Physiologically based pharmacokinetic model (PBPK) for the halofantrine cardiac effect prediction - proof of concept study towards the system for the antimalarial drugs cardiac safety assessment

Sebastian Polak[1,2], Barbara Wiśniowska[2]

[1]Simcyp Ltd (part of Certara), UK, [2]Unit of Pharmacoepidemiology and Pharmacoeconomics, Jagiellonian University, Poland

Background

Malaria remains a serious health burden across the world especially in the under-developed countries. The interest in the assessment of cardiotoxicity of antimalarial drugs has recently been renewed. Antimalarial drugs help to cure the disease yet, at lese some can, carry serious safety problems due to cardiac arrhythmias, possibly fatal, in both adults and children. The aim of this study was to establish a model based cardiac safety assessment framework. Halofantrine which is considered an effective treatment for multi-drug resistant falciparum malaria has demonstrated arrhythmogenic potential, including torsade de pointes and patients deaths, was chosen as an example.

Methods

Average clinical data describing halofantrine (HAL) and its active metabolite N-desbutylhalofantrine (DB-HAL) concentration change in time after single oral dose of 500 mg was derived from the Charbit et al. [1]. Plasma concentration values and their standard deviation after graph digitization were used as input for the simple empirical two-compartmental model to simulate individual concentrations for 12 virtual individuals to mimic the clinical trial scenario. After correction for the plasma protein binding (fu=0.004 for both moieties), the simulated individual plasma exposure was directly used as input (parameter concentration in the Hill equation). Information about the concentration dependent main ion currents inhibition triggered by the two entities, in a form of IC50 (micromoles) values were derived from the literature or predicted using QSAR models (Table 1).

Table 1. IC50 values against main cardiac ion channels. *predicted

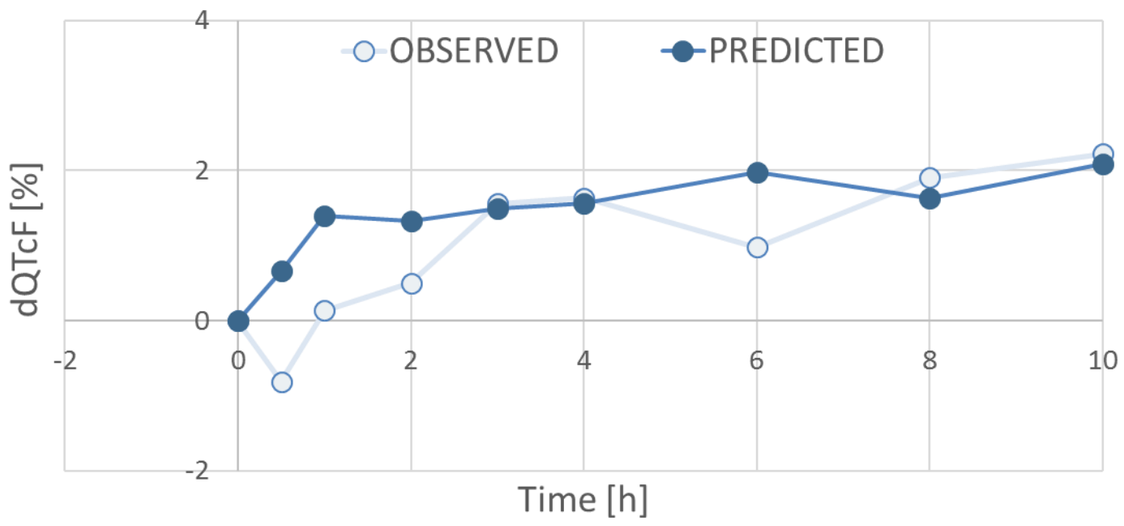
	IKr	INa	ICa
HAL	0.0216	331.2	1.9
DB-HAL	0.0717	6.71*	6.55*

The inhibition factors for specific currents were calculated using the Hill equation. The Cardiac Safety Simulator (CSS) v2.1 was used to simulate the drug-triggered ECG modification [2]. ten Tusscher model of human cardiac electrophysiology in a one-dimensional, heterogeneous string of ventricular epicardial, midmyocardial, and endocardial cells setting was used during the study [3].

