Electrocardiography and Repolarization Abnormalities in Cardiac Safety: Benefits and Limitations of Fully Automated Methods for QT Measurement

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Abstract

During early phase drug safety trials in humans, prolongation of the rate-corrected QT interval has become a surrogate marker for heterogeneity of ventricular repolarization that can cause potentially fatal arrhythmic events. "Thorough QT" studies have been designed to test for clinically significant QT prolongation by new drugs, with "positive controls" used to assess sensitivity of the method Measurement of the QT interval may be done manually, automatically, or by adjudication of selected automated samples. Automated measurement of QT is improving, but in the absence of a universally accepted ECG definition of the end of the T wave, QT measurements have become proprietary engineering solutions that differ among ECG core labs and among algorithm developers. Alternative measures of repolarization beyond QT interval alone might further increase the benefit of fully automated ECG algorithms in drug safety testing.

1.   Introduction

QT interval prolongation (the time from the onset of the QRS complex to the end of the T wave of the ECG waveform) has become a surrogate marker for heterogeneity of ventricular repolarization that can lead to fatal ventricular arrhythmias such as torsade de pointes and ventricular fibrillation [1]. As a consequence, drug safety evaluation during the development of new molecular entities has evolved to include pre-clinical assessment, early phase "Thorough QT" (TQT) testing in normal subjects where possible, and aftermarket surveillance [2,3].

Detection of a QT prolongation signal in pre-clinical testing or during early phase development in humans may result in termination of further development of the drug, even when it is efficacious. Even with early phase evaluation of the QT prolonging effects of a new drug, a low incidence of prolongation of the QT due to genetic polymorphisms and drug interactions in susceptible individuals may result in a significant number of post-marketing sudden deaths [1]. Widely used drugs that have been removed from the market because of QT prolongation and sudden death include Seldane and Cisipride.

Accordingly, much academic, pharmaceutical, and regulatory attention has become focused on drug-related changes in repolarization, and specifically on the QT interval. This discussion will focus on the QT interval in humans, methods for quantifying the change in QT interval in response to drugs, and the value and limitations of computer-assisted electrocardiography in evaluating repolarization changes related to cardiac safety.

2.   The QT interval of the ECG

The electrocardiogram represents the body surface projection of uncancelled electrical activity of the heart during the cardiac cycle, as measured by any pair of electrodes comprising a lead and displayed as voltage versus time. Within the ventricles, depolarization spreads through specialized conduction tissue to depolarize the myocardium from near apex to base and radially from endocardium to epicardium. Repolarization begins in the epicardium and then in the endocardium. The QRS complex of the ECG represents ventricular depolarization and the T wave represents ventricular repolarization. The QT interval is defined as the duration from the onset of the QRS complex to the end of the T wave. It corresponds closely to the systolic ejection period of the heart; the end of the T wave therefore occurs just at the beginning of diastole

3.   Long QT and cardiac safety

Heterogeneity of repolarization occurs when some areas of the myocardium repolarize with marked differences in timing and variations in voltage. When this occurs, it is possible for spontaneous depolarizations in early repolarizing tissue to initiate abnormal propagation of electrical impulses through ventricular myocardium in various stages of electrical restitution. This process can initiate waves of sustained abnormal activation such as torsade de pointes and ventricular fibrillation.   When

there is heterogeneity of repolarization, the T wave of the ECG may be distorted and prolonged. However, the surrogate nature of QT prolongation on the body surface ECG for actual heterogeneity of repolarization must be emphasized: there can be QT prolongation without heterogeneity when all cells are uniformly delayed in repolarization, and also heterogeneity within the ventricle without prolongation of the QT.

Repolarization in the ventricles is highly dependent on the function of a number of cardiac channels involved with the generation of individual action potentials. One of the most important cardiac channels is known as IKr, the rapid outward rectifying current that governs much of the rate of repolarization in the heart. IKr function may differ in different parts of the heart, and when there is a partial loss in function, localized areas of repolarization delay within the heart may result in QT prolongation on the surface ECG. Genetic alteration of IKr function is responsible for one type of congenital QT prolongation that can be associated with underlying heterogeneity of repolarization and a predisposition to arrhythmogenesis. Heterogeneity of repolarization can also be acquired in people without clicnically apparent congenital long QT syndromes, commonly in the presence of drugs that reduce IKr function. When this occurs, the QT interval on the surface ECG may be prolonged, and the risk of arrhythmias in this setting is often covariate with the magnitude of QT prolongation.

In this way, drugs that significantly prolong the QT interval can cause fatal arrhythmogenesis and sudden death. In response to these observations, formal evaluation of propensity for QT prolongation has become an important component of safety testing of new drugs.

4.   The "thorough QT" study

Elements of an appropriate "Thorough QT" (TQT) study for detecting significant QT prolongation during early phase drug testing in normal subjects are outlined in the International Committee on Harmonization document E14 and expanded in questions addressed by the US Food and Drug Administration [2,3]. The goal of the TQT study is to guide further assurances of cardiac safety and surveillance intensity if and when a drug is approved for marketing.

