
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 0.09
0.09 0.09 0.09 0.09 //Kps
0.09 //CL
0.09 //CL_Ki
0.09 //kon
0.09 //Rmax
0.09 //Ka

[OMEGA] @correlation
0.0862 //vmax_rifa
0.389 0.121 //km_rifa

[OMEGA]
0.00616 //v_rifa
0.108 //ka_rifa
0.136 //mtt_rifa
0.474 //n_rifa

[OMEGA]
0.0351 //iovkm_rifa occ1
0.0351 //iovkm_rifa occ other than 1
0.0940 //iovv_rifa occ1
0.0940 //iovv_rifa occ other than 1
0.276 //iovka_rifa occ1
0.276 //iovka_rifa occ other than 1
0.0244 //iovf_rifa occ1
0.0244 //iovf_rifa occ other than 1

[TABLE]
capture CP = Cvenous/BP;
capture GENO = GENO;
capture WEIGHT = weight;
capture CP_RIFA = cp_rifa;
capture CLINT = Clint_ind;
capture dos = last_dose;
capture DELTA = delta;
capture CL_RIFA = cl_rifa;
capture BIO_RIFA = f_rifa;