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The Potential Role of the J-T_{peak} Interval in Proarrhythmic Cardiac Safety: Current State of the Science From the American College of Clinical Pharmacology and the Cardiac Safety Research Consortium

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Sudden death resulting from drug-induced proarrhythmia is one of the most feared complications in pharmaceutical medicine.[1] Of particular interest in the domain of proarrhythmic cardiac safety is torsade de pointes (torsade). Torsade is a rare polymorphic ventricular arrhythmia that typically occurs in self-limiting bursts that can lead to symptoms of dizziness, palpitations, syncope, and seizures, but also an arrhythmia with potentially catastrophic consequences: drug-induced torsade can occasionally progress to ventricular fibrillation and sudden cardiac death.[2] Following multiple drug withdrawals worldwide due to proarrhythmic concerns in the late 1980s to early 2000s, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) released 2 guidelines, ICH S7B (nonclinical investigations) and ICH E14 (clinical investigations), that were subsequently adopted by regulatory agencies in multiple geographic jurisdictions. These have since become essential features of the cardiac safety regulatory landscape. Unfortunately, although these guidelines successfully prevented drugs with unrecognized torsadogenic liability from reaching the market, there have been unexpected consequences for both drug developers and patients. The ICH S7B/E14 guidelines focus on drug-induced reductions in a single cardiac potassium ionic repolarizing current, I_{Kr} (referred to here as hERG current because it flows through the ion channel whose α-subunit is encoded by *hERG*), and associated prolongation of the QT/QTc interval as seen in humans during clinical pharmacology trials including thorough QT assessment as per ICH E14. Since the adoption of the S7B/E14 guidelines, it has become clear that a large proportion of drug candidates block the hERG channel. As a consequence, it is believed that many potentially useful therapeutics have been terminated during nonclinical screening and development programs because of their effect on hERG and potential QT liability. Additionally, many drug candidates that proceed to clinical development but then show a small degree of QT/QTc prolongation in early-phase clinical pharmacology trials have been discontinued from development.[3] Although this may initially appear to be efficient drug development, hERG current block and QT/QTc prolongation alone are not specific biomarkers for torsade. There

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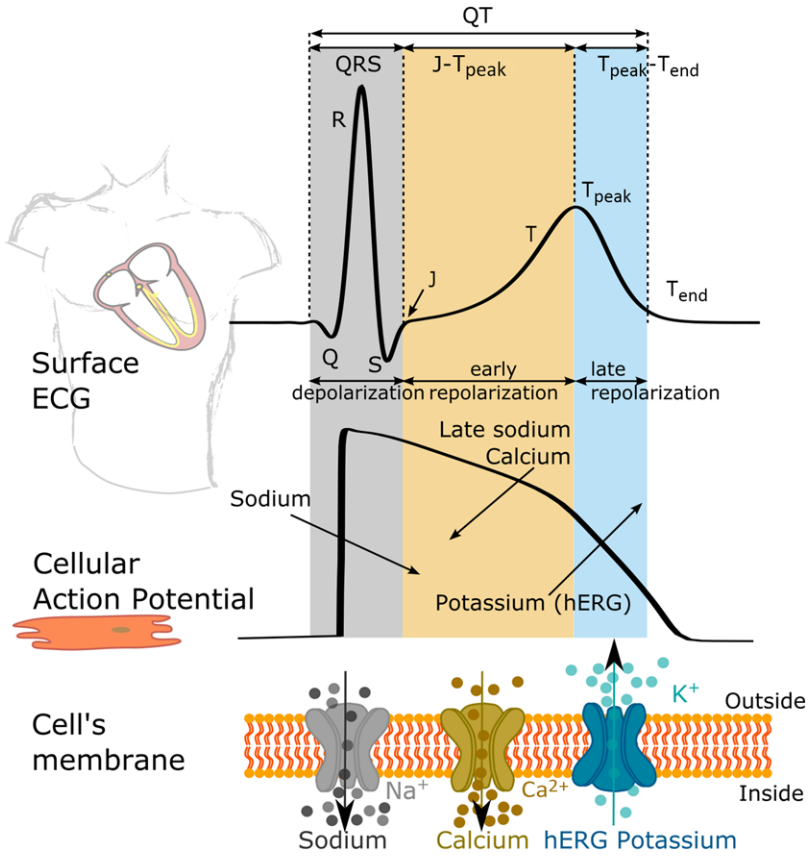

Figure 1. The J-T_{peak} interval and ionic currents of interest during cardiac depolarization and repolarization. Figure adapted from Vicente et al.[22]

are examples of drugs (eg, ranolazine, verapamil) that prolong the QTc interval but are associated with a very low risk for torsade[4] because they block other currents (eg, late sodium and/or L-type calcium). As a consequence, many candidates that might have demonstrated important therapeutic benefits and might have had an overall favorable cardiac safety profile probably have not reached the market and hence have not improved public health. In recent years, therefore, there has been considerable interest in identifying more informative ECG cardiac safety biomarkers.

