Effects of Antiarrythmic Drug Lidocaine on Ventricular Electrical Activity. A Computer Modelling Study

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Abstract

Lidocaine is a class Ib antiarrythmic drug that acts blocking the fast sodium current. In this work, a mathematical model of lidocaine effects has been developed. This model has been incorporated to the Luo Rudy model of guinea pig ventricular action potential and the effect of different basic cycle lengths (BCL) and concentrations of drug on the action potential characteristics has been studied.

Our results show that at BCL 300 ms lidocaine reduces maximum current sodium to 7% and 39% for10 μM and 100 μM respectively. If we increase BCL, the blockade is reduced. In addition, lidocaine reduces the maximal upstroke velocity, for BCL 500 ms the inhibition is 0.9 %, 7 % and 38 % for 1μM, 10 μM and 100 μM respectively. This reduction depends on BCL. Conduction velocity is also affected by lidocaine, It is reduced to 4% and 23% for 10 μM and 100 μM respectively (BCL 300 ms); lower concentrations do not affect the conduction velocity.

1. Introduction

Lidocaine is a class Ib antiarrhythmic drug, that blocks the sodium channel of the cardiac ventricular cells [1]. It is known that lidocaine induces depression of sodium current (I_{Na}) [2] and of maximal upstroke velocity ($\dot{V}_{max}$) of ventricular action potentials [3,4]. The blockade developed by lidocaine is stimulation rate dependent; which is called *use dependence*, the block is increased when the stimulation frequency is incremented [5,6].

Experiments have shown that most of sodium channels open very briefly and then undergo activation during the first few milliseconds of the action potential or pass directly into the inactivated state. Binding studies provide direct information about binding of the drug to different states of the channel. It was found that the blockade was mainly produced during inactivated state. The inactivated state block was mainly developed slowly over a time frame of several hundred of milliseconds [7].

Lidocaine is used in the treatment of ventricular cardiac arrhythmias and cardiac arrest with ventricular fibrillation, specially with acute ischemia, but it is not useful in the treatment of atrial arrhythmias [8].

Although there are two available methods to study numerically the behaviour of drugs, we choose the Guarded Receptor Theory (GRT) in order to consider apparent shifts in channel inactivation and receptor affinity as the result of gated regulation of the diffusion path between the unbound drug poll abd the channels binding site [9]. Experimental results suggest that variations of peak I_{Na} during repetitive stimulation are voltage sensitive shifts in equilibrium between unblocked and blocked channels. The GRT postulated fixed drug-receptor affinity but with limited access to the receptor site. This theory considers the kinetics of channel blocking agents to be composed of two processes: coupling of drug to a binding site and the effect of channel gate conformations on drug access to the binding site [9].

The main objective of the present work is to develop a mathematical model of the sodium channel block by lidocaine in guinea pig ventricular cells and to study its effects on action potential characteristics for different concentrations and basic cycle lengths (BCL).

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 this model the sodium current is expressed as:

$$I_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h \cdot j \cdot (V - E_{Na}) \qquad (1)$$

Where $\bar{g}_{Na}$ is the maximum conductance, m^3,h and j are channel gates, V is the membrane potential and E_{Na} is the reversal potential [10].

We have used the Guarded Receptor Hypothesis to model the lidocaine effect on sodium channel, where interaction between drug and ion channel can be represented by

$\Leftrightarrow$

If b(t) represents the fraction of drug-complexed channels, the time-dependent fraction of drug-complexed channels is described by:

$$\frac{db}{dt} = k \cdot [Drug] \cdot (1-b) - l \cdot b \qquad (2)$$

Where k y l are forward and reverse rate constants and [Drug] is the drug concentration.

Early studies of drug revealed that the presence of lidocaine reduces the maximum sodium current when the stimulation frequency was increased, suggesting that the block is use dependent [11]. We suggest the following model (figure 1) of blockade of sodium channel by lidocaine, in accordance with experimental studies that have shown drug–receptor interaction mainly in inactivated state.

We consider that lidocaine is a neutral drug, assuming that the binding is controlled by the activation gate (m^3), whereas unbinding is independent of membrane voltage, and therefore the drug unbinds in all the states.

