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Mechanistic Physiologically Based Pharmacokinetic (PBPK) Model of the Heart Accounting for Inter-individual Variability: Development and Performance Verification

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ABSTRACT

Modern model-based approaches to cardiac safety and efficacy assessment require accurate drug concentration-effect relationship establishment. Thus, knowledge of the active concentration of drugs in heart tissue is desirable along with inter-subject variability influence estimation. To that end, we developed a mechanistic physiologically based pharmacokinetic model of the heart. The models were described with literature-derived parameters and written in R, v.3.4.0. Five parameters were estimated. The model was fitted to amitriptyline and nortriptyline concentrations after an intravenous infusion of amitriptyline. The cardiac model consisted of 5 compartments representing the pericardial fluid, heart extracellular water, and epicardial intracellular, midmyocardial intracellular, and endocardial intracellular fluids. Drug cardiac metabolism, passive diffusion, active efflux, and uptake were included in the model as mechanisms involved in the drug disposition within the heart. The model accounted for inter-individual variability. The estimates of optimized parameters were within physiological ranges. The model performance was verified by simulating 5 clinical studies of amitriptyline intravenous infusion, and the simulated pharmacokinetic profiles agreed with clinical data. The results support the model feasibility. The proposed structure can be tested with the goal of improving the patient-specific model-based cardiac safety assessment and offers a framework for predicting cardiac concentrations of various xenobiotics.

Introduction

Accurate prediction of drug effect is valuable in terms of both safety and efficacy. The establishment of the concentration-effect relationship plays a central role in pharmacodynamic (PD) modeling.[1] Therefore, in the first step, the pharmacokinetic (PK) profile should be captured. Cardioactive drugs may trigger their effects by binding to receptors, enzymes, or other targets from either the extracellular or intracellular side of the sarcolemma. Therefore, knowledge of a drug concentration at its site of action (in myocardium, in this case) is strongly needed to comprehend the exposure-response relationship[2] and avoid the bias of the hysteresis effect in response versus time profiles.[1,3] This problem is a matter of scientific curiosity that has a practical significance. PK compartmental models were developed to describe drug myocardial disposition.[4-6] Although they can serve the purpose of PK/PD modeling, they are drug-specific. In addition, such link models are based on steady state concentration-response profiles[7] and are characterized by parameters with limited physiological meaning at best. Against this background, physiologically based pharmacokinetic (PBPK) models track drug disposition over time in compartments that reflect specific organs and tissues, which provides quantitative insight into the physiological processes that drugs undergo. PBPK model parametrization provides compound-independent anatomical and physiological knowledge, which offers a universal mechanistic framework for PK prediction in tissues of interest.[8,9] Furthermore, this "bottom-up" approach allows for a priori prediction of the inter-individual variability that results

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from physiology diversity in a population.[9-11] It is especially important in light of a U.S. Food and Drug Administration briefing document[12] that has indicated that the estimation of the effects of various intrinsic and extrinsic factors on a drug's PK and PD is one of the crucial tasks in the drug development process. Regarding cardiac modeling, the supportive role of PBPK in drug exposure assessment was directly expressed.[7,13]

We recently proposed a 4-compartment cardiac model nested in the full PBPK structure,[14] which aimed to be the first PBPK heart model published as a basis for predicting drug distribution within cardiac tissue. The model that we propose in this study goes further and has overcome the limitations that previously arose. The provided structure is fully mechanistic, accounts for cardiac metabolism, passive diffusion and active transport in heart tissue, and distinguishes between extracellular and intracellular spaces. It has been integrated with a submodel for metabolites and allows for the estimation of cardiac concentration of both parent compound and metabolites with inter-individual variability. Thus, it offers a promising basis for effective cardiac concentration prediction. We used the models to predict the concentration-time profiles in plasma and the heart for amitriptyline (as a model drug) and its main metabolite, nortriptyline, after an amitriptyline infusion.

Materials and Methods

PBPK Model Building

The model was written as a set of ordinary differential equations. The model building process covered the following steps:

(1) Defining the compartments of interest for the parent compound and the metabolite,
(2) Model parametrization assuming a reference human,
(3) Unknown parameters value optimization,
(4) Inclusion of inter-individual variability in a healthy Caucasian population in the model parameters.

