Analyzing Thorough QT Study 1 & 2 in the Telemetric and Holter ECG Warehouse (THEW) using Hannover ECG System HES® : A validation study

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Abstract

Following the ICH E14 clinical evaluation guideline [1], the measurement of QT/QTc interval prolongation has become the standard surrogate biomarker for cardiac drug safety assessment and the faith of a drug development. In Thorough QT (TQT) study, a so-called positive control is employed to assess the ability of this study to detect the endpoint of interest, i.e. the QT prolongation by about five milliseconds. In other words the lower bound of the one-sided 95% confidence interval (CI) must be above 0 [ms]. Fully automated detection of ECG fiducial points and measurement of the corresponding intervals including QT intervals and RR intervals vary between different computerized algorithms. In this work we demonstrate the ability and reliability of Hannover ECG System (HES®) to assess drug effects by detecting QT/QTc prolongation effects that meet the threshold of regulatory concern as mentioned by using THEW database studies namely TQT studies one and two.

1. Introduction

The fully automated detection of the fiducial points and the corresponding measurements of the ECG intervals can be carried out on global, representative or raw ECG waveforms [2]. Unlike fully manual reading techniques, automated cardiac algorithms are considered to be reproducible, robust and consistent. Thorough QT studies are preferred area of application for such automatic algorithm to save time and money. However, validating automated ECG algorithms is a necessity to build trust and acceptance from drug safety authorities. Hannover ECG System HES® is one of the well-renowned and well-reputed ECG analysis and interpretation programs worldwide. Since 1971, HES® has been continuously developed and improved by leading cardiologists, biomedical engineers and computer scientists from all over the world [3]. HES® HOLTER is able to provide beat-to-beat classification including normal beats, Premature Ventricular Contractions (PVC), Premature Supra-Ventricular Contractions (PSVC) and Artifact beats for the long-term and ambulatory ECG recordings [4, 5]. Among many other features, it is able to calculate number of *period*-to-*period* ECG wave intervals and durations including $QT_{interval}$, $RR_{interval}$, heart rate corrected $QT_{interval}$. The term *period* in HES® is defined as limited and fixed period of time and typically assigned to the value of ten seconds. In this work, HES® HOLTER automatic QT interval detection has been validated using positive control and placebo Holter redcordings in *Thorough QT Study # 1* (TQT1) [6] and *Thorough QT Study # 2* (TQT2) [7] from THEW database [8]. Both of these studies are double-blind, randomized, placebo-controlled and multi-arm cross-over Holter-based TQT trials. Moxifloxacin was administrated in both studies to build the positive controls. Usually the positive control is employed in a TQT study as mentioned in order to test the sensitivity for a method of detecting QT/QTc prolongation by five milliseconds. If the method employed is able to detect such QT/QTc prolongation by the positive control, then that method will constitute evidence of finding the QT effect and prolongation in the on-drug recordings of the study. The sample sizes of TQT1 and TQT2 studies are 35 and 72, respectively. In TQT1 study, ten scheduled time points were localized, namely one time point at compound administration time (denoted as "0 H"), one time point at one-hour pre-dose "-1 H" and eight post-dose time points starting from one-hour post-dose "1 H" through eight-hour post-dose "8 H", consecutively. Eleven scheduled time points were were localized in TQT2 study, namely one-hour pre-dose "-1 H", 30-minutes pre-dose "-0.5 H", compound administration at "PREDOSE", one-hour through six-hour post-dose "1 H" to "6 H", eight-hour pre-dose "8 H" and twelve-hour pre-dose "12 H". For the assessment of drug effect, calculation of double delta differences was performed for RR, QT/QTc changes

from the baseline in both studies. Baseline was considered from start of recording to the time of compound administration and was characterized by the median of differences. The single delta differences are calculated by baseline subtraction from all time segments. Furthermore, double delta difference was built by subtracting placebo single delta from the scheduled time-matched Moxifloxacin single delta for each study subject. Finally, double delta differences were characterized by mean, median, Standard Error of the Mean σ_M and 95% CI per hour. Further detailed information about the validation method used in this work will be addressed in the following section.

