

Interpreting the Interval

J Rick Turner of Quintiles ECG Services looks at the design, methodology, analysis and interpretation of the ICH E14 thorough QT/QTc study

There is considerable interest in drug safety in many countries, including the US (1). Cardiac safety has assumed a central role in drug safety evaluation for two reasons. Firstly, cardiac adverse drug reactions are typically serious and can be fatal, as was seen for various drugs that were removed from the market in the 1980s and 1990s. Secondly, these fatalities prompted regulatory attention and the development of the ICH Guidelines S7B (2) and E14 (3), released in 2005. These guidelines formalised nonclinical and clinical assessments of an investigative drug's proarrhythmic liability, and they have been adopted by regulatory agencies in Canada, Europe and the US.

While other cardiac and cardiovascular adverse drug reactions are certainly receiving regulatory attention (4), assessment of proarrhythmic liability remains a central component of preapproval assessments. Recent 'question and answer' documents have provided further regulatory commentary on this issue (5-7). This article therefore focuses specifically on the ICH E14 'Thorough QT/QTc Study' or TQT study, a clinical trial dedicated to evaluating a drug's liability to prolong the QT interval in a tightly controlled environment. It is widely acknowledged that QT interval prolongation is neither a perfect nor the only indicator of a drug's proarrhythmic liability, but its evaluation is currently required by regulatory agencies.

Following a brief overview of salient characteristics of the QT interval, the design, conduct, statistical analysis, and interpretation of the TQT study are discussed. Statistical aspects are explained in a simplified and relatively succinct manner, with reference made to more detailed sources.

THE QT INTERVAL

Figure 1 is a stylistic representation of the QT interval. It represents the time,

expressed in milliseconds, between the onset of the QRS complex and the offset of the T-wave, and therefore encompasses depolarisation and repolarisation of cardiomyocytes. Should a drug lead to delayed repolarisation, an occurrence of clinical concern that is associated with certain potentially fatal arrhythmias, the QT interval will be prolonged, as shown in red in Figure 1.

Perspective on the magnitude of the QT interval can be gained by considering values following a supine rest period. After such a period, the normal QT interval ranges for males and females can be meaningfully represented as 400-450 milliseconds and 400-470 milliseconds, respectively (8). Since everyday activities such as eating, sleeping and exercise can affect the QT interval, there can be considerable variation, up to 75 milliseconds, across a 24-hour period (9,10).

'CORRECTING' THE QT INTERVAL FOR HEART RATE

In addition to the QT interval *per se*, ICH Guideline E14 discusses a parameter called QTc, QT 'corrected' for heart rate. The QT interval is affected by heart rate. Additionally, the phenomenon of hysteresis is observed, whereby the change in QT interval does not happen contemporaneously with the precipitating change in heart rate: the time lag can be several minutes.

Various correction formulae are therefore used to 'correct' for heart rate in an attempt to remove its influence. These include the Fridericia and Bazett formulae. In both cases, the same formula is used for all subjects – a

process that generates QTc values designated as QTcF and QTcB, respectively. The value QTcI represents a subject-specific correction methodology in which previously obtained data from each subject are used on a subject-by-subject basis.

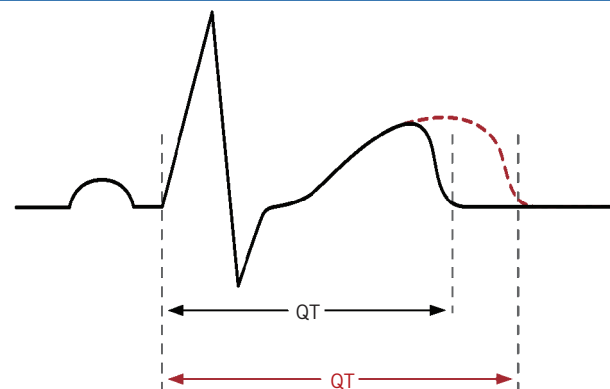
DESIGN OF THE THOROUGH QT/QTc STUDY

The TQT study typically employs healthy adult subjects and the following treatment arms:

- The proposed therapeutic dose of the study drug
- A suprathreshold dose of the study drug that is several multiples of the proposed therapeutic dose
- A placebo
- A positive control that is known to increase the QT/QTc interval

The suprathreshold dose is intended to mimic what may happen in the worst case scenario should the drug be approved and prescribed for patients. This scenario involves patients who have compromised metabolism or excretion and patients taking other medications, each of which may lead to greater than intended concentrations of the drug in the body. It should be noted that there are situations in which administering a suprathreshold dose may be impractical or unethical, for example, when studying compounds with

Figure 1: Stylistic representation of the QT interval and QT prolongation



inherent dangers such as oncologic agents. Rock and colleagues recently discussed alternative approaches in such cases (11).

The positive control is used to establish assay sensitivity. It is critical to demonstrate that the study's methodology is capable of detecting drug-induced QT/QTc prolongation if the drug does indeed have a true influence. The antibacterial agent moxifloxacin is commonly used, since its administration leads to a predictable increase in QT/QTc of around five to eight milliseconds at C_{max}, a prolongation that is not considered harmful. ECGs are captured at various times following the administration of moxifloxacin, with particular attention falling on time points shortly before, at, and shortly after T_{max}.

Determining the most informative TQT study design for a given drug requires fundamental knowledge of its human pharmacokinetic profile. This knowledge includes C_{max} and T_{max}, since the QT/QTc interval must be assessed shortly before, at, and shortly after T_{max}, as well as some later time points, typically including 24 hours after drug administration. The number of timepoints must be determined and included in the study protocol. While there is no precise agreed-upon number, 11 to 15 are representative values.