These cross-over or parallel design studies examine placebo and baseline adjusted change in rate-corrected QT intervals in ECGs that are taken in accord with the pharmacodynamic and pharmacokinetic effects of the drug under evaluation. In practice, QT prolongation of regulatory concern is about 5-10 ms, with increased concern as the prolongation becomes longer. Therefore, a "negative" TQT study is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of drug on the QTc (the rate-corrected QT interval) excludes 10 ms. This provides assurance that the mean effect of the study drug is not > 5 ms. If the upper bound of the mean exceeds 10 ms of QTc prolongation, the study is termed "positive."

Further, a "positive control" arm of a TQT study is strongly recommended to establish confidence that the QT measurement method has adequate sensitivity to detect small increases in QT interval, so that false negative studies do not result from limited test performance. This is accomplished with placebo and baseline adjustment of QT intervals measured in the study population after use of a drug that is known to cause QT prolongation in normal subjects, but to only a small degree and with rare complications. A common example of such a drug, widely used in TQT testing, is the antibiotic Moxifloxacin, which increases mean QT by about 5-10 ms in normal volunteers. The "positive control" is detected by the study measurement methodology when the lower bound of the one-sided 95% confidence interval for the QTc is above 0.

TQT studies are expensive to perform, in terms of logistics and costs of analysis. Greater precision of QT measurement can reduce the number of subjects required for statistically significant "negative" and "positive control" arms of the study. At present, QT interval measurements in TQT studies are generally manually adjudicated rather than fully manual or fully automated, but since cost and efficiency are relevant to sponsors, fully-automated QT methods are of increasing interest.

5.   The computer and QT measurement

Recent thorough QT studies have involved as many as 10,000 individual ECGs just for the moxifloxacin and placebo data of the "positive control" study arms. In practice, computerized assistance with ECG management and measurement is essential for practical, timely completion of these studies, even when all ECGs are reviewed and adjusted by a trained over-reader.

Short of fully automated QT measurement, there are a number of ways that modern digital electrocardiographs can improve QT evaluation.   Computer-assisted averaging of single leads over time (generally 10 seconds during routine electrocardiography) can produce a "representative" complex for that lead that reduces noise and respiratory variation that affect individual complexes. In addition, computer-assisted "global complex" formation from the 12 simultaneously-acquired and temporally-aligned "representative complexes" can reduce positional and lead placement variability of single ECG leads. This allows the earliest onset of the QT interval in any lead to be used for measurement in combination with the latest offset of the QT interval in any other lead. This determines the QT interval that exists in the underlying 3-dimensional projection of

repolarization to the body surface, eliminating isoelectric projection that might exist in any single lead. Because single lead measurements systematically underestimate true QT (Figure 1), global measurement of intervals has been recommended for routine use in digital electrocardiography [4].
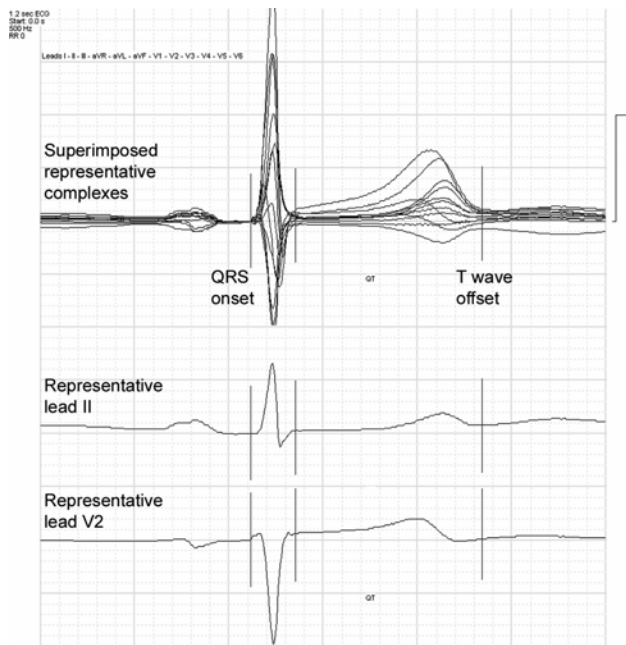

Figure 1. Superimposition of 12 simultaneously acquired single lead averaged complexes (top) allows detection of earliest QRS onset and latest T wave offset in the underlying ECG signal projected to the body surface. In contrast, single lead averaged complexes (lead II, middle, and lead V2, bottom) have isoelectric components of the waveforms that would underestimate the true QT interval. From Kligfield, et al [5]

6.   Fully-automated QT measurement

Fully-automated measurements of the QT interval will vary with methodology and accuracy of the underlying algorithm. Several issues require consideration. A major problem of full-automated measurement is shared with manual measurement of the QT: surprisingly, there is no uniformly accepted medical definition of the end of the T wave. This includes whether measurement should be global or single lead and what method should be used to find the end of the repolarization wave. As a consequence, QT measurements vary with the individual ECG reader or with the engineering solution of the individual algorithm developer or ECG device manufacturer.

