Simulation of pharmacokinetics of amitriptyline and nortriptyline and their common effect on human cardiac electrophysiology in healthy population

Zofia Tylutki[1], Sebastian Polak[1,2]
zofia.tylutki@doctoral.uj.edu.pl

[1] Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland, [2] Simcyp (a Certara Company) Limited, Sheffield, UK

OBJECTIVES

In assessing drug triggered cardiac effect the parent drug and its metabolites' exposure in cardiac tissue seems to be of particular interest, although drug level in plasma is the most commonly used as the effective concentration surrogate. The aim of the study was to simulate drug influence on the electrophysiology of human cardiomyocytes in the population, taking into account individual PBPK model-predicted drug and its metabolite concentrations both, in heart and plasma. Amitriptyline and nortriptyline were used as the model substances.

METHODS

Amitriptyline time-concentrations profiles in plasma and heart tissue were simulated in a whole-physiologically-based pharmacokinetic (PBPK) model with four-compartment heart model nested in [1]. The model has been extended with the intra- and extracellular spaces in cardiac model and minimum-PBPK model for the metabolite [2] consisted of 4 compartments (plasma, heart, liver, and rest of the body) of physiological volumes and blood flows. 3 parameters of minimum PBPK model were fitted to the clinical data on amitriptyline and nortriptyline plasma concentrations. The simulation scenario followed study methodology by Pickup et al. [3]. The models were written in R v.3.3.2. After defining the dose amount (single oral dose of 75 mg), number of individuals (8), number of females (0), and age range (20 – 28) the sex- and age- dependent physiological model parameters were randomized to account for inter-individual variability. The seed was set to 1111. 10 iterations of simulation were run. Predicted individual free concentrations of amitriptyline and nortriptyline both, in plasma and the heart (with no distinction of cardiac compartments), were combined with patient-specific parameters and in vitro ion channel inhibition to simulate pseudoECG traces in Cardiac Safety Simulator (CSS) [4], and ΔQTcB as an ultimate endpoint. The build-in to CSS ten Tusscher model [5] was used as a biophysical description of cardiac myocytes. Inter- and intra-individual variability was simulated at this stage with the use of individually predicted cardiomyocytes volume, area, capacitance, and circadian-dependent plasma electrolyte concentrations and heart rate.

Values of unbound fractions of amitriptyline and nortriptyline in plasma (fu_p) and heart tissue (fu_h), and CSS input IC_{50} [mcM] [6] (concentration of a drug that is required for 50% current inhibition) used in the simulations are presented in Table 1.

Table 1. Values of CSS input parameters referring to current inhibition and protein binding for amitriptyline and nortriptyline

Drug	Current	IC_{50} [μM]	Model	fu_p	fu_h
Amitriptyline	$I_{ca(L)}$	21.9	CHO	0.054	0.0013
	I_{Kr}	1.801	CHO		
	I_{Na}	3.5	HEK		
Nortriptyline	I_{Kr}	2.27	HEK	0.083	0.001

RESULTS

The ranges of the mean difference between the length of QTcB after drug administration and at baseline (ΔQTcB) simulated for free plasma and free heart were as follows: from -3.04 ms (1 h postdose) to 6.14 ms (6 h postdose), and from -3.22 ms (1 h postdose) to 4.21 ms (6 h postdose). Mean of observed and simulated ΔQTcB values together with their standard deviations are presented in Figure 2.

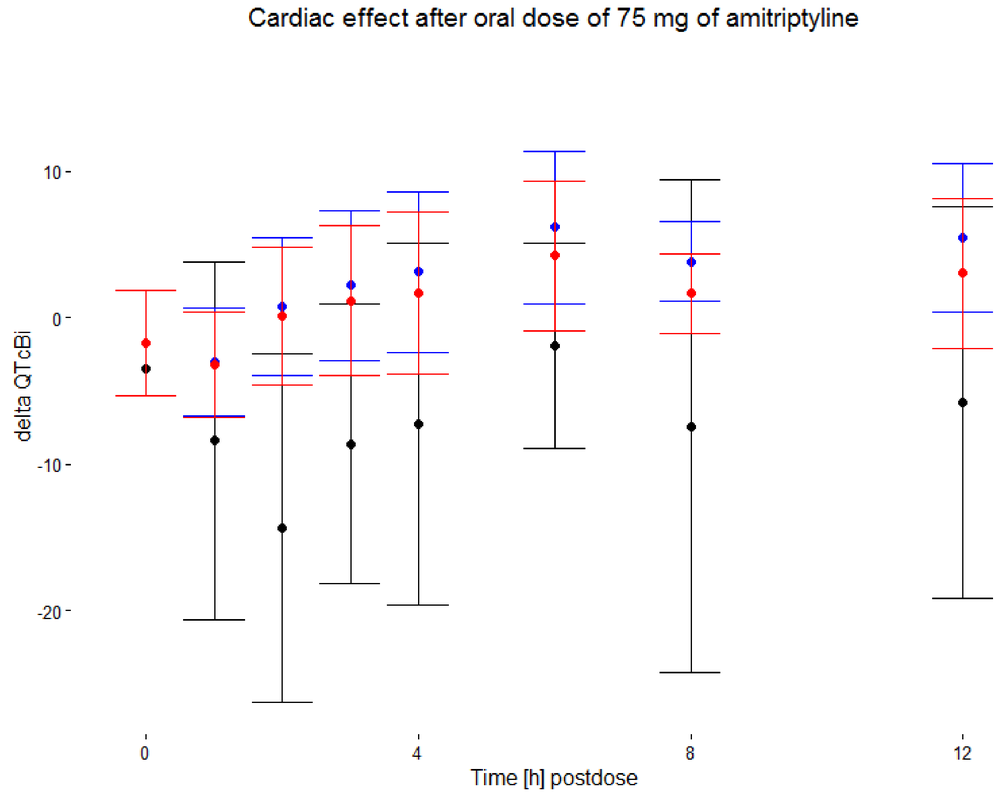

Figure 2. Mean values with SD of ΔQTcB [ms] observed [3] (in black), simulated in CSS with the use of free plasma concentrations predicted in PBPK model (in blue), simulated in CSS with the use of free cardiac concentrations predicted in PBPK model (in red)

