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A New Paradigm for Predicting Risk of Torsades de Pointes during Drug Development:

Commentary On: "Improved Prediction of Drug-Induced Torsades de Pointes Through Simulations of Dynamics and Machine Learning Algorithms"

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Introduction

The drug-induced long QT syndrome (diLQTS) describes a clinical entity in which administration of a drug produces marked prolongation of the QT interval on the ECG, and a morphologically distinctive polymorphic ventricular tachycardia, termed Torsades de Pointes (TdP). Risk factors for the development of TdP include: QT prolonging drugs; female gender; bradycardia; electrolyte disturbances (hypokalemia, hypomagnesemia); recent conversion to normal (sinus) rhythm; and congenital LQTS.[1]

The molecular mechanisms underlying diLQTS have been greatly informed by studies of the congenital LQTS, in which mutations in genes that encode any number of ion currents result in abnormal cardiac ion channel function manifest as QT interval prolongation and risk for sudden cardiac death (SCD) due to TdP. In contrast, the mechanism by which drugs cause acquired LQTS is almost always due to block of the rapid component of the delayed rectifier potassium current, I_{Kr}. Although several cardiovascular drugs are reported to cause diLQT and risk of TdP, there are also many non-cardiovascular drugs, such as cisapride, erythromycin, and methadone that are also commonly shown to prolong cardiac action potential duration (APD), and predispose to TdP. Given the importance of identifying individuals susceptible to diLQTS and SCD, the screening of new drugs for torsadogenic potential has become a significant regulatory concern and the subject of increased scrutiny in drug development.[2] DiLQTS and the resultant risk for TdP is also the most common reason for withdrawal of medications from the market. Furthermore, the FDA mandates in-hospital initiation of dofetilide, a QT-prolonging drug, due to its torsadogenic toxicity. Thus, there is an urgent need to develop an accurate predictive model to stratify diLQTS/TdP risk in susceptible individuals.

Towards accomplishing this goal, *in silico* models have become a valuable tool in the stratification of TdP risk. Alterations in the human ether-a-go-go (hERG) (now known as *KCNH2)* encoding I_{Kr} have largely been ascribed to be the dominant repolarization current involved in QT interval prolongation and risk of TdP. Therefore, many of the early *in silico* models of TdP risk have attempted to model effects of drug binding-related changes in I_{Kr}.

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For example, Di Veroli *et al.* used an *in silico* Markov model to predict I_{Kr} repolarization current in Chinese hamster ovary (CHO) cells and predict alterations in action potential (AP).[3] These data allowed for the prediction of drug binding kinetics which may be useful in the characterization of new drugs with potential for QT interval prolongation. Patients who are genetically susceptible to QT prolongation are exceptionally prone to developing TdP, and as such, merit special consideration from *in silico* based prediction models. For example, Hoefen *et al.* recently demonstrated a computational model of LQT1 in which the estimation of SCD risk was linked to cellular electrophysiologic functions of LQT1-linked mutations versus wild type controls.[4] Using a 1-dimensional "cable" model to represent ventricular heterogeneity, these investigators determined that a transmural repolarization increase of 10 msec in adult LQT1 patients was 35% more likely to experience an adverse cardiac outcome. These novel studies incorporated multiple predictors of APD prolongation, including the late sodium current $I_{Na\text{-}L}$ and the slow delayed rectifier potassium current I_{Ks}, and used these factors to predict adverse events independent of traditional ECG parameters. However, selecting only adult survivors of LQT1 phenotype, and the fact that APD is determined by a combination of membrane and intracellular signaling events involved in excitation-contraction coupling were significant limitations of this model.[5] Additionally, Moreau *et al.* have developed an *in silico* model of LQT3 involving an increased persistent sodium current I_{Na} from clinically relevant mutations in *SCN5A*, the gene encoding the cardiac sodium channel. This model was used in tandem with biophysical characterization in TsA201 cells to confirm the arrhythmogenic potential of gain-of-function *SCN5A* mutations, and also to validate mexiletine, a sodium-channel blocker, as a targeted treatment modality for these patients. Thus, *in silico* modeling has become a valuable adjunct to the diagnosis and treatment of TdP risk in susceptible patients.

