A PROSPECTIVE, SINGLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, CROSSOVER STUDY TO ASSESS THE PERFORMANCE OF AUTOMATED AND MANUAL METHODOLOGIES FOR DETECTING QTC INTERVAL PROLONGATION

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Abstract

BACKGROUND: Although the computer-assisted, manual approach is the established method for detecting QTc interval prolongation in thorough QT studies, newer automated techniques may offer increased efficiency and speed and decreased variability. Performance characteristics of contemporary automated and manual methods have not been well studied prospectively.

METHODS: This was a prospective, single-blind, placebo-controlled, randomized, crossover study in 24 healthy volunteers. The effects of moxifloxacin 400 mg on the QTc interval were assessed using a new fully automated system (QTinno, NewCardio, Inc) and a computer-assisted, manual approach using a single interpreting cardiologist (HeartSignals, Social & Scientific Systems, Inc). The Surveyor Telemetry Central System (Mortara Instrument, Inc) was used to collect the raw 12-lead ECG dataset for both analyses. Maximum mean placebo-corrected change from baseline QTcF (ΔQTcF) was estimated by repeated measures analysis of averaged replicates by each method.

RESULTS: QT data from 23 completed subjects at 30 time points during the 2 treatment periods resulted in 3450 and 2028 replicates by the automated and manual methods. Adequacy of the study sensitivity (lower bound of the 95% confidence interval of ΔQTcF greater than 5 msec) was confirmed by both methods at multiple time points. The maximal mean ΔQTcF and 90% CIs were 14.3 (11.2-17.5) and 12.7 (9.4-16.0) msec and occurred at 1.5 and 3 hr using the automated and manual methods, and both were similarly precise with a RMSE of 6.4 and 6.7 msec, respectively. Categorical analyses of the QT data from the 2 methods yielded similar results.

CONCLUSION: The automated and manual methods for evaluating moxifloxacin-induced QTc prolongation demonstrated a high and comparable degree of precision, and each was successful in demonstrating assay sensitivity for a positive control.

Introduction

The thorough QT/QTc (TQT) study was established to ensure that all new drugs are comprehensively evaluated for QT prolongation (1,2). Comparisons of manual, computer-assisted, and automated methodologies for TQT studies have demonstrated that both approaches give reliable and reproducible results; one reported lower variability with the automated method (3) and another reported lower availability with a semi-automated approach (4).
The current study was designed to evaluate both an automated system and an established, computer-assisted, manual system that is currently used for QT interval measurement.

Methods

Study Design: This was a single-center, single-blind, placebo-controlled, 2-period, crossover study to assess the effect of moxifloxacin 400 mg on the QTc interval using the automated system (QTinno, NewCardio, Inc) and a computer-assisted, manual approach using a single interpreting cardiologist (HeartSignals, Social & Scientific Systems, Inc). Subjects participated in 2 treatment periods separated by a 1-week washout. Subjects received moxifloxacin 400 mg or placebo after an 8-hr fast. Subjects had baseline ECGs performed 5 times over 5 minutes at each of 3 predose time points (0.75, 0.5, and 0.25 hr) and then 5 times at each of 12 time points from 0.5 hr through 24 hr postdose. Moxifloxacin was assayed using a validated LC/MS/MS method with a lower limit of quantification of 0.025 µg/mL.
QT Measurements: The Surveyor Telemetry Central System (Mortara Instrument, Inc) was used to collect the raw 12-lead ECG dataset for both analyses. The automated system was used to measure QT and QTcF of all 5 replicates at each time point. The manual approach was initially to measure QT and QTcF of the 2nd through 4th replicate. The cardiologist was blinded to the treatment sequence and time order of the ECGs. Based on objective criteria, the 1st or 5th replicate was used in place of another, if fewer than 3 optimal replicates were reported after the initial read. QTcF of each replicate was calculated from QT and RR. Intervals of each method were summarized by the arithmetic mean for data listings, summary, and analysis.

Statistical Methods: The following analyses were performed separately using manual or automated QT intervals.

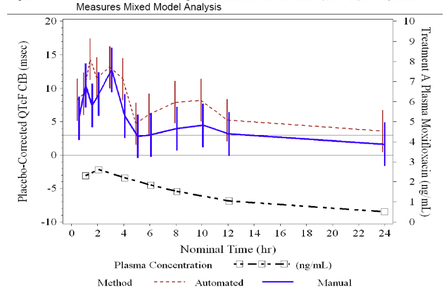
Change from baseline QTcF (ΔQTcF) was fit by mixed model analysis of variance to evaluate residual standard deviation (model SD or square root mean-square error) and assay sensitivity. This was adequate if the lower bound of at least one 95% one-sided confidence interval (CI) for the mean placebo-corrected ΔQTcF was greater than 5 msec.
An outlier analysis was performed to detect individual HR < 50 bpm and ΔQTcF or ΔQT ≥ 30 msec or ≥ 60 msec.

