VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2011, Vol. 18, No. 4, pp. 401–410

ISSN 1897–5593

Improving the precision of QT measurements

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Abstract

Background: *Accurate and precise QT interval measurement is very important for both regulatory and drug developmental decision making. These measurements are often made using a manual or semi-automated technique, and the associated variability necessitates sample sizes of around 50 to 70 subjects in thorough QT/QTc studies. The purpose of this study was to compare the reproducibility and precision of a semi-automated (SA) method and a high-precision (HPQT) technique for ECG extraction and QT interval measurement on two thorough QT/QTc (TQT) studies conducted in compliance with ICH E14.*

Methods: *Data from 35 healthy subjects from two different crossover TQT studies on treatment with placebo and moxifloxacin was analyzed. Both methods examined the RR and QT intervals measured in lead II or the lead with the highest quality T-wave on a single beat basis using the QT algorithm included in the COMPAS software package. ECGs were measured at a protocol-specific timepoint.*

Results: *The effect of moxifloxacin on the QTc interval was highly reproducible in the two studies, and assay sensitivity was met with both methods. Pairwise comparison of QTcF values between methods demonstrated high agreement with no bias, small mean differences (below 1.5 ms) and narrow limits of agreement. HPQT improved the precision of the QTc measurement by 31% in Study I (standard deviation of ΔQTcF: SA 8.9 ms; HPQT 6.3 ms) and by 15% in Study II (SD: SA 9.7 ms; HPQT 8.3 ms).*

Conclusions: *The HPQT QT measurement technique detected the effect induced by moxifloxacin with the same accuracy as SA techniques, and with clearly improved precision. More precise QTc measurement has important implications in terms of lowering the likelihood of false positive results and/or reducing the sample size in TQT studies, as well as improving the utility of QT assessment in early clinical development.* (Cardiol J 2011; 18, 4: 401–410)

Key words: thorough QT study, QTc interval, electrocardiogram, moxifloxacin

Editorial p. 341

Introduction

With the advent of the International Conference for Harmonization (ICH) E14 guidance to assess the QT/QTc interval in so-called thorough QT (TQT) studies [1], there is increasing emphasis on accurate and precise measurement of the QT interval. The QT interval is the single regulatory biomarker used to assess the risk of arrhythmia due to drug-induced impaired cardiac repolarization leading to the rare and sometimes fatal drug-induced,

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Received: 31.03.2011 Accepted: 17.05.2011

polymorphic ventricular tachycardia, torsades de pointes. To demonstrate that a drug does not prolong the QT interval to such an extent that there is a safety concern, a TQT study should statistically exclude an effect of the drug on the placebo-controlled change-from-baseline QTc (ΔΔQTc) exceeding 10 ms. To demonstrate the sensitivity of the study, i.e. its ability to detect a small QTc prolongation, a positive control that mildly prolongs the QTc interval, usually moxifloxacin, is included [2].

Currently, most central ECG laboratories use a so-called semi-automated (SA) measurement technique: the placement of the calipers for interval measurement is decided by a computer algorithm and the measurements are thereafter adjusted by the reader. Typically, the intervals from three consecutive beats in each of three ECG strips at each protocol timepoint are measured. The process is often overseen by a cardiologist, who also performs the assessment of T wave morphology changes. The use of the SA measurement technique results in a variability of the primary endpoint (ΔΔQTc) that often requires a sample size of the TQT study exceeding 50 subjects. With eight to ten (and sometimes more) timepoints post-dosing with triplicate ECG recordings in each of four treatment groups/arms, this can result in a total of 6,000 or more ECG tracings.

To simplify and accelerate the analysis of such a large number of ECGs, scientists have been focusing on the development of more precise QT measurement techniques than those usually provided in regular commercial ECG equipment for clinical practices [3]. A more precise QT measurement technique would have several important advantages. Firstly, when the sample size of the TQT study is unchanged, a higher precision of measurements improves the power of the study, thereby minimizing false positive results. Using larger amounts of ECG data permits the implementation of newer beat-to-beat methodologies [4]. Alternatively, fewer subjects are needed to obtain the same statistical power in TQT studies, which are designed to exclude a threshold effect (10 ms). Finally, with a more precise technique, QT assessment can be done with greater confidence in early clinical studies which have been designed for other purposes, and include far fewer subjects.

Certain features of drug-induced impaired cardiac repolarization are more complex to measure and evaluate, such as changes of T and U wave morphology. Gross changes are observed mainly with potent, selective blockers of the delayed rectifier potassium current, IKr [5], while less pronounced changes, such as those observed with moxifloxacin, require more sophisticated computer algorithms to be detected [6]. In consequence, the ICH E14 guidance requires an assessment of any T wave morphology changes caused by the investigational drug in a TQT study. A SA method handles this through visual inspection and scoring of such changes. Currently, it seems advisable to incorporate this assessment in any new technique intended for use in TQT studies or other studies where QT assessment may be an important secondary objective [7].

