Simulating pharmacokinetic and pharmacodynamic impact of the drug formulation on the human cardiac safety by applying in vitro – in vivo extrapolation approach

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Purpose of the study

Changing formulation of marketed drugs may influence drug pharmacokinetics and hitherto their safety. The aim of this study was to simulate drugs' formulation effect on electrophysiology of human cardiomyocytes. Diclofenac (DICLO) given as hydroxypropyl-β-cyclodextrin (HPβCD) novel IV formulation [Carr 2013] and dolasetron (DOL) given as PO and IV formulations [Hunt 1995, Hunt 1996] were used as the model drugs.

Methods

For DICLO and HPβCD clinically observed average plasma concentrations were directly utilized and simulation was repeated 10 times [Carr 2013]. For dolasetron Simcyp (V13.1) compounds were developed with the use of the available ADME data and simulated individual plasma concentrations of DOL together with its two main metabolites, namely hydrodolasetron (HDOL) and hydroxyhydrodolasetron (OH-HDOL) after IV and PO dose were utilized. For both cases concentrations were corrected for protein binding (fu as presented in Table 1).

Cardiac Safety Simulator (CSS) V1.0 was used to simulate pseudoECG signal [Glinka 2014]. CSS input data included exposure data as described above and IC_{50} values describing ionic currents inhibition (μM) presented in Table 1.

Table 1. In vitro ionic currents inhibition IC_{50} and fu values

Compound	Current	IC_{50}	Source/Method	fu	Source
DICLO	IKr	30.00	Kristof 2012 / dog CM	0.005	Kurkov 2012
	IKs	40.00	Kristof 2012 / dog CM		
	ICaL	12.89	Yarishkin 2009/rat CM		
HPβCD	IKr	2500.0	Polak 2011 / QSAR	1	Assumed
DOL	IKr	4.09	Kuryshev 2000 / HEK	0.25	Anzemet product sheet
	IKs	31.01	Polak 2011 / QSAR		
	INa	38.00	Kuryshev 2000 / HEK		
HDOL	IKr	8.32	Kuryshev 2000 / HEK	0.25	Anzemet product sheet
	IKs	13.75	Polak 2011 / QSAR		
	INa	8.50	Kuryshev 2000 / HEK		
OH-HDOL	IKr	2.15	Kuryshev 2000 / HEK	0.25	Assumed
	IKs	24.94	Polak 2011 / QSAR		
	INa	3.02	Polak 2011 / QSAR		

Simulations were set to mimic clinical trials and the following were simulated: for HPβCD-diclofenac combination 37.5 and 75mg PO doses were considered. Cardiac effect for 70 healthy individuals (55.75% male) with mean age 23.3 years (range 18-49) was simulated [Carr 2013]. Inter-occasion variability was accounted for by using drugs concentration from various time of the day. For intravenously given DOL two dose ranges namely 2.5-3.0, 3.5-5.0 mg/kg were taken under consideration. Exposure was simulated within Simcyp platform for 16 healthy male individuals [Hunt 1995]. For orally taken DOL exposure after five doses namely 25, 50, 100, 150, 200 mg for 6 healthy male individuals was simulated within Simcyp [Hunt 1996]. ΔQTcF (DICLO) and QTcB (DOL) respectively were used as the ultimate endpoints.

Results

For DICLO lack of statistically significant differences between the predicted and observed in vivo values of ΔQTcF was confirmed for both doses using t-Welsh test ($p>0.05$). The mean ΔQTcF at each time point was beyond 5 ms (FDA regulatory threshold) as presented in Figure 1.

