Comparison of Highly-Automatic versus FDA-Submitted QT Measurements for the Detection of Moxifloxacin Induced Prolongation of the QTc Interval

R Handzel[1,3], C Garnett[2], M Li[2], S McNitt[3], S Polonski[3], X Xia[3], JP Couderc[3]

[1]Department of Biomedical Engineering, University of Rochester, Rochester, NY, USA
[2]CDER, Food Drug Administration, Department of Human and Health Services, USA
[3]Heart Research Follow-up Program, Cardiology Department, University of Rochester Medical Center, Rochester, NY, USA

Abstract

In this study, we investigated the ability of a QT algorithm to detect small drug-induced QT interval prolongation by adopting a "highly-automatized" approach. In a set of 8,911 digital ECGs, we analyzed the drug-concentration profile of computerized QTc to the measurements submitted to the Food and Drug Administration (FDA) by pharmaceutical companies. The RR and QT intervals were measured using lead II based on a QT algorithm included in the COMPAS software package developed at University of Rochester Medical Center, NY. When comparing the time-dependent effect of the drug on the QTc interval the automatic technique produced results similar to the measurements reported by contract research organizations to the Agency (FDA).

1. Introduction

A dose-dependent prolongation of the QTc interval is used as a marker of drug cardiotoxicity. The assessment of the propensity of a new compound to prolong the QTc interval is based on results from clinical trials specifically designed to investigate this endpoint: the thorough QT studies (TQTs).

The TQTs generally follow a placebo-controlled, crossover design. A positive control group is used to assess if the study relies on a QT measurement technique that can detect small drug-induced QT/QTc prolongation [1].

Moxifloxacin is used as a positive control substance in TQTs and it produces an approximate 10 msec prolongation of the QTc interval following a single oral dose of 400 mg [2,3]. This dose is considered to be safe even though it is known to generate moderate QTc prolongation. In this study we investigated how our highly-automatic QT technique performs in comparison to QTc measurements submitted to the FDA in regular thorough QT studies.

2. Methods

2.1. Study population

This study included a total of 8,911 HL7 XML ECG files that were extracted from the FDA ECG Data Warehouse under a collaborative arrangement between the FDA and the University of Rochester, NY. All sixty-six enrolled individuals were females. The data were fully de-identified. The study was a longitudinal four-arm crossover and on day –1 ECGs were recorded over 12 hours (0, 0.5, 1.5, 2, 3, 4, 5, 4.5, 6, 8, 12 hours). Day 1 recordings began pre-dose for both moxifloxacin and placebo and were recorded over 72 hours (0.5, 1.5, 2, 3, 4, 5, 4.5, 6, 8, 12, 24, 48, 72 hours). A set of 4,930 ECGs were recorded during day 1 of the protocol.

The XML files were de-identified and proprietary information were removed from the XML files: equipment used to record the ECGs, name of the company that realized the ECG measurements, and all ECG fiducial points. Our group obtained access to the ECG signal information only. The clinical information related to demographic and the link between ECG files, patients and study arms were provided in separate files sent by the FDA under confidence disclosure agreement.

The comparison between the QTc measurements from the COMPAS software and from the Agency was conducted by the FDA. Only the final results were sent back to the University as they are described in the results section.

2.2. Scalar ECG measurements

COMPAS is a software package developed at University of Rochester which integrates various methods to analyze the repolarization segment from the surface ECGs [4]. In this study, a simple QT measurement technique was implemented using a least square fitting technique. The terminal portion of the T-wave was defined as the crossing point between the fitted line and the isolelectric reference.

First, the R-peaks are detected based on template correlation technique applied to the lead with highest amplitude of R wave. The QRS template is extracted from the beats which are detected using the first derivative method. Second, a FIR low-pass filter with 21 coefficients is applied to remove the high frequency noise component from the ECG signal (Fc= 25 Hz). Third, the baseline wander is corrected by the cubic spline interpolation method after locating the isoelectric points using detected R peaks. Finally, we developed a QRS complex and J point detector based on prior work from Zong at al. [4].

The end of the T-wave is determined by finding t_c first, which is the time at which the second half of T wave has the maximum slope. The searching of t_c starts at the apex of T-wave (t_a) and ends at t_f or half the length of the T wave when detection of t_f failed. The t_f is the point at which the sign of the linear regression slope changes. This is a modified version of the tangent method described by Lepeschkin and Surawicz [5]. We reported the QT interval duration from lead II exclusively [6].

The tangent line is centered at t_c, and four points to both sides of t_c are used to form the fitted line applying the least square method. The QT interval for each beat was heart rate corrected using the Fridericia's formula [7].

