Abstract

Drug-induced inhibition of the cardiac hERG potassium channel is assumed to predict delayed cardiac repolarization (DR). The consequent QP prolongation is a surrogate marker of torsade de points (TdP), a potentially lethal arrhythmic outcome. Drugs with effective therapeutic plasma concentrations (ETPC) within 15-fold of their hERG IC50, thought to be dangerous despite the fact that multiple ion channel effects (MICE) can mitigate DR. Here we demonstrate that a logistic regression model, which integrates effective IC50s for TdP with much greater certainty than the hERG safety ratio (IC50_ETPC) alone. Safety ratios were calculated for 43 drugs (19 long-term and 24 short-term) from multiple classes by dividing their hERG, Nav1.5, and Cav1.2 IC50 values by each drug’s ETPC. Two logistic regression models were constructed: one using the hERG IC50_ETPC ratio alone (Model 1), the other integrating hERG IC50_ETPC, Nav1.5 IC50_ETPC, and Cav1.2 IC50_ETPC data (Model 2). The predictive power of each model was evaluated by performing leave-one-out validations. Each model’s accuracy to discriminate +TdP and −TdP drugs was determined by comparing their receiver-operator characteristics (ROC, true vs. false positive rates). Model 1 had a 52% False Positive Rate associated with a 90% True Positive Rate and a ROC area under the curve (AUC) of 0.74. Model 2 significantly improved accuracy showing a 14% False Positive Rate associated with a 90% True Positive Rate and a ROC AUC of 0.88. We propose that models that incorporate quantitative drug effects on multiple cardiac ion channels will be robust nonclinical predictors of cardiac risk.

Introduction:

The challenge is to identify drugs early in development that may cause torsade de points (TdP), a serious polymorphic ventricular tachycardia that can lead to sudden death. The frequency of TdP may be <10−4 for non-cardiac drugs cannot be reliably detected in clinical trials. The risk of sudden death may become apparent only during marketing surveillance. QT prolongation has been chosen as a surrogate marker for TdP because TdP is always associated with a prolonged QT interval but the QT-TDP linkage is incomplete and the hERG channel (hERG, Cav1.2 and Nav1.5) IC50 values for 41 drugs were collected from the literature and ChanTest’s internal database. The average Effective Therapeutic Plasma Concentrations (ETPC) were collected from the literature or calculated from Cmax and % protein binding values. In the logarithmic plots above, the hERG IC50/ETPC value is the vertex of each line segment, the Nav1.5 IC50/ETPC value is the point at the end of each blue line segment and the Cav1.2 IC50/ETPC value is the point at the end of each orange segment. Drugs were characterized as torsadogenic (left panel) or non-torsadogenic (right panel) according to information found in Redfern et al. (Categories 1-3 = TdP, Categories 4-5 = TdP, Arizona CERT database and reported cases. The dashed line shows Redfern’s criteria of 30% for torsadogenic drugs. One can see that not all of the torsadogenic drugs have hERG IC50 values that are less than 30 fold above the ETPC and some non-torsadogenic drugs have hERG IC50/ETPC ratios that are less than 30. The plots above reveal that with very few exceptions, the +TdP and −TdP drugs can be qualitatively distinguished from each other by their multi- ion channel IC50/ETPC profiles. In general safe drugs have IC50/ETPC values for the depolarizing currents close (within one order of magnitude) to hERG IC50/ETPC values.

1. The ECG and Cardiac Action Potential are Formed by Many Different Ion Channel Currents

Ion channel (hERG, Cav1.2 and Nav1.5) IC50 values for 41 drugs were collected from the literature and ChanTest’s internal database. The average Effective Therapeutic Plasma Concentrations (ETPC) were collected from the literature or calculated from Cmax and % protein binding values. In the logarithmic plots above, the hERG IC50/ETPC value is the vertex of each line segment, the Nav1.5 IC50/ETPC value is the point at the end of each blue line segment and the Cav1.2 IC50/ETPC is the point at the end of each orange segment. Drugs were characterized as torsadogenic (left panel) or non-torsadogenic (right panel) according to information found in Redfern et al. (Categories 1-3 = TdP, Categories 4-5 = TdP, Arizona CERT database and reported cases. The dashed line shows Redfern’s criteria of 30% for torsadogenic drugs. One can see that not all of the torsadogenic drugs have hERG IC50 values that are less than 30 fold above the ETPC and some non-torsadogenic drugs have hERG IC50/ETPC ratios that are less than 30. The plots above reveal that with very few exceptions, the +TdP and −TdP drugs can be qualitatively distinguished from each other by their multi- ion channel IC50/ETPC profiles. In general safe drugs have IC50/ETPC values for the depolarizing currents close (within one order of magnitude) to hERG IC50/ETPC values.

2.) hERG Is Not The Best Predictor of TdP When Drug Affects Multiple Ion Channels

Many torsadogenic drugs potently and selectively inhibit hERG ion channel current. However, hERG blockers that have effects on multiple ion channels, are not always torsadogenic. Verapamil, which is used to treat high blood pressure and angina, is a multiple ion channel blocker that inhibits hERG very potently (IC50 = 143 nm). Verapamil inhibits the two major depolarizing currents, ICaL and ICaNa, offsetting the hERG block and avoiding delayed repolarization. There are no reported incidents of TdP since it has been on the market. Compounds that have multiple ion channel effects should be identified as early as possible during drug development.

3.) +TdP and −TdP Drugs Characterized by Their Ion Channel IC50/ETPC Profiles

4.) Model Based on Multiple Ion Channel Effects Is More Predictive of TdP

We created two predictive logistic regression models: The first model was developed with hERG IC50/ETPC data and the second with hERG IC50/ETPC + Nav1.5 IC50/ETPC + Cav1.2 IC50/ETPC data. Cross validation of each model was performed to classify drugs as either +TdP or −TdP. The first logistic regression model using only hERG classified the drugs, displaying an overlapping of the +TdP and −TdP groups, 11 false positives and 1 false negative. In contrast, the second model effectively separated the +TdP and −TdP groups and resulted in only 3 false positives and 2 false negatives.

Conclusions:

1) Some hERG blockers (IC50/ETPC values lower than 30) are safe drugs when they also block calcium and/or sodium currents.
2) Logistic regression models that include multiple ion channels are better predictors of cardiac risk than models including hERG block alone.
3) Drug misclassification is most probably due to inadequacy of TdP classification or drug effects on other channels involved in cardiac excitability.