Assessment of the sensitivity of detecting drug-induced QTc changes using subject-specific rate correction

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Published in

J. Electrocardiol. 2012, 45, no. 6, pp. 541-545

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Conflict of interest:

None of the authors has any conflict of interest.

Abstract

Aims: To quantify the sensitivity of QT heart-rate correction methods for detecting drug-induced QTc changes in thorough QT studies.

Methods: 24h Holter ECGs were analyzed in 66 normal subjects during placebo and moxifloxacin delivery (single oral dose). QT and RR time series were extracted. Three QTc computation methods were used: (1) Fridericia's formula, (2) Fridericia's formula with hysteresis reduction, and (3) a subject-specific approach with transfer function-based hysteresis reduction and three-parameter non-linear fitting of the QT-RR relation. QTc distributions after placebo and moxifloxacin delivery were compared in sliding time windows using receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) served as a measure to quantify the ability of each method to detect moxifloxacin-induced QTc prolongation.

Results: Moxifloxacin prolonged the QTc by 10.6 ± 6.6 ms at peak effect. The AUC was significantly larger after hysteresis reduction (0.87 ± 0.13 vs 0.82 ± 0.12, $p<0.01$) at peak effect, indicating a better discriminating capability. Subject-specific correction further increased the AUC to 0.91 ± 0.11 ($p<0.01$ vs Fridericia with hysteresis reduction). The performance of the subject-specific approach was the consequence of a substantially lower intra-subject QTc standard deviation (5.7 ± 1.1 ms vs 8.8 ± 1.2 ms for Fridericia).

Conclusion: The ROC curve provides a tool for quantitative comparison of QT heart rate correction methods in the context of detecting drug-induced QTc prolongation. Results support a broader use of subject-specific QT correction.

Introduction

Regulatory agencies require intensive evaluations to identify drugs with arrhythmogenic potential and the risk of syncope and/or sudden death. Monitoring the QT interval (a measure of total duration of depolarization and repolarization) on the ECG has become mandatory. Marketed drugs have been withdrawn or restricted and the development of others has been interrupted because of QT interval prolongation. Validation and comparison of QT measurement techniques is therefore crucial in the context of drug evaluation.[1]

Correction of QT intervals for heart rate is necessary to provide a single intrinsic physiological value that can be compared before and after drug delivery and between subjects. The challenge is to design robust signal processing techniques to reliably define the end of the T-wave and estimate the QTc from ECG recordings. Standard formulas for the corrected QT (QTc) such as Bazett's[2] do not fully reproduce the complexity of the dependence in the preceding interbeat intervals (RR) and ignore inter-subject variability and memory effects (slow adaptation to abrupt changes in heart rate). Previous studies have demonstrated the importance of more elaborate subject-specific rate correction formulas on the accuracy of QTc measurements as well as its impact on the reliability of prolonged QT detection.[3-7] This paper aims at providing further arguments to advocate the use of Holter monitoring combined with subject-specific QT correction in clinical studies.

Moxifloxacin is an antibacterial agent which causes QTc prolongation and is often used as active comparator for drug tests.[8] In this study, we used ECG recordings previously collected

during a thorough QT study with placebo and moxifloxacin delivery. We developed an approach based on the receiver operating characteristic (ROC) curve[9] to assess the sensitivity of different QTc computation methods (Fridericia and subject specific) to detect drug-induced QTc prolongation. The results obtained underline the necessity of hysteresis reduction and subject-specific correction.

Methods

Clinical protocol

ECG signals of a thorough QT study with crossover design (database "Thorough QT Study #2", E-HOL-12-0140-008) were obtained from the Telemetric and Holter ECG Warehouse (Rochester, NY). In 66 normal subjects, 24-hour standard 12-lead Holter ECGs (1000 samples per sec) were recorded during placebo delivery as well as during QT-prolonging drug (moxifloxacin) delivery. The two treatments were separated by a washout period of at least one week. During each session, a single dose was delivered orally after one hour of rest that served to define baseline conditions in the ECG. Moxifloxacin plasma concentration was measured 1h, 2h, 3h, 4h, 5h, 6h, 8h, 12h, 23h and 24h postdose.

