Dronedarone's Efficacy in Preventing Arrhythmias During Myocardial Ischemia or Short QT Syndrome: A Computational Study

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Abstract

The mechanisms underlying dronedarone's role in the genesis of cardiac arrhythmias remain unclear under relevant pathological conditions such as the myocardial ischemia condition and the short QT Syndrome condition. This study aims to provide a deeper understanding of dronedarone's therapeutic potential, particularly in the context of myocardial ischemia-induced arrhythmias or KCNJ2 D172N mutation-induced short QT syndrome (SQT3). Simulation results suggest that under the SQT3 condition, dronedarone produced a significant prolongation of the action potential duration with the concentrations of dronedarone increased. In contrast, the ability of high concentrations of amiodarone to prolong the action potential duration was actually worse than low concentrations. The maximal slopes of action potential duration restitution curve and effective refractory period restitution curve were decreased in the presence of dronedarone or amiodarone, which decreased instability of re-entrant excitation waves, indicating antiarrhythmic effects of dronedarone and amiodarone on D172N mutation. Significant differences exist in the frequency and concentration-dependent effects between amiodarone and dronedarone. Our results provide possible explanations for the efficacy of dronedarone and amiodarone.

1. Introduction

Pharmacological therapy is the primary modality to protect against arrhythmias [1, 2]. However, to date, data regarding pharmacological treatment in myocardial ischemia and the short QT Syndrome (SQT3) are limited. The genetic KCNJ2-linked short QT syndrome (SQT3) is identified as a genetic mutation, in which aspartic acid is replaced by asparagines at position 172 in the Kir2.1 potassium channel (D172N). Although dronedarone's effectiveness as a Class III antiarrhythmic agent in preventing atrial fibrillation recurrence in patients with persistent AF is well-established, the effects of dronedarone under the myocardial ischemia condition and the SQT3 syndrome condition have not been fully understood.

Therefore, this study aimed to evaluate and compare the potential effects of dronedarone in comparison to amiodarone on ventricular electrical activities at cellular and tissue levels under the above two pathological conditions, by using multi-scale models of human ventricular electrophysiology. Electrophysiological remodeling, based on experimental data of myocardial ischemia or Kir2.1 D172N mutation-induced changes, was emulated and incorporated into a human ventricular model, respectively. Subsequently, the effects of dronedarone were integrated into the constructed models to analyze their influence on electrophysiological alterations in ventricular cells, in comparison with amiodarone. These results may provide theoretical insights into the possible pharmacological agent for treating patients with myocardial ischemia or SQT3.

2. Methods

2.1. Model Development

The ten Tusscher et al. [3] model of the human ventricular AP was used for this study. According to the experimental data, the ionic currents of the ischemic cells were remodeled as shown in Table1. The electrophysiological behavior of a single cell can be described as following ordinary differential equation (ODE):

\[
\frac{dV_m}{dt} = - \frac{I_{ion} + I_{stim}}{C_m}
\]  

(1)

where \( V \) is transmembrane voltage, \( C_m \) is the membrane capacitance, \( I_{stim} \) is the externally applied stimulus current, \( t \) is time, \( I_{ion} \) is the sum of ionic currents as described in the following equation:

\[
I_{ion} = I_{Na} + I_{Kr} + I_{to} + I_{Ks} + I_{CaL} + I_{SatCa} + I_{NaK} + I_{Pca} + I_{Pc} + I_{hCa} + I_{hNa} + I_{K1}
\]

(2)

Where \( I_{K1} \) was modified to incorporate experimental data of Priori et al. [4] on SQT3 KCNJ2 D172N mutation-induced changes. SQT3 is identified as a
genetic mutation, in which aspartic acid is replaced by asparagines at position 172 in the Kir2.1 potassium channel (D172N). The $I_{K_1}$ model formulation is described by

$$I_{K_1} = G_{K_1} \frac{K_0}{5.4} \left( e^{-x_{K_1 e}} (V_m - E_{K_1}) \right)$$

$$x_{K_1 e} = \frac{\alpha_{K_1}}{\alpha_{K_1} + \beta_{K_1}}$$

D172N:

$$\alpha_{K_1} = \frac{0.1}{1 + e^{-0.05(V - E_{K_1})}}$$

$$\beta_{K_1} = \frac{3e^{-0.002(V - E_{K_1})} + e^{-0.08(V - E_{K_1})}}{1 + e^{-0.006(V - E_{K_1})}}$$

$$G_{K_1} = 11.3 \frac{nS}{\mu F}$$

where $G_{K_1}$ is the maximal channel conductance of $I_{K_1}$, $x_{K_1 e}$ is the time-independent inward rectification factor, $K_0$ is the extracellular potassium concentration.

### 2.2. Modelling drug-channel interaction

The effect of drug on blocking an ion channel can be simulated using a blocking factor $V$ that reduces the maximum conductance of the targeted ion channel. Mathematically, $V$ is expressed as:

$$V = \frac{1}{1 + (D/IC_{50})^{nH}}$$

where $D$ is the drug concentration, $IC_{50}$ is the drug concentration of 50% blockade of the binding site and $nH$ is the Hill coefficient.