Linear regression estimates of ΔQTcF vs. time-matched moxifloxacin plasma concentrations were estimated by separate mixed models (repeated over nominal time, subject random) fit to ΔQTcF following moxifloxacin, ΔQTcF following placebo, and placebo-corrected ΔQTcF.
The Bland-Altman analysis of QTcF difference (automated – manual) included estimates of the mean difference and limits of agreement (LoA) that were 1.96 x SD of the individual differences. Scatter plot figures of individual difference vs. the mean of the 2 QTcF values are presented with slope estimates,

Results

QT data from 23 completed subjects at 30 time points during the 2 treatment periods resulted in 3450 and 2028 replicates by the automated and manual approaches. Adequacy of the study sensitivity (lower bound of the 95% confidence interval of ΔQTcF greater than 5 msec) was confirmed by both methods at multiple time points. The maximal mean ΔQTcF and 90% CIs were 14.3 (11.2-17.5) and 12.7 (9.4-16.0) msec and occurred at 1.5 hr and 3 hr using the automated and manual methods (Figure 1). Assay sensitivity was demonstrated at a greater number of time points via the automated method, although these values persisted beyond the expected decay curve for moxifloxacin.

Figure 1 Placebo-corrected Change from Baseline QTcF Mean (90% CI) of Repeated Measures Mixed Model Analysis



The manual and automated approaches were similarly precise with √(MSE) or intrasubject SD of 6.4 msec and 6.7 msec, respectively (Table 1). The proportion of variance attributed to subject differences was also similar between methods, 0.45 and 0.34.

Table 1. Residual Variance of QTcF Change from Baseline, Intersubject Variance, and Variance Ratio

QT Measure	Model MSE	Intra-subject SD	Inter-subj. Var	Inter-subject SD	Repeat-ability
ΔQTcF (msec, automated)	41.5	6.4	74.8	8.6	0.45
ΔQTcF (msec, manual)	44.4	6.7	67.1	8.2	0.34

Intrasubject SD is used to estimate sample size and precision of crossover study.
Intersubject SD is used to estimate sample size and precision of parallel groups study.
Benefit of crossover design increases with Repeatability [1 – (intra-/inter- Var ratio)]

Categorical analyses of the QT data from the 2 methods yielded similar results. Very few outliers were detected and these events typically were not common between methods (Table 2):

Table 2. Interval Outliers Detected by Categorical Analysis

	Moxifloxacin		Placebo		Common
Interval Outlier Events(Subjects)	Auto	Man	Auto	Man	Events
Predose HR < 50 bpm	8(4)	7(5)	0	3(2)	5/10
Postdose ΔQT (30, 60) msec	1(1)	0	3(1)	0	0
Postdose ΔQTcF (30, 60) msec	0	0	0	0	-
Postdose HR < 50 bpm	10(3)	10(3)	8(5)	8(5)	12/36

No ECG had ΔQT or ΔQTcF > 60 msec by either methodology.

The association between ΔQTcF by manual and automated methods and time-matched plasma moxifloxacin concentrations was positive and statistically significant. The association may have been due, in part, to a trend over time: The regression of post-placebo ΔQTcF on time-matched plasma concentrations of the moxifloxacin treatment were also statistically significant with a slightly lower slope. (Table 3 and Figure 2a).

Figure 2a Change from Baseline QTcF vs. Plasma Moxifloxacin Concentration

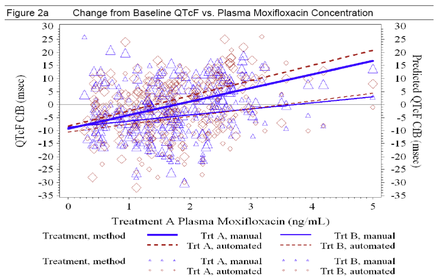


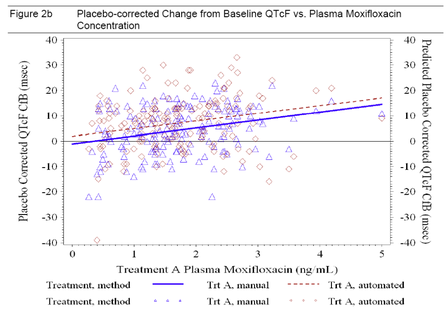
Table 3. Association between ΔQTcF and Time-matched Plasma Moxifloxacin

	Intercept		Slope	
QT Measure	Estimate	p-value	Estimate	p-value
Automated				
Moxifloxacin ΔQTcF [1]	-8.17	<0.001	5.81	<0.001
Moxifloxacin – Placebo ΔQTcF[2]	1.93	0.372	3.04	<0.001
Placebo ΔQTcF [1,3]	-10.46	<0.001	2.98	<0.001
Manual				
Moxifloxacin ΔQTcF [1]	-9.21	<0.001	5.20	<0.001
Moxifloxacin – Placebo ΔQTcF[2]	-1.11	0.537	3.16	<0.001
Placebo ΔQTcF [1,3]	-8.61	<0.001	2.34	0.002

[1]Represented in Figure 2a. [2]Represented in Figure 2b. [3]Regression of ΔQTcF following placebo treatment on time-matched plasma concentrations following moxifloxacin.

