**Introduction**

The evaluation of cardiotoxicity is a crucial aspect of drug development. Current regulatory guidelines for drug safety require the measurement of IKr channel block in vitro and QT interval prolongation in vivo to assess the arrhythmic risk of a drug. However, it has become evident that these markers alone are insufficient to predict cardiotoxic behavior accurately. A new paradigm has been proposed, which combines in vitro studies that measure the drug's effect on different ionic channels and in-silico models of cardiac myocyte electrophysiology. This report evaluates the cardiotoxicity of Ritonavir using the MATLAB program provided.

**Methodology**

The effect of Ritonavir on the different ionic channels was modeled using a pore block model, which reduces the channel conductance based on the available half-maximal inhibitor concentration, IC50, and Hill coefficient, n, using the formula:

where FB is the fraction of channel block.

To evaluate the cardiotoxic effect, the electrophysiological variability inherent in the cardiac tissue was considered by using a population of models approach. The file mask.mat contains channel conductance multiplying factors corresponding to ten different models of ventricular myocytes. Each column of the file corresponds to an ionic channel in the O'Hara model.

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| --- | --- | --- |
| Gna | Hill Coeff. | 1 |
| IC50 (μM) | 27.96163 |
| GNaL | Hill Coeff. | 0.7 |
| IC50 (μM) | 7.175 |
| Gto | Hill Coeff. | 1 |
| IC50 (μM) | ∞ |
| GKr | Hill Coeff. | 1 |
| IC50 (μM) | 5.157 |
| GKs | Hill Coeff. | 1 |
| IC50 (μM) | ∞ |
| GK1 | Hill Coeff. | 1 |
| IC50 (μM) | ∞ |
| GNaCX | Hill Coeff. | 1 |
| IC50 (μM) | ∞ |
| GNaK | Hill Coeff. | 1 |
| IC50 (μM) | ∞ |
| GCaL | Hill Coeff. | 1.3 |
| IC50 (μM) | 8.228 |
| EFTPCmax (μM) | | 0.4369 |

For each of the ten models, the effect of Ritonavir was evaluated for four different concentrations: 1x, 2x, 10x, and 100x [EFTCP] (a total of 40 simulations). The stimulation protocol consisted of stimulating with a current 1.5x the stimulation threshold 500 times with a BCL=800ms and analyzing the last three beats. A pro-arrhythmic behavior was considered if alternans in the APD90 were observed, abnormal repolarizations appeared, or APD prolongation of more than 25% (with respect to control).