The steady-state plasma concentration of amiodarone is reported to range between 1 and 2mg/mL, corresponding to 1.55-3.11 mM [5]. The therapeutic concentration of dronedarone is reported to be between 84 and 147ng/mL, corresponding to 0.15-0.26 mM [6]. To simulate the actions of dronedarone and amiodarone, we used the simple pore block theory, by which the maximal channel conductance of the targeted channel(s) was reduced by various percentages according to the dose of the drugs (as shown in Table 2).

#### Table 1. Model parameters under control and ischemic conditions

<table>
<thead>
<tr>
<th></th>
<th>$[K^+]_0$(mM)</th>
<th>gCaL(%)</th>
<th>gNa(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.4</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ischemia</td>
<td>8.0</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

### 3. Results

#### 3.1. Simulations in Myocardial Ischemia

Simulation outcomes revealed that myocardial ischemia shortened the action potential duration (APD) of ventricular myocytes, increased the resting membrane potential, and decreased the action potential amplitude. Both dronedarone and amiodarone prolonged the APD of ischemic ventricular myocytes without altering the resting potential of ischemic ventricular cells (Figure 1). Specifically, 0.1 μM and 0.3 μM dronedarone increased APD by 11.38% and 15.90% under normal conditions and 12.21% and 16.25% under ischemia conditions, 1 μM and 3 μM amiodarone increased APD by 9.44% and 14.12% under normal conditions and 8.31% and 11.56% under ischemia conditions. Under ischemic conditions, an increase in dronedarone concentration significantly increased APD in ventricular cells, while amiodarone did not.

![Figure 1. Action potentials in ventricular cells under (a) control and (b) ischemic conditions.](image-url)
3.2. Simulations in SQT3

Alternations to \(I_{K1}\) due to SQT3 mutations accelerated the repolarization phase of APs as shown in figure 2. The D172N mutation resulted in shortening of APD. The measured APD\(_{90}\) was 298ms for the ventricular cells (Figure 3) in WT, which was shortened to 258ms in D172N condition. The abbreviated APD resulted largely from increased \(I_{K1}\) during the late phase of AP repolarization as shown by the time course of \(I_{K1}\) in figures 2. The resting membrane potential remains unchanged.

The effects of drug interactions simulated on APD prolongation from the ventricular cells under D172N condition are summarized in figure 3. APD\(_{90}\) in D172N the presence of 1, 3μM amiodarone, and 0.1, 0.3μM dronedarone, respectively. Dronedarone produced a significant prolongation of APD\(_{90}\) with the concentrations of dronedarone increased. However, the ability of high concentrations of amiodarone to prolong APD was actually worse than low concentrations. Both dronedarone and amiodarone prolonged the APD in D172N condition without altering the resting potential of ventricular cells.

![Figure 2. Simulations of \(I_{K1}\) in ventricular cells under the WT and D172N conditions.](image)

![Figure 3. Effects of low and high doses of amiodarone and dronedarone on human ventricular cells. (a) APs under the WT and D172N conditions in the presence of amiodarone and dronedarone. (b) Corresponding APD\(_{90}\) histogram.](image)

The APD reduction and the effective refractory period (ERP) reduction were rate-dependent (Figure 4(a)-(b)) in ventricular cells. Across the range of diastolic intervals studied, the measured APD\(_{90}\) and ERP were smaller in the D172N condition than in the WT condition. In addition, the action potential duration restitution curve (APD-R) and the effective refractory period restitution curve (ERP-R) relationships were steepened by the mutation, as indicated by the observed increase in the maximal slope of the APD-R curves and ERP-R curves (Figure 4(c)-(d)). In ventricular cells, the measured maximal slope of the APD-R and ERP-R curves were increased by the D172N mutation.

As an increased steepness of APD-R and ERP-R curves is believed to be associated with increased instability of re-entrant excitation waves, the KCNJ2 D172N mutation increases the risk of arrhythmias. The maximal slopes of APD-R and ERP-R curves were decreased in the presence of dronedarone or amiodarone, which is associated with decreased instability of re-entrant excitation waves [17], indicating antiarrhythmic effects of dronedarone and amiodarone on D172N mutation.

![Figure 4. (a) APD restitution curves in ventricular cells under WT and D172N conditions. (b) ERP restitution curves in ventricular cells under WT and D172N conditions. (c) Measured slopes of APD-R curves in ventricular cells under WT and D172N conditions. (d) Measured slopes of ERP-R curves in ventricular cells under WT and D172N conditions.](image)

4. Conclusion

Our simulations indicate that both dronedarone and amiodarone prolonged the AP in ischemic condition and D172N condition without altering the resting potential of ventricular cells. Under ischemic conditions, an increase in dronedarone concentration significantly increased APD in ventricular cells, while amiodarone did not. In D172N condition, dronedarone produced a significant prolongation of APD with the concentrations of
dronedarone increased. In contrast, the ability of high concentrations of amiodarone to prolong APD was actually worse than low concentrations. In ventricular cells, the measured maximal slope of the APD-R and ERP-R curves were increased by the D172N mutation, which increases the risk of arrhythmias. The maximal slopes of APD-R and ERP-R curves were decreased in the presence of dronedarone or amiodarone, which decreased instability of re-entrant excitation waves, indicating antiarrhythmic effects of dronedarone and amiodarone on D172N mutation. Significant differences exist in the frequency and concentration-dependent effects between amiodarone and dronedarone. Our results provide possible explanations for the efficacy of dronedarone and amiodarone.

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References


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