

Effects of the Antiarrhythmic Drug Dofetilide on Myocardial Electrical Activity: A Computer Modelling Study

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Abstract

Dofetilide selectively inhibits the rapid component of the delayed potassium current (I_{Kr}). In this work, a mathematical model of dofetilide effects on I_{Kr} has been developed. This model has been incorporated to the Luo and Rudy (II) model of guinea pig ventricular action potential and the effect of different dofetilide concentrations on the action potential characteristics has been studied. Our results show that the steady-state block of I_{Kr} is dose-dependent with a block of 10%, 53% and 92% for 1 nM, 10 nM and 100 nM of dofetilide respectively ($IC_{50} = 8.7$ nM). This increment of I_{Kr} block when the concentration increases induces a prolongation of APD also in a dose-dependent way. We observed prolongations of APD_{90} of 13% and 28% for 10 nM and 100 nM of dofetilide respectively. In agreement with experimental results, the interaction between dofetilide and the receptor in the channel presents slow kinetics and reverse use-dependence in our model.

1. Introduction

The antiarrhythmic efficacy of drugs that induce prolongation of action potential duration (APD), through the blockade of the delayed rectifier current, I_K , has been widely probed in reentrant arrhythmias. In different species, as guinea pig, I_K consist on two components: a slowly activating component, I_{Ks} , and a rapidly activating component, I_{Kr} , sensitive to E-4031 or sotalolol [1]. Dofetilide is an antiarrhythmic drug that specifically blocks the rapid component of the delayed rectifier potassium current I_{Kr} [2-4]. In 1999, the U.S. Food and Drug Administration (FDA) approved dofetilide for the treatment of persistent atrial fibrillation and flutter. Dofetilide is classified as a pure class III antiarrhythmic agent because it produces only prolongation of action potential duration (APD), without any effect on the resting membrane potential, action potential amplitude or maximum rate of depolarization [4]. The effect of dofetilide on APD has been recorded in different myocardial tissues and species [5,6]. In all the myocardial tissues, blockade of I_{Kr} by dofetilide induces a higher

prolongation of APD, and hence, of the QT interval, as the concentration of dofetilide increases. Prolongation of APD is related with the increment of refractory period in cardiac tissue.

While the efficacy of dofetilide as antiarrhythmic drug is related to the increment in refractoriness, the prolongation of QT may trigger the polymorphic ventricular tachycardia called *torsade de pointes* [7]. Different studies have found antiarrhythmic action of dofetilide in preventing and terminating ventricular tachycardias [8] and in the prevention of atrioventricular re-entrant tachycardia [9]. It has been also suggested that dofetilide may be useful in reducing the frequency of multiple episodes of monomorphic ventricular tachycardia and in increasing the efficacy of antitachycardia pacing in patients with implantable cardioverter-desfibrillator [10].

Dofetilide is a potent blocker of I_{Kr} . An IC_{50} in the nanomolar range has been experimentally measured in guinea pig ventricular myocytes, namely 8.7 nM [11] and 31 nM [4]; 3.9 nM in rabbit ventricular myocytes, [3]; 11 nM in mouse AT-1 cells [12] and 12 nM in HERG expressed in human cells [13]. These results are consistent with radioligand ($[^3H]$ dofetilide) binding affinity studies that show high-affinity sites associated with I_{Kr} with IC_{50} values of 28 nM [14] and 31 nM [15].

Experimental evidences suggest that the interaction between the drug and the receptor in the channel is produced in the open state (open channel block) rather than in the closed state [3, 13, 16]. Once the block has been produced, the effect persists during a long period at rest, suggesting that the drug does not dissociate when the channel is closed; the drug seems to be trapped within the channel [3, 16]. It has been recently suggested that dofetilide interacts with the channels in both the open and the inactivated states [17]. The interaction between dofetilide and receptor presents a very slow kinetics [11,13] and exhibits reverse use-dependence [2,16]. The increment in the dofetilide dose enhances the reverse-use dependence [2].

The main objective of the present work is to develop a mathematical model of the I_{Kr} block by dofetilide and to study the effect of different concentrations on the action potential characteristics.

2. Methods

In this work, the mathematical model of the cardiac action potential developed by Luo and Rudy (phase II) was used in order to simulate the guinea pig ventricular action potential. In 1995, they improved the model by replacing the I_K by its two components I_{Ks} and I_{Kr} [18]. The formulation of the I_{Kr} current is based on the experimental data obtained by Sanguinetti and Jurkiewicz [1]. They proposed I_{Kr} channels with three possible states: Closed (C), Open (O) and Inactivated (I).



The formulation of I_{Kr} in de model [18] is expressed as

$$I_{Kr} = G_{Kr \max} X_r R (V - E_{Kr})$$

where V is the membrane potential, E_{Kr} is the reversal potential, $G_{Kr \max}$ is the maximum conductance of I_{Kr} , X_r is the activation gate and R is the time-independent inactivation gate. For a detailed description of the current see reference [18].

