Investigation of the Pro-arrhythmic Effects of Domperidone by a Simulation Study

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Abstract

Recently, it was reported that domperidone might be associated with a high risk of sudden cardiac death. However, the underlying mechanism is not clear. This study investigated the pro-arrhythmic effects of domperidone using a multi-scale biophysically detailed computational model of the heart developed by ten Tusscher et al.

Based on experimental data of Benoit Drolet et al., the pharmacological effect of domperidone was simulated by dose-dependent I_{kr} blocking. AP profiles, conduction velocity of electrical excitation waves, pseudo electrocardiograms and vulnerable window at tissue level were analyzed to further investigate the effects of domperidone on cardiac electrophysiology.

It was shown that domperidone significantly and dose-dependently prolonged action potential duration and QT interval, slowed down conduction velocity and augmented vulnerable window. With the increase of drug concentration, domperidone increased the incidence of action potential alternans and augmented the vulnerability of genesis of unidirectional conduction.

This study shows that domperidone has profound and dose-dependent pro-arrhythmic effects on cardiac electrophysiological properties at cellular and tissue level.

1. Introduction

Domperidone, an alternative to cisapride, is commonly used to treat gastrointestinal disorders. However, it was reported that similar to cisapride, domperidone might be associated with a high risk of ventricular arrhythmias and sudden cardiac death (SCD). In a recent epidemiological study, the odds ratio for SCD with domperidone was reported to be 3.72, which increased to 11.4 for daily doses > 30 mg [1].

Recently, modelling of cardiac drug adverse effects in silico was used to investigate drug effect on arrhythmias. Drug effects were integrated into mathematical models of cardiac electrophysiology, such as by adaptation of ion channel conductivities of the model to the dose-dependent inhibition of these currents. Then, the effects, which are measured at the ion channel, cell, tissue or even organ level, for example by voltage clamp, optical mapping etc., can be simulated computationally. Through this method, cardiac toxicity of the drug can be assessed by simulating and analyzing a series of biomarkers, such as action potential duration, electrocardiograms and vulnerable window.

In this study, we evaluated the pro-arrhythmic effects of domperidone by simulating reliable biomarkers on a multi-scale biophysically detailed computational model of the human heart.

2. Material and methods

2.1. Ventricular model

The mathematical model of human ventricular action potential developed by ten Tusscher *et al*. [2] in 2006 was used in this study. This model computationally reproduced the electrophysiology of different types of ventricular cells, including endocardial, M and epicardial cells.

- *Single cell model*

A schematic graph shown in Figure 1 illustrates the transmembrane ion flux of single cell model, which includes ion channels and ion pumps across the cell membrane. In addition to ionic channels in the membrane, intracellular calcium dynamics was also included in the model [2].

The governing equation of the cellular AP can be described as:

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m} \quad (1)$$

where V_m (mV) is transmembrane voltage, t (ms) is time, I_{ion} is the sum of ionic currents as desdribed in equation 2, I_{stim} (pA) is the externally applied stimulus current, and C_m(pF) is the membrane capacitance. More details of parameters and equations of the model can be found in Ref. [2].

$$I_{ion} = I_{Kr} + I_{Ks} + I_{Kl} + I_{to} + I_{Na} + I_{bNa} + I_{CaL} + I_{bCa} + I_{NaK} + I_{NaCa} + I_{pCa} + I_{pK} \quad (2)$$

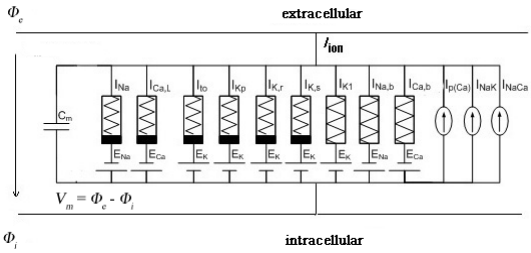

Figure 1. A schematic graph of the transmembrane ion fluxes in a ventricular cell [2].

- One-dimensional tissue strand model

The one-dimensional (1-D) strand tissue model was illustrated in Figure 2, consisting of 100 cells in a row with a total length of 16.5 mm. The number of endocardial cells, M cells and epicardial cells were 25, 35 and 40 respectively, similar to that used by Zhang *et al.* [3].

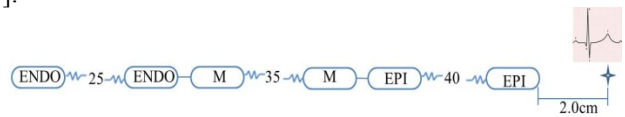

Figure 2. 1-D human ventricular tissue model of 100 cells consisting of endocardial, M and epicardial cells [2].

The governing equation of the 1- D ventricular tissue model was described by equation 3:

$$\frac{\partial V}{\partial t} = \nabla \cdot D\nabla V - \frac{I_{\text{stim}} + I_{ion}}{C_m} \quad (3)$$

where V_m (mV) is transmembrane voltage, t (ms) is time, D is the diffusion tensor, ∇ is the grandient operator, I_{ion} is the sum of ionic currents as described in equation 2 previously, I_{stim} (pA) is the externally applied stimulus current, and C_m(pF) is the membrane capacitance.

