Modeling and Simulation Approach for Assessing Proarrhythmic Potency of the Non-Cardiological Drugs

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Abstract

The study aimed to assess the usefulness of the modeling and simulation approach for the proarrhythmic potency of the non-cardiological drugs prediction. Ability to mimic population effect with use of the virtual population generator on the QTc value was tested. ToxComp version 1.5 (www.tox-comp.net) with ten Tuscher human cardiomyocyte model (1D string - Epi/M/Endo - 20/30/50%) was used to mimic the clinical study and formoterol was chosen as a model drug (Lecaillon study - 8 males/4 females, mean age[SD] – 24[6]). Simulation time was set to 10 seconds and the QTc [ms] value with Fridericia correction was chosen as an endpoint. Obtained simulation results were compared with clinical study outcomes. None of the differences between observed and predicted values were statistically significant (t-test). Current study proves that such phenomena can be predicted with use of the mathematical models working on the population level.

1. Introduction

Recently published data proves that the data safety remains an issue. Such phenomena occur regardless of more and more careful evaluation of the potential toxic effects of the investigated compounds. On the other hand, cautious safety profile testing results in high failure rate at various levels of drug development.

According to the available sources cardiotoxic (proarrhythmic) effect remains one of the main reasons of the drug related toxic effects [1]. There are several available models utilized for the drugs proarrhythmic potency assessment at various levels of the drug development. The most commonly utilized and probably most reasonable pathway includes in vitro models where the human ionic channels are heterologously expressed in non-human (i.e. XO, CHO) and human (i.e. HEK) cells, in vivo/ex vivo animal studies where suggested species are used for the whole heart drug influence evaluation and currently best available yet costly and still not perfect clinical studies - thorough QT/QTc studies (TQTs). The role of the latter one is to establish whether the studied drug influences the myocardial repolarization that might potentially lead to the Torsade de Pointes arrhythmia (TdP) but it should be noted that there is a range of problems and potential pitfalls connected with such studies including choice of the dose, positive control, and other elements including default endpoints correction by heart rate (QT/QTc). In recent years more and more effort is put toward using in silico methods and better utilizing the in vitro studies results. As QSAR models being relatively easy to develop (depending mostly on the data range and quality rather than algorithms proposed) could be utilized as a very early screening tools it brings a concept of wider implementation of the mechanistic models mimicking the human heart physiology. The in vitro – in vivo extrapolation (IVIVE) of the drug pharmacodynamics effect has been adopted from the pharmacokinetic studies where such paradigm is already a well-established technique. Platform allowing for the extrapolation of the in vitro measured, drugs triggered inhibition of various ionic channels to the human population has been developed, is freely available (ToxComp) and its' existing modules of the virtual population generator are now progressively expanded.

The main objective of this study was to assess the usefulness of the modelling and simulation approach for the proarrhythmic potency of the non-cardiological drugs prediction. Ability to mimic population effect applied with use of the virtual population generator on the QTc value was tested.

2. Materials and methods

Modelling and simulation approach was utilized to assess the potential proarrhythmic potency of the non-cardiological drugs. Formoterol was chosen as the model compound. The drug is electrophysiologically inactive yet influences beta-adrenergic system and indirectly plasma potassium concentration. Both of these factors can

influence the human ECG and subsequently QT.

2.1. Clinical study

Results of the clinical study published by Lecaillon [2] were mimicked in the simulations. The design was an open-label, single-dose pharmacokinetic and safety/tolerability study in healthy volunteers. Each volunteer inhaled one dose of formoterol fumarate as dry powder capsules for inhalation via a single-dose powder inhaler (120 µg). Included in the trial population were 12 healthy volunteers (eight males and four females) with a mean with (SD) age of 29 (6) years and they were mimicked in a virtual study with use of the virtual population simulator [3]. The study endpoints included pharmacokinetic and pharmacodynamics parameters from which drug plasma concentration (PK) and QT corrected with a Bazett formula were digitized and used as the observed values.

Blood collection and effects (pulse, QTc) measurement times were: 0, and 30 min, and 1, 2, 3, 4, 6, 8, and 12 h post-dose. Those times were also used for simulations.

2.2. Software

ToxComp is a freely available platform for the vitro – in vivo extrapolation of the cardiotoxic effect distributed under the GNU-GPLv3 license [4]. The core of the system consists of the ten Tusscher model describing human left ventricular cardiomyocyte electrophysiology [5]. Main difference and advantage at the same time, as compared to other solutions lies in the application of the population approach. Virtual population simulator uses the empirical models combining demographic (age, gender) and physiological (plasma ions concentration, cardiomyocyte volume etc.) parameters. It allows for simulation of the inter-individual variability within the population.

For a one-dimensional string of cells the forward Euler method is used to integrate model equations and results are used to calculate a pseudo-ECG. A space step and a time step are by default set to $\Delta x=0.01$ mm and $\Delta t=0.01$ ms.

Software is based on Java platform solutions both to develop the user interface and core source code. Interface to control the application was designed and created in JavaFX, a language which comes from a family of Java solutions. Its main advantages are built in set of basic controls and simplified syntax which allows for rapid creation of sophisticated user interface behavior available on multiple devices.

Solution based on Java code allows the use of robust object-oriented techniques, while maintaining satisfactory performance and memory management.

2.3. Simulation settings

Physiological parameters describing the virtual volunteers involved in a clinical trial include plasma ions concentration (K^+, Na^+, Ca^{2+}) and parameters describing cardiomyocytes (volume, area, electric capacitance) and sarcoplasmic reticulum volume. Heart wall thickness was simulated with use of the Sjögren model [6]. It was assumed that the cells distribution in a heart wall was as follows: epicardium 20%, midmyocardium 30% and endocardium 50% of the cells respectively.