Computation of QTc time series

An automatic fiducial point detector was applied to each recording in the database in order to identify the markers defining the onset of the QRS (Qon), the peak of ventricular

activation (R), the end of repolarization (Toff) and to extract the RR and QT interval time series.[7] These time series were processed to estimate the QT/RR relation. We used a subject-specific, nonlinear, transfer function-based correction method to compute the QTc time series from Holter ECG recordings.[7] This QT/RR model includes 5 parameters: 3 describing the static QT-RR relationship[3] and 2 representing memory/hysteresis effects that intervene in the calculation of effective RR values.[6] Eight different QT-RR curve fitting functions (linear, power law, exponential, logarithm, arctangent, hyperbolic tangent, hyperbolic arcsine and hyperbolic arccosine) were tested for each subject, similarly to the work of Malik *et al*.[3] Hysteresis reduction took into account an instantaneous response (the RR interval of the previous beat) and a slow response (time constant adjusted to each subject, typically about 2 min) in order to define the effective RR interval (RReff) as a linear combination of past RR values. A parameters identification procedure was designed to minimize QTc fluctuations and enforce zero correlation between QTc and effective RR.[7] Each patient-specific correction formula was estimated based on QT and RR time series extracted during placebo delivery (24h of data) and was applied to both placebo and drug delivery in the same subject.

In addition to the subject-specific QTc (QTc,S), Fridericia's correction formula[10] was used to compute the QTc,F time series (= $QT/RR^{1/3}$). Fridericia's formula was also applied to a weighted sum of the RR time series to take into account memory effects (improved Fridericia, QTc,FI = $QT/RRavg^{1/3}$, where RRavg is the average RR interval over the previous 120 beats).

Analysis of QTc time series

QTc time series were analyzed in one-hour sliding time windows (10 min shifts between consecutive windows). The ΔQTc time series was defined as QTc minus the mean QTc during the first window (predose control window). The ΔΔQTc in each time window was defined as the difference between the mean ΔQTc during drug delivery and that during placebo delivery.[8]

In each time window, the distributions of ΔQTc during drug and placebo delivery were compared. Mean and standard deviation of ΔQTc were documented for each window. To quantify the relevance of the differences in mean ΔQTc, the ROC curve[9] between the placebo and drug ΔQTc distributions was computed for each subject and for each window. This is equivalent to trying to diagnose whether a beat comes from the drug or placebo recording using a threshold on the ΔQTc value. The area under the ROC curve (AUC) represents the reliability of this prediction, or, equivalently, measures how different the drug and placebo ΔQTc distributions are. The AUC is equal to the probability that the ΔQTc of a random beat after drug delivery is larger than that of a random beat after placebo delivery.[9] It is also related to the Mann-Whitney U test. As compared to a paired t-test, the advantage of the AUC is that it converges to a finite value for large sample sizes, while the p-value could become very small, thus hindering the comparison of different QT correction approaches.

These analyses were performed for each of the three definitions of the QTc (subject-specific, Fridericia and improved Fridericia).

Results

Drug-induced QTc prolongation

Figure 1A describes moxifloxacin pharmacokinetics; plasma concentration (mean ± SD) is displayed as a function of time and is in agreement with previous data[11, 12] although a bit slower, possibly due to over-encapsulation or food intake. Note that drug was delivered at hour 1. Maximum plasma drug concentration was determined by performing a curve fitting with a sum of two exponentials. Peak plasma concentration was reached at time 4.4 hours.