2. Methods

2.1. Rational

2.1.1. Automatic Holter ECG analysis

HES® Holter automatic algorithm performs the analysis on long-term ECG or ambulatory ECG signals in five main steps. In the first stage, the ECG signal will be pre-conditioned and denoised out of high-frequency components and baseline distortion in order to get analyzed correctly in the further steps. The heart beats are localized and classified in the second step. In the third step, so-called local representative dominant heart beats are derived from each channel within the actual time-interval of ECG signal. The local representative dominant beat for a given channel is calculated by averaging all intrinsic and normal beats of that channel after time-alignment them to their R_{peak} points. HES® Holter algorithm is designed to deal with long-term ECG signals on time-interval basis, which has typically 10-second duration. Furthermore, in the fourth step, a so-called global representative dominant beat is calculated by averaging all previously derived local representative dominant beats, and is delineated by detecting its main fiducial points namely P_{onset}, P_{offset}, QRS_{onset}, R_{peak}, QRS_{offset} and T_{offset}. Time intervals and wave durations are measured from the fiducial points: $PR_{segment}$, $PR_{interval}$, $RR_{interval}$ $QRS_{duration}$ and $QT_{interval}$. Further derivations are: heart rate-corrected QT intervals QT_{cB} and QT_{cF} based on Bazett's and Fridericia's formulae, respectively. In the fifth step, cardiac events are characterized based on heart-beat classifications and the analysis of the beat-to-beat $RR_{interval}$ values, see figure 1.

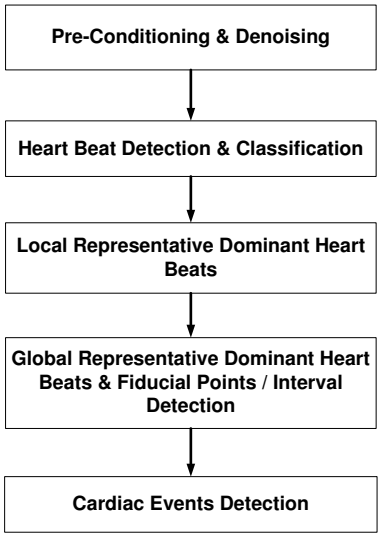

Figure 1. The workflow diagram for HES® HOLTER algorithm implemented in this work

2.1.2. Heart rate corrected $QT_{interval}$ calculation

Since $QT_{interval}$ is heart-rate dependent, correction methods are needed to remove the heart rate influence in order to make $QT_{interval}$ values comparable. The most common correction methods for $QT_{interval}$ are *Bazett* and *Fridericia*, denoted as QT_{cB} and QT_{cF}, respectively. Another well-known approach for $QT_{interval}$ correction in TQT studies is called individual $QT_{interval}$ correction and denoted as QT_{cI}. This methodology applies linear regression on $QT_{interval}$ values and their corresponding $RR_{interval}$ values for each individual participant in the clinical study during pretreatment and placebo phases. That is, $QT_{interval}$ values and the corresponding $RR_{interval}$ data are used to fit a separate linear regression and derive the related regression coefficients for each individual prior the drug administration and during placebo phase. Afterwards, the calculated coefficients will be applied on $QT_{interval}$ and $RR_{interval}$ data in the post-treatment phase to each participant on an individual basis in order to calculate the individual corrected $QT_{interval}$,i.e. QT_{cI}. In [9], it is mentioned, that QT_{cI} has been used routinely in TQT studies so far. Furthermore, it is recommended to consider QT_{cI} as the primary endpoint of TQT studies in assessing the effect of new drugs on cardiac repolarization [9].

2.1.3. Single delta calculation for $QT_{interval}$

Single Delta $QT_{interval}$ is denoted as $\Delta QT_{interval}$. It estimates the differences in $QT_{intervals}$ of two ECG signals for any given individual. These two ECG signals can be either time-matched and recorded in two different days or they can be time-unmatched and recorded sequentially and continuously, that is two consecutive periods in the same ECG recording. Typically, the first ECG signal is recorded when the subject is off drug. It is

also called pre-dose ECG signal or baseline ECG signal, whereas the second ECG signal is acquired right after the drug administration. Therefore it is called post-dose or on-drug ECG signal. In case of time-matched recordings, the $QT_{intervals}$ of the baseline ECG signal will be subtracted from the corresponding $QT_{intervals}$ of the post-dose ECG signal. And in case of time-unmatched recordings, a representative $QT_{interval}$ (usually the mean or median of all $QT_{intervals}$ in the baseline signal) will be subtracted from all $QT_{intervals}$ of the post-dose and pre-dose ECG signal(s). In this work, time-unmatched recording approach is applied.

2.1.4. Double delta calculation for $QT_{interval}$

Double Delta $QT_{interval}$ is denoted as $\Delta\Delta QT_{interval}$. Like the calculation of single delta $QT_{interval}$, $\Delta\Delta QT_{interval}$ assesses the differences between the $\Delta QT_{interval}$ in two time-matched ECG signals. The first ECG signal is basically the output of Δ calculation for $QT_{interval}$ or $QT_{interval}^{corrected}$ as illustrated in section 2.1.3, whereas the second ECG signal is the ECG signal with placebo effect time-matched as mentioned with the first signal.

