Comparison of Six Commonly Used QT Correction Formulæ and Three Parameter Estimation Methods

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Methods for Estimating the QT Correction Factor

Three computing methods have been proposed to estimate the correction factor for these six correction formulæ: Golden section interaction procedure, Ordinary regression model estimated by least square approach and Mixed model estimated by maximum likelihood approach.

Mixed model approach - performed worst in terms of all five performance indices: the QTc-RR correlation, the absolute regression slope of QTc/RR, RMSE, standard deviation of range of QTc. These values were statistically significantly different from 0 (P=0.001). Therefore, the mixed model failed to make QTc values independent of RR values.

Simulation Study (Example 2)

In this example, a dataset was simulated for individual QT-RR patterns according to a proposed strategy [7]. The aim of the simulation was to get a range of possible performances. The simulation results were generally in agreement with those observed for Example 1 (Table 2). Two observations are particularly worth commenting on. The golden section procedure generated QTc values that were totally uncorrelated to RR for all six formulæ (mean values of the estimated absolute individual correlation coefficients and regression slopes were always equal to zero). The parabolic QT correction formulæ produced QT intervals with the smallest mean variation when QTc intervals were uncorrelated to RR intervals.

4-way Crossover Study (Example 3)

This example is different from Example 1 in that it contains off-drug ECGs and on-drug ECGs, e.g. here we simulate the evaluation of various QT correction formulæ under the real-life scenario of a thorough QT study. The results were consistent with those observed from Example 1 and 2. However, there was a marked difference in means of absolute correlation coefficients between the golden section approach and two regression approaches. The means of p generated by the golden section approach were zero for all six correction formulæ but the mean values of p generated by the least square regression model and mixed model were statistically significantly different from zero (P=0.001) for all six correction formulæ.

Discussion

The results from 225 individual off-drug QT-RR profiles from the 4 clinical trials (Example 1) demonstrated that the golden section approach always provides the best correction factor for all six correction formulæ in terms of QTc-RR relationship. The mean absolute values of correlation coefficients and slopes for the 225 subjects were equal to zero meaning that the golden section approach generated QTc values that were invariant of heart rate regardless of correction formulæ. The results from the simulated ECG data (Example 2) confirmed the above observation. Even for the on-drug ECG dataset (Example 3), the golden section approach also yielded zero correlation coefficient and near zero slope for all six correction formulæ. The parabolic model (Model 3) produces QTc intervals which are independent of RR and with the smallest variation in terms of standard deviation and range - smallest mean range of QTc from the golden section (37.915 msec), largest mean range of QTc for the hyperbolic model (39.073 msec).

Conclusions

- In conclusion, the golden section procedure always finds the correction factor that makes QTc totally independent of RR for all six correction formulæ.
- In particular the parabolic correction formulæ (QTc=QT×RR) also generates QTc values with the smallest variation for both off-drug and on-drug ECGs.
- It is therefore recommended that parabolic correction formulæ should be used to correct QT for heart rate in clinical studies and that its correction factor (α) should be estimated using the golden section approach.
- In contrast, least square regression model and mixed model may use a correction formulæ that fails to make the QTc independent of RR and should be avoided when defining the best correction factor.

References


QT interval on an electrocardiogram (ECG) trace is an important and widely used surrogate parameter to assess drug safety since prolongation of cardiac repolarization and QT interval is associated with various serious arrhythmias namely Torsade de Point (TdP) [1].

The duration of QT interval is affected by many factors including age, gender, various medical conditions, and most importantly by heart rate (HR) [1,2]. The QT interval varies with HR; the faster the HR (or the shorter the RR interval [RR=R0+HR]), the shorter the QT interval.

This effect is so pronounced that QT measurements have to be corrected for heart rate. These values are referred to as corrected QT interval (QTc). The QTc interval represents the QT interval at a standardised heart rate of 60/min. The goal of heart rate correction is to provide QTc interval values that are independent of the corresponding RR interval values.

Over the past several decades, many correction formulæ have been proposed. However, there is lack of systematic assessment of the sensitivity of formula parameters and validation of the corrected QT intervals.

Aims

The aim of this analysis was to compare six commonly used QT correction methods and three parameter estimating methods.

These methods were applied to four off-drug ECG datasets, a simulated dataset and one on-drug ECG dataset.

Six commonly used QT correction formulæ

Deriving a QT correction formulæ involves two steps:

1. Step: Fitting a model with two regression parameters (α, β) to describe the QT-RR relationship, e.g. QTc=αRR+β.
2. Step: Using the fitted model to derive a correction formulæ so that QTc=QT/RRα+β.

Bazett fitted a parabolic regression model QTc=RRα+β and derived the following correction formulæ, QTc=QT×RRα+β [3]. Using a similar strategy, Fridericia developed an alternative correction formulæ, QTc=QT×RRα+β [4]. By fitting a simple linear regression model using the Framingham heart data, Sage et al suggested a so-called Framingham formulæ: QTc=QT×(1-RR)αβ [5].

All the above proposed models for QT-RR relationships are in fact special cases of the following six most commonly used regression models (Table