In this study, we compared a standard SA measurement technique using three replicates from pre-determined times within each ECG timepoint to a high-precision measurement technique (HPQT, iCardiac Technologies, Rochester, NY, USA), which uses computer derived QT measurements while maintaining human oversight of quality and of scoring of T/U wave morphology changes. We wanted to test the hypothesis that this approach would result in more precise QT measurement while maintaining the ability to detect the QT prolongation induced by a single dose of moxifloxacin. We compared the two methods on data from two TQT studies conducted in compliance with the ICH E14 guidelines. ECGs from placebo and moxifloxacin treatment arms were included in the analysis, and the effect of moxifloxacin on the ΔΔQTcF was analyzed using a time-matched approach.

Methods

Study datasets

Study I, conducted by Pfizer (Sandwich, UK) was a double-blind, randomized, five-way crossover TQT study in 35 healthy volunteers (30 males, five females). Subjects were 18 to 55 years of age with a mean body weight of 75.3 kg (53.6 to 96.6 kg) and body mass index (BMI) between 18 and 30 kg/m^2. All subjects were screened for clinically relevant abnormalities in their medical history, were physically examined, including blood pressure and pulse rate, and were required to have normal baseline ECG with QTc interval < 430 ms for males and < 450 ms for females. The ECGs were recorded using the Philips Holter recording system and the EASI lead configuration (Philips Health Care, San Francisco, CA, USA). The lead equivalent to Lead II was used for interval measurements. ECGs were extracted at the following timepoints on the day of dosing: –1.5, –1, –0.5 hours pre-dose, and 1, 2, 3, 4, 6 and 8 hours post-dose. Subjects were in the semi-recumbent position at rest for 10 min prior to ECG timepoints. Moxifloxacin was administered as an open-label, single 400 mg tablet.

Study II was a double-blind, randomized, four-way crossover TQT study in 70 healthy volunteers. From this study, ECGs from the placebo and moxifloxacin arms from 35 subjects (20 males, 15 females) were randomly selected from one of the databases (E-HOL-12-0140-008) of the Telemetric and Holter ECG Warehouse [8]. Twelve-lead ECGs were obtained using the Mortara H12+ Holter (Mortara Instrument, Milwaukee, WI, USA) and Lead II was used for interval measurements. ECGs were extracted at the following timepoints on the day of dosing: –1, –0.5, –0.25 pre-dose, and 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose. Blinding of moxifloxacin was ensured through encapsulation and a single dose of 400 mg was given.

At the core ECG laboratory (iCardiac Technologies), the same reader measured all ECGs from the same subject with both measurement methods. Readers were blinded to timepoints and treatments. For both methods (SA and HPQT), ECG intervals were measured using COMPAS, a software package developed at the University of Rochester Medical Center, Rochester, New York, USA [7].

Semi-automated QT method: ECG selection and over-reading method

In Study I, three replicate 10-s ECGs were extracted at 4 min, 2 min, and 10 s prior to each nominal timepoint.

In Study II, three replicate 10-s ECGs extracted at 4 min, 2 min and 0 s prior to each nominal timepoint. The QT/QTc intervals were measured on three consecutive complexes from each ECG chosen by analysts and the mean values from these three complexes were computed. A replicate ECG was non-evaluable when three sequential usable beats could not be obtained from the replicate. For each selected beat, the analyst adjusted the calipers placed by COMPAS as required, following the standard approach for SA methodology. The mean of the values from the three replicates was reported as the QT/QTc values for each timepoint.

High-precision QT method

Ten ECG replicates were selected from among non-overlapping 10-s ECGs available at each timepoint. The selection process was based on a 'confidence score' designed as a combination of quality metrics including beat stability, heart rate changes, and signal-to-noise estimates. Heart rate stability is a factor varying between 0% and 100%. It represents the percentage of beats within a replicate ECG with a preceding RR value within a 'stable' range defined as ± 10% of the mean RR from the previous 5 min period. In Study I, ten ECG replicates were extracted within a 10 min window immediately prior to each nominal timepoint. In Study II, ten ECG replicates were selected within a 5 min window centered on each nominal timepoint. The COMPAS algorithm measured the QT interval in all beats within a replicate. Beats were flagged for analysts' overread if an extremely small or large RR, QT, QTcF, QTcF beat-to-beat change, or RR beat-to-beat value was observed. All 'low confidence' beats were reviewed manually by the ECG analyst, using pass/fail criteria, i.e. an accepted interval was included in the analysis, whereas a failed one was not used.