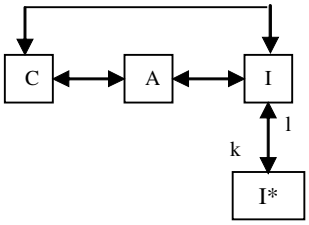

Figure 1. Block diagram for lidocaine in guinea pig ventricular cells.

Subsequently the kinetics is described by:

$$\frac{db}{dt} = k \cdot \left(m^3 \cdot (1 - h \cdot j)\right) \cdot [Drug] \cdot (1-b) - l \cdot b \qquad (3)$$

The response of sodium channel in presence of lidocaine is determined by the stimulation frequency. So with periodic excitation, the time course of each stimulus is shown to be exponential, with a rate and steady state that is linearly dependent on the stimulation frequency. This relationship can be exploited and leads to a simple estimation procedure for the association rates [12]. Consequently we applied this method to the experimental results obtained by Clarkson [13] in guinea pig to find the association and dissociation constants k = 20 ms^{-1} M^{-1} and l = 6.3 x 10^{-4} ms^{-1}, and thereby K_d = 31 x 10^{-6} M.

The effect on Na current is described by:

$$I_{Na} = \bar{g}_{Na} \cdot m^3 \cdot h \cdot j \cdot (1-b) \cdot (V - E_{Na}) \qquad (4)$$

3. Results and Discussion

In order to study the effect of lidocaine on sodium current, we applied trains of stimuli at different BCLs and concentrations.

Simultaneous recordings of sodium current (I_{Na}), maximal upstroke velocity ($\dot{V}_{max}$), action potential duration (APD_{90}) and conduction velocity (CV) are shown for different lidocaine concentrations. Figure 2 shows that, I_{Na} peak was -377 µA/µF in normal condition (before application of drug), while in the presence of lidocaine the depression on I_{Na} was evident. With a BCL of 300 ms the I_{Na} value was reduced to -347 and -227 µA-/µF for concentrations of 10 µM and 100 µM lidocaine respectively. This means that the inhibitory effect on sodium current was around 8 % and 39 % respectively.

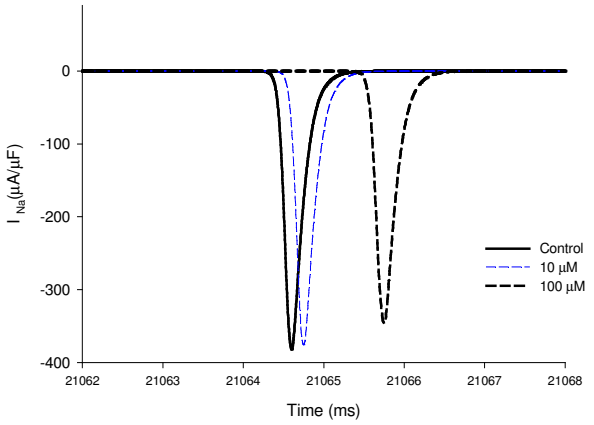

Figure 2. Effect of lidocaine concentration on I_{Na} for a BCL 300 ms

At a BCL 1000 ms, the I_{Na} was reduced to 2 % and 17 % for 10µM and 100µM respectively. Our model reproduces the use-dependent property of blocking by lidocaine. Additionally we can observe that the sodium current was triggered later when lidocaine was used than in control conditions.

The effect of lidocaine on $\dot{V}_{max}$ is illustrated in figure 3. For 1 µM the $\dot{V}_{max}$ was reduced to a 3 % while for 100 µM the reduction was of 22 %.

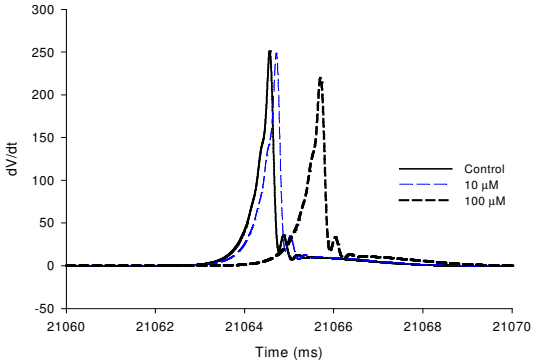

Figure 3. Effects of lidocaine on maximal upstroke velocity of action potential for a BCL 1000 ms.