Results

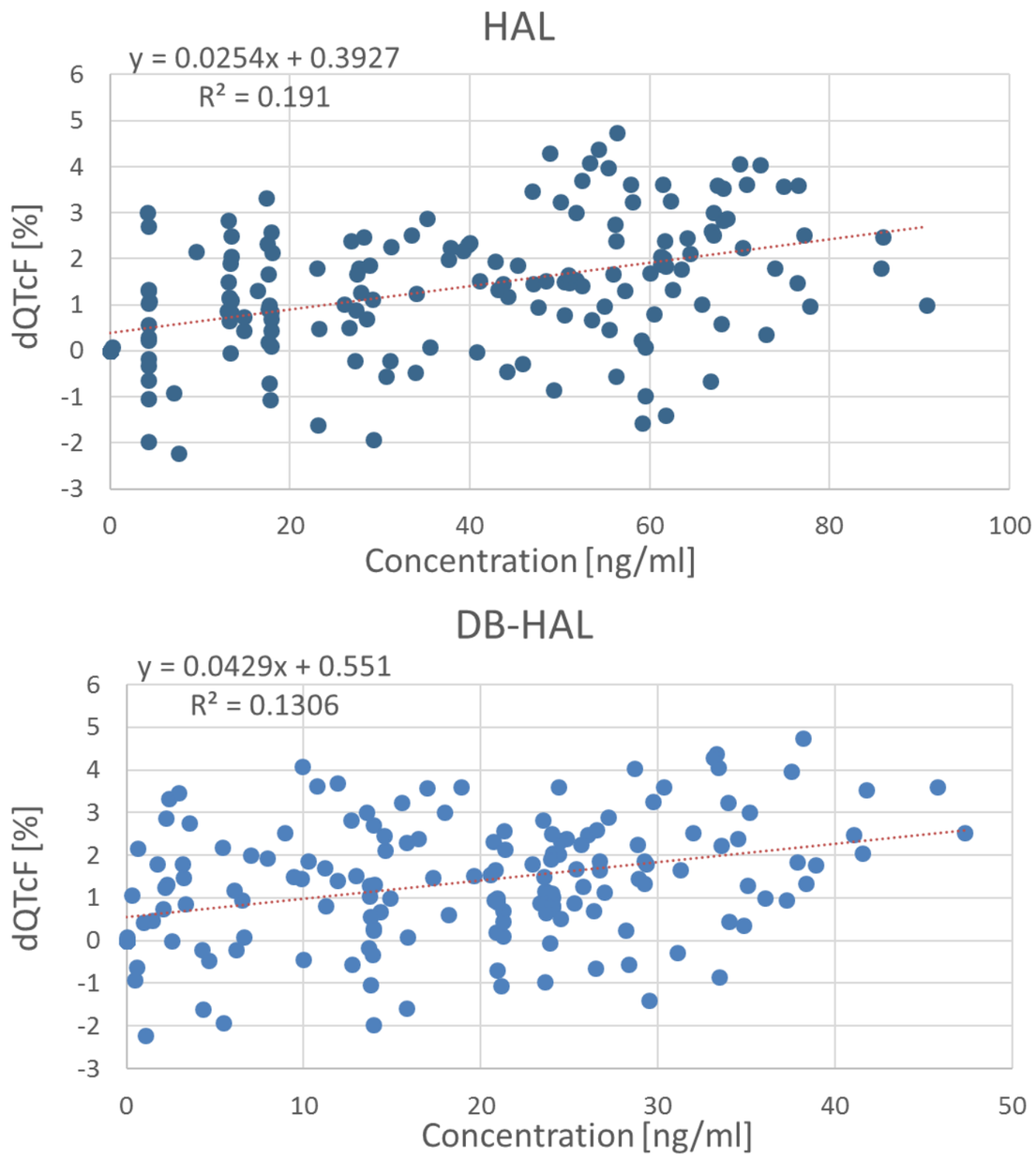
The predicted results expressed as the QT (corrected with the use of Fridericia correction formula) change relative to baseline were compared against the observed values of the same character (Figure 1).

Figure 1. Mean observed and predicted QTc values.



The clinically observed maximum of QTc increase reached 2.6% which is in line with the simulated value of 2.4%.

Figure 2. Concentration–effect relationship for HAL and DB-HAL.



This study aim was to assess whether a mechanistic model of human cardiac electrophysiology can be applied to antimalarial drug safety assessment. The middle-out approach (in vitro currents inhibition data combined with clinical exposure information) were used to predict cardiac effect of the halofantrine and its active metabolite.

- For the tested concentrations halofantrine did not prolong the QT above 5% as compared against the baseline yet the prolongation effect was concentration-dependent and the developed current model can be used to assess potential clinical effect in higher doses and concentrations.
- The obtained results show that mechanistic modelling and simulation approach can be utilized for the safety assessment.

[1] Charbit B. et al. Pharmacokinetic and pharmacodynamic interaction between grapefruit juice and halofantrine. Clin Pharmacol Ther. 2002 Nov;72(5):514-23.

[2] www.certara.com/software/pbpk-modeling-and-simulation/cardiac-safety-simulator/

[3] ten Tusscher K. et al. Cell model for efficient simulation of wave propagation in human ventricular tissue under normal and pathological conditions. Phys Med Biol. 2006 Dec 7;51(23):6141-56.