In consequence, and in contrast to the SA method, there was no mixing of manually adjusted values with computer-measured values. T wave morphology assessment with the HPQT method was performed entirely manually (visually) on beats from three replicates which were chosen based on high quality criteria. The process was overseen by a cardiologist, who also performed the final quality control.

The median values of the QT/QTc intervals from all analyzed beats were calculated for each replicate ECG. A replicate ECG was deemed non-evaluable when there were fewer than three usable beats in the replicate. The mean of the evaluable replicate median values was reported as the QT/QTc values for that timepoint.

Statistical analysis

The ECG data was analyzed using a linear mixed effects model with the following covariates: time (categorical), treatment, time-by-treatment interaction, and the baseline value of QTcF. The response was the post-dose QTcF after baseline adjustment, for which the average of the pre-dose ECG timepoints was used. Subject was included as a random effect. The estimates of ΔΔQTcF values and their two-sided 90% confidence intervals (CI) were then calculated based on the fitted linear mixed effects model. The standard deviation of the ΔQTcF values for each nominal timepoint was also provided and the possible reduction in the sample size estimation was illustrated.

Pairwise comparison of the QTcF values at all timepoints obtained from semi-automated and high-precision methods was carried out via the method proposed by Bland and Altman [9]. The mean of the differences and the limits of agreement (defined as ± 1.96 standard deviations [SD] of the differences) were calculated. The mean difference indicates any potential bias of one method over another, and the limits of agreement indicates the variability in the

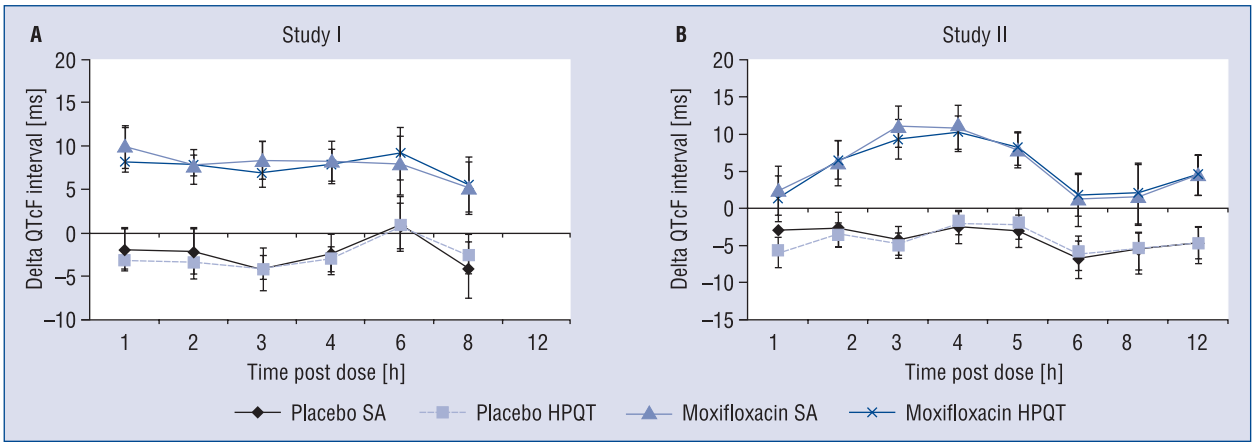

Figure 1. ΔQTcF across timepoints following dosing with either placebo or 400 mg moxifloxacin; **A, B.** Mean (± 90% two-sided confidence interval) changes in QTcF occurring in Study I (n = 35) and Study II (n = 35), respectively; SA — semi-automated; HPQT — high-precision QT interval measurement.

differences. A linear regression analysis of the means and differences between the two methods was performed and associated 95% CI of the fitted slopes were given to show the potential linear trends between the two variables.

To compare the time-matched QTcF measurements, the time-matched mean difference in QTcF between the moxifloxacin and placebo groups after baseline adjustment (ΔΔQTcF) was used as the endpoint, as per E14 guidance [1, 2]. Assay sensitivity based on ΔΔQTcF after dosing of moxifloxacin was tested at 1, 2, 3 and 4 hours, and deemed to have been met if the lower bound of the CI exceeded 5 ms at any of these timepoints, after adjustment for multiplicity using two common approaches, Hochberg's procedure [10] and Bonferroni correction [11].

Outlier analyses were used to determine the number and percentage of subjects that had QTcF interval increases from baseline of > 30 ms to 60 ms and > 60 ms. Each subject was considered having an outlier value based on the most extreme value across all of the timepoints.

The study was approved by the local bioethical committee and all patients gave their informed consent.

