Advances in Assessing Drug-induced Torsade de Pointes and the Comprehensive In Vitro Proarrhythmia Assay (CiPA)

An FDA/CSRC/HESI-sponsored Think Tank Meeting was convened in Washington, DC, on May 21st & 22nd, 2018, to discuss the latest data from the Comprehensive In Vitro Proarrhythmia Assay (CiPA) Initiative. This Synopsis provides a very high level report of results presented.

The four components of CiPA collectively seek to characterize more clearly the torsadogenic risk of drugs by providing a more comprehensive assessment of a drug’s effect on multiple cardiac ionic currents rather than just hERG. In vitro assessment of drug-induced effects on ionic currents focuses primarily on hERG, late sodium, and L-type calcium (calcium) currents. In silico computer modeling integrates individual ion channel data to predict the clinical risk of Torsade. ECG biomarkers, e.g., the heart rate-corrected J-Tpeak interval (J-Tpeakc), are studied in Phase 1 clinical trials to check for unanticipated effects compared with nonclinical ion channel data and in silico modeling predictions. In vitro drug effects on human induced pluripotent stem cell-derived ventricular cardiomyocytes can be optionally examined for the same purposes.

Twenty-eight ‘gold standard drugs’ were used to evaluate the CiPA paradigm, representing a varied spectrum of multiple electrophysiological mechanisms, including multichannel blocking drugs (hERG and late sodium and/or calcium block). Each drug was ranked on clinically demonstrated high, intermediate, or low risk of Torsade. Two subsets were then created: 12 training drugs (four high Torsade risk, four intermediate risk, and four low risk) to be used in in silico model development and optimization; and 16 validation drugs (four high Torsade risk, seven intermediate risk, and five low risk) to be used in model validation.

In Silico Modeling Approach and Validation Results
The development and validation process first involved the selection of a base cardiomyocyte model (O’Hara-Rudy model, 2011) modified for dynamic-drug block of hERG. The effects of 12 CiPA training drugs on seven cardiac current currents in heterologous expression systems were used for model optimization and metric development. The optimized model (including risk classification thresholds) was frozen for use in the subsequent validation exercise, which utilized the remaining 16 CiPA validation drugs to generate a Torsade Metric Score (qNET) used to assess the model’s ability to categorize drugs correctly into Torsade risk categories.

The validation process used two different ionic current datasets, one containing manual patch clamp data for all three currents (obtained at 37°C), and a second ‘hybrid’ dataset consisting of manual hERG data along with automated patch clamp measurement of calcium and late sodium (the latter two obtained at room temperature). The Torsade Metric Score performance was evaluated via receiver operating characteristic (ROC) curves, with the area under the curve (AUC) values representing the probability of correctly ranking a higher risk drug above a lower risk drug. In general, the ability to discriminate low (or high) risk drugs vs. other category drugs was excellent (AUC > 0.9) for both datasets.

Human Induced Pluripotent Stem Cell-derived Cardiomyocytes
Results from the CiPA Myocyte Validation Study were presented. Two statistical models were used to evaluate the ability of two commercially available cell lines to categorize the torsadogenic
risk of 28 blinded CiPA drugs across 15 sites using multielectrode array and voltage-sensing dye approaches, and to define sources of response variability. Three of seven predictors tested (drug-induced cellular repolarization arrhythmia, prolongation of repolarization at any concentration, and prolongation of repolarization at clinical exposures) were most useful in drug categorization. In general, the incidence of cellular repolarization arrhythmias paralleled the categorization risk, with most high risk drugs inducing arrhythmia-like events. All high risk drugs induced repolarization prolongation. Intermediate risk drug-induced changes in repolarization were less than for high risk drugs. In contrast, five of nine low risk drugs induced repolarization duration shortening, while others minimally prolonged repolarization. Estimated drug-induced repolarization prolongation at Cmax was the highest for ibutilide, dofetilide, quinidine, and vandetanib in the high risk category. Intermediate risk drugs induced moderate repolarization prolongation at Cmax, with five of nine low risk category drugs shortening repolarization at Cmax.

Logistical and ordinal regression models were able to discriminate Torsade risk categories, with ROC-based AUC values ranging above 0.8 (good to excellent range). There was some limitation in classifying late sodium-blocking drugs into the low risk category. Site variability was lower than variability induced by cell line, and both sources of variability were lower than the contribution provided by drug concentration, demonstrating the overall utility of the model across multiple sites and cell lines.

Phase I ECG Biomarker(s) under CiPA
Results of a new prospective clinical trial were presented at the Think Tank. The primary objective of Part 1 (parallel study) was to confirm that concentration-response analysis of the electrocardiographic QTc and J-Tpeakc intervals in Phase I clinical pharmacology studies can be used to confirm that balanced ion channel-blocking drugs (ranolazine, verapamil, and lopinavir/ritonavir) do not cause J-Tpeakc prolongation, and predominant hERG-blocking drugs (chloroquine) do cause J-Tpeakc prolongation. As expected, the predominant hERG blocker (chloroquine) prolonged both ΔΔQTc and ΔΔJ-Tpeakc, while the balanced ion channel blockers (ranolazine, verapamil, and lopinavir/ritonavir) prolonged ΔΔQTc and had flat or negative ΔΔJ-Tpeakc slopes. The primary endpoints were met for chloroquine, verapamil, and lopinavir/ritonavir, while ranolazine displayed a flat J-Tpeakc slope with an upper confidence bound 2 msec above the prespecified threshold of 10 msec for ΔΔJ-Tpeakc.

A second part of the study investigated whether diltiazem (calcium block) mitigates QTc prolongation by dofetilide (selective hERG block) by shortening J-Tpeakc. In combination with dofetilide, diltiazem did not shorten QTc (not meeting primary the endpoint), but did shorten J-Tpeakc. The lack of QT shortening with diltiazem is unclear, but may be due to indirect effects (e.g., autonomic response from decreased blood pressure or increased ventricular loading from PR interval prolongation). Of note, verapamil and lopinavir/ritonavir (which have hERG and calcium block) prolonged QTc without prolonging J-Tpeakc in Part 1 of the study.

Summary
Results from validation endeavors for each of the CiPA components were presented, thus setting the stage for further discussion with the ICH S7B/E14 Discussion Group and the potential opening of a ‘Question & Answer’ document to address how the principles outlined in CiPA can be implemented in a standardized manner.