Population level simulation of the action potential as a system for the drugs pro-arrhythmic potency classification

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Purpose of the study

One of the biomarkers of drugs pro-arrhythmic potency is based on the analysis of early afterdepolarizations (EADs) in action potentials (AP). The aim of current work was to assess the possibility to derive EAD numbers from AP signal simulated at the population level and its application for the drugs pro-arrhythmic potency assessment.

Methods

Healthy volunteers (age 18-75; n=60) midmyocardial cells electrophysiology were simulated with use of Simcyp Cardiac Safety Simulator (CSS) V 1.0 in the virtual trial. O'Hara-Rudy model mimicking human physiology was utilized [O'Hara 2012]. Each simulated action potential was analyzed and number of patients with early after depolarizations (EADs) present for each tested concentration was reported after normalization by the maximum available number namely 60. Positive EAD signal was defined as the higher than 0 difference between the number of the first derivative sign changes of baseline (lowest concentration) and concentration of interest. Logarithm of IC_{50} value (pIC50) being a parameter of Hill equation (assuming n = 2) correlating active concentration and number of EADs in the population of 60 individuals was used as the classifier. The thresholds were established based on the simulated data to maximize all 4 classes separation. 9 active concentrations (1E-4 - 1E4 µM) were tested. 20 drugs, 5 from each of 4 TdP-risk categories according to Credible Meds (A=known TdP risk, B=possible TdP risk, C=conditional TdP risk, D=no TdP risk) were randomly selected for the experiment from the complete list as presented in Table 1 [CredibleMeds.org]. Validation was done with the use of 8 additional drugs. Drug-induced current density changes were realized by reduction of the maximal conductance of main cardiac ion channels, based on the in vitro data. The IC_{50} values for each drug and current were retrieved from the available literature (tox-portal.net) as presented in Table 1.

Table 1. List of drugs for 4 TdP risk classes and their in vitro ionic currents inhibition IC_{50} values

I/E	Class	Drug	in vitro IC_{50} [µM]							
			I_{Kr}		I_{Ks}		I_{Na}		I_{CaL}	
Interpolation	Drugs with known TdP risk	Bepridil	0.035	Kirsch 2004	6.2	Wang 1999	3.7	Mirams 2011	1.4	Balasubramanian 2009
		Cisapride	0.026	Kirsch 2004	3.39	Lacerda 2001	337	Kramer 2013	11.8	Kramer 2013
		Dofetilide	0.01	Champeroux 2011	1000	Champeroux 2011	1020	Champeroux 2011	1023	Champeroux 2011
		Flecainide	1.05	Du 2011			0.9	Penniman 2010	27.1	Kramer 2013
		Quinidine	0.82	Kirsch 2004	1000	Champeroux 2011	16.6	Mirams 2011	19.82	Champeroux 2011
	Drugs with possible TdP risk	Aripiprazole	0.24	Huang 2010						
		Clozapine	2.5	Lee 2006			15.1	Kramer 2013	3.6	Kramer 2013
		Nicardipine	1.3	Champeroux 2011	10	Champeroux 2011	4.3	Champeroux 2011	0.25	Champeroux 2011
		Risperidon	0.25	Champeroux 2011	1000	Champeroux 2011	102	Mirams 2011	125	Champeroux 2011
		Tamoxifen	0.198	Chiu 2004						
	Drugs with conditional TdP risk	Diphenhydramine	2.6	Kirsch 2004	132	Khalifa 1999	41	Mirams 2011	228	Mirams 2011
		Doxepin	6.5	Duncan 2007						
		Galantamine	760.2	Vigneault 2012						
		Metronidazole	1340.2	Kramer 2013			2073.2	Kramer 2013	177.9	Kramer 2013
		Trazodon								
	Drugs with no known TdP risk	Amoxiciline	50000	Yao 2008						
		Captopril	1000	Polonchuk 2013						
		Propranolol	9	Champeroux 2011	1000	Champeroux 2011	5	Champeroux 2011	21	Champeroux 2011
		Sulfametoxazol	2200	Saenen 2007						
		Zolpidem	65.5	Jehle 2013						
Extrapolation	Drugs with known TdP risk	Astemizole	0.0009	Zhou 1999			3	Kramer 2013	1.1	Kramer 2013
		Droperidol	0.0322	Drolet 1999			22.7	Kramer 2013	7.6	Kramer 2013
	Drugs with possible TdP risk	Apomorphine	2.4	Hurst 2003						
		Alfuzosin	17.7	Mannikko 2010						
	Drugs with conditional TdP risk	Amoxapine	5.1	Obers 2010						
		Desipramine	1.39	Ekins 2002			1.52	Mirams 2011	1.71	Mirams 2011
	Drugs with no known TdP risk	Verapamil								
		Metoprolol	145	Kawakami 2006						

References

O'Hara-Rudy 2011; CredibleMeds.org; Kounas 2005

Results

The thresholds allowing for best possible discrimination of 4 analyzed classes are presented in Table 2. Based on the developed model 15 from 20 compounds (75%) were correctly classified: A-4/5, B-3/5, C-4/5, D-4/5 respectively. All incorrectly classified records were allocated single class above or below of the original one (Table 3 and Figure 1).

