Development of a Permeability-Limited Cardiac Physiologically-Based Pharmacokinetic Model for Predicting Cardiac Exposure

Zofia Tylutki[1,2], Ciarán Fisher[1], Mark Holbrook[1], Sebastian Polak[1,2]

[1] *Certara UK Limited, Simcyp Division, QSTS, Sheffield, United Kingdom* [2] *Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland*

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Permeability-limited **cardiac PBPK model** can be used to predict **local drug concentration** in the heart tissue

Background & Objective

- Physiologically-based pharmacokinetic (PBPK) models can be used to predict local tissue concentrations, specifically the concentration within the target tissues of toxic endpoints.
- Cardioactive drugs may trigger their effects by binding to receptors, enzymes, or other targets from either the extracellular or intracellular side of sarcolemma.
- Sarcolemma may act as a permeability barrier, and so active transport may contribute to drug distribution within cardiac tissue, as many efflux and influx transporters are known to be expressed in human cardiac tissue.
- The local myocardial drug concentration may not only be affected by uptake or efflux, but also the metabolic activity of the heart as cytochrome P450 enzymes are expressed in cardiac tissue.
- A multi-compartment permeability-limited model of a heart was developed to address these issues [1,2].
- Implementation of the developed heart model in the Simcyp PBPK Simulator (Certara UK Ltd., UK) will facilitate further model verification, wider application, and iterative refinement of the model.

Methods

- The PBPK model of heart was written as a set of ordinary differential equations in R environment, v.3.4.1 [3]. Numerical solutions were computed using *deSolve* library.
- Most of the model parameters were literature derived.
- The inter-individual variability was included in model parametrization.
- Amitriptyline (AT) and its main metabolite – nortriptyline (NT), served as model compounds for model performance verification.
- Model performance verification was through two approaches:
  1. By simulating the PK of AT or AT and NT observed in clinical studies and clinical cases described in the literature. The results were compared with experimentally observed data.
  2. By treating the PBPK model predicted AT and NT cardiac concentrations as the active drug fraction surrogate, and using it in simulations of the AT triggered cardiac electrophysiological effect in clinical studies and clinical cases described in the literature where AT was administered orally:
     - In therapeutic doses
     - In supratherapeutic doses.

  For simulations of the electrophysiological effect the Cardiac Safety Simulator (CSS) (Certara UK Ltd., UK) was used.

Results

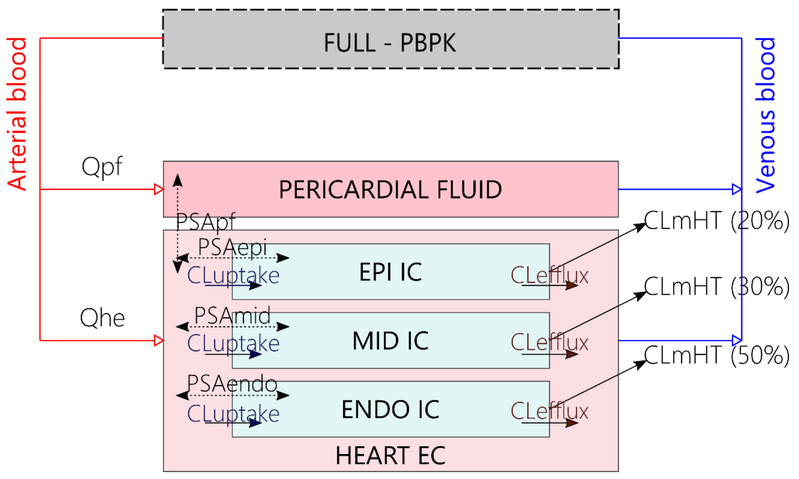
MODEL STRUCTURE

- The developed heart PBPK model comprises five compartments representing:
  - The pericardial fluid,
  - Heart extracellular water (HEART EC),
  - Epicardial intracellular fluid (EPI IC),
  - Midmyocardial intracellular fluid (MID IC),
  - Endocardial intracellular fluid (ENDO IC).
- Active transport and cardiac metabolism are incorporated into the model (Fig 1).
- To predict NT (metabolite) concentration, a minimal PBPK, rather than whole-body (full) PBPK model was applied.

MODEL PERFORMANCE VERIFICATION

- In terms of predicting PK of AT and NT after AT given intravenously (Fig 2) or orally (Fig 3), the simulated concentrations in most cases were within two-fold of the experimental values. The compared metrics were: mean of concentrations, AUC, and C_{max}.
- In terms of predicting AT triggered cardiac electrophysiological effect (Fig 4):
  - When AT was administered in therapeutic doses, the simulated mean ΔQTc did not exceed 5 ms in either of the assessed time points, as in the clinic.
  - In cases of AT intoxications the effect of QTc interval prolongation and increase in heart rate was mimicked in simulations.