Genetic variability had a reflection in a simulation as the most commonly occurring in the Caucasian population hERG channel polymorphism (namely K897T) was simulated by modification of the gating parameters in the cardiomyocyte model.

Heart rate values for various times of the day where simulated with use of the in house developed model, correlating the individuals age and gender with the observed heart rate. Randomly drawn values were further corrected by the drug concentration to mimic the drug related change in the heart rate.

As the in vitro inhibition data were not available extended QSAR models were used to predict I_{Kr} current inhibition for various formoterol concentrations expressed in micromoles and was considered as negligible. Adrenergic stimulation and following plasma potassium decrease were simulated by the terbutaline concentration dependent decrease of the stimulation period and plasma potassium depletion. Sjögren model was used to simulate the age dependent heart wall thickness. QTc [ms] value with Fridericia correction was chosen as an endpoint and compared with the observed values (after the recalculation from Bazett to Fridericia corrected QTc). QTc calculation was based on the in-house derived algorithm analysing ECG morphology with use of the first derivative threshold method. First and last QRS elements were excluded from the analysis for the sake of the computational stability. Final QT interval value was calculated as the mean of the remaining QRS derived QTs. t-Student test ($p=0.05$) was used to assess the significance of the difference between observed vs. predicted values.

All simulations were carried out for 10 000 ms and were repeated 10 times for every individual and concentration, and the average value (SD) is reported.

3. Results

3.1. Heart rate and plasma potassium concentration

Table 1 and 2 contain the crucial physiological parameters describing virtual population. As they were randomly drawn and further corrected by drug

concentration their accordance with observed values was carefully checked.

Table 1. Observed versus simulated values of the heart rate [beats/min] reported as mean (SD).

Time [h]	Observed RR	Simulated RR
0	65 (9)	66 (16)
0.5	78 (11)	75 (13)
1	77 (13)	74 (7)
2	75 (13)	80 (10)
3	74 (13)	84 (14)
4	73 (12)	80 (14)
6	91 (11)	82 (14)
8	82 (10)	80 (10)
12	82 (8)	72 (15)

Table 2. Observed versus simulated values of the plasma potassium in [mM] reported as mean (SD).

Time [h]	Observed K^+	Simulated K^+
0	4.37 (0.25)	4.39 (0.3)
0.5	3.79 (0.39)	3.88 (0.39)
1	3.64 (0.43)	3.73 (0.27)
2	3.53 (0.34)	3.63 (0.21)
3	3.65 (0.29)	3.6 (0.25)
4	3.66 (0.31)	3.63 (0.27)
6	3.7 (0.31)	3.88 (0.35)
8	3.9 (0.24)	3.92 (0.25)
12	4.18 (0.28)	3.94 (0.44)

Both of the above presented physiological parameters remain in a good agreement with the simulated values. Thus it can be assumed that the physiological environment was properly represented and such settings could be applied for the ECG simulation.

3.2. QTc

Heart rate corrected QT value was the final endpoint of the safety arm of the study. Table 3 presents comparison between observed and simulated together with the p values from the t-Student test.

Table 3. Observed versus simulated values of the QTcF values [ms] reported as mean (SD).

Time [h]	Observed QTcF	Simulated QTcF	p
0	382 (17)	358 (29)	0.11
0.5	391 (21)	378 (22)	0.32
1	382 (21)	380 (15)	0.84
2	392 (19)	388 (16)	0.70
3	389 (23)	396 (20)	0.63
4	392 (18)	387 (28)	0.72
6	385 (15)	387 (28)	0.89
8	391 (18)	385 (18)	0.60
12	385 (22)	372 (23)	0.32

4. Discussion

All simulated QTcF values for formoterol study fall in the observed ±10% ranges. The differences between observed and predicted QTcF values were not statistically significant.

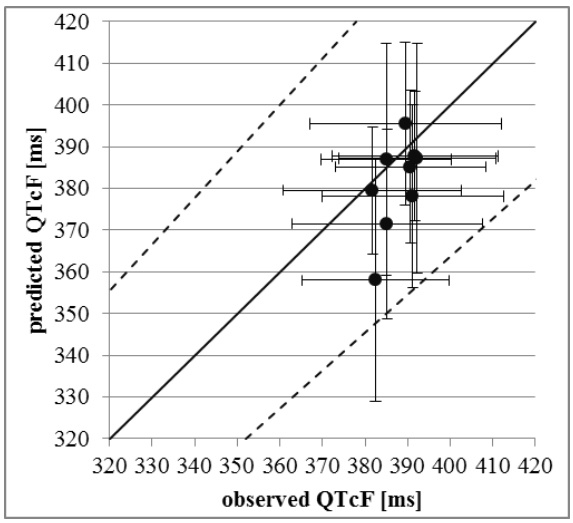

Fig.1. Predicted vs. observed values of QTcF. Bars represent standard deviations (SD) and the dashed line is ±10% range.

The most likely reason for the observed error is caused by the differences in the simulated and clinically observed heart rate and plasma potassium concentration. Nevertheless in all phases simulated corrected QTc values similarly to the observed clinical results lie below 500 ms which is a warning border.

5. Conclusions

The results suggest that the modelling and simulation approach could provide valuable quantitative insight into the cardiological effect of the electrophysiologically inactive, non-cardiological drugs.

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