The differences in the development of use-dependent block on $\dot{V}_{max}$ to different BCLs and concentrations are shown in table 1.

BCL (ms)	10 µM	100 µM
300	8.5 %	47 %
500	7.5 %	38 %
1000	3.2 %	22 %

Table 1 Reduction of $\dot{V}_{max}$ for different BCLs

These data are similar to different experimental results [14,15,16]. In figure 4 experimental data recorded for BCL = 1000 ms (▲) are compared with data obtained using our model (●). Our results confirm the use-dependent effect of lidocaine on $\dot{V}_{max}$.

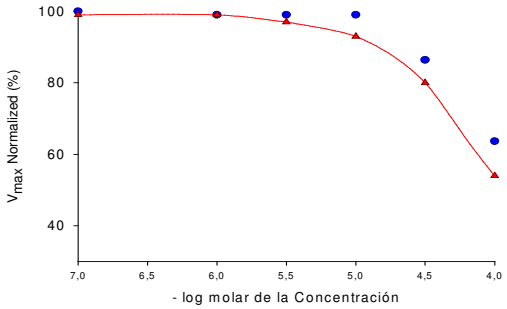

Figure 4. Comparison of the computer predicted values for $\dot{V}_{max}$ obtained in the presence of lidocaine (●) against experimental data (▲). For a BCL 1000 ms.

Action potential duration at 90% repolarization (APD_{90}) was unaffected by lidocaine in the tested range of concentrations. In figure 5, we can observe that the highest concentration did not produce a significant change on APD_{90}, likewise, high frequencies did not change this parameter (Table 2). APD_{90} was prolonged only 2 % for 100 µM.

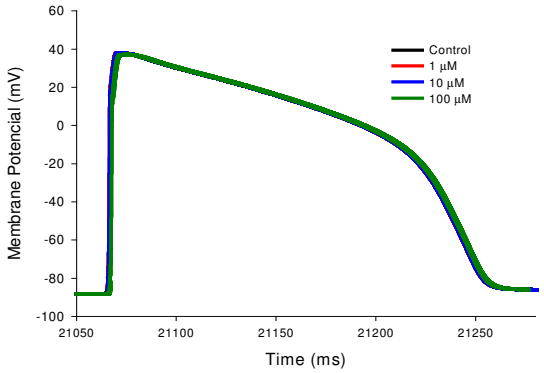

Figure 5. Effect of lidocaine on action potential duration for a BCL 300 ms.

	APD_{90}			
BCL (ms)	Control	1 µM	10 µM	100 µM
300	132	131	132	143
500	153	153.5	154	159
1000	174	174	174.8	177

Table 2. Effects on the duration of action potential

Similarly to $\dot{V}_{max}$ and I_{Na}, the conduction velocity (CV) was decremented, when the drug concentration was increased. With a BCL of 500 ms the CV was reduced to 0.41 m/s and 0.35 m/s for 1µM and 100 µM respectively and to 0.41 m/s and 0.38 m/s for the same concentrations for a BCL of 1000 ms. Figure 6 shows the changes in CV induced by different lidocaine concentrations, expressed as a function of BCL.

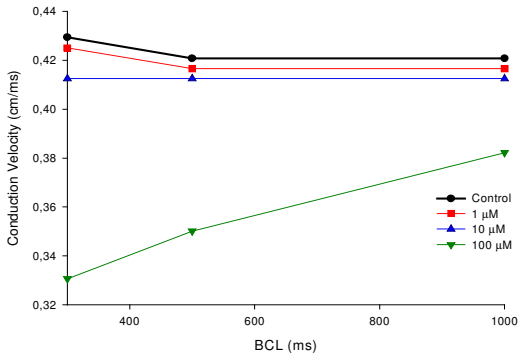

Figure 6. Decrement in conduction velocity induced by different lidocaine concentrations at different BCLs.

4. Conclusions

In the present study, we have proposed a model to characterize the behaviour of lidocaine in ventricular

cells of guinea pig. The model is based on experimental results and takes into account the experimental evidence that shows that the interaction of the drug with the channel occurs in the inactivated state. We can observe that blockade is concentration and frequency dependent.

Lidocaine reduces I_{Na}, $\dot{V}_{max}$ and conduction velocity in high concentration. APD_{90} is not affected by lidocaine in the tested range of concentrations.

Acknowledgements

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