The QTc,S during the control hour was 389.3 ± 23.2 ms before placebo delivery and 390.7 ± 21.9 ms before drug delivery ($p = 0.73$, paired t-test, $n = 66$ subjects), suggesting the stability of QTc measurement over a week. Figure 1B shows the ΔQTc,S time series (mean ± SD in each 1-hour window) with patient-specific heart rate correction for placebo and moxifloxacin, as well as the ΔΔQTc,S time series (ΔQTc,S drug minus ΔQTc,S placebo), for all the windows. The use of ΔΔQTc reduces subject-specific circadian variations.[1] The amplitude and the decay of the resulting ΔΔQTc,S curve is similar to that from Malik et al.[8] obtained using moxifloxacin intravenous injection. The maximum ΔΔQTc,S was found at time 4.6 hours (average over all the subjects). The ΔΔQTc curves obtained with the three methods were similar (less than 1 ms discrepancy, as shown in Fig. 2), mainly because heart rate was not significantly affected by moxifloxacin ($p = 0.08$, repeated measures ANOVA). The standard deviation of ΔΔQTc was 7.6 ± 0.9 ms for the two Fridericia methods and 6.5 ± 0.8

ms for the subject-specific method. For subsequent detailed statistics, the distributions of ΔQTc were analyzed in the window from time 4.1 to 5.1 hours, where the peak effect was identified.

Reliability of the detection of QTc prolongation

Figure 3 compares the ΔQTc distributions after placebo and moxifloxacin delivery in one subject, for the 1-hour window centered at time 4.6 hours. The ΔQTc distributions were obtained with three different methods: Fridericia's (Fig. 3A), improved Fridericia's (Fig. 3B) and subject-specific (Fig. 3C). Both hysteresis reduction (Fig. 3B vs A) and subject-specific correction (Fig. 3C vs B) decreased the spread of ΔQTc and the overlap between placebo and moxifloxacin ΔQTc distributions. Intra-individual ΔQTc variability (standard deviation of the ΔQTc time series over 24h) in the placebo study was 8.8 ± 1.2 ms for Fridericia, 6.9 ± 1.3 ms for improved Fridericia and 5.7 ± 1.1 ms for the subject-specific method, demonstrating the increased stability over time of the subject-specific QTc.[3, 5, 7] During drug delivery, intra-individual ΔQTc variability in one-hour time windows was respectively 9.0 ± 1.4 ms, 7.2 ± 1.4 ms and 5.8 ± 1.1 ms for the three methods.

This improvement in the ability to discriminate between the two distributions can be quantified using the ROC curves (Figs. 3D, E and F). In this example, the AUC is considerably increased, suggesting that the subject-specific method has a higher sensitivity for detecting changes in QTc.

The statistics of AUC over all subjects provides a quantitative measure to compare the correction methods in the context of QTc prolongation detection. Figure 3G shows median

AUC time series during 24 hours. During the control interval (first hour), the AUC remains near 0.5 (placebo and moxifloxacin ΔQTc distribution cannot be discriminated). After drug delivery, the AUC increases. The AUC is significantly higher for improved Fridericia as compared to standard Fridericia ($p<0.001$, repeated measures ANOVA), demonstrating the importance of hysteresis reduction. Using subject-specific heart rate correction formula led to even larger values for AUC ($p<0.02$ with respect to improved Fridericia). The improvement was however insignificant during the night (around time 20 hours in Fig. 3G), where heart rate is closer to 60 bpm (no correction needed).

Population-based relevance of QTc prolongation

Another way to evaluate the clinical relevance of drug-induced QTc prolongation is to compute for each subject the mean ΔQTc in the interval around time 4.6 hours during placebo and moxifloxacin delivery (peak effect). The accuracy of the parameter ΔQTc for classifying between the placebo and the moxifloxacin group can also be quantified using a ROC curve. The subject-specific method had the largest AUC (0.96 vs 0.94 for Fridericia's method) and enables the discrimination between placebo and moxifloxacin based only on the ΔQTc with a sensitivity of 92% and a specificity of 94% using a threshold at 3.5 ms. This means that in this clinical study a ΔQTc of more than 3.5 ms was a good indication that the subject had taken moxifloxacin.

