TQT Studies: Their Impact on Drug Development and the Key Elements of a Successful TQT Study

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Introduction

Thorough Q1/QcT (TQT) studies are an indispensable part of the development of new chemical entities (NCE). These studies show that their outcome has major impact on a drug development program. However, these studies are relatively novel and the general view is that TQT studies are expensive to conduct.

A body of emerging evidence is providing some guidance as to how to optimise the design of these studies.

In this paper we have reviewed 14 publications from 2004 to 2009 and extracted QT data and their Confidence Interval values as an indicator of data quality.

Regulatory Guidance

The first going body to issue guidance was the European Agency for the Evaluation of Medicinal Products, (EMEA) released a paper in 1997. This proposed experimental, non-clinical/clinical models for the consideration of assessing QT prolongation1.

Health Canada issued a guidance document in 2001 relating to the assessment of QT prolongation potential of non-antiarrhythmic compounds. It listed the non-clinical and clinical methodologies to be used in the development of NCE2.

Definitive guidance was provided from an expert working group, (EWG), of the International Conference of Harmonization, (ICH) releasing the ICH Topic E14 guideline which was brought into operation and adopted by the European Union and The United States in 20053.

A Q&A document released by the FDA in 2008 provided further clarification on a number of emerging issues as studies were being reported and submitted4.

TQT Studies: Tackling concept, design, conduct, analysis and interpretation

A positive signal in a TQT study does not mean that a NCE will cause Torsades de Pointes (TdP) with the associated risk which was brought into operation and adopted by the EWG4.

The early conduct of a TQT study is desirable but the cost of some study designs may be prohibitive given the high attrition rates5.

There are three key elements all of which are of an equal importance for the successful outcome of these studies:

1. Study Design
2. Clinical Conduct and ECG recordings
3. Analysis of ECG data sets

Design of TQT Studies

There are a number of designs that have been proposed for the best conduct of a TQT study. This paper has looked at studies which appear to have produced the best quality results, using an oral 400mg dose of moxifloxacin. It is important when considering the conduct of a TQT study to remember that no ‘One Size Fits All’ and that each medicine has specific characteristics which necessitate a custom fitted design.

However, there are certain design features in a TQT study which will work better than others across different designs. Numerous study designs and ECG assessment methodologies have been tried and submitted for regulatory acceptance. In July 2009 35 TQT studies were listed on http://clinicaltrials.gov. We have identified 1 study in 2003, 2 each in 2004 and 2005, 5 in 2006, 6 in 2007, 15 in 2008 and 4 in 2009. The outcome of these and other published studies in conjunction with the published guidelines is providing a growing pool of options for the design of future studies and allow the identification of common features which appear to perform better than others.

The quality of TQT studies is assessed by the performance of a positive control the use of which is recommended by the ICH-E14 guideline5. The capability of the study to detect QTc prolongation can be greatly enhanced by the use of a concurrent control, e.g. a positive control (non-antiarrhythmic pharmaceutical) to establish assay sensitivity. The positive control should have an effect on the QT interval of at least 5ms (i.e. an effect that is close to the QTc prolongation that represents the threshold of regulatory concern).

The extent of the prolongation caused by this positive control is then usually expressed by the point estimate at the time point of the greatest effect. It is usual in later publications that the 90% or 95% two-sided confidence interval would be given. The size of this confidence interval is a derivative of the variability of the data caused by either physiological variation on experimental error. The narrower the confidence interval the better the quality of the study results.

Clinical Conduct

Due to the unfavourable signal to noise ratio, TQT studies often include large numbers of volunteers to compensate for this. There are only a relatively few sources of experimental errors specific to TQT studies:

1. Poor signal quality (low sampling rate, interferences) making it difficult or impossible to define the on or offset of the QT interval
2. Hysteresis resulting in an over-estimation of the rate corrected QT interval

Many suggestions have been made to improve the quality of the ECG signal and numerous methods have been proposed to perform much better than those performed in parallel groups and or using holder when considering the width of the confidence interval. When comparing cross-over trials only, then the sample size seems positively related to a narrow CI.

ECG Analysis

The size of the effect on QT of a 400mg oral dose of moxifloxacin has now been investigated intensively and presumably is better described than for any other medicine. A post hoc analysis6 of holder recordings taken during a study administering an intravenous 400mg dose of moxifloxacin has further added to our understanding of its effect on QT. Considering only publications where the lower bound of the 90% CI is greater than 5ms, there are more than two-fold increase of QTc prolongation (range 8-17.5) following a 400mg dose of moxifloxacin, which is around 90% bio-available. The QTc prolongation has been reported to be 18ms in lean healthy subjects following a 60 minute iv infusion of 400mg moxifloxacin7.

Various methods of ECG analysis have been applied: different baseline corrections, manual, semi-automated and fully automated methods of QT interval measurement, different means of arriving at a numeric value for a given time point. This diversity of analysis methods may explain some of the observed differences. The width of the CI intervals range from 2 to 15ms, a 15ms CI may not be explained by sample size alone8, as some studies used the same sample size to detect the anticipated effect.

In our view, automatic reading of digitally recorded 10 second 12-lead ECGs with subsequent computer aided over reading is the current gold standard. There are still differences in opinion on how this is best done. Not only QT intervals but all ECG parameters (PR, QRS, T-wave morphology) need to be analysed and reported.

It is beneficial for a QcT study to be performed under one roof in its entirety. ECG data does not need to be transferred and it is easier to maintain consistent effective quality systems using multiple feedback loops.

References

12. 25. Comparison of semiautomated and fully automated methods for QT measurement during a thorough QT/QTc study: Hysteresis19 arises from the lag time between QT interval and numerous methods have been proposed to compensate for this. There are only a relatively few sources of experimental errors specific to TQT studies.