The regression of placebo-corrected ΔQTcF on time-matched plasma concentrations had similar slopes by automated and manual methods and the slightly higher automated results had an intercept approximately 3 msec higher than those by the manual method (Figure 2b).

Figure 2b Placebo-corrected Change from Baseline QTcF vs. Plasma Moxifloxacin Concentration



The summary of QTcF automated – manual differences suggest that intervals by the automated method were typically 8.3 msec to 9.8 msec lower than intervals by the manual method. The slightly negative slope estimate for QTcF following the placebo treatment suggests a trend toward smaller differences at higher QTcF. The CI for all other slopes include 0, consistent with no trend. The QTcF limits of agreement (LoA) range from 13.8 msec for ΔQTcF following moxifloxacin to 15.7 msec for QTcF following moxifloxacin. (Table 4, Figure 3a)

Mean ΔQTcF following moxifloxacin was typically 2.4 msec higher by the automated method, while ΔQTcF following placebo was 0.8 msec lower by the automated method compared to Δ intervals by the manual method. Table 4 shows a similar pattern for QT as for QTcF. (Figure 3b)

Table 4. Bland-Altman Analysis of QTcF, ΔQTcF, QT and ΔQT

		Summary of Auto – Manual		Slope vs. Averaged Methods	95% CI	
Interval	Treatment	Mean msec	LoA msec	Estimate	Lower	Upper
QTcF	Moxifloxacin	-8.3	15.7	0.04	-0.03	0.10
	Placebo	-9.8	15.3	-0.11	-0.17	-0.04
ΔQTcF	Moxifloxacin	2.4	13.8	-0.01	-0.10	0.09
	Placebo	-0.8	14.8	0.02	-0.09	0.13
QT	Moxifloxacin	-8.2	13.9	0.03	-0.00	0.07
	Placebo	-9.6	14.0	0.01	-0.03	0.05

Table 4. Bland-Altman Analysis of QTcF, ΔQTcF, QT and ΔQT

		Summary of Auto – Manual		Slope vs. Averaged Methods	95% CI	
Interval	Treatment	Mean msec	LoA msec	Estimate	Lower	Upper
ΔQT	Moxifloxacin	2.5	12.4	0.01	-0.03	0.05
	Placebo	-0.2	13.0	0.04	-0.01	0.09

LoA, limits of agreement (1.96 SD of differences)

Figure 3a Bland-Altman Analysis of QTcF

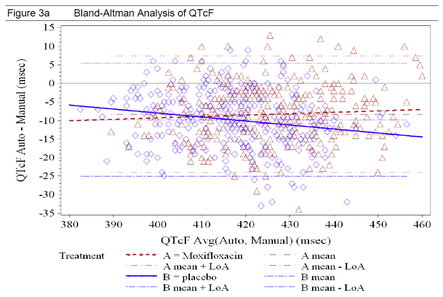
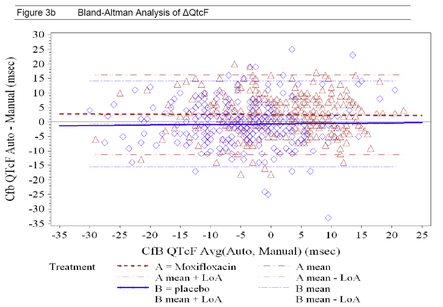


Figure 3b Bland-Altman Analysis of ΔQTcF



Discussion and Conclusions

This study was intended to establish the value of automated and computer-assisted, manual approaches in order to assess performance characteristics of technologies that are acceptable to the FDA and other regulatory agencies for detecting cardiac safety signals in drug development. The automated and manual approaches for evaluating moxifloxacin-induced QTc prolongation demonstrated a high and comparable degree of precision. Each was successful in demonstrating assay sensitivity for a positive control and yielded similar results with respect to categorical outlier analysis.

Both automated and computer-assisted, manual approaches have the ability to detect QT interval prolongation in drug development. The optimal selection of either methodology will depend upon a number of factors including drug characteristics and the population being studied.

References

1. International Conference on Harmonisation. ICH Harmonized Tripartite Guideline E14. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic
Drugs. 12 May 2005.

2. Bloomfield DM, et al. The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. Clin Pharm Ther 2008;84:475-80.

3. Fosser C, et al. Comparison of manual and automated measurements of the QT interval in healthy volunteers: an analysis of five thorough QT studies. Clin Pharm Ther 2009;86:503-6.

4. Tyl B, et al. Comparison of Semiautomated and Fully Automated Methods for QT Measurement During a Thorough QT/QTc Study: Variability and Sample Size Considerations. J Clin Pharmacol 2009;49:905-905.