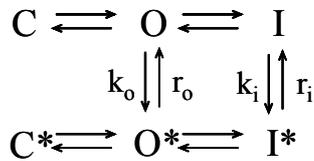
The blocking activity of dofetilide was simulated using the "guarded receptor hypothesis" [19], and its effect on the current was represented by introducing the factor $(1-b)$ in the I_{Kr} formulation (where b is the fraction of channels blocked by the drug). This model of drug action assumes a drug binding to a constant affinity channel receptor guarded by the gating mechanism of the channel, unaltered by the drug. Thus, the new formulation of I_{Kr} taking into account the effect of dofetilide is

$$I_{Krb} = (1-b) G_{Kr \max} X_r R (V - E_{Kr})$$

Both the I_{Kr} model and the cellular model (including the new I_{Krb} formulation) was written in ACSL language, using Gear stiff algorithm to solve the nonlinear system of differential equations.

3. Results and discussion

In accordance with experimental studies that have shown drug-receptor interaction in open and in inactivated states, but not in closed states, and that the drug is trapped when the channel closes. We suggest the following model of blocking I_{Kr} by dofetilide



where (*) indicates the drug-channel binding states, k_o and k_i are the association rate constants, and r_o and r_i are the dissociation rate constants (with open and inactivated states respectively). We consider that the forward coefficients are equal for the open and inactivated states and that the reverse coefficients are also equal. Then,

$$k_o = k_i = k \quad \text{and} \quad r_o = r_i = r$$

From this model, the blocking factor b can be calculated as

$$\frac{db}{dt} = \{X_r R + (1-R)\} \{k[D](1-b) - rb\}$$

We used the dissociation constant $r=0.0036s^{-1}$, obtained by Duff *et al* [14], using radioligand ($[^3H]$ dofetilide) binding affinity studies, for the high-affinity sites identified in guinea pigs ventricular myocytes. From the value IC_{50} of 8.7 nM recorded by Weerapura *et al* [11], we estimated the association rate constant k , ($IC_{50}=r/k$), as $k=0.4137 \mu M^{-1}s^{-1}$.

These values are similar to those obtained in different experimental conditions as: $k=0.6 \mu M^{-1}s^{-1}$ [13] and $k=0.1 \mu M^{-1}s^{-1}$ and $r=0.003s^{-1}$ [15]

In order to test the dofetilide-channel binding model, we applied voltage-clamp protocols of stimulation to the I_{Krb} model.

In Figure 1, the evolution of the normalized current (I_{Krb}/I_{Kr}) when a voltage clamp protocol (from -40 mV to 0 mV) was applied to the I_{Krb} model for a dofetilide concentration of 50 nM is shown. The symbols represent the experimental results obtained by Weerapura *et al* [11] and the solid line shows the results of the I_{Krb} model. The model indicates that the I_{Krb} decays with a time constant of 41 s very close to that recorded experimentally (36.6 s)

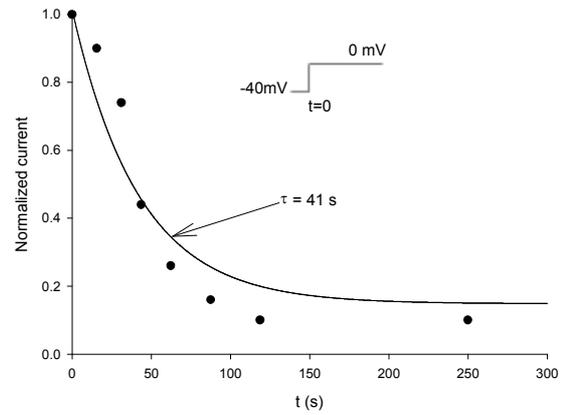


Figure 1. Voltage clamp protocol (indicated in the figure) was used to compare the experimental results obtained when dofetilide 50 nM is applied to ventricular guinea pig cells. Symbols correspond to experimental results, the line is the evolution indicated by the I_{Krb} model

In Figure 2, the same voltage clamp protocol was applied, this time from -80 mV to +10 mV, for different concentrations of dofetilide ([D]), in the range from 1nM to 1 μ M. It is possible to observe that the block is faster when the dofetilide concentration increases. For this voltage-clamp protocol, the time constant for a [D]= 300 nM resulted from the model is 7.5 s (plot not shown), closed to recorded experimentally (5.2 s) by Snyders *et al* [15].

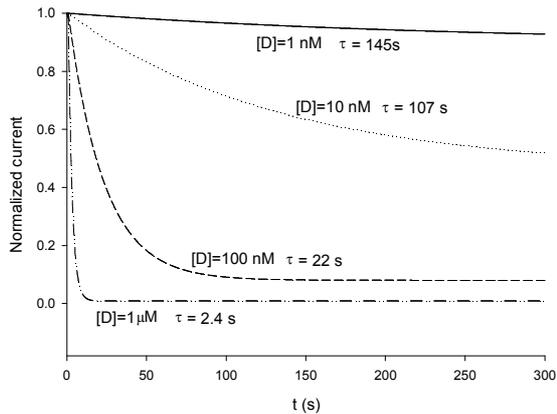


Figure 2. Time course of blocking (from the I_{Kr} model) for different concentrations of dofetilide, when a voltage clamp protocol (indicated in the figure 1, but from -80mV to +10 mV) is used.