2.3. Statistical analysis

For each ECG, the QT interval was measured in all available beats and the median was computed to yield one value for each ECG. Since each individual had triplicate ECGs for each time point in the study, the mean of these was calculated. This value at time zero was defined as baseline and subtracting it from the treatment values gives ΔQTc.

$$\Delta QTc_{moxi} = QTc_{moxi-baseline}$$
$$\Delta QTc_{placebo} = QTc_{placebo-baseline} \quad \text{(Eq. 1)}$$

To account for the placebo effect, ΔQTc_{placeo} was subtracted from ΔQTc_{moxi}. The mean of this difference was calculated for each time point.

$$\Delta\Delta QTc = mean(\Delta QTc_{moxi} - \Delta QTc_{placebo}) \quad \text{(Eq. 2)}$$

When statistically comparing the curves describing the QT profiles across time between the two measurements, we used a mixed-effects linear model for repeated measures. The model had no intercept and used an unstructured covariance structure as this model showed the best goodness-of-fit. The secondary analysis based on Bonferroni multiplicity adjustment was used to compare measurement at each time point, significance level below 0.005 was considered statistically different.

2.4. Quality assessment

A quality assessment process was performed on all 8,911 ECG tracings which involved three levels. First, the ECG tracings were determined to be readable or unreadable. Unreadable files were discarded by COMPAS for a number of reasons that prevented it from being measured (flat T-wave for example, were defined as anything under the threshold of 0.05mV). Next, the remaining files that had values outside of the manually specified ranges (QTc [340-515]msec and RR [500-1350]msec) were labeled as outliers. The remaining high quality files were analyzed for peculiar values following criteria described in Eq. 4.

IQR = 75 Quartile – 25 Quartile
Potential Outliers: > 75 Quartile + 1.5 IQR (Eq. 3)
< 25 Quartile – 1.5 IQR

Finally, any ΔQTc values that were out of the range (-30 to 30 mec) were manually checked. All the outliers were manually examined. Based on the ECG and measurement quality, the QT interval were kept, corrected or rejected.

3. Results

3.1. Subjects

Sixty-one of the healthy participating females were fully analyzed in this study with ages ranging from 39 to 64 years. No other information about the volunteers was disclosed. Two individuals had all baseline ECGs measurements in the ΔQTc outliers that were all of bad quality and rejected. In these two individuals ΔΔQTc could not be calculated and were excluded from the analysis.

3.2. ECG selection process

We describe below the number of ECGs used in the study. We defined three groups: the outliers (5.2%), the rejected tracings from the analysis (4.1%). These percentages were based on the set of ECGs used for the analysis i.e. excluding Day -1 (44.7%).

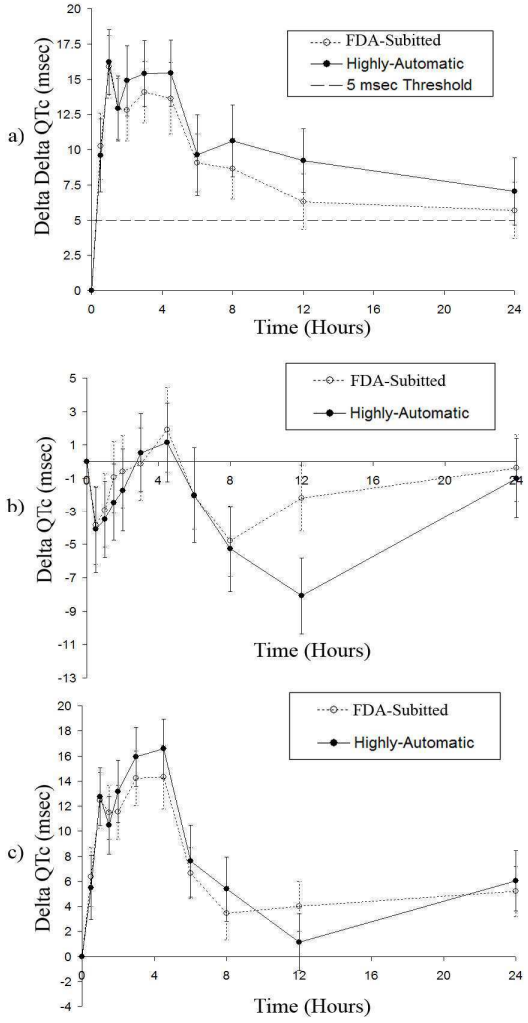

Figure 1: Highly-automatic and FDA-submitted measurements plotted with the 90% CI for all three plots: a) ΔΔQTc, b) ΔQTc_{moxi}, and c) $\Delta QTc_{placebo}$

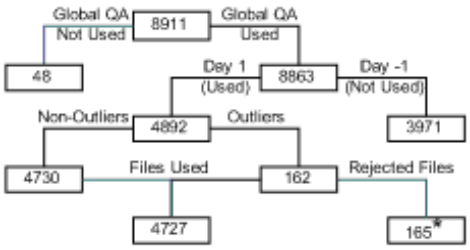

Figure 2: t_0 on day 1 was used as the baseline and day -1 was not used. Note: The * indicates a greater value than the files analyzed because baseline ECG tracings for two individuals were discarded.

3.3. Comparing QTc measurements

At the expected maximum moxifloxacin concentrations between 1 and 3 hours post-dose both the highly-automatic and the FDA-submitted measurements were associated with similar QTc prolongation (see Table 1). It is the Agency expectation that the ΔΔQTc at time 12 be roughly 50% of the ΔΔQTc at max concentration. Both methods consistently revealed such a profile.

