Making Sense of Biostatistics: Assessing Drug Cardiac Safety  
By J. Rick Turner and Lawrence Satin

We introduced the assessment of drug safety in general terms in our December 2008 column. This column focuses on the assessment of one aspect of drug safety: an investigational drug’s proarrrhythmic liability, i.e., its propensity to promote cardiac arrhythmia (irregular heartbeat). While it is neither a perfect nor the only indicator of proarrrhythmic liability, the clinical evaluation of drug-induced QT interval prolongation is the focus of the 2005 ICH Guideline E14 (see also the related “Questions and Answers” document, 2008).

Figure 1 presents a stylistic representation of the surface electrocardiogram (ECG), and also the QT interval and QT interval prolongation (in red).

![Figure 1: The electrocardiogram](image)

In each heartbeat, the QT interval is the length of time from the onset of the QRS complex to the offset of the T-wave. It is the time taken for cardiac cells to depolarize (contract) and repolarize (get ready to contract again). The duration of the QT interval varies with each heartbeat, albeit only by few milliseconds (msec). After resting supine, the normal ranges for males and females are 400-450 msec and 400-470 msec, respectively.

Since the QT interval is inversely related to heart rate (shortening as heart rate increases) irrespective of other influences, it can “corrected” for heart rate by several statistical methodologies, leading to the term QTc. QT/QTc prolongation is considered an indicator of delayed repolarization, a phenomenon that is associated with potentially lethal cardiac arrhythmias.

A Thorough QT/QTc Study, or “TQT study,” assesses an investigational drug’s propensity to prolong the QT/QTc interval. The ICH E14 Guideline does not provide unequivocal formulaic instructions on the conduct of a TQT study, and various complex statistical methodologies are employed by research scientists. This column explains the statistical fundamentals in a simplified and relatively succinct manner.
One commonly used experimental design for a TQT study is a cross-over design, in which all subjects complete all four treatment arms:

- A positive control treatment that is known to increase the QT/QTC interval.
- The proposed therapeutic dose of the study drug.
- A supratherapeutic dose of the study drug that is several multiples of the therapeutic dose. This scenario represents plasma concentrations that could occur, for example, in patients with liver function impairment or taking other medications that may enhance the effects of the drug.
- A placebo treatment.

The purpose of the positive control is to establish assay sensitivity. It has to be demonstrated that the experimental setting and methodology used for the study is capable of detecting an increase in drug-induced QT/QTC intervals when the treatment has a true influence. The antibacterial agent moxifloxacin is commonly used, since its administration leads to a predictable increase in QT/QTC of around 5-8 msec at Cmax (recall our discussions of the drug-concentration profile in the January 2009 column), 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 Tmax. Tmax is well documented for moxifloxacin.

To establish assay sensitivity, we need to demonstrate that our experimental methodology can detect moxifloxacin-induced QT/QTC prolongation. The following null hypothesis (H₀) and research hypothesis (H₁) are used:

\[ H_0: \Delta < 5 \text{ msec} \]
\[ H_1: \Delta > 5 \text{ msec} \]

where \( \Delta \) is the mean difference between subjects’ responses to moxifloxacin and placebo in QT/QTC prolongation. The null hypothesis is tested by the placement of the lower bound of a one-sided 95% confidence interval (CI) on the mean difference point estimate for each of the measurement times. Assay sensitivity is demonstrated by rejection of the null hypothesis in favor of the research hypothesis. This rejection occurs if the lower bound of the one-sided 95% CI for any of the measurement times is above 5 msec. This occurrence indicates that we have good statistical evidence that our experimental methodology will be able to detect QT/QTC prolongation induced by the investigational drug if it truly exists.

Once this evidence has been provided, the data for the therapeutic dose and supratherapeutic treatment arms can be analyzed. ECGs are captured at various measurement times following the drug’s administration, with particular attention on time points shortly before, at, and shortly after Tmax. In this case, first-in-human trials will have established the investigational drug’s Tmax fairly accurately. For both doses, the following null hypothesis (H₀) and research hypothesis (H₁) are used:

\[ H_0: \Delta \geq 10 \text{ msec} \]
\[ H_1: \Delta < 10 \text{ msec} \]

where \( \Delta \) is the mean difference between subjects’ responses to the drug and placebo in QT/QTC prolongation. The null hypothesis is tested by the placement of the upper bound of a one-sided 95% CI on the mean difference point estimate for each of the measurement times for each of the doses. An increase in QTc below the limit of regulatory concern, an upper bound of 10 msec, is demonstrated by the rejection of the null hypothesis in favor of the research hypothesis. This rejection occurs if the upper bounds of the one-sided 95% CIs for all measurement times for both doses lie below 10 msec. In this case, ICH E14 refers to the study as a negative study. If one of the upper bounds lies at or above 10 msec, the study is deemed to be a positive study.
Interpretation of the results of a TQT study is more subtle than the dichotomous terms “negative” and “positive” suggest. It is fair to say that the greater the overall degree of QT/QTc prolongation, the greater the regulatory concern, and that a positive study means the sponsor will be expected to conduct more extensive cardiac monitoring in later clinical trials. However, a drug-induced increase of 10 msec or more does not equate precisely to the drug being proarrhythmic, and therefore does not necessarily equate to the drug failing to receive marketing approval. Regulatory agencies employ benefit:risk analysis in their marketing decisions, and by that time have a tremendous amount of data to inform their decision. The greater the severity of the drug’s indication, and the fewer available treatments there are, the more likely it is to be approved for a given degree of QT/QTc prolongation. If approved, the drug’s labeling will carry information for physicians and patients concerning its degree of QT/QTc prolongation.

References


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