Discussion

Drug effects are subject-specific, especially if the oral dose is not body weight-dependent, as in our dataset. The QT-RR relationship is also subject-specific.[3, 5] The use of advanced QT correction techniques decreases the consequence of the latter source of inter-patient variability and facilitates the identification of QTc changes. Hysteresis reduction is particularly effective at decreasing the variance of QTc distributions (Figs. 3A to C). In addition to its low computational complexity, the improved Fridericia method offers a significant upgrade as compared to the standard Fridericia's formula in terms of its ability to identify QTc changes. Subject-specific nonlinear QT-RR formulas with multiple adjustable parameters further improve the results (Fig. 3). Subject-specific methods are well adapted to long recordings with significant variations in heart rate (e.g. day vs night). Their application to short (< 1 min) ECG signals is however limited. Since 136 twelve-lead 24-hour ECGs were analyzed, semi-automatic validation of the QT interval was used (outlier detection). In our experience, more careful, manual validation may further reduce QTc variance. Alternatively, advances in automatic validation techniques would help improve the accuracy of the analysis of long Holter recordings.

Small circadian variations in the QTc (< 5 ms) were observed in the placebo study. Note that the protocol started at 7 am for all subjects and that they ate and slept at roughly the same time. These variations may be due to the influence of the autonomic nervous system, but also to the limitations of the model whose parameters are assumed to be constant along the day. These observations confirm the value of a placebo control group to account for

subject-specific circadian variations, as recommended by Malik et al.[1] The choice of one-hour time windows for the analysis was based on measured moxifloxacin pharmacokinetics. Studying drugs with faster pharmacokinetics or intravenous injection would require shortening the length of sliding windows.

The clinical relevance of QTc measurement is to detect differences in QTc between two groups (e.g. drug vs placebo). In order to quantify the reliability of QTc definition and computation methods, we took the opposite approach: trying to retrospectively infer information about the group from QTc values. Assuming that a difference in QTc between two groups is expected (as is the case with moxifloxacin), the AUC reflects the contrast between the two groups obtained from QTc statistics only. Prospective prediction of the group from QTc values is however beyond the scope of our method.

Evaluating the sensitivity of QT correction methods to detect physiological or drug-induced QTc changes is a critical validation step for a correct interpretation of thorough QT studies. In combination with dedicated statistical tools such as ROC curves, available ECG databases such as the Rochester initiative THEW provide a framework to test, validate, compare and improve ECG processing techniques.

Acknowledgements

Data used for this research was provided by the Telemetric and Holter ECG Warehouse of the University of Rochester (THEW), NY.

This work was supported by the Heart and Stroke Foundation of Québec (FMCQ) and the Fonds de la Recherche du Québec – Santé (FRQS).