Results

Changes in QTcF interval from baseline

Both SA and HPQT produced very similar change-from-baseline QTcF (ΔQTcF) in all treatment arms and at all timepoints in both studies (Fig. 1). In Study I, the difference between methods of the mean ΔQTcF ranged over timepoints from 0 to 1.6 ms in the placebo arm and between 0.1 to 1.7 ms for moxifloxacin. In Study II, the difference between mean ΔQTcF for SA and HPQT ranged from 0.1 to 3 ms (at 1 h) for placebo and between 0 and 1.8 ms for moxifloxacin.

Time-matched placebo-adjusted changes in QTcF

Placebo-corrected ΔQTcF (ΔΔQTcF) changes were in strong agreement for both studies, and mean differences between SA and HPQT methods were less than 2.4 ms for Study I and less than 2.0 ms for Study II at all timepoints (Table 1). In Study I, the mean ΔΔQTcF was above 10 ms between 1 and 4 hours after dosing with both methods. The lower bound of the CI was above 5 ms at all timepoints with HPQT and at all timepoints except 6 hours with SA, where the largest difference of means between methods was observed (2.4 ms). The largest mean ΔΔQTcF for Study II was seen at 3 hours with both methods; ΔΔQTcF was above 10 ms at 3, 4 and 5 hours with SA and at 2, 3, 4 and 5 hours with HPQT. The lower bound of CI exceeded 5 ms at 2 to 6 and 12 hours post-dosing with both SA and HPQT.

When Hochberg's procedure was used to adjust for multiplicity for the 1 through 4 hours timepoints, assay sensitivity was determined at all four timepoints with both methods in Study I. Using Bonferroni, assay sensitivity was determined at all four timepoints for HPQT and three timepoints for SA (1, 3, and 4 h post-dose). In Study II, assay sensitivity was determined at three timepoints with HPQT (2, 3, and 4 h post-dose) and two timepoints with SA (3 and 4 h post-dose) with both methods for adjustment. Overall, when adjusted for multiplicity, assay sensitivity for the study was achieved with both SA and HPQT.

Table 1. ΔΔQTcF [ms] across timepoints after 400 mg oral moxifloxacin.

Study	Time	Mean	N	SE	90% CI		Mean	N	SE	90% CI	
					Lower	Upper				Lower	Upper
I		Moxifloxacin SA					Moxifloxacin HPQT				
	1	11.8	34	1.7	8.9	14.6	11.4	34	0.9	9.8	13.0
	2	10.0	34	2.1	6.4	13.6	11.4	34	0.8	10.0	12.7
	3	12.5	34	1.7	9.5	15.4	10.9	34	1.2	8.9	12.9
	4	10.8	34	1.9	7.6	13.9	10.7	34	1.4	8.4	13.1
	6	6.0	29	2.3	2.1	9.9	8.4	29	1.8	5.5	11.4
	8	9.7	32	2.4	5.7	13.8	8.4	32	1.9	5.2	11.6
II		Moxifloxacin SA					Moxifloxacin HPQT				
	1	5.3	35	2.4	1.3	9.3	7.3	35	2.5	3.2	11.5
	2	8.9	35	1.9	5.6	12.2	10.1	35	1.4	7.7	12.4
	3	15.3	35	2.0	11.9	18.8	14.3	35	1.5	11.8	16.7
	4	13.2	35	2.2	9.5	16.9	12.2	35	1.8	9.2	15.3
	5	11.2	34	1.9	8.0	14.3	10.6	34	1.4	8.2	13.1
	6	9.4	34	2.5	5.1	13.7	8.7	34	1.9	5.5	11.8
	8	6.7	34	2.1	3.2	10.2	7.7	34	1.7	4.8	10.5
	12	9.1	33	1.9	6.0	12.3	9.3	33	1.2	7.3	11.3

SE — standard error; CI — confidence interval; SA — semi-automated; HPQT — high-precision QT interval measurement