We identified a trend toward a slightly higher mean ΔΔQTc value from the highly-automatic method in comparison to the FDA results. The largest mean difference of 2.9 msec occurred 12 hours post-dose. A mixed linear model was used to test the null hypothesis that the two measurement techniques yield the same mean value at each time point in favor of the alternative hypothesis that they yield significantly different mean values. This analysis failed to reject the null hypothesis i.e. it failed to show that the two average profiles are different (p=0.12).

While p-value is 0.046 for hour 2, 0.023 for the hour 4.5 and 0.016 for the hour 12, none of these time point reached the Bonferroni adjusted significance level of 0.005.

4. Discussion and conclusions

Fully automatic QT measurements have not been used in thorough QT studies because none of the current algorithms are considered as precise as the human readings. In this study, we assume that most of the QT interval measurements realized by computers are valid and it is only a small fraction of these measurements that needs to be visually checked, corrected or rejected. Under such assumptions, we implemented a validation study for a highly computerized approach i.e. a method in which we identified a small subset of the computer outputs to be manually reviewed and accepting all other ones (highly-automatic method).

In other studies comparing automatic measurements to manual techniques, automatic methods did not consistently revealed a higher or lower trend [8,9].

Darpo et al. [8] have reported results from three TQTs comparing manual to two commercial measurement techniques. Only two of these studies

had comparable designs to the one we report (study 2 had a time match crossover design and was not used). On average, the highly-automatic measurements led to very similar standard error in comparison to these studies. The average standard errors were 1.5 and 1.4 msec for highly-automatic and FDA-submitted methods, respectively. In the report from Darpo et al., study 1 had average standard error values of 2.4 and 1.9 msec when using commercial systems. Darpo's third study was slightly different in that its baseline ECGs were taken at three separate times pre-dose and had an average standard error value of 1.3 msec.

Table 1: Highly-automatic versus FDA-submitted means and 90% two-sided confidence interval (CI).

	Highly-Automatic		FDA data	
Time (Hours)	Mean	90% CI Width	Mean	90% CI Width
1	16.2	4.6	15.9	4.4
1.5	12.9	4.6	12.9	4.4
2	14.9	5.0	12.8	4.4
3	15.4	4.6	14.1	4.3
12	9.2	4.5	6.3	4.0
24	7.0	4.7	5.7	4.0

4.1. Limitations

Even though both methods had very similar means and CI, the data at 12 hours post-dose had a difference of 2.9 msec. This discrepancy between the highly-automatic and FDA-submitted methods could not be checked since we did not have access to FDA-submitted QT data. The FDA supplied the subjects' ID that had the largest difference between the two methods. These ECG tracings were examined and were found to be of good quality. Thus, we were not able to understand where these differences were coming from. No further analysis could be conducted regarding this discrepancy but this small difference did not raise any concerns form the Agency.

4.2. Conclusion

The highly-automatic measurements of a standard set of 12-lead ECG strips were equivalent to the measurements provided to the FDA by pharmaceutical companies. We conclude that highly-automatic QT measurement methods should be considered as an alternative approach in drug-safety studies.

Acknowledgements

We would to thank Dr. Norman Stockbridge for his support. This work has been partially funded from NIH-RO1 grant #1160743209.

References

[1] ICH Harmonized Tripartite Guideline E14. The Clinical evaluation of QT/QTc interval prolongation and proarrhytmic potential for non-antiarrhythmic drugs [online]. Available from URL: http://www.fda.goc/cderIGuidance16885(nl.htm [accessed 2008 May 21]

[2] Culley C, Lacy M, et al. Moxifloxacin: Clinical Efficacy and Safety. Am J Health Syst Pharm 2001;58:379-88.

[3] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. 2005. DIA meeting, Washington DC, May 2005.

[4] Courderc J, Vaglio M, et al. Electrocardiographic method for identifying moxifloxacin-induced ventricular repolarization abnormalities. Computers in Cardiology 2006;33:705-8.

[5] Zhong W, Moody GB, Jiang D. A Robust Open-source Algorithm to Detect Onset and Duration of QRS Complexes. Computers in Cardiology 2003;30:737-740.

[6] Waktare J, Hnatkova K, et al. Optimal Lead Configuration in the Detection and Subtraction of QRS and T Wave Templates in Atrial Fibrillation. Computers in Cardiology 1998;25:629-32.

[7] Lepeschkin E, Surawicz B. The Measurement of the Q-T Interval of the Electrocardiogram. Circulation 1952;6:378-88.

[8] Darpo B, Agin M, Kazierad D, et al. Man Versus Machine: Is There an Optimal Method for QT Measurements in Thorough QT Studies?. J Clin Pharmacol. 2006;46:508-612.

[9] Kligfield P, Hancock E, Helfenbein E, et al. Relation of QT Interval Measurements to Evolving Automated Algorithms from Different Manufacturers of Electrocardiographs. Am J Cardiol. 2006;98:88-92.

Address for correspondence

Robert M. Handzel
University of Rochester
CPU Box 274020
Rochester, NY 14627-4020, USA
Robert.M.Handzel@gmail.com