The following general assumptions were made: the compartments are homogenous, the physiological model structure-related parameters are time-independent, and the equilibrium between the blood and tissues is reached immediately. Full PBPK and minimum PBPK models were developed for the parent compound and the metabolite, respectively.

Definitions of all model parameters are presented in Supplementary Material 1.

Full PBPK and the Heart Model

To predict the parent compound PK, we maintained the scaffold structure of the full PBPK that we previously established,[14] having adopted it from the study by Jones and Rowland-Yeo.[8] Only a few model parameters were redefined. The values of all full PBPK system–related input parameters for an average human are presented in Supplementary Material 1. Tissue to plasma partition coefficients (Kps) were calculated according to the Rodgers-Rowland equation.[15,16] Kp_{re_ami}—the tissue to plasma partition coefficient for remaining tissues in the body that were lumped into the "rest" compartment in the full PBPK model was fixed at 1. The assumptions of perfusion rate-limited kinetics, the equilibrium between total drug concentrations in the tissue and in the plasma at steady state, and nonlinear hepatic metabolism according to Michaelis-Menten enzyme kinetics are valid.

The PBPK heart model was nested in the whole-body PBPK. The proposed cardiac structure was assumed to consist of 5 compartments: pericardial fluid (PF), heart extracellular compartment (HEART EC), and epicardial intracellular (EPI IC), midmyocardial intracellular (MID IC), and endocardial intracellular (ENDO IC) compartments, which were linked under the assumption of permeability-limited kinetics. Cardiac metabolism is to occur in intracellular compartments. Drug distribution within cardiac tissue, both by passive diffusion and active transport, was considered.

Model parameters were derived from the literature, and because the verified cardiac model structure is one of the original results of the study, it is presented in the Results section.

Minimum PBPK Model

For the metabolite time-concentration profile predictions, we adapted the minimal PBPK model extended with the hepatic compartment.[17] The metabolite formation was assumed to occur in both the liver and heart compartments. The clearance was assigned to the liver compartment (hepatic clearance—CL_{hep}) and central compartment (nonhepatic clearance—$CL_{non\text{-}hep}$). The model parameters were literature-derived and consistent with parameters describing full PBPK blood flows, organ volumes, and Cytochromes P450 (CYPs) abundance (Supplementary Material 1). Tissue to plasma partition coefficients (Kps) were calculated according to the Rodgers-Rowland equation.[15,16] The assumptions were the same as for the full PBPK model, that is, perfusion rate-limited kinetics, the equilibrium between total drug concentrations in the tissue and in the plasma at steady state, and nonlinear hepatic metabolism according to Michaelis-Menten enzyme kinetics.

Drug-Related Parameters

The simulations were run for amitriptyline and its metabolite, nortriptyline. The literature-derived values of parameters used in the study are presented in Table 1. Kinetic parameters of amitriptyline and nortriptyline biotransformation for respective CYPs isoforms[31,32] are published in Supplementary Material 1.

Model Fitting

The values of 5 parameters could not be found in the scientific literature. Thus, they had to be estimated. The unknown parameters included Kp_{re_nor}—the tissue to plasma partition coefficient for remaining tissues in the body that were lumped into the "rest" compartment in the minimal PBPK model; fuh_{ami}—the fraction of amitriptyline actively transported to hepatocytes; fuh_{nor}—the fraction of nortriptyline actively transported to hepatocytes; CL_{efflux}—the active efflux transport at the membranes of cardiomyocyte (intracellular) compartments [L/h]; and CL_{uptake}—the active uptake transport at the membranes of cardiomyocyte (intracellular) compartments [L/h].

The model was fitted simultaneously to the following:

(1) Individual concentrations of amitriptyline and nortriptyline in venous blood observed in a healthy man, age 21, weighing 83 kg after intravenous infusion of 43 mg of amitriptyline,[26]
(2) Two fixed data points of amitriptyline total concentrations in heart tissue assumed to be equal at steady state *Kphe* times more than in plasma. The simulated steady state drug plasma concentration was achieved after a 200-h infusion of amitriptyline.

The parameter start values as well as the upper and lower bounds used in the fitting process are presented in Table 2.