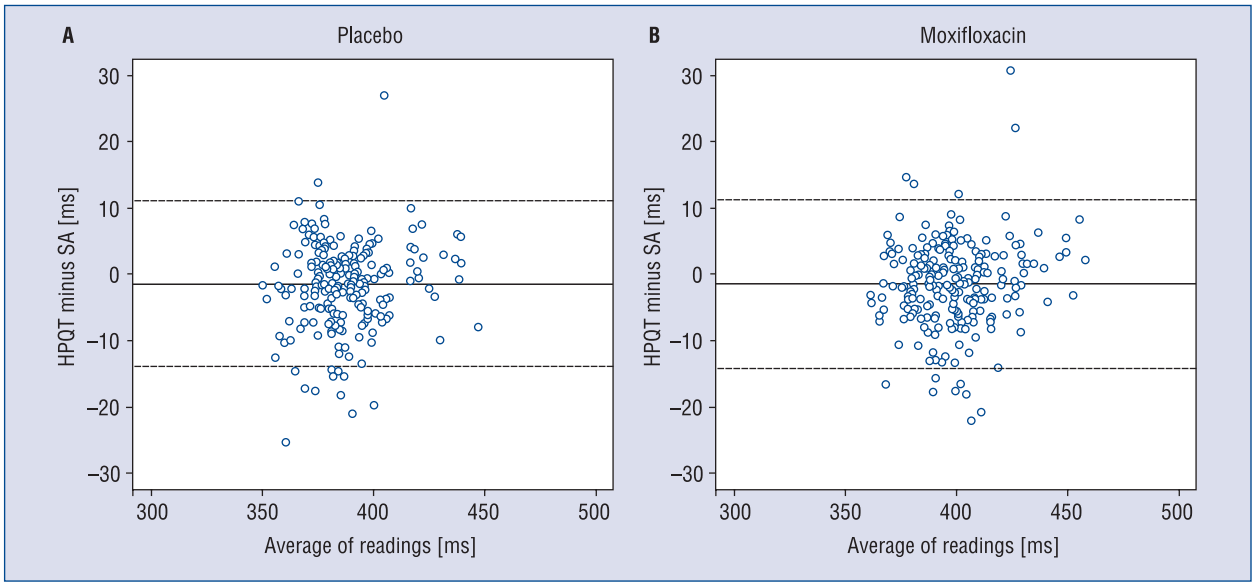

Figure 2. Pairwise comparison of QTcF intervals generated by high-precision (HPQT) and semi-automated (SA) measurements from Study I. Solid line represents mean difference for all timepoints between methods bounded by 1.96 standard deviation (dotted line) for 35 subjects given either placebo (**A**) or moxifloxacin (**B**).

Pairwise comparison via the Bland-Altman analyses

Bland-Altman plots over all pairwise differences of QTcF intervals measured with SA and with HPQT demonstrated good agreement between methods (Figs. 2, 3). The mean of the pairwise differences was below 1.5 ms in Study I and below 0.8 ms in Study II, with limits of agreement below 12.7 ms and 11.3 ms, respectively (Table 2). In both studies, the slopes of the regression lines characterizing the relationship between the pairwise difference of QT measurements and their average

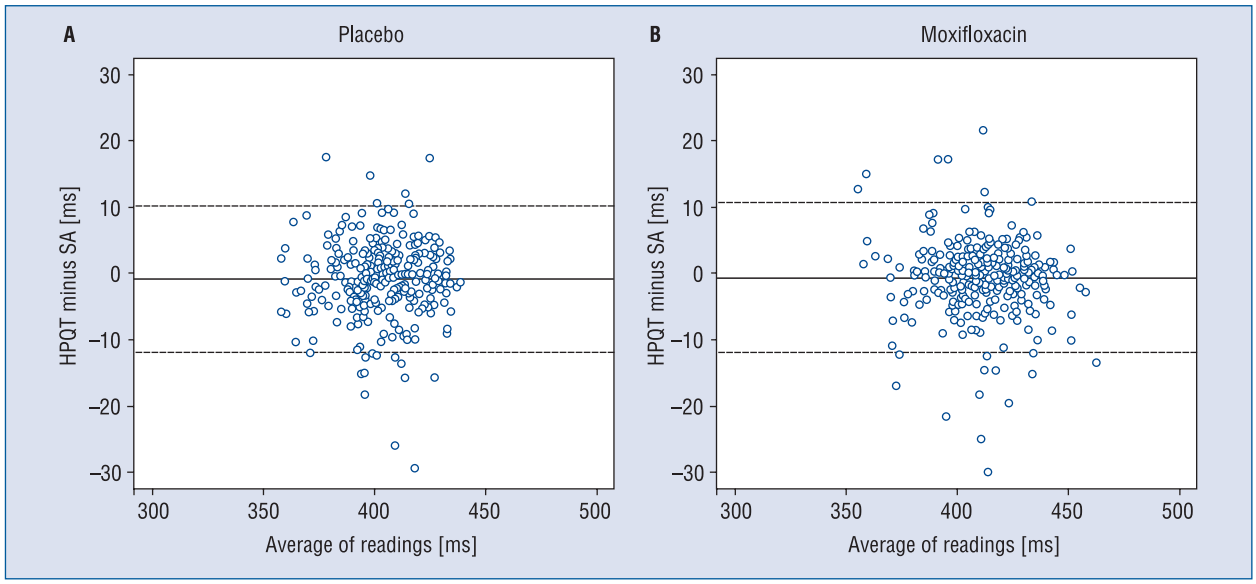

Figure 3. Pairwise comparison of QTcF intervals generated by high-precision (HPQT) and semi-automated (SA) measurements from Study II. Solid line represents mean difference for all timepoints between methods bounded by 1.96 standard deviation (dotted line) for 35 subjects given either placebo (**A**) or moxifloxacin (**B**).

