Available online at www.sciencedirect.com

ScienceDirect

Journal of Electrocardiology xx (2016) xxx – xxx

JOURNAL OF Electrocardiology

www.jecgonline.com

Evolving regulatory paradigm for proarrhythmic risk assessment for new drugs

Jose Vicente, PhD, [a,*] Norman Stockbridge, MD, PhD, [b] David G. Strauss, MD, PhD [a]

[a] *Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, MD, USA*
[b] *Division of Cardiovascular and Renal Products, Office of New Drugs, U.S. Food and Drug Administration, Silver Spring, MD, USA*

Abstract Fourteen drugs were removed from the market worldwide because their potential to cause torsade de pointes (torsade), a potentially fatal ventricular arrhythmia. The observation that most drugs that cause torsade block the potassium channel encoded by the human *ether-à-go-go* related gene (hERG) and prolong the heart rate corrected QT interval (QTc) on the ECG, led to a focus on screening new drugs for their potential to block the hERG potassium channel and prolong QTc. This has been a successful strategy keeping torsadogenic drugs off the market, but has resulted in drugs being dropped from development, sometimes inappropriately. This is because not all drugs that block the hERG potassium channel and prolong QTc cause torsade, sometimes because they block other channels. The regulatory paradigm is evolving to improve proarrhythmic risk prediction. ECG studies can now use exposure-response modeling for assessing the effect of a drug on the QTc in small sample size first-in-human studies. Furthermore, the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative is developing and validating a new *in vitro* paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential. Under CiPA, the prediction of proarrhythmic potential will come from *in vitro* ion channel assessments coupled with an *in silico* model of the human ventricular myocyte. The preclinical assessment will be checked with an assessment of human phase 1 ECG data to determine if there are unexpected ion channel effects in humans compared to preclinical ion channel data. While there is ongoing validation work, the heart rate corrected J–T_{peak} interval is likely to be assessed under CiPA to detect inward current block in presence of hERG potassium channel block.

Keywords: QTc prolongation; J–T_{peak}c; T-wave morphology; Torsade de pointes; hERG block; Multi-ion channel block

Fourteen drugs were removed from the market worldwide because of their potential for heart rate corrected QT interval (QTc) prolongation and/or torsade de pointes (torsade) [1], a potentially fatal ventricular arrhythmia [2]. In the 1990s, there was an increasing recognition that non-cardiac drugs could cause torsade. In response to this drug-induced torsade epidemic two guidances for industry were established: the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S7B [3] and the ICH E14 [4]. The ICH S7B recommends an *in vitro* assay to assess whether a compound and its metabolites block the potassium channel encoded by the human *ether-à-go-go* related gene (hERG). The ICH E14 guidance describes a specific clinical study, the so-called thorough QT study.

The thorough QT study assesses whether the drug prolongs QTc in healthy subjects. More specifically, the guidance states that "the threshold level of regulatory concern [...] is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms" [4]. This analytic methodology originally outlined in ICH E14 requires assessing the effect of the drug on QTc at many time points after administration of a supratherapeutic dose. This results in the requirement for enrolling a large number of subjects to ensure sufficient statistical power to rule out a QTc prolongation of 10 ms, and the thorough QT study became the largest clinical pharmacology study in drug development. Pharmaceutical sponsors often performed this study late in drug development at the end of Phase 2, which is inefficient and sometimes leads to late stage attrition of a new drug.

* Corresponding author at: U.S. Food and Drug Administration, 10903 New Hampshire Ave, WO62-1125B, Silver Spring, MD 20993.
E-mail addresses: pepoviru@gmail.com, jose.vicente@fda.hhs.gov

http://dx.doi.org/10.1016/j.jelectrocard.2016.07.017
0022-0736/

Exposure-response analysis in first-in-human studies for QT assessment

Early in the conduct of thorough QT studies FDA and pharmaceutical sponsors began applying exposure-response analysis to QT studies. It was recognized that drugs blocking the hERG potassium channel exhibit a linear relationship between drug concentration and QTc prolongation (at least when the effects on QT are small) and the amount of QTc prolongation at maximum drug concentration (Cmax) could be predicted from the exposure-response model [5,6]. In order to validate this approach, a collaboration between the Consortium for Innovation and Quality in Pharmaceutical Development and the Cardiac Safety Research Consortium (IQ-CSRC) was formed to design a clinical study in healthy subjects to demonstrate that robust ECG monitoring and exposure-response analysis of data generated from first-in-human single ascending dose (SAD) studies can be used *in lieu* of the by-time-point analysis previously accepted for a thorough QT study [7]. This type of study would not include a pharmacological positive control, thus, it would not be considered a thorough QT study.