A crossover or parallel study design can be employed, depending on which is considered more advantageous. The central benefit of the crossover design is that each subject serves as his or her own control, thereby reducing intersubject variability for estimates of effects on QT/QTc. This allows a smaller number of subjects to be employed to achieve the required statistical power, which means the study will cost less to complete. In some cases, however, a parallel design is the better choice. This includes drugs for which a long period is needed to reach steady state, or which have a long half-life (making long washout periods between treatments necessary). It also includes the delayed appearance of metabolites, which may themselves prolong the QT/QTc interval, even if the parent form of the drug does not.

METHODOLOGICAL CONSIDERATIONS

ICH Guideline E14 states that the increase in QT/QTc interval of regulatory concern is 'around' five milliseconds. The operational definition of 'around five milliseconds' involves placing the upper bound of a one-sided 95 per cent confidence interval (CI) on the mean difference point estimates (drug minus placebo) obtained in the study for the therapeutic dose and for the supratherapeutic dose. If any upper bound breaches 10 milliseconds, the drug is deemed to have prolonged the QT/QTc interval by the degree of regulatory concern.

As noted earlier, while QT values for healthy adults at rest are around 400 to 470 milliseconds, various factors that occur throughout a day can influence this interval, causing it to vary by as much as 75 milliseconds in a 24-hour period. In addition to this intrasubject variability, there is also considerable intersubject variability. Detecting a systematic (drug-induced) signal of less than 10 msec against this background noise presents enormous methodological challenges.

TQT studies are therefore advisably conducted in well-prepared wards within residential medical centres or clinical pharmacology units, where maximum methodological and environmental control can be exerted. Subjects' eating, drinking, sleeping and physical activity should be strictly controlled. The use of televisions, mobile phones and all other electronic communication devices should not be allowed. Meals should be given approximately 90 minutes before ECGs are captured, and these measurements should occur after a rest period and before blood draws to facilitate determination of pharmacokinetic parameters are made. Typically, three ECGs (triplicates) are captured at each timepoint, and values averaged for analysis purposes.

STATISTICAL ANALYSIS

As noted earlier, assay sensitivity must first be established. It must be demonstrated that the study's methodology can detect the QT-prolonging influence of moxifloxacin. The following null hypothesis (H₀)

and research (alternate) hypothesis (H_R) are used:

- H₀: $\Delta \leq 5\text{msec}$
- H_R: $\Delta > 5\text{msec}$

Δ is the mean difference between subjects' responses to moxifloxacin and placebo in QT/QTc prolongation. The null hypothesis is tested by placing the lower bound of a one-sided 95 per cent CI on the mean difference point estimate for each measurement time. Assay sensitivity is demonstrated by rejection of the null hypothesis in favour of the research hypothesis. This rejection occurs if the lower bound for any of the measurement times is greater than five milliseconds. This occurrence provides compelling statistical evidence that the study's methodology will detect QT/QTc prolongation induced by the investigational drug if it truly exists.

If assay sensitivity is established, the data for the therapeutic dose and supratherapeutic treatment arms can be analysed. For both doses, the following null and research hypotheses are used:

- H₀: $\Delta \geq 10\text{msec}$
- H_R: $\Delta < 10\text{msec}$

Δ is the mean difference between subjects' responses to the drug and placebo in QT/QTc prolongation. For each of the doses, the null hypothesis is tested by placing the upper bound of a one-sided 95 per cent CI on the mean difference point estimate for each measurement time. An increase in QT/QTc below the limit of regulatory concern is demonstrated by the rejection of the null hypothesis in favour of the research hypothesis. This rejection occurs if the upper bounds of the one-sided 95 per cent CIs for all measurement times for both doses lie below 10 milliseconds. In this case, ICH E14 deems the study a 'negative study.' If one or more of the upper bounds lies at or above 10 milliseconds, the study is deemed positive. This dichotomous terminology is discussed further shortly.

While these descriptions of the statistical hypotheses are conceptually accurate, the actual statistical analysis is more complex. Since multiple timepoints are analysed, the issue of multiplicity needs to

be considered, and the intersection union test is typically employed. The null hypothesis is actually the union of several hypotheses: that the difference between drug and placebo is greater than or equal to 10 milliseconds for at least one of the time points studied. The research hypothesis is the intersection of several hypotheses: that the difference between drug and placebo is less than 10 milliseconds for all time points studied.

INTERPRETATION

Interpretation of the results of a TQT study is more subtle than the previously mentioned dichotomous terms 'negative' and 'positive' suggest. The greater the degree of QT/QTc prolongation, the greater the regulatory concern, and a positive study means that the sponsor will be expected to conduct more extensive cardiac monitoring in later clinical trials. However, it is also the case that the greater the severity of the drug's indication, and the fewer available treatments there are, the more likely a drug is to be approved for a given degree of QT/QTc prolongation. Benefit-risk analysis is therefore a crucial aspect of a regulatory agency's deliberations when considering granting marketing approval. If approved, the drug's labelling will carry information concerning its degree of QT/QTc prolongation.

CONCLUSION

ICH Guideline E14 details the TQT study, a clinical trial dedicated to assessing a drug's propensity to prolong the QT/QTc interval. This article has provided a brief overview of the trial's design, conduct, analysis and interpretation (12,13).

As noted earlier, while evaluation of QT and proarrhythmic liability is a key component of cardiac safety evaluation, it is not the only one. A broader discussion of cardiac safety is provided by Turner and Durham (14). Additionally, a recent editorial (15) accompanying the Rock *et al* paper cited earlier (11) overviews the work of the Cardiac Safety Research Consortium (CSRC). As discussed on its website, the CSRC is a collaborative enterprise whose mission is "to advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment

based upon the principles of the FDA's Critical Path Initiative as well as other public health priorities" (16).

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