2.1.5. Confidence limits for the sample mean

The confidence limits of the confidence interval provides a lower and upper limit for the sample mean, in which the true mean should fall. For instance, a confidence interval with 95% coefficient means that the true mean should fall within at least 95% of the intervals of the samples collected in the long run.

2.2. Main procedure

All subjects in both studies were analyzed based on the the following procedure. For a given subject, placebo Holter recording and the pre-drug/post-drug recording (positive control Holter) are first processed using HES® HOLTER program as illustrated in the section 2.1.1. As result, the corresponding *period*-to-*period* $RR_{interval}$ along with $QT_{interval}$ values will be derived and the corresponding *period*-to-*period* QT_{cB}, QT_{cF} and QT_{cI} values are computed as presented in the section 2.1.2. Afterwards, *period*-to-*period* ΔQT_{cB}, ΔQT_{cF}, ΔQT_{cI}, $\Delta\Delta QT_{cB}$, $\Delta\Delta QT_{cF}$ and $\Delta\Delta QT_{cI}$ will be calculated for the whole duration of the recordings as explained in the sections 2.1.3 and 2.1.5, respectively. Finally, the time-matched mean values, median values, σ_M values, the lower and upper bounds of the one-sided 95% CI values (LCL95% and UCL95% respectively) for $\Delta\Delta QT_{cB}$, $\Delta\Delta QT_{cF}$ and $\Delta\Delta QT_{cI}$ differences are obtained for all subjects at the time points of each study after taking Not-a-Number (NaN) values out of the calculation.

3. Results

The sample mean, sample median, σ_M, LCL95% and UCL95% results of $\Delta\Delta QT_{cI}$ at the ten scheduled time points obtained from TQT1 and at the eleven scheduled time points obtained from TQT2 are illustrated in table 1 and in table 2, respectively.

Table 1. The results of $\Delta\Delta QT_{cI}$ obtained from TQT1

Time Point	Mean [ms]	Median [ms]	σ_M [ms]	LCL95% [ms]	UCL95% [ms]
-1 H	-0.36	0.54	0.64	-1.87	1.15
0 H	0.86	1.95	1.20	-1.96	3.69
1 H	9.79	9.22	1.41	6.46	13.11
2 H	11.07	10.16	1.59	7.34	14.81
3 H	12.29	12.73	1.74	8.20	16.38
4 H	3.82	4.06	1.91	-0.67	8.32
5 H	1.13	2.59	2.02	-3.61	5.86
6 H	1.11	0.94	2.23	-4.12	6.34
7 H	2.98	6.26	2.37	-2.58	8.53
8 H	5.98	7.31	2.97	-1.01	12.96

Figure 2 and figure 3 show the mean and the 95% CI results of $\Delta\Delta QT_{cI}$ at the scheduled time points of TQT1 and TQT2, respectively. In TQT1, the average of double delta difference at the point of largest $\Delta\Delta QT_{interval}$ prolongation is 12.0 [ms], the σ_M is 2.56 [ms] and the time at the maximum effect is around the third hour of the post-drug period. The time course of the drug effect using $\Delta\Delta QT_{cB}$ looks a bit different with a maximum of 14.0 [ms] and σ_M of 1.88 [ms] observed between the second and the third hours after drug administration. $\Delta\Delta QT_{cF}$ shows a maximum QT_{cF} prolongation between the second and third hour in post-drug period (PDP), the maximum mean value of $\Delta\Delta QT_{cF}$ is 12.9 [ms] with σ_M of 1.68 [ms] at around the third hour of PDP. A similar result was observed for $\Delta\Delta QT_{cI}$ with 12.3 [ms] with σ_M of 1.88 [ms] with a maximum at hour three after drug administration.