Table 2. Summary of Bland-Altman analyses.

Study	Treatment	Mean difference [ms]	Limits of agreement [ms]	Slope (95% confidence interval) [ms]	P value for slope
I	Placebo	–1.5	12.5	0.04 (–0.00, 0.09)	0.08
	Moxifloxacin	–1.4	12.7	0.04 (–0.00, 0.09)	0.08
II	Placebo	–0.8	11.1	0.00 (–0.04, 0.04)	0.94
	Moxifloxacin	–0.7	11.3	–0.02 (–0.06, 0.01)	0.17

value were not significantly different from zero (Table 2). This demonstrates that the agreement of QT measurements between the HPQT and SA methods is consistent across the overall range of QT values.

Comparison of standard deviation of the ΔQTcF

In Study I, the SD for ΔQTcF was lower for HPQT than for SA at all timepoints on placebo, and for all except one (8 h) on moxifloxacin. The mean SD of ΔQTcF across treatments and timepoints was reduced from 8.9 ms with SA to 6.3 ms with HPQT (31% reduction), and the reduction was larger in the placebo arm (41%) than in the moxifloxacin arm (21%). In Study II, the level of reduction of SD seemed smaller. The SD of ΔQTcF was lower at all timepoints on both treatments with HPQT, with the reduction ranging from 2% to 32%. The mean SD for both treatments and all timepoints was reduced from 9.7 ms to 8.3 ms, a reduction of 15% (Fig. 4).

Outlier analyses

For both studies, there were no subjects with QTcF increases from baseline of > 60 ms after placebo or moxifloxacin. In Study I, no subjects on placebo, and one subject in the moxifloxacin arm, had a ΔQTcF measured by HPQT between 30 and 60 ms. In Study II, one subject on placebo had a ΔQTcF measured by SA between 30 and 60 ms. On moxifloxacin, eight subjects had ΔQTcF values between 30 ms and 60 ms as measured by SA, and four subjects when using HPQT.

Discussion

This study compared a standard semi-automated (SA) technique, which is commonly used by central

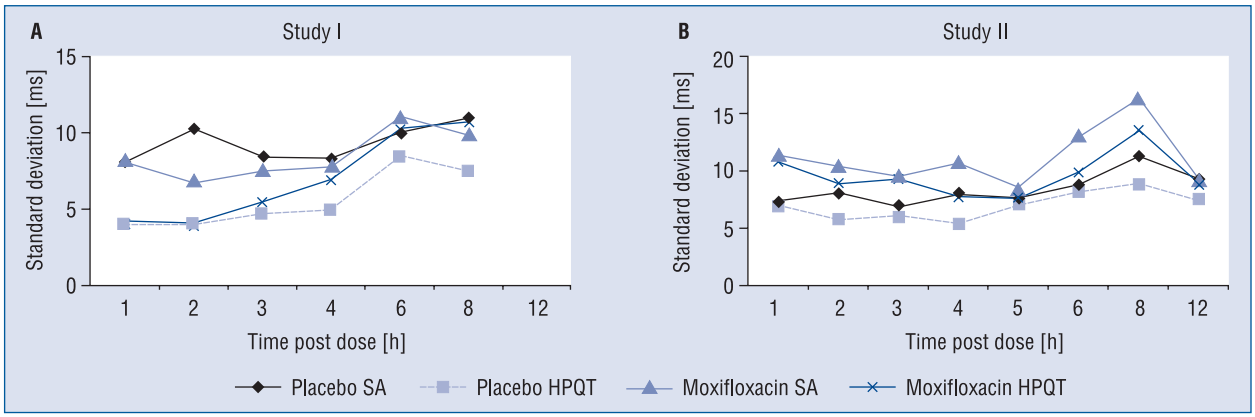

Figure 4. Comparison of standard deviations of ΔQTcF values [ms] after placebo and moxifloxacin. Values represent mean standard deviation at each timepoint from 35 subjects in each study and treatment group; SA — semi-automated; HPQT — high-precision QT interval measurement.

ECG laboratories, with a high-precision technique (HPQT) for QT interval measurement in healthy volunteers. Data from two thorough QT (TQT) studies was analyzed using the same computer algorithm for the QT interval measurements, which were done by the same reader at the core lab.

Our results demonstrate that both methods detected the QTc prolongation caused by a single-dose of moxifloxacin with very similar level and timing of the peak effect (Table 1); with both methods, the 'assay sensitivity' test requirements were met [1, 2]. The bias between methods using Bland-Altman plots and analyses was negligible. Importantly, the precision of the QT measurement, as determined by the SD of the ΔQTcF, was reduced by HPQT by, on average, 31% and 15% in Studies I and II, respectively.

