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

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Introduction

Thorough QT/QTc (TQT) studies are an indispensible part of the development of new chemical entities (NCE). These studies are significant and 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 QTcF data and their Confidence Interval values as an indicator of data quality.

Regulatory Guidance

The first governing body to issue guidance was the European Agency for the Evaluation of Medicinal Products, (EMEA) releasing a 'Points to Consider' document in 1997. This proposed experimental, non-clinical/clinical models for the consideration of assessing QT prolongation[1].

Health Canada issued a guidance document in 2001 relating to the assessment of QT prolongation potential of non anti-arrhythmic compounds. It listed the non-clinical and clinical methodologies to be used in the development of NCE's[2].

Definitive guidance was provided from an expert working group, (EWG), of the International Conference of Harmonization, (ICH) releasing the ICH Topic E 14 guideline which was brought into operation and adopted by the European Union and The United States in 2005[3].

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 submitted[4].

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 of sudden death but it has, however, a major impact on the development of a NCE.

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

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 studies. 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.

Table 1
showing the variability of QT measurements expressed by the width of the 90% or 95% Confidence Interval around ΔΔQT after a 400mg single dose of moxifloxacin administered as positive control. Data extracted from TQT studies published between 2004 and 2009[6-11, 13-18]. Only studies reporting a Confidence Interval around the Moxifloxacin-Placebo difference are reported. Studies reported by Dixon, Harada and Taubel were conducted at Richmond Pharmacology Limited in London, UK.

Year	Autor (et al.)	Subjects (N)	Design	ECG Recording	Baseline Correction	QTcF	CI Lower	CI Upper	CI ΔU-L	CI %
2008	**Dixon**	152	cross over*	bed side	PA	14.8	13.5	16.1	**2.6**	90
2004	Morganroth	58	cross over	bed side	PA	*8	*6	*9	*3	90
2009	**Harada**	46	cross over	bed side	TM	11.3	9.5	13.1	**3.6**	90
2009	**Taubel**	62	cross over	bed side	TM	12.0	10.1	14.0	**3.9**	**95**
2008	Davis	61	cross over	bed side	PA	13.7	11.5	15.8	**4.3**	90
2009	Tyl†	62	cross over	holter	TM	17.5	14.7	• 20.3	**5.6**	90
2008	Ayalasomayajula	**315**	parallel	holter	TM*	16.5	13.5	19.4	**5.9**	90
2009	Zhang	**44**	cross over	bed side	TM*	13.2	10.2	• 16.2	**6.0**	90
2008	Iwamoto	**31**	cross over	holter	PA	11.1	7.5	14.7	**7.2**	90
2008	Rosillon	**184**	parallel	holter	TM	12.4	8.6	• 16.2	**7.6**	90
2004	Harris	23	cross over	bed side	TM	5.9	2.0	9.8	**7.8**	**95**
2005	Serra	188	parallel	bed side	TA	6.2	**1.3**	11.2	**9.9**	90
2009	Modi (study 1)	48	cross over	holter	PA	7.8	2.8	12.9	**10.1**	**95**
2008	Bloomfield	20	cross over	holter	TM*	17.0	10.7	23.4	**12.7**	90
2009	Modi (study 2)	48	cross over	holter	PA	8.2	1.1	15.8	**14.7**	**95**

PA = Pre Dose Average (of study day) | **TA** = Time Averaged (from a baseline day) | **TM** = Time Matched (to a baseline day)
•reconstructed from the one-sided 95% CI | *decimal points not reported | †Moxifloxacin given as a 1-hour i.v. infusion

The quality of TQT studies is assessed by the performance of a positive control the use of which is recommended by the ICH-E14 guideline[5]: "The confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent positive control group (pharmacological or non pharmacological) to establish assay sensitivity. The positive control should have an effect on the mean QT/QTc interval of about 5ms (i.e., an effect that is close to the QT/QTc effect that represents the threshold of regulatory concern, around 5 ms)."

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 derivate of the variability of the data caused by either physiological variation on experimental bias; in other words the narrower the confidence interval the better the quality of the study results.

Table 1 shows design and key results from data published during the last five years. The first eight publications use a two-sided Confidence Interval (CI) of 90%. It is intrinsically narrower than the two-sided 95% CI which has been used in six publications shown at the bottom of the table. In three of the studies only the lower boundaries of the 95% CI have been reported; the upper boundary has been reconstructed for the above comparison.

The table clearly shows that studies using a cross-over design and multiple standard bed side 12-lead ECG appear to perform much better than those performed in parallel groups and or using holter 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.

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[12]:

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 for subsequent data cleansing[6, 8, 11, 12, 14, 16, 17]. Sufficient training and robust processes combined with constant supervision and quality control is required to produce consistently high quality ECG traces over a period of time.

Hysteresis[19] arises from the lag time between QT interval adaptation which takes some time and the decrease in the RR interval which is immediate whenever the heart rate increases. In 10 second 12-lead bed side ECG traces, these distortions of the QTc interval may go undetected and there is no means of retrospectively cleaning the data. 12-lead holter recordings with subsequent extraction of ECG "snap-shots" used for analysis should theoretically address this problem.

More work is needed to establish whether the surprisingly poor performance of studies using 12-lead holter recordings may be due to the inappropriate selection of snapshots, poor clinical control or indeed other factors.

Average to poor quality of ECG traces results in a greater degree of subsequent ECG analysis. This can be avoided by careful quality checks at the time of producing the data.

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 analysis[12] of holter 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 boundary of the 90/95% CI is greater than 5ms, a more than two-fold increase of QTcF has been described (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 moxifloxacin[12].

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 alone[6, 13] 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 cardiologist over reading is the current gold standard. There are still differences in opinion 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 QTc 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.

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