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Prediction of QT changes in humans incorporating *in vitro* data into physiologically based cardiomyocyte cell model - a case study on inhibition of multiple cardiac ion currents by tolterodine and its metabolite

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Introduction

There are various models and techniques available to identify the risk of QT prolongation liability at preclinical level, including widely accepted *in vitro* systems. However, there exists a translation gap in quantitative extrapolation of the *in vitro* cardiac safety data, typically collected at the preclinical level, to the clinical situation. Rules of thumb, decision trees and expert systems available to qualitatively (yes/no) predict clinical QT prolongation in humans or at best to guide type of assays to be carried out at next level of assessment. Physiologically based biophysically-detailed models of cardiac physiology that can characterise influence of various ion channels on the electrophysiology of human cardiomyocyes can bridge translational gap in cardiac safety assessment and allow extrapolation of *in vitro* ion channel activity of a drug to human situation incorporating physiological, demographic, genetic and circadian variability. Such mechanistic model is implemented in the Cardiac Safety Simulator (CSS, previously ToxComp) [1,2].

Purpose:

To study the impact of considering only I_{Kr} (rapid delayed rectifying current) or all ion channel currents inhibition by Tolterodine (TOL) with and without its electro-physiologically active metabolite 5-hydroxymethyl tolterodine (5-HMT) on prediction of clinical QT prolongation of Tolterodine using the CSS platform. The bio-relevance of total versus free plasma concentration for QT prolongation effect was also studied.

Materials and Methods

All simulations were run in the ToxComp version 1.4 (which is now incorporated into the CSS v1.0). Total and free mean maximum human plasma concentrations (C_{max}) of TOL and 5-HMT in both CYP2D6 extensive metaboliser (EM) and poor metaboliser (PM) subject groups after 4 mg b.i.d. oral dose of TOL were obtained from literature [3]. *In vitro* IC_{50} values of both TOL and 5-HMT towards I_{Kr}, I_{Na}, (sodium current) and I_{CaL} (late calcium current) were obtained from the literature and reported in Table 1. The predicted QT prolongation (ΔQTcF) was then compared with the reported Thorough QT (TQT) study results [3].

Table 1. IC_{50} values of TOL and its 5-HMT with respect to I_{Kr} (rapid delayed rectifying current), I_{Na} (sodium) and I_{CaL} (late calcium current).

Cardiac Ion Channel Current	IC_{50} Value (µM)	
	Parent (TOL)	Metabolite (5-HMT)
I_{Kr}	0.011	0.5
I_{Na}	5	15
I_{CaL}	0.143	0.15

Results and Discussion

The simulated QT prolongation (ΔQTcF) of the combined population (EM+PM) with various inputs are shown in Table 2 and compared with the clinical data. When the inhibitory activity of only parent drug towards only I_{Kr} current and total plasma concentration was used as bio-relevant concentration (**SIM1**), the predicted QT prolongation was significantly higher than clinically observed QT prolongation. The predictions were improved when free plasma concentration of TOL and information for all ion channels were used (**SIM4**); however it was still almost two fold higher than the clinically observed values. When the electrophysiological activity of the active metabolite was incorporated into the model (**SIM8**), the clinically observed response was recovered very well. As per table 1, the metabolite is relatively less potent than TOL at inhibiting I_{Kr}, hence QT prolongation was not significant in EMs whereas it was considerably larger in PM subjects (**SIM8**).

Table 2. Predicted QT prolongation response at various simulation inputs compared with reported clinical QT prolongation response

Study	SIM1	SIM2	SIM3	SIM4	SIM5	SIM6	SIM7	SIM8	Clinical
Operating concentrations to drive QT	Total	Free	Total	Free	Total	Free	Total	Free	
In vitro $IC_{50\%}$ input	Only I_{Kr}	Only I_{Kr}	I_{Kr}, I_{Na}, I_{CaL}	I_{Kr}, I_{Na}, I_{CaL}	Only I_{Kr}	Only I_{Kr}	I_{Kr}, I_{Na}, I_{CaL}	I_{Kr}, I_{Na}, I_{CaL}	
Choice of active moiety (Parent alone or with Metabolite)	Only Parent	Only Parent	Only Parent	Only Parent	Parent + Metabolite	Parent + Metabolite	Parent + Metabolite	Parent + Metabolite	
ΔQTcF (ms) for CYP2D6 EMs	24.66	-4.35	43.05	11.01	30.83	7.12	6.79	-1.8	NA*
ΔQTcF (ms) for CYP2D6 PMs	52.83	6.49	7.87	10.02	47.16	13.15	1.27	9.77	NA*
ΔQTcF (ms) Overall^	37.34	0.53	27.22	10.57	38.18	9.83	4.31	3.41	5.6

QTcF is the QT interval corrected for heart rate using Fridericia correction method; NA- Not available; * Separate estimate of ΔQTcF for EM and PM groups were not provided in reported clinical study. ^ Clinical study comprised of 45% PM population, hence for simulation results ΔQTcF overall is calculated considering 45% of subjects as PM as opposed to natural frequency of ~8%.

Conclusions:

Physiologically based models such as those incorporated in the Simcyp CSS provide capability to combine available *in vitro* information for parent and metabolite or co-administered drugs to provide reliable prediction of clinical QT response of particular therapy and helps to bridge the currently existing translational gap in quantitative extrapolation of the *in vitro* cardiac safety assessment to the clinical scenario.

References:

[1] Polak et al. 2012, Computing in Cardiology, 39, 789; [2] Glinka and Polak 2012, Bioinformation, 8, 1062; [3] Malhotra et al., 2007, CPT, 81, 377