The J-T_{peak} Interval: What It Is and Why It Is Important

The J-T_{peak} interval is the time from the end of the QRS complex to the peak of the T-wave, corresponding to early repolarization (see Figure 1). As for QT interval measurements, J-T_{peak} interval measurements are corrected for heart rate to yield J-T_{peak}c. J-T_{peak}c has been identified as a potentially useful biomarker that can differentiate QT-prolonging drugs that block inward currents (eg, late sodium, calcium) in addition to hERG from predominant hERG blockers.[5] Also shown in Figure 1, T_{peak}-T_{end} corresponds to late repolarization, which is discussed in subsequent sections. These are the ECG biomarkers of specific interest in this article.

Drug-induced ventricular repolarization delay and the risk of torsade are not due solely to hERG block but, rather, are dependent on a balance of multiple inward and outward ionic currents active during the ventricular action potential that, taken together, define ventricular repolarization. With regard to drug-induced torsade, the 2 most important currents in addition to hERG are inward depolarizing currents: the late sodium current and the L-type calcium current (see also Figure 1). Blocking of these currents in animals,[6,7] human cells,[8] and in in-silico models[9] shortens the action potential duration of cardiac cells in the ventricle and prevents the occurrence of early afterdepolarizations, which are the trigger of torsade.[10,11] Moreover, mexiletine (late sodium block) mitigated recurrent torsade caused by acquired long-QT syndrome in a recent clinical study.[12] Hence, in the presence of QTc prolongation due to drug-induced block of hERG current, multi-ion channel–blocking drugs that also block these inward currents to an equipotent extent as hERG have a lower risk of inducing torsade ("balanced" ion-channel blockers) compared with drugs that block only hERG channels (predominant hERG blockers).

The Comprehensive in Vitro Proarrhythmia Assay (CiPA) initiative[13,14] is driven by an international consortium comprising multiple collaborators from industry, academia, and regulatory agencies and is coordinated by the Health and Environmental Sciences Institute (HESI). The CiPA initiative is investigating new strategies that have the potential to improve the prediction of torsade risk. Although the first components of CiPA fall in the nonclinical domain (drug-induced effects on multiple isolated human depolarizing and repolarizing currents, in-silico modeling of cellular human ventricular activity, and optional checking for unanticipated findings using human induced pluripotent stem cell–derived cardiomyocytes), a fourth component is the examination of drug-induced effects on ECGs rigorously recorded during well-controlled early-phase clinical pharmacology studies. The primary assessment methodology is concentration-response modeling with a focus on a wider range of ECG components including J-T_{peak}c, except for drugs in which this approach may not be appropriate (eg, a nonlinear relationship between drug concentration and ECG changes). The primary goal is to assess for unanticipated ECG effects (eg, changes in QTc, QRS, PR, as well as J-T_{peak}c) compared with the nonclinical assessment that might occur due to human-specific metabolites, differences in expected protein binding/tissue concentration, or other factors. It is noted that potent L-type calcium block can prolong the PR interval (and thus needs to be clinically evaluated), although late sodium block does not have a major effect on atrioventricular conduction.

Overall, CiPA's multiple goals and potential areas to impact drug discovery, development, and therapeutic use include guiding predictions regarding the nature of a potential proarrhythmic risk of balanced ion channel–blocking drugs with demonstrated hERG block and/or QTc prolongation and providing more informative drug labels for new and currently marketed drugs.[14]