Table 2. Threshold values

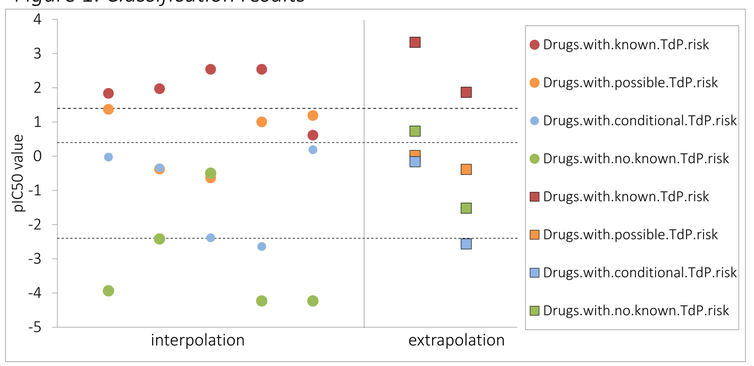
Class	pIC50	
Drugs with known TdP risk	∞	1.4
Drugs with possible TdP risk	1.4	0.4
Drugs with conditional TdP risk	0.4	-2.4
Drugs with no known TdP risk	-2.4	-∞

At the validation stage (extrapolation) based on the developed model 3 of 8 compounds (38%) were correctly classified: A-2/2, B-0/2, C-1/2, D-0/2 (single class above or below of the original one except of Verapamil).

Table 3. Classification results and pIC50 values after fitting to Hill equation

I/E	Original class	Drug	PREDICTION	
			pIC_{50}	Classified as
Interpolation	Drugs with known TdP risk	Bepridil	1.836	Drugs with known TdP risk
		Cisapride	1.973	Drugs with known TdP risk
		Dofetilide	2.540	Drugs with known TdP risk
		Flecainide	2.540	Drugs with known TdP risk
		Quinidine	0.613	Drugs with possible TdP risk
	Drugs with possible TdP risk	Aripiprazole	1.369	Drugs with possible TdP risk
		Clozapine	-0.376	Drugs with conditional TdP risk
		Nicardipine	-0.637	Drugs with conditional TdP risk
		Risperidon	1.002	Drugs with possible TdP risk
		Tamoxifen	1.189	Drugs with possible TdP risk
	Drugs with conditional TdP risk	Diphenhydramine	-0.027	Drugs with conditional TdP risk
		Doxepin	-0.342	Drugs with conditional TdP risk
		Galantamine	-2.387	Drugs with no known TdP risk
		Metronidazole	-2.639	Drugs with conditional TdP risk
		Trazodon	0.189	Drugs with conditional TdP risk
	Drugs with no known TdP risk	Amoxiciline	-3.939	Drugs with no known TdP risk
		Captopril	-2.422	Drugs with no known TdP risk
		Propranolol	-0.499	Drugs with conditional TdP risk
		Sulfametoxazol	-4.234	Drugs with no known TdP risk
		Zolpidem	-4.234	Drugs with no known TdP risk
Extrapolation	Drugs with known TdP risk	Astemizole	-0.342	Drugs with known TdP risk
		Droperidol	-2.387	Drugs with known TdP risk
	Drugs with possible TdP risk	Apomorphine	-2.639	Drugs with conditional TdP risk
		Alfuzosin	0.189	Drugs with conditional TdP risk
	Drugs with conditional TdP risk	Amoxapine	-3.939	Drugs with conditional TdP risk
		Desipramine	-2.422	Drugs with no known TdP risk
	Drugs with no known TdP risk	Verapamil	-0.499	Drugs with possible TdP risk
		Metoprolol	-4.234	Drugs with conditional TdP risk

Figure 1. Classification results



Discussion & Conclusions

Proposed model offers good classification quality. The incorrectly classified drugs during the model building stage include: Quinidine (A classified as B), Clozapine and Nicardipine (B classified as C), Metronidazole (C classified as D), Propranolol (D classified as C). The only case of the risk class lowering namely metronidazole has only limited evidence of QT prolongation in the elderly, multidrug treated patients [Kounas 2005].

As the validation stage both drugs with known TP risk were properly classified. Among 5 misclassified compounds only one, namely Verapamil, was moved 2 classes up from *no risk* to *possible TdP risk* category. Potential reasons for the misclassification lie in drug specific (lack of the metabolites effects and physiological parameters modification), system specific (physiological parameters were only partially included i.e. no circadian variability) and methodology/algorithm specific reasons (single cell simulation, multiple sources of the currents inhibition data). Further research will include more drugs in each class.