In Figure 3, the steady-state blockage effect of different concentrations of dofetilide on the I_{Kr} (a) and on the action potential (b) are shown. For all the simulations, the cellular model was stimulated, until the steady-state was reached, with a rectangular current pulse with an amplitude 1.5 times the diastolic threshold and a duration of 2 ms. Only the magnitudes associated to the last stimulation pulse are shown. From the figure, it is observed that as the concentration of dofetilide is increased from 1nM to 1 μ M, the maximum value (peak) of I_{Kr} decreased from APD₉₀ 10% to 99%, and, as a consequence of the I_{Kr} block, the APD₉₀ increases from 2% to 29%. The theoretical values obtained using the model are in agreement with the experimentally recorded ones. Yang *et al* [20] obtained an increment of 26% of APD₉₀, when guinea pig papillary muscles were treated with dofetilide (100 nM). Similar values have been obtained experimentally in other species. Baskin *et al* [5] recorded an increment of isolated ferret ventricular ERP of approximately 10-20 % for different values of dofetilide concentration (10 nM-10 μ M). Recently, Hua *et al* [6] observed that dofetilide (10 nM) increased APD₉₀ at 1Hz by 24%, in isolated guinea pig Purkinje fibers. The higher blocking effect observed in Purkinje fibers is due to the fact that dofetilide is more potent in Purkinje fiber than in ventricular muscle.

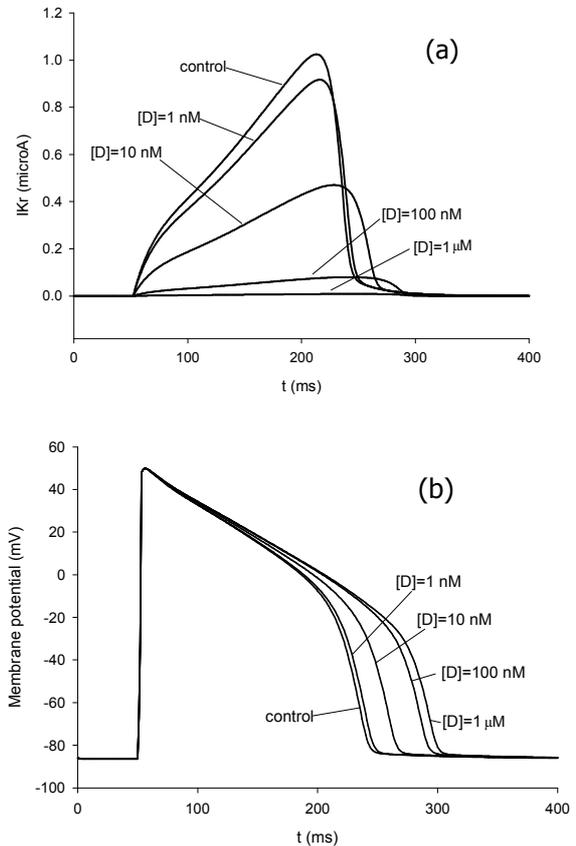


Figure 3. Effect of dofetilide concentration on I_{Kr} (a) and on the action potential (b) obtained with the model.

The model proposed reproduces the reverse use-dependence effect of dofetilide. Due to this effect, the prolongation of action potential duration increases when the stimulation frequency is reduced. In Figure 4 it is possible to observe the increment in APD₉₀ induced by different concentrations of dofetilide at different pacing cycle length.

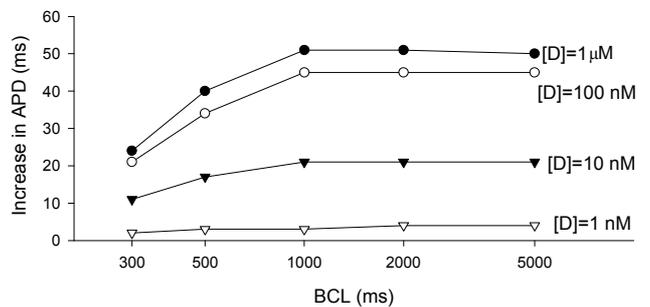


Figure 4. Increment in APD₉₀ induced by different dofetilide concentrations at different basic cycle length (BCL).

From the results shown in the figure, it is possible to observe that the dofetilide presents reverse use-dependence in all range of concentration tested (1 nM to 1 μ M). Even more, when the concentration of dofetilide increases, the reserve use-dependent is enhanced. However, for BCL higher than 1000 ms the increment of APD₉₀ does not change significantly with the BCL. This behaviour is very similar to the observed experimentally [2], see Figure 3 in reference [16].

4. Conclusions

A model of the dofetilide-I_{Kr} binding has been presented. The model is based on experimental results and takes into account the recent experimental evidence that suggest an interaction between dofetilide and the membrane receptor when the channels are in both, open and inactivated state, and that indicate that the drug is trapped when the channel is in closed state. The block kinetics and the increment of APD₉₀ for different concentrations of dofetilide are in good agreement with experimental results. The model also reproduces the reverse use dependence behaviour observed in this drug.

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