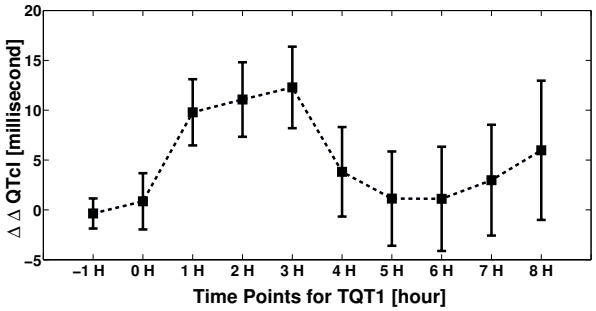

Figure 2. The mean and the 95% CI values of $\Delta\Delta QT_{cI}$ at the time points of TQT1

In TQT2, the biggest $\Delta\Delta QT_{interval}$ prolongation has been observed at hour 3 with 6.0 [ms] and σ_M of 2.76 [ms],

Table 2. The results of $\Delta\Delta QT_{cI}$ obtained from TQT2

Time Point	Mean [ms]	Median [ms]	σ_M [ms]	LCL95% [ms]	UCL95% [ms]
-1 H	-0.23	-1.07	0.61	-1.455	0.98
-0.5 H	-0.02	-0.25	0.61	-1.249	1.19
PRE-DOSE	0.26	0.68	0.71	-1.16	1.69
1 H	3.42	2.80	1.24	0.93	5.91
2 H	6.86	7.30	0.91	5.02	8.69
3 H	7.51	6.16	1.13	5.25	9.78
4 H	8.24	8.82	1.06	6.12	10.37
5 H	6.58	6.64	1.23	4.11	9.05
6 H	6.36	5.73	1.12	4.11	8.62
8 H	5.00	3.35	1.05	2.88	7.12
12 H	6.26	5.35	1.29	3.67	8.84

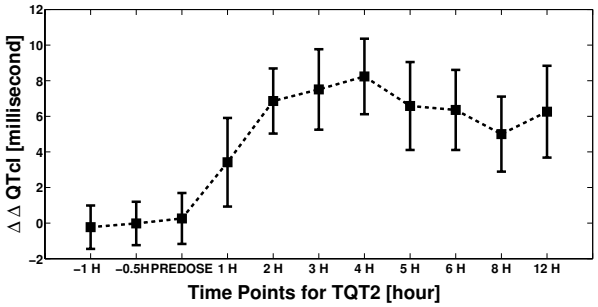

Figure 3. The mean and the 95% CI values of $\Delta\Delta QT_{cI}$ at the time points of TQT2

while $\Delta\Delta QT_{cB}$ showed the biggest effect of 10.8 [ms] and σ_M 1.68 [ms] at hour 4 in PDP. The biggest effect of $\Delta\Delta QT_{cF}$ has been observed at hour 4 either: 9.0 [ms] with σ_M of 1.22 [ms]. $\Delta\Delta QT_{cI}$ results showed the largest QT prolongation at 4 hours with a prolongation of 8.3 [ms] and σ_M of 1.06 [ms].

When we compared the time course between TQT1 and TQT2, the overall picture of the drug effect was similar up to hour three in PDP, but different after that time. While $QT_{interval}$ prolongation distinctly dropped after three hours in TQT1,significant delta delta-differences were effective until hour 12, whichever $QT_{interval}$ correction method was applied.

Moxifloxacin Plasma level was only available for TQT2. We investigated on the agreement of average time course of $\Delta\Delta QT_{cI}$ and mean plasma level over time and found an excellent agreement, see figure 4.

4. Discussion and conclusions

The results achieved are very well in the range of the phase-I studies with Moxifloxacin as a reference drug. Purpose of a positive control drug arm is to prove a sufficient assay sensitivity to detect a drug related "positive" signal of $QT_{interval}$ prolongation. The QT_c effect time course

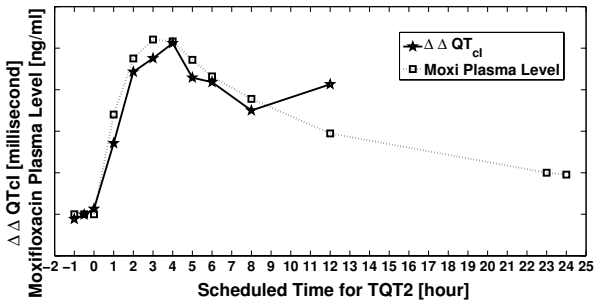

Figure 4. Moxifloxacin Plasma level and the average time course of $\Delta\Delta QT_{cI}$ in TQT2

caused by Moxifloxacin is usually a rising plasma level which goes hand in hand with $QT_{interval}$ prolongation, reaching its peak between 2 and 4 hours under oral administration, and then gradually reducing $QT_{interval}$ effect. Our result demonstrates that the HES® HOLTER with its fully automated ECG analysis is a useful tool in the evaluation of TQT studies. Theoretical claim that $QT_{interval}$ should follow the plasma concentration has been confirmed by our analysis result. we interpret this finding as a strong indicator of reliability of HES® algorithm.

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