Variation in automated QT measurement can be shown to occur among algorithms, both between successive generations of algorithms within individual manufacturers

and also between manufacturers. A recent study found that, for the same ECGs, global QT measured by the most recent algorithms of the two largest manufacturers of automated electrocardiographs in the US were 15 and 26 ms longer than the QT measured by their prior generation algorithms [6]. Of note, all four of these algorithms remain in current use, so that it is evident that fully-automated QT measurements from different eras cannot be compared without systematic error. Indeed, use of an earlier fully-automated algorithm prior to drug use and a later algorithm after use would result in an obviously false positive QT prolongation effect that would invite unwarranted regulatory concern. Conversely, use of different generation fully-automated algorithms in the reverse sequence would eliminate the likelihood of detecting all but the most extreme QT prolongation. It is therefore essential that all automated algorithms used in serial study of QT intervals, whether TQT or simple comparison of surveillance ECGs, must be constant.

Although the latest generation of fully-automated algorithms from these two large manufacturers had closely comparable mean values for global QT measurement in the study population (only 1.8 ms mean difference), the large standard deviation of the difference of 132 ms indicates considerable differences for individual data comparisons within the group. On further examination, the mean individual absolute differences in fully-automated QT were twice as large in patients with any type of abnormality on the ECG compared with those with normal ECGs [6]. This highlights the dependence of automated measurements on the separate engineering solutions for QT definition by different manufacturers and algorithm developers. Therefore, if fully-automated methods are ultimately used for cardiac safety studies, whether one or another of these algorithm might perform better or best for cardiac safety studies

7.   Benefits and limitations

Evidence is emerging for the feasibility of conducting TQT studies using fully-automated methods [7,8]. The benefits of fully-automated measurement of QT intervals include reduction in time and cost of ECG analysis during cardiac safety studies. Limitations include inevitable inclusion of erroneous automated measurements in the analysis, which can increase required sample size to achieve statistical significance in TQT studies. Although it might be possible to exclude some erroneous measurements that exist in recognized high noise environments, the ultimate effect of such exclusion on study sensitivity and specificity will vary with the algorithm and will require testing for each algorithm.

As an example of feasibility of fully-automated TQT analysis, Figure 2 illustrates the double delta QTc from the moxifloxacin-placebo arm of a pharmaceutical

company TQT study submitted to the US FDA and released to the Cardiac Safety Research Consortium (CSRC), a public-private partnership established under the FDA Critical Path Initiative [9]. Fully-automated global QT reanalysis of the digitized ECGs submitted by the sponsor, with no manual adjudication, successfully identifies the positive control double-delta QTc effect as established in the E14 guidance.
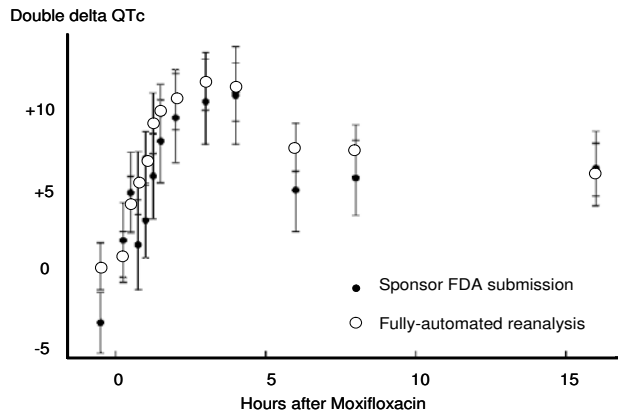

Figure 2. Fully-automated reanalysis of digitized ECGs from an FDA-submitted positive control TQT evaluation, showing global double delta QTc in comparison with the original sponsor single lead, manually adjudicated measurements

Future study will clarify the role of fully-automated QT analysis in drug safety study. Progress in that direction will benefit from continued development of QT measurement algorithms, with competition according to sensitivity and precision. Serial application of more than one fully-automated QT measurement algorithm might allow final adjudication of only major discrepancies to optimize time, cost, and accuracy of safety studies.

8. Beyond QT

As noted, QT prolongation is a surrogate for, and not equivalent to, heterogeneity of repolarization. Further, separate from depolarization and the QRS complex, the QT interval is only a unidimensional measurement of the duration of cardiac repolarization. But in reality, cardiac repolarization has multidimensional characteristics that are not represented by the simple unidimensional duration of the QT alone. A number of alternative measures of cardiac repolarization may provide new and better insights into cardiac safety, including T wave area, T wave amplitude, T wave symmetry, T wave shape and notching, T wave vectors, and derived correlates of ventricular action potentials, among others. All go well beyond the QT interval alone.

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