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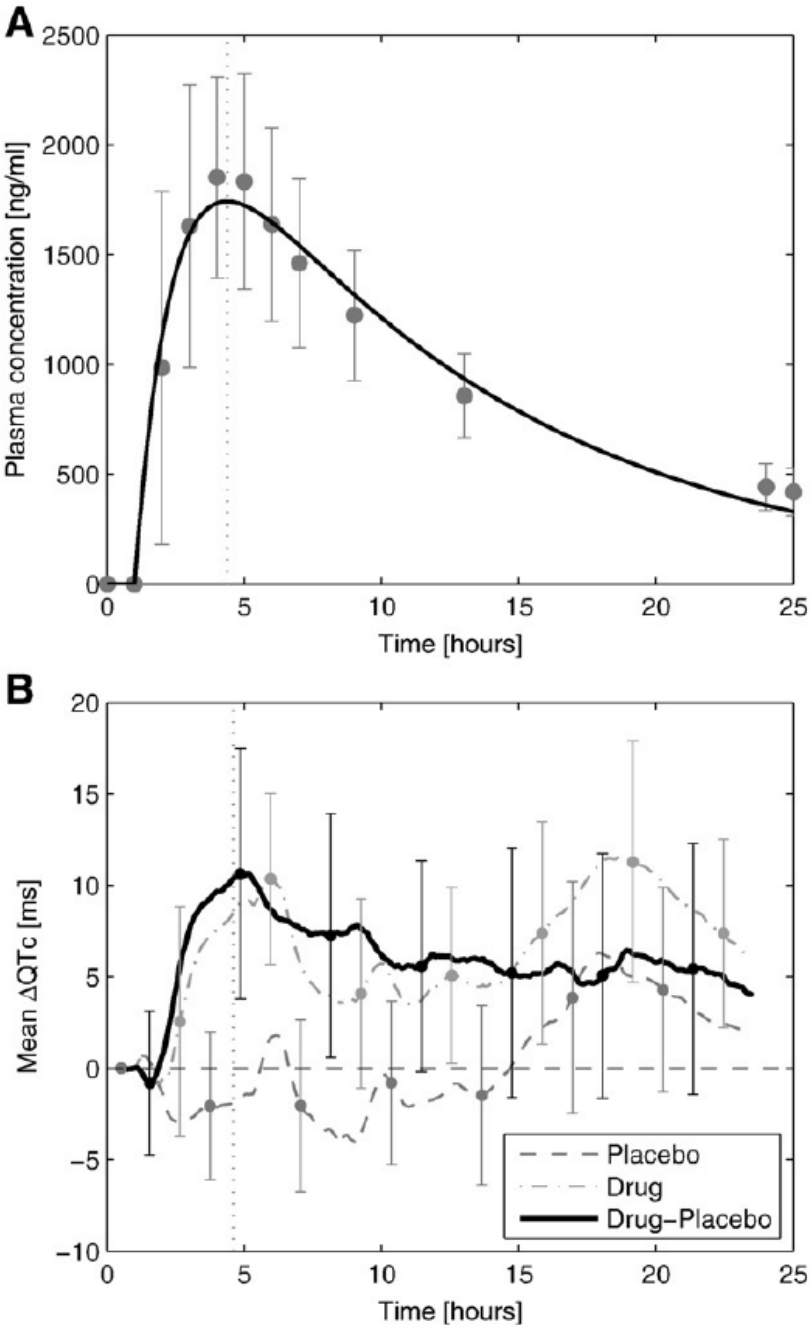

Figure 1: (A) Plasma moxifloxacin concentration averaged over all the subjects (mean ± SD). The solid curve is a fit with a sum of two exponentials. (B) Mean ΔQTc for placebo, moxifloxacin and their difference (ΔΔQTc). Dotted vertical lines show peak plasma concentration and average time of peak ΔΔQTc.

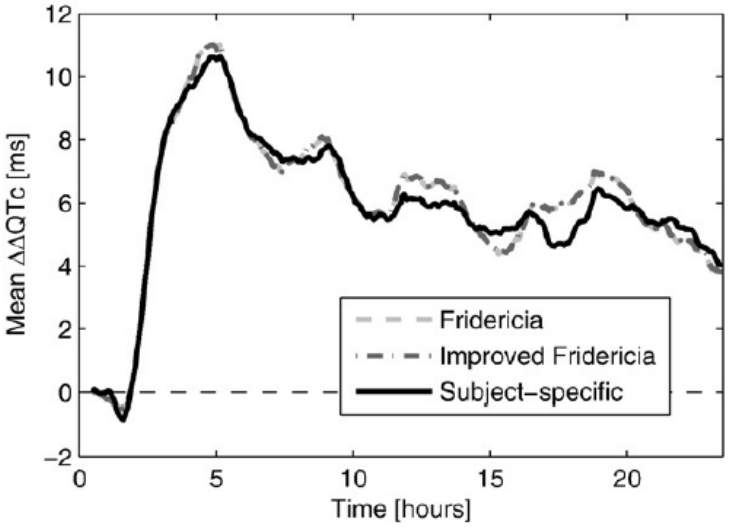

Figure 2: Time course of mean ΔΔQTc for the three different heart rate correction methods.