When comparing methods for extraction and analysis of ECG data, the ICH Q&A document, issued in 2008 [2], discusses several approaches which we have employed in the present study:

— looking at the peak and time course of the mean ΔΔQTcF effect of the positive control;
— determining whether the study is sufficiently sensitive to detect a 5 ms ΔΔQTcF effect;
— performing a pairwise comparison using Bland-Altman plots.

Finally, we have also compared the precision of the two methods, since an improvement has an important impact on the power of the QT assessment.

Peak and time course of ΔΔQTcF of the positive control. In studies in healthy volunteers, it is important to ensure that emerging methods result in similar levels of drug-induced QTc prolongation when compared to available methods. It is less critical that the absolute QTc values are identical. A single-dose of 400 mg moxifloxacin is the most widely-used positive control in TQT studies and causes an effect on the ΔΔQTc of about 8 to 15 ms [12–14]. The peak effect in our studies was 12.5 ms and 11.4 ms for SA and HPQT, respectively, in Study I, and 15.3 ms and 14.3 ms in Study II. The full time course of ΔΔQTcF was comparable between methods, with a largest difference at any timepoint of 2.4 ms in Study I and 2.0 ms in Study II. The level and timing of the moxifloxacin QTc peak effect in our studies was consistent with that observed in other studies using manual, SA or fully automated ECG measurement approaches [14–17]. Clearly, both traditional (e.g. fully manual and SA) and more modern ECG techniques, paired with strict handling and standard experimental conditions at the clinical sites, seem to enable the detection of a relatively small QTc effect in healthy volunteer studies of a size that is often used in TQT studies, i.e. 40 to 60 subjects [18–21].

Assay sensitivity. A TQT study's 'assay sensitivity' has been defined as the ability to statistically detect an effect level close to the threshold of 'regulatory concern' (5 ms), i.e. the lower 90% confidence bound should exceed 5 ms [1]. On our datasets from two TQT studies, both SA and HPQT clearly met the assay sensitivity criterion at several timepoints; when adjusted for multiplicity for 1 through 4 hours post-dosing, the assay sensitivity test was met at three to four timepoints with HPQT and at two to four timepoints with SA. This is also the case in most TQT studies where the peak effect of moxifloxacin often reaches 10 ms or more, and most methods for QT measurement are precise enough to result in a confidence interval that exceeds 5 ms with commonly used sample sizes.

In instances where this criterion is not met, it can be caused by either a lower-than-expected peak effect of moxifloxacin or a low precision of the QT measurements. An example of failed assay sensitivity due to low precision of the QT measurement was recently provided in the publication by Morganroth et al. [18] from a TQT study with silodosin, an alpha-blocker, conducted in 55 healthy male volunteers. The peak effect of moxifloxacin was in the expected range (peak ΔΔQTcI of 9.6 ms), but the CI was very wide (12.6 ms), translating into a SD of ΔΔQTcI of approximately 18 ms. This meant that the lower bound of the CI never exceeded 5 ms and therefore, assay sensitivity as defined by ICH E14 [1, 2] was not met. However, it should be noted that many factors in the conduct of a study can contribute to the overall QT variability.

Pairwise comparison using Bland-Altman plots. These plots allow pairwise comparison of absolute QTc measurement. The strength of this analysis is that it can disclose a bias between methods that correlates with the absolute QTc value, i.e. whether differences between methods tend to grow with increasing QTc intervals. Such a difference between methods within a range of QTc intervals that will be closely scrutinized for any degree of prolongation would obviously be of concern, and raise questions in regard to which method represents the most accurate QTc measurement [16, 17]. In our study, the regression line through all data pairs showed either a non-significant, very shallow slope or no slope at all, which is comforting.

The 'limits of agreement' (LoA) of the Bland-Altman plots describe the variability of the pairwise differences between compared methods and is often defined as ± 1.96 SD of these differences. There are no well-defined boundaries for acceptability using this approach. However, a LoA below ± 15 ms seems to indicate good agreement [15–17, 22–24]. In our two studies, the LoAs were well below this level, indicating an excellent agreement between methods. To some extent this is confirmed by the low mean of the differences, which were less than 1.5 ms on both placebo and moxifloxacin in both studies.

