In Silico Prediction of the Drug Overdose Consequences at the Heart Electrophysiology Level

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Abstract

The aim of the study was to simulate the possible clinical situation of the drug overdose and to assess its electrophysiological consequences, and thus to move the M&S approach to the patient's bedside level. Cardiological consequences of citalopram overdose were simulated with use of the ToxComp system.

Physiology of the 36-yo woman, 33 hours post suicidal ingestion, with high serum citalopram (477 ng/mL) and its metabolite desmethylcitalopram (123.2 ng/mL) concentration was simulated. Ionic current inhibition data were either taken from the literature or predicted with use of the extended QSAR models. Total ionic currents inhibition was simulated as the sum of inhibitions. Plasma ions concentrations and heart rate rhythm were taken from the clinical report (Tarabar 2008). QTc [ms] value with Fridericia correction was the endpoint. Four scenarios were tested assuming that either I_{Kr} current only or $I_{Kr}+I_{Ks}$ currents are affected with various heart rates.

The comparison of the observed vs. simulated QTcF values for four tested scenarios was as follows: (1) I_{Kr}/102 bpm - 524/469; (2) I_{Kr}/150 bpm - 515/511; (3) $I_{Kr}+I_{Ks}$/102 bpm – 524/487; (4) $I_{Kr}+I_{Ks}$/150 bpm – 515/524. ToxComp system predicted the electrophysiological consequences of citalopram overdose. Results indirectly suggest the role of the drug triggered multiple currents inhibition instead of dealing with hERG channel only.

1. Introduction

The in silico methods are more and more commonly used for the drug toxicity prediction, beginning from the QSAR models which can be used at the early stages of the drug development up to the mechanistic models describing human cardiac cells physiology. The first group namely models correlating quantitatively or semi-quantitatively structural parameters of chemicals with their chosen activities or properties are used for the screening purposes due to ease of use and high-throughput abilities. At the same time their use at the later stages is limited and mechanistic models are more commonly utilized as they allow for more detailed insights into the studied phenomena (i.e. drugs – biological structures relation). One of the well-known in silico realized paradigms include the in vitro measured data into the in vivo situation. Most advanced models enable to translate the wet-labs observed phenomena to the human population in vivo. Such concepts are utilized in various areas including drug pharmacokinetics dealing with the drugs and their derivatives fate in the body as well as pharmacodynamics where the chemicals influence on the biological structures is investigated.

Having well characterized modelling and simulation methods already applied for the drug development the question arises whether we could transfer it further to the patients' bedside and to predict clinical consequences of the drug usage dependent on the dosage scheme.

The aim of the study was to simulate the possible clinical situation of the drug overdose and to assess its heart electrophysiological consequences, and thus to move the M&S approach to the patient's bedside level.

Citalopram is an orally administered antidepressant agent which is counted among so called selective serotonin reuptake inhibitors (SSRI). Mechanism of its action is connected with the increase of the serotonin concentration in certain parts of the central nervous system. Apart from the other routes citalopram is predominantly metabolized in the liver to the desmethylcitalopram which is pharmacologically active.

2. Materials and methods

Modelling and simulation approach was utilized to assess the potential proarrhythmic potency of the drug used out of the label scheme. Citalopram was chosen as the model compound due to its electrophysiological activity which can be counted as a downside of the non-cardiological drug. It is also believed that the cardiotoxic metabolite may be co-responsible for chemicals triggered

arrhythmia and for that reason desmethylocitalopram was included into the simulation.

2.1. Clinical observation

According to the clinical report published by Tarabar [1] a 36-year-old woman was presented to the hospital complaining of shakiness, numbness in the arms, and palpitations. She was suspected a suicide attempt two days before, when she ingested 50 tablets of citalopram (20 mg each). Most important results of the clinical and laboratory examinations are presented in Table 1.

Table 1. Patient clinical and laboratory examinations results.

Parameter	Value	Unit
Plasma sodium	133	mM
Plasma potassium	3.1	mM
Plasma calcium	2.3	mM
Blood pressure	84/44	mmHg
Pulse	102-150	beats/min

The above listed values were applied for the simulation. Straight after the hospital admission ECG control was done. The corrected QT interval (Bazett's formula) ranged between 572 to 600 ms.

Patients serum citalopram concentration measured approximately 33 hours post-ingestion was 477 ng/mL (1.47 μM) and the desmethylcitalopram concentration was 123.2 ng/mL (0.4 μM). Both concentrations were used for the simulation.

2.2. Software

ToxComp is a freely available platform for the vitro – in vivo extrapolation of the cardiotoxic effect distributed under the GNU-GPL license [2]. The core of the system consists of the ten Tusscher model describing human left ventricular cardiomyocyte electrophysiology [3]. 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 patient 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 [4]. 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. It was assumed that patient doesn't carry any hERG channel polymorphism, and wild type genetic variant was used.

Heart rate values were simulated based on the previously reported values (102 and 150 beats/minute).

Literature reported I_{Kr} current inhibition data for citalopram were used [5]. As the in vitro inhibition data were not available for all cases the extended QSAR models were used to predict the citalopram triggered I_{Ks} current inhibition as well as the descitalopram triggered I_{Kr} and I_{Ks} curent inhibition [6]. All values expressed as the Hill equation parameter namely IC_{50} [μM] and n are shown in Table 2.

Table 2. In vitro ionic channels inhibition.

Drug	Ionic current	IC_{50} (n)	Source
Citalopram	I_{Kr}	3.97 (0.75)	Exp [5]
	I_{Ks}	6.45 (1)	Est [6]
Desmethylcitalopram	I_{Kr}	1.75 (1)	Est [6]
	I_{Ks}	5.36 (1)	Est [6]

There were two scenarios tested where either I_{Kr} was the only affected current or both outward potassium currents I_{Kr} and I_{Ks} were inhibited as suggested by the QSAR models results.

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. As the study describes casuistic case with one patient involved, no statistical analysis was carried out.

All simulations were carried out for 10 000 ms.

3. Results

Table 3 and Table 4 present the results of four possible scenarios simulations as compared with the clinically observed values.

Table 3. Simulated vs. observed results compared (Bazett formula correction).

Scenario	Pulse	Observed	Predicted
I_{Kr}	102	572	513
	150	600	598
$I_{Kr} + I_{Ks}$	102	572	532
	150	600	612

Table 4. Simulated vs. observed results compared (Fridericia formula correction).

Scenario	Pulse	Observed	Predicted
I_{Kr}	102	524	469
	150	515	511
$I_{Kr} + I_{Ks}$	102	524	487
	150	515	524

4. Discussion

Obtained results suggest that simulation approach can be used for the patients clinical effects prediction at the bedside level. The experimental results describing the in vitro I_{Ks} current inhibition for the investigated drugs were not available but it was assumed that they can be affected by citalopram and its metabolite. $I_{Kr} + I_{Ks}$ scenario results which are closer to the observed values than I_{Kr} only scenario support such assumption. The IC_{50} values were predicted with use of the previously developed QSAR model, so the experimentally measured values could further improve the QTc prediction.

Citalopram is a weak L-type calcium channel inhibitor and according to one of the theories such effect helps to prevent arrhythmia in the therapeutic doses and concentrations due to the QT interval shortening. Not-reported internal results of the simulation with the I_{CaL} current affected shows lack of influence and negligible effect.

5. Conclusions

ToxComp system predicted the electrophysiological consequences of the citalopram overdose. Clinical effect of the two active substances, parent drug and its metabolite was properly mimicked. Results indirectly suggest the role of the drug triggered multiple currents inhibition rather than hERG channel inhibition only.

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