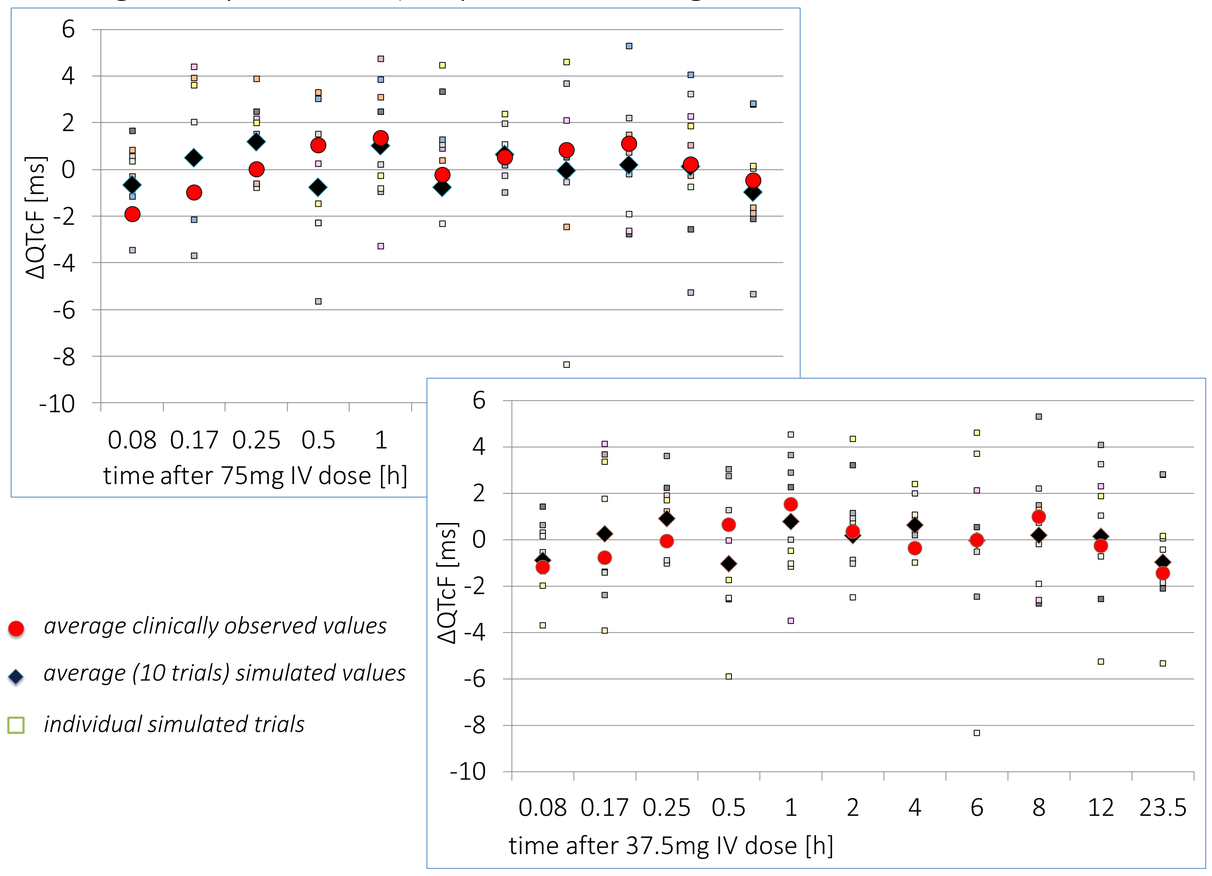

Figure 1. Observed vs. predicted ΔQTcF values for two DICLO+HPβCD doses

For DOL simulation results confirmed concentration-QTcB trend for PO formulation in the tested doses range with lack of statistically significant differences between the predicted and observed in vivo values in t-Welsh test ($p>0.05$) for separate doses (Figure 2).

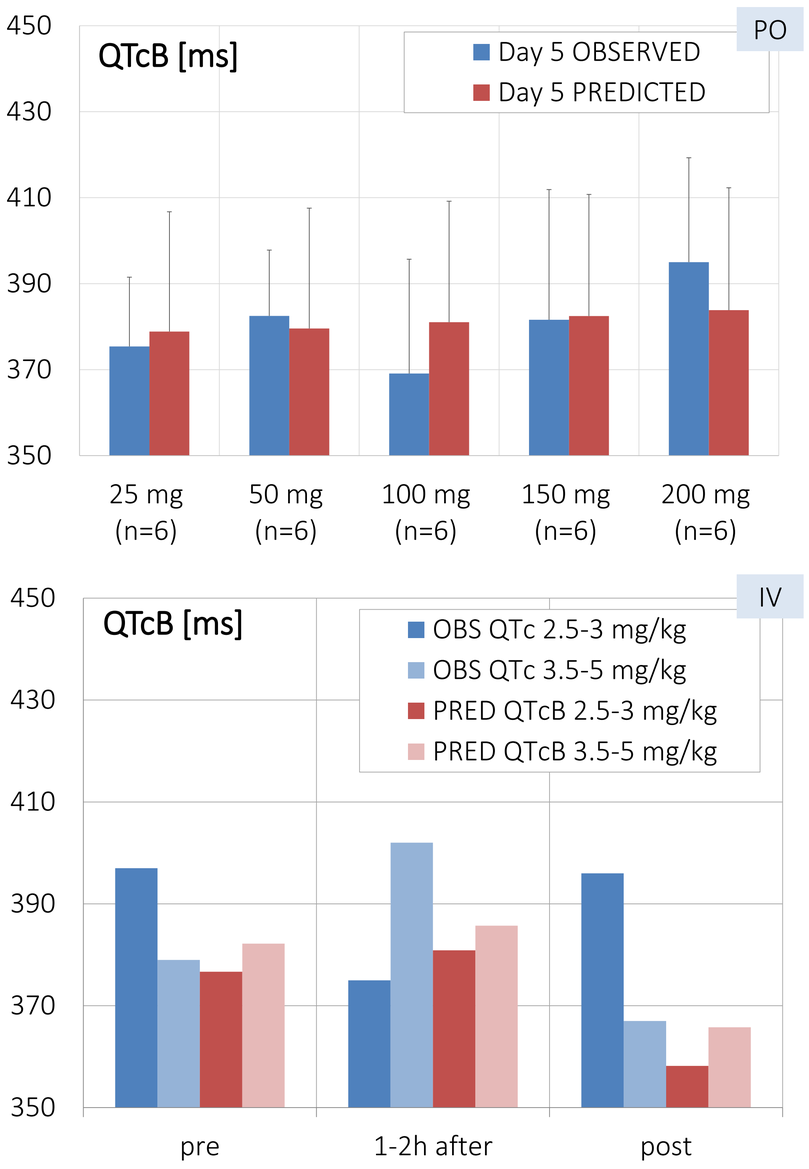

Figure 2. Observed vs. predicted QTcB values for two DOL formulations given IV and PO

Conclusions

The results of this study support predictive abilities of the in silico simulations. If such approach is properly used such methods can accurately anticipate the consequences of various scenarios including those where clinical effect can be potentially modulated by the drug formulation and its excipients.

References

Carr 2013 ClinTher 35(5):647-658; Glinka 2014 ComputBiolMed: 7:20-26; Kristof 2012 PLOSOne 7(12): e53255; Yarishkin 2009 KoreanJPhysiolPharmacol; 3(6):437-42; Polak 2011 AppSoftComp 11(2):2611-2617; Kurkov 2012 JPharmSci 101(12):4402-4408; Anzemet PRODUCT MONOGRAPH (products.sanofi.ca/en/anzemet.pdf)