Recent clinical studies, including a retrospective analysis of 34 thorough QT studies and 3 prospective clinical trials including 11 drugs and 5 drug combinations, have provided evidence that the absence of significant J-T_{peak}c prolongation in the presence of QTc prolongation may be a useful "ECG signature" of a balanced ion channel–blocking drug.[15–18] Drugs that predominantly block the hERG channel prolong QTc by prolonging both J-T_{peak}c and T_{peak}-T_{end}, whereas drugs that block the hERG channel along with calcium and/or late sodium channels prolong QTc by prolonging T_{peak}-T_{end} with limited or no effect on the J-T_{peak}c interval. For example, dofetilide, quinidine, and moxifloxacin (predominant hERG blockers) prolong QTc by prolonging both J-T_{peak}c and T_{peak}-T_{end}, whereas ranolazine (a balanced hERG and late sodium blocker), verapamil (a balanced hERG and L-type calcium blocker), lopinavir/ritonavir (blocker of hERG, L-type calcium, and late sodium), and drug combinations of dofetilide (hERG blocker) with lidocaine or mexiletine (late sodium blockers) prolonged QTc by prolonging T_{peak}-T_{end} but not J-T_{peak}c. As already noted, verapamil and ranolazine have not been shown to cause torsade despite >15 years of use, even though both prolong the QTc interval.[4,18] Thus, conceptually, such an "ECG signature," in conjunction with preclinical ion channel data and in-silico modeling, might have a role in distinguishing mechanistically different profiles that are clinically relevant to safety-related decision making such as torsade risk. As discussed below, this signature might be informative during individual drug development and to assess targeted drug combinations, or both.

Evidence of the Usefulness of J-T_{peak} Interval in Assessment of Cardiac Safety

J-T_{peak}c was first identified as a potential biomarker to differentiate QT-prolonging drugs with different ion channel effects in a retrospective analysis of 34 thorough QT studies.[15] In this analysis it was found that predominant hERG blockers prolonged both the QTc and J-T_{peak}c, but hERG blockers that also blocked the L-type calcium and/or late sodium currents (balanced blockers) prolonged QTc without prolonging J-T_{peak}c. This "ECG signature" was confirmed in a prospective clinical study. In that study,[16] known predominant hERG blockers (dofetilide and quinidine) prolonged J-T_{peak}c (and QTc), whereas balanced blockers (ranolazine and verapamil) did not prolong J-T_{peak}c (ranolazine prolonged QTc, and verapamil did not in this single-dose study). The mechanism of action associated with balanced ion channel block (hERG + late sodium) was verified in a second prospective clinical study.[17] That study demonstrated that late sodium block (lidocaine or mexiletine) shortens QTc prolongation caused by hERG block (dofetilide) by shortening the J-T_{peak}c interval. Thus, this drug combination of a predominant hERG blocker combined with a late sodium current blocker resulted in a similar ECG signature as observed with ranolazine administered alone. An arm to assess whether calcium block (diltiazem) could shorten QTc prolongation by hERG block (moxifloxacin) was also included in this study. Diltiazem did not shorten moxifloxacin-induced QTc prolongation, although study design limitations confounded this analysis.

A total of 12 ECG biomarkers including T-wave morphology, vectorcardiographic biomarkers, and alternative measures of repolarization duration were also assessed in the prospective studies previously described. Analyses using concentration-response models as well

as an analysis based on the area under the receiver operating characteristic curve showed that the J-T_{peak}c was the best biomarker to differentiate balanced ion channel block from predominant hERG block.[5,19] In addition, analyses using different J-T_{peak}c ECG methods by other research groups showed similar results.[20,21] These findings suggest that J-T_{peak}c might be used to differentiate QTc-prolonging drugs with predominant hERG block versus balanced ion channel block.

Under CiPA, a drug that is predicted nonclinically to be a balanced ion channel blocker (and low torsade risk) based on CiPA's in-silico model torsade risk prediction (Torsade Metric Score), clinical ECG data may then be used to determine whether there are unexpected ion channel effects in humans compared with the in vitro ion channel data. Specifically, the absence of J-T_{peak}c prolongation would be consistent with balanced ion channel block.

A third prospective study was conducted[18,22] to (1) confirm that concentration-response analysis using QTc and J-T_{peak}c ECG data from small-sample clinical pharmacology studies can be used to confirm that balanced ion channel–blocking drugs do not cause J-T_{peak}c prolongation; and (2) to test the hypothesis that calcium channel block can reduce QTc prolongation from hERG block by shortening the J-T_{peak}c interval. Overall, results suggest that the absence of drug-induced J-T_{peak}c prolongation seems consistent with balanced ion channel block.