Eq. 1 and 3 was numerically solved by the forward Euler method with a time step of 0.02ms and a space step of 0.15mm.

2.2. Effects of domperidone on ion channel gating

In general, the dose-dependent inhibition of ion channel conductivities induced by drugs can be quantitatively simulated by modifying the IC_{50} and nH value, which correspond to changes of the half-maximal inhibitory concentration and the slope of the Hill curve during drug application [4]. The interaction between drug molecules and ion channels can be mimicked by equitation 4 [5].

$$\frac{g_j}{g_{Control,j}} = 1/[1 + \left(\frac{D}{[IC_{50}]_j}\right)^{nH}] \quad (4)$$

where $g_{control,\ j}$ (nS/pF) is the conductivity of ion channel j without drug-induced modification, g_j (nS/pF) is the conductivity of ion channel j with drug-induced modification, D (mol/L) is the concentration of drug, $[IC_{50}]_j$ (mol/L) is the IC_{50} value, and nH is the Hill values.

As for domperidone, it mainly inhibited the rapid delayed rectifier potassium current I_{Kr}. In order to determine the dose-dependent effect of domperidone, I_{Kr} blocking were was simulated at different concentrations of domperidone. Based on the experimental data of Benoit Drolet *et al.* [6], in the simulation, the IC_{50} was 0.162μmol·L^{-1}, nH was 0.99 and the concentration values were 10, 30, 100 300 to 1000nmol/L. The simulated ion channel conductivity reductions corresponding to various domperidone concentrations were shown in Table 1. Then the effect of ion channel conductivity reduction induced by domperidone was incorporated into ventricular model.

Table 1. The ion channel conductivity reductions relative to domperidone concentrations

Domperidone concentrations (nmol·L^{-1})	I_{Kr} conductivity reductions
0.00	100%
0.01	94%
0.03	84%
0.10	62%
0.30	35%
1.00	14%

2.3. Biomarkers

In the present computational study, a series of biomarkers were calculated to evaluate the influence of domperidone. At cellular level, action potentials (APs) were evoked with a basic cycle length (BCL) of 1000ms, and effects of domperidone on action potential duration (APD) and APD_{90} restitution (APDR) curves were calculated. At tissue level, effects of domperidone on conduction velocity (CV) of electrical excitation waves, pseudo electrocardiograms (pseudo-ECG) [7] and vulnerable window (VW) were quantified.

3. Results

Figure 3 demonstrated the APs simulated of ENDO cells evoked using S1-S2 stimulus protocol with BCL of 1000ms at different concentrations of domperidone. With

the increase of domperdione concentrations, APD was gradually prolonged. Table 2 summarized electrophysiological changes induced by domperidone in ENDO cells, including variations of action potential amplitude (APA), max depolarization velocity (dV/dt_{max}), APD_{90}, $APD_{90}/APD_{90,\ Control}$. It is demonstrated that high concentration of domperiodone has insignificant effects on APA and dV/dt_{max}. The simulation results of domperidone in M and EPI cells were similar to that in ENDO cells (Data not shown).

The simulation results indicated that domeridone had a more significant effect in the recovery phase of action potential and higher concentrations longer APDs which was associated with higher risk of arrhythmogensis.

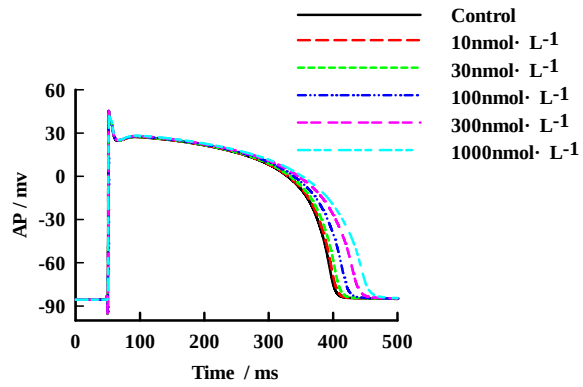

Figure 3. Action potentials recorded from ENDO cell, evoked by S1-S2 stimulus protocol with BCL of 1000ms

Table 2. Effect of domperidone on ENDO cell: APA, dV/dt_{max}, APD_{90}, $APD_{90}/APD_{90,\ Control}$

Domperidone concentrations/ ($nmol \cdot L^{-1}$)	APA/ mv	dV/dt_{max}/ ($v \cdot s^{-1}$)	APD_{90}/ ms	$\triangle APD_{90}$/ $APD_{90,Control}$
0	129.020	396.4	347.9	0
10	129.025	396.4	350.8	0.8%
30	129.033	396.3	355.8	2.3%
100	129.052	396.2	367.6	5.7%
300	129.077	396.4	383.9	10.3%
1000	129.098	396.6	398.5	14.5%

APDRs of ENDO cells were calculated using S1-S2 stimulus protocol (Fig. 4). With the increase of domperidone concentration, the slope of APD90 restitution curves increased towards shorter diastolic intervals, which potentially increased the genesis of action potential alternans.