CONCLUSIONS

Simulated ΔQTcB value did not exceed 5 ms (value of regulatory concern) in neither of the assessed time points if the cardiac concentration of amitriptyline and nortriptyline predicted in full PBPK model was used as an active concentration surrogate. The simulated study was negative regarding a threshold pharmacologic effect on myocardial repolarization which was in accordance with in vivo observations [3]. The results of this study support the predictive abilities of in silico simulations as well as PBPK modeling.

REFERENCES

[1] Tylutki, Z, Polak, S. Scientific Reports, 7 (2017): 39494.
[2] Cao, Y, Jusko, W. Journal of Pharmacokinetics and Pharmacodynamics, 39 (2012): 711-723.
[3] Pickup, AJ et al. Journal of Cardiovascular Pharmacology, 4 (1982): 575-83.
[4] Glinka, A, Polak, S. Toxicology Mechanisms and Methods, 25 (2015): 279-286.
[5] ten Tusscher, KH et al. Am J Physiol Heart Circ Physiol 286 (2004): H1573–89.
[6] Polak, S et al. BMC Pharmacology and Toxicology 13.1 (2012): 6.

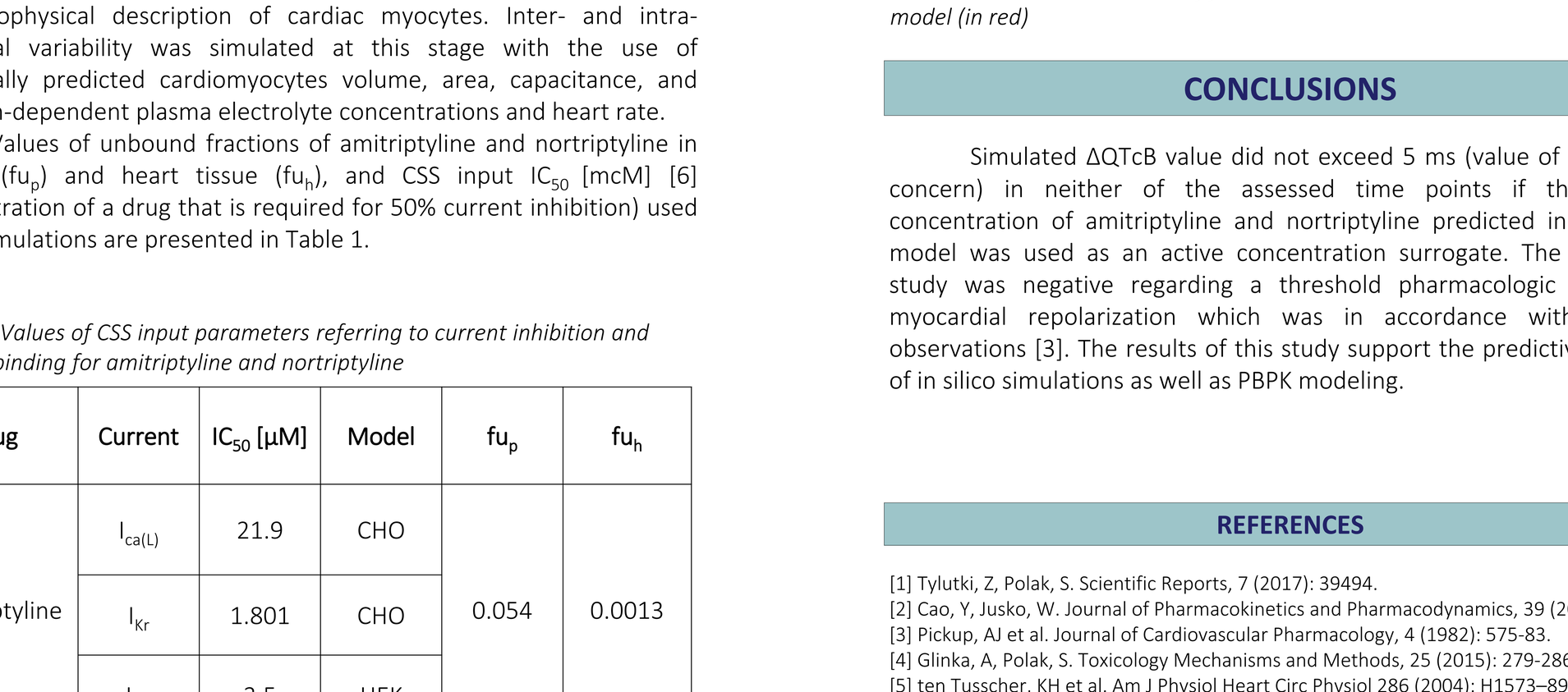

Figure 1. One out of ten simulation results of PK of amitriptyline (left plot) and nortryptyline (right plot). Points with error bars represent mean and SD of observed concentration [3]. Lines stand for individual simulated PK profiles