There is now a wealth of data supporting the hypothesis that the underlying molecular mechanisms of diLQTS not only involve I_{Kr}-block but also other cardiac ion currents. Lu *et al.* examined the role of phosphoinositide 3-kinase (PI3K) signaling pathway in modulating ventricular repolarization.[6] They showed that inhibitors of tyrosine kinase or PI3K increased APD in canine cardiac myocytes that was reversed by intracellular infusion of phosphatidylinositol 3,4,5-triphosphate. The inhibitors not only decreased I_{Kr} but also I_{Ks}, the L-type calcium current $I_{Ca,L}$, the peak sodium current I_{Na}, and increased the late sodium current $I_{Na\text{-}L}$. The *in vitro* studies were augmented by computer modeling of the canine ventricular AP that demonstrated that the drug-induced change in any one current accounted for <50% of the increase in APD. Furthermore, a knock-out mouse model lacking the PI3K p110 α-catalytic subunit exhibited a prolonged APD and QT interval that were in part due to an increase in $I_{Na\text{-}L}$. Thus, downregulation of PI3K signaling pathway directly or indirectly via tyrosine kinase inhibition leads to prolongation of the QT interval mediated in part by modulating multiple cardiac ion channel.[6] This may be one explanation for why some tyrosine kinase inhibitors used in the treatment of cancers are associated with increased risk for QT prolongation and TdP. A more recent study by *Yang et al.* confirmed the role of $I_{Na\text{-}L}$ in generating ventricular arrhythmias associated prolongation of the APD through the PKI3K signaling pathway. Although not all QT-prolonging drugs designated as torsadogenic I_{Kr}-blockers demonstrated this effect.[7] Furthermore, this study also highlighted the urgent

need to develop new screening tools to evaluate the torsadogenic potential during the drug development stage.

In silico modeling allows for facile testing of new drugs with potential risk for diLQTS. However, each model is limited not only by its underlying assumptions but also the experimental data used to validate the model. For example, in addition to AP prolongation related to membrane-associated ion channels, arrhythmogenic potential from pathological intracellular calcium handling also plays a significant role in TdP risk. Interestingly, some antiarrhythmic agents classically described as sodium channel blockers e.g., flecainide, have subsequently been shown to stabilize the cardiac ryanodine receptor (RyR2), further reducing arrhythmia risk.[8] Also, intracellular calcium overload is associated with alterations in the sodium-calcium transporter function (NCX), further modulating I_{Na}, and APD. Thus, although hERG is a major contributing factor in TdP risk, other cardiac ion channels and intracellular calcium handling also play a significant role in TdP, and need to be considered when performing *in silico* modeling.

In a study published in this issue of *Clinical Pharmacology & Therapeutics*,[9] Lancaster and Sobie address the importance of multi-channel drug effects for *in silico* modeling in the prediction of TdP risk. They used a Quantitative Systems Pharmacology approach to discriminate between torsadogenic and non-torsadogenic drugs based on published cellular electrophysiological studies in ventricular myocytes. In all, 86 drugs and 3 human ventricular myocyte models were compared, and 331 electrophysiologic variables were evaluated including both membrane-associated parameters, and intracellular data (calcium transients). The investigators found that this combined approach has a greater predictive value (96%) for drug-induced torsadogenic potential than previous models that only considered hERG blockade. Interestingly, 2 parameters, APD_{50} and diastolic $[Ca^{2+}]$ have approximately the same accuracy as the above approach, and may be more suitable for a "shotgun" approach to rapidly determining TdP risk in a high-throughput drug screening model. This model is not only scalable at differing drug concentrations and can be modeled in synthetic susceptible populations, but also shows widespread applicability and appeal when predicting TdP risk.

Although elegant, this *in silico* model does not yet incorporate physiologic variations in APD, such as is found in diurnal variability,[10] congenital LQTS,[4] or sex-based differences in repolarization. Other limitations relate to: assumptions in ion channel interactions and more 'simple' pore-block models of drug action, which do not assess channel blocking kinetics or state-dependent drug binding; failure to incorporate specific effects on the $I_{Na\text{-}L}$ in the current mathematical models as improved representations of this current may improve classifier performance; and the 'simplicity' of the model which fails to capture the true complexity of TdP generation. However, despite these limitations, the model does incorporate a large amount of cellular electrophysiological data from 3 independent sources and applies this to predictive modeling of TdP risk with 96% predictive accuracy for TdP potential. Thus, the study provides the most accurate pre-clinical model to date for the discovery of torsadogenic potential, and will be a very useful adjunct to predict risk of new drugs used in potentially susceptible populations.

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