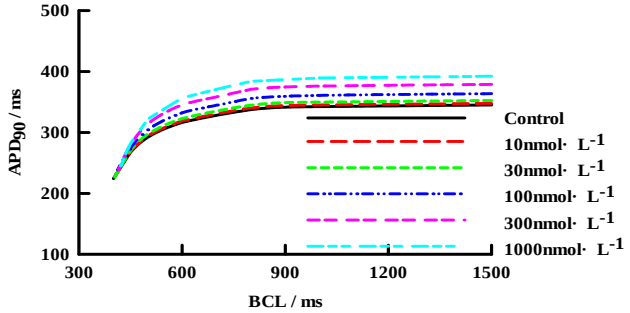

Figure 4. APDR recorded from ENDO cell, evoked by S1-S2 stimulus protocol

In 1-D tissue model, pseudo-ECGs were calculated using S1-S2 stimulus protocol with BCL of 1000ms as shown in Figure 5. It was shown that QT interval was gradually prolonged with increasing domperidone concentrations, indicating the pro-arrhythmia effect of domperidone.

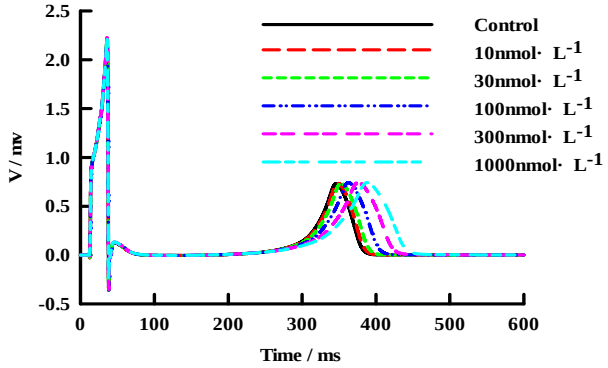

Figure 5. Pseudo-ECG recorded from 1-D tissue model, evoked by S1-S2 stimulus protocol with BCL of 1000ms

In order to further examine the effect of domperidone on AP conduction, the conduction velocity (Fig. 6) and vulnerable window (Fig. 7) were examined in 1-D strand simulations at different concentrations of domperidone. Compared to the control condition, the measured CV decreased gradually with the increase of domperdione concentrations while the measured VW increased by 7.9% and 18.6% respectively with 100 and 300nmol/L domperidone. With reduced CV and augmented VW, domperidone promoted the gensis of unidirectional conduction in response to a premature stimulus, which was pro-arrhythmic.

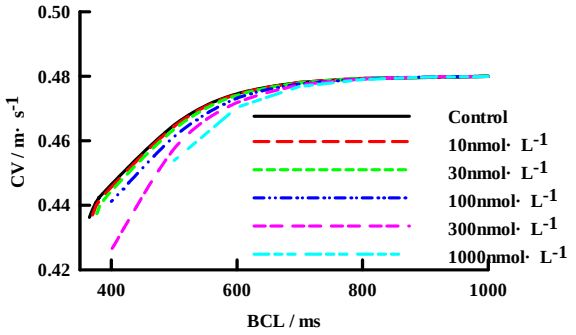

Figure 6. CV restitution curve recorded from 1-D tissue model, evoked by dynamic stimulus protocol

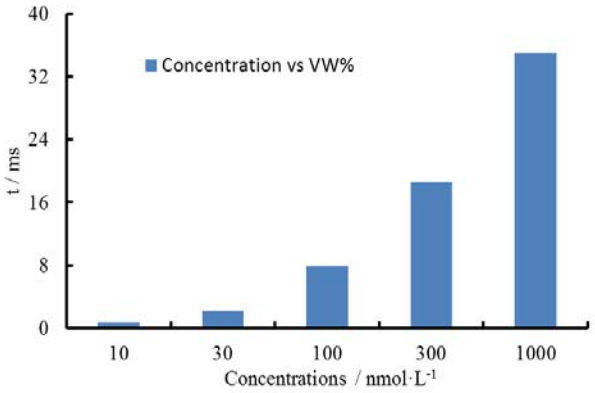

Figure 7. The VW increase ratio compared to $VW_{control}$

4. Discussion and conclusion

Our simulation results showed that domperidone prolonged APD and QT interval significantly and dose-dependently. At 100nmol/L, domperidone prolonged APD by 5.7% and QT interval by 6.8%, which boosted to 10.3% and 12.8% respectively at 300nmol/L. With the increase of drug concentration, the slope of APD_{90} restitution curves increased towards shorter diastolic intervals, increasing the risk of inducing action potential alternans at fast pacing rate. In 1-D strand simulations, domperidone slowed down CV and augmented VW, which tended to generate unidirectional conduction in response to a premature stimulus.

In conclusion, domperidone has profound and dose-dependent effects on cardiac electrophysiological properties at cellular and tissue level. It increases APD and QT interval, augments tissue's vulnerability for genesis of unidirectional conduction. All of these effects are pro-arrhythmic. The results based on computational study shed light on the mechanisms of pro-arrhythmic effects of domperidone, providing a potential target for future anti-arrhythmic drug development.

Acknowledgements

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