Precision of QT measurement. Using ECGs extracted from the same timepoints from two TQT studies, HPQT improved the precision of the QTc measurement by up to 61% per timepoint in Study I and by up to 32% in Study II. The level of improvement seemed clearly larger in Study I, in which the precision was improved by 41% in the placebo arm and by 21% in the moxifloxacin arm; overall, the SD of ΔQTcF was reduced from 8.9 ms to 6.3 ms, a 31% improvement. The improvement in Study II was 17% on placebo and 13% on moxifloxacin and the mean SD of ΔQTcF across timepoints was reduced from 9.7 ms to 8.3 ms, a 15% improvement of the precision. These differences between Studies I and II illustrate that precision is not only about QTc measuring technique. Many other factors can also influence the end result.

The precision of QTc measurement can be estimated from published TQT studies by looking at the width of the ΔQTc or ΔΔQTc. Table 3 summa-

Table 3. Precision of ΔQTc in recently published TQT studies.

Study	N	Design	QTc	Mean ΔΔQTc [ms]	ΔΔQTc CI [ms]	Width of CI [ms]	SD of ΔQTc [ms]	Method
Morganroth et al. 2010 [18]	47	P	QTcF	9.6	3.3 to 15.9	12.6	18.4	SA
Moore et al. 2010 [19]	41	XO	QTcF	14.1	9.7 to 18.5	8.8	12	Manual
De Kam et al. 2010 [21]	82	XO	QTcI	20.8	UB 23.1	4.6	8.9	Manual
March and Cardi 2009 [28]	51	P	QTcI	9.4	UB 14.0	9.2	14	SA
Poordad et al. 2009 [29]	60	XO	QTcF	10	6.9 to 13.1	6.2	10.2	SA
Vandemeulebroecke et al. 2009 [30]	73	XO	QTcF	10.3	7.8 to 12.7	4.9	8.9	Manual
Dalen et al. 2010 [25]	35	XO	QTcX	10	7.5 to 12.5	5.0	6.3	Eclysis
Tyl et al. 2009 [17]	62	XO	QTcF	17.4	LB 13.5	7.8	13.1	Fully automated
	62	XO	QTcF	19.9	LB 16.9	6.0	10.1	SA1
	62	XO	QTcF	17.5	LB 14.7	5.6	9.4	SA2

CI — 90% confidence interval; P — parallel; XO — crossover; QTcX — study-specific QTc correction; QTcI — subject-specific QTc correction; UB — upper bound of 90% CI; LB — lower bound of 90% CI; SA — semi-automated

rizes some key parameters of recently published TQT studies in healthy volunteers, for which we have estimated the precision of ΔQTcF using this approach. Again, it should be emphasized that such a head-to-head comparison between studies entails many components that are not influenced by the measuring technique, and results should therefore be interpreted cautiously. Within this limitation, it seems that the precision of the HPQT technique on our studies (6.3 ms and 8.3 ms) is better than in the published studies using manual or SA techniques, in which the SD ranges from 8.9 ms to 18.4 ms. The most precise estimate in Table 3 is seen with the Eclysis technique in the publication by Dalen et al. [25], which also resulted in very good precision of ΔQTc (SD: 6.3 ms); this measurement technique is also a computerized, highly precise approach, which analyzes much more ECG data than conventional SA or manual techniques, with some human oversight [26]. Interestingly, in a recent study comparing SA to fully automated methods in 62 healthy volunteers, the variability was higher with the fully automated technique (SD for ΔQTcF on moxifloxacin: 13.1 ms) than with two tested SA techniques (SD: 10.1 and 9.4 ms) [16]. These results, combined with those from our study, indicate that some degree of human oversight and intervention, as employed in HPQT methods, may be the optimal way to improve the precision of QT measurement, while also providing an evaluation of T wave morphology changes.

Precision matters for two important reasons:

1. Using more precise techniques for QTc measurement allows for substantially improved power of TQT studies, which enables reduction of the sample size or the risk of false positive results. As an example, improving the precision of ΔQTcF from 9.3 ms to 7.3 ms would allow a reduction of the sample size from 58 to 37 subjects, with unaltered power (90%) and assumptions.
2. More precise estimates of the QTc interval will allow implementation of these techniques in early clinical studies. Combined with concentration effect modeling, precise estimates of QTc effect may substantially improve the ability to detect QTc prolongation early in the development process, and may eventually replace the TQT study [27].

Conclusions

A high-precision technique for the extraction of ECGs and the measurement of QT intervals was highly comparable to a conventional SA technique in terms of the QTc effect induced by the positive control, and resulted in a clear improvement of the precision of the QTc estimate in two separate TQT studies.

Acknowledgements

This study was funded through iCardiac Technologies. BD, AF, and JPC are the Global Medical Director, the Vice President of Cardiovascular Safety, and the Chief Technology Officer, of iCardiac Technologies, respectively. MZ, AS, MT and AZ are employed by iCardiac Technologies. The authors would like to acknowledge the critical comments and implementation efforts of Sasha Latypova, Executive Vice President of iCardiac Technologies.

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