Figure 1: The structure of the multicompartmental PBPK heart model nested in the full-PBPK model



Discussion

- Knowledge of cardiac active drug concentration at the site of action, myocardium, is important. Direct measurements may pose problems which can be overcome through PBPK modelling and simulation of drug concentrations which can inform cardiac safety assessment.
- The multi-compartmental model structure described here is parametrized with human relevant physiological data and reflects the heart anatomy in its structure.
- Despite model assumptions, the results of population PBPK–QSTS analysis indicate that the proposed model is a promising structure for further development and verification.
- A prototype model has been implemented in R, and is now being implemented in the human Simcyp PBPK Simulator (Certara UK Ltd., UK) as part of the TransQST project.

Figure 2: Simulated Amitriptyline (AT) and Nortriptyline time-concentration profile after AT infusion pooled collectively.

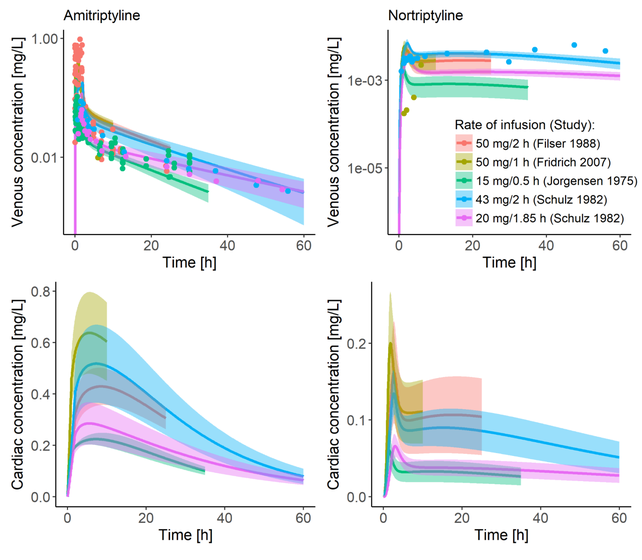


Figure 3: The ratio of predicted mean concentrations to observed mean concentrations of Amitriptyline (red dots) and Nortriptyline (blue dots)

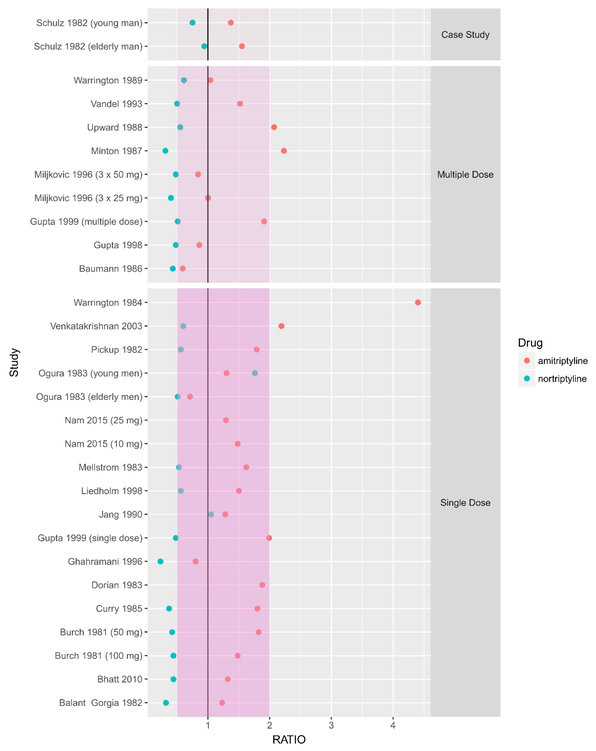
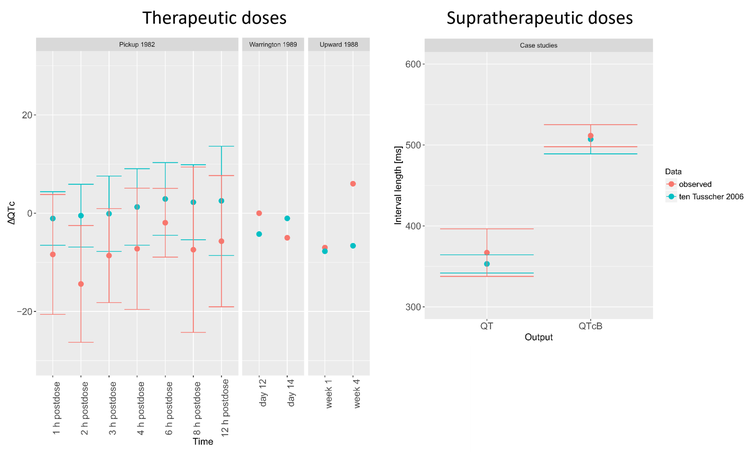


Figure 4: The results of PBPK-QSTS modeling in ten Tusscher [4] ventricular cardiomyocyte cell model implemented in CSS compared to clinically observed values.



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This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116030. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.