Utility of J-T_{peak} Analysis: Methodological and Clinical Needs

Successful employment of J-T_{peak}c requires its reliable assessment. Different definitions of the peak of the T wave can be found in the literature, and these are of particular relevance in the presence of notched and flat T waves.[23] Choice of the measurement lead is also of potential importance. Johannesen and colleagues[23] described an automated measurement methodology using the vector magnitude lead and compared it with prior semiautomated measurements. Concordance of measurements was high, and the automated results led to the same conclusions about the electrophysiological mechanisms of the drug compounds studies. The algorithm has been released as open-source software.[24]

Given the ability of the J-T_{peak}c to differentiate predominant hERG blockers from those with additional L-type calcium channel or late inward sodium block, it can now be explored to gain additional insight into drugs associated with QTc prolongation. Potential areas for research include further evaluations on the optimal method to correct for drug-induced heart rate increases and potentially other methods to analyze effects on J-T_{peak}c. More experience with this parameter with additional drugs will be informative, and drug developers should be encouraged to share data with the pharmaceutical community in a precompetitive manner. This will be particularly valuable when there are CiPA-compliant ion channel data.

Although the J-T_{peak}c analysis has significant potential, fit-for-purpose application and acceptance by regulatory authorities remain to be explored. In addition, assurance that balanced channel blocker profiles are clinically meaningful in the safety profile of new compounds will be important. The CiPA initiative, which identifies a fit-for-purpose staging of investigations, is an excellent start, as these studies may be performed early in a drug candidate's development. This will decrease the risk that a low–torsade risk QT prolonger is not prematurely terminated. Another key question for J-T_{peak}c is in how it can be integrated into current approaches to ECG safety assessment across various stages of new compound development and if it is useful in animal cardiac in vivo studies. Sponsors should be specifically encouraged, when possible, to conduct cardiac safety assessments in the standard first-in-human study. This study, which generally incorporates the largest dose range of any phase 1 study, could represent opportunities to incorporate ECG assessments into the initial clinical development program in a cost-effective way. Concentration-response modeling of QTc and J-T_{peak}c data, using various multiple-dosing regimens, could then allow a complete assessment of the cardiac safety profile of the multi–ion channel-blocking drug candidate. Of note, multi-ion channel effects may portend other proarrhythmic liabilities that would require an integrated ECG assessment (eg, QTc, PR, QRS, J-T_{peak}c). In addition, multi–ion channel effects may result in nonlinear concentration-ECG relationships that make concentration-response analysis challenging for individual new molecular entities. Thus, as has been done for concentration-QTc modeling,[25,26] recommendations and best practices on how to plan and conduct concentration-response analysis for J-T_{peak}c and other ECG biomarkers will be required in the future.

Dialogue without consensus on a number of remaining issues has been encouraged through a Cardiac Safety Research Consortium/Health and Environmental Sciences Institute/U.S. Food and Drug Administration public meeting.[14] Opinions varied on how much more clinical experience is needed to understand the implications of this method or to support recommendations on its use before widespread implementation. Although questions were raised concerning its implications for assessing torsade risk, the use of this biomarker independent of preclinical CiPA assessments is not recommended. It is important that additional data be gathered to answer outstanding questions.[14]

Finally, if the additional data being gathered lead the current discussions to consensus supporting the adoption and use the J-T_{peak}c methodology in the future, such adoption will not mean that research into this important area is complete. On the contrary, sponsors should be encouraged to allow open access to both nonclinical and clinical data as this method is used (with due considerations for intellectual property) in the precompetitive arena. It is only in this way that the field will further advance.

In summary, J-T_{peak}c represents a potentially important advance in the assessment of a new drug's ion channel effects as part of its proarrhythmic potential assessment under CiPA. Although remaining issues need to be addressed before adoption of the J-T_{peak}c methodology, there is significant potential value in including this new approach to complement the QT assessment of drugs with multi–ion channel effects under the CiPA paradigm. Although the current ICH E14 framework has done an excellent job of identifying drugs with potential proarrhythmic effects, it unfortunately may have resulted in the premature discontinuation of otherwise safe and effective drugs, based on a 1-dimensional assessment of hERG data and associated QTc data. The CiPA paradigm, which includes ion channel assessments, in-silico modeling, and clinical assessment of the QTc and J-T_{peak}c intervals, as well as other ECG biomarkers, may provide an efficient, cost-effective pathway for the development of drugs with low torsade risk and better inform the need for intensive ECG monitoring in phase 3 trials.

Disclosure Statements

Drs Vicente, Strauss, and Noveck report no relevant disclosures. Dr Upreti is an employee and shareholder at Amgen. Dr Fossler is an employee and shareholder at Trevena, Inc. Dr Sager has disclosed consulting relationships with ERT, BioTelemetry Research, iCardiac, Charles River, and AnaBios.

Disclaimer

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