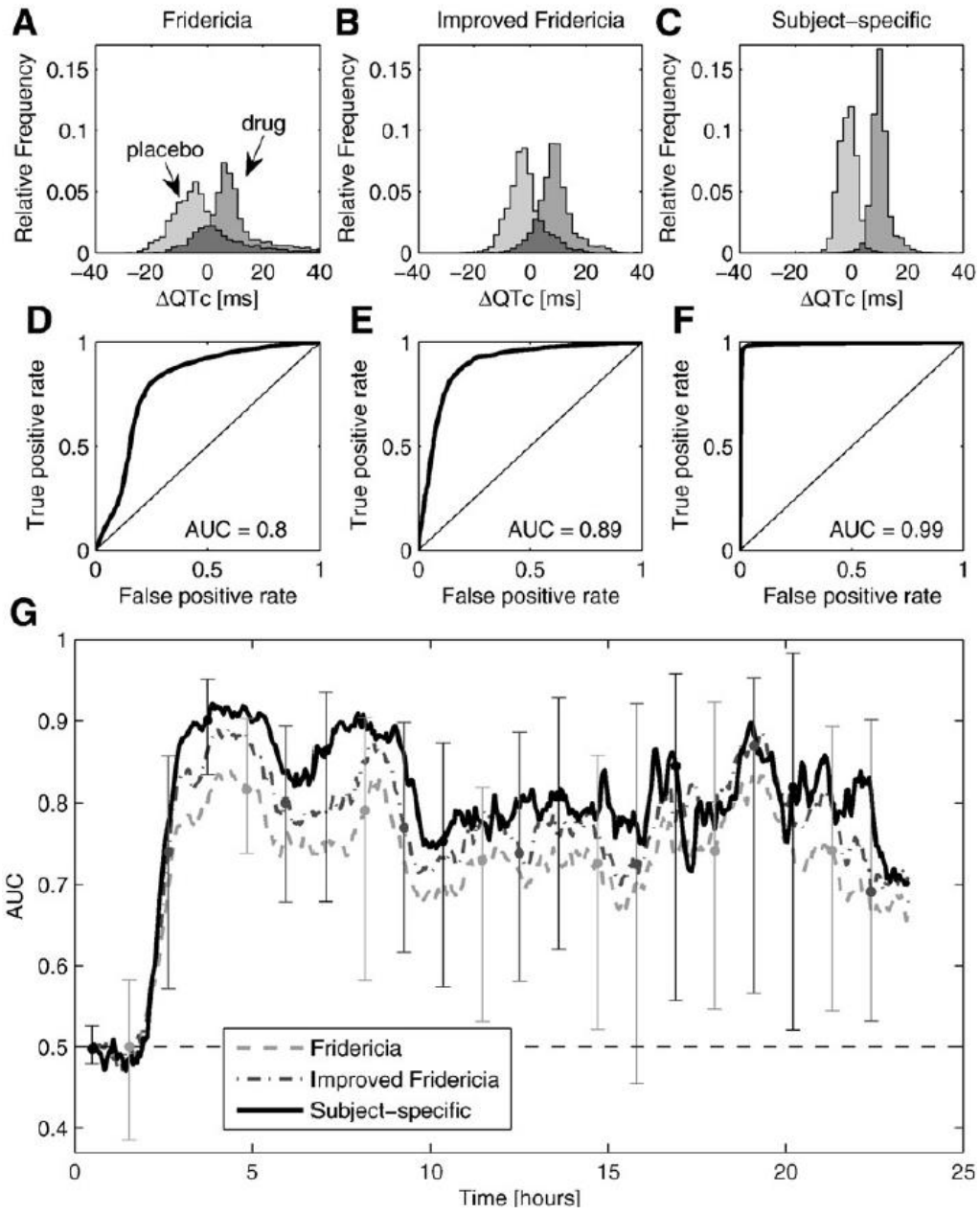

Figure 3: ΔQTc distributions at peak effect (1-hour window around time 4.6 hour) in one subject during placebo and moxifloxacin delivery, obtained using Fridericia's (A), Improved Fridericia's (B) and subject-specific correction formula (C). The darker region represents the overlap between the two distributions. The corresponding ROC curves are displayed in panels D, E and F. The area under the ROC curve (AUC) is indicated. (G) Evolution of the

median of the AUC, for the three correction methods. The first and third quartiles are shown as error bars for some data points displayed as dots.