The IQ-CSRC study met its primary end point to detect QTc prolongation in 5 drugs that had a small effect on QT and to confirm an absence of QTc prolongation in a drug with no effect on QT. The concept of applying exposure-response analysis in a small sample size to assess potential for QTc prolongation for new drugs has been applied in a few cases [8–11], and at least in one scenario this resulted in a waiver for a thorough QT study [8].

In December 2015, the questions and answers section of the ICH E14 guidance was updated to support the use of exposure-response modeling as a primary end point for assessing the effect of a drug on the QTc interval. Because this approach makes use of all drug concentration and ECG measurements from all time points, significantly smaller sample sizes can be used making it feasible to incorporate QT assessment into a first-in-human study rather than running a separate thorough QT study. There are some circumstances under which the exposure-response analysis cannot be used. For example, when the QTc effect is not a direct function of plasma concentration because delayed effects (*e.g.* the drug prolongs QT as a result of hERG trafficking or accumulation into myocardial tissues), when it is not possible to reach the highest clinically relevant exposure or when the drug has heart rate effects [12]. However, this approach does not address the distinction between QTc prolonging drugs that cause torsade and QTc prolonging drugs that do not cause torsade.

The need for mechanistic approaches for torsade risk assessment

Since the implementation of ICH S7B and ICH E14 guidances in 2005, no new marketed drugs have been associated with unacceptable risk of torsade. Thus, this has been a successful strategy from a torsade risk management standpoint. On the other hand, the extreme focus on hERG and QTc has resulted in drugs being dropped from development, sometimes inappropriately [1]. This is because not all drugs that block the hERG potassium channel or prolong QTc cause torsade. For example, there are marketed drugs like amiodarone [13], ranolazine [14] and verapamil [15] that block the hERG potassium channel and prolong QTc but have minimal risk for torsade because they block additional inward currents. Drugs like these may have not made it to the market under the current regulatory paradigm because pharmaceutical sponsors may have stopped the development of these drugs due to proarrhythmic potential concerns. Therefore, there is a need to improve the lack of specificity of the hERG assay and QTc prolongation for prediction of actual torsade risk.

While the most common mechanism of drug-induced QTc prolongation is the block of the hERG potassium channel in the membrane of ventricular cells, there are multiple ion channel currents in addition to hERG that regulate repolarization of ventricular cells in the heart [16] (Fig. 1). Nonclinical studies have demonstrated that block of inward current (inward late sodium current (I_{NaLate}) or inward L-type calcium current (I_{CaL})) prevents the occurrence of early afterdepolarizations (EADs) associated with drug-induced hERG potassium channel block [17,18]. This can explain why some QTc prolonging drugs that block inward currents in addition to the hERG potassium channel have minimal torsade risk.

The Comprehensive *in vitro* Proarrhythmia Assay (CiPA)

The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative is developing and validating a new *in vitro* paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential of drugs [16]. This is a global effort with involvement from FDA, the Cardiac Safety Research Consortium (CSRC), the Health and Environmental Science Institute (HESI), the Safety Pharmacology Society (SPS), the European Medicines Agency (EMA), Health Canada, Japan National Institutes of Health Sciences (NIHS), Japan Pharmaceuticals and Medical Devices Agency (PMDA), industry and academia. CiPA proposes a mechanistically driven assessment of (i) *in vitro* drug effects on multiple ion channels (ii) coupled with an *in silico* model of human cardiac myocytes with (iii) verification of predicted responses in human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) and (iv) confirmation of ion-channel current effects in phase 1 clinical studies (Fig. 2).

The nonclinical ion channel, *in silico* modeling and stem cell derived cardiomyocyte assays will be validated by a set of 28 drugs that were classified by a compound selection committee into categories of high, intermediate and low risk of drug-induced torsade. The primary prediction of proarrhythmic risk will be based on the *in silico* model. Clinical phase 1 ECG assessment will be used to determine if there are unexpected ion channel effects compared to the preclinical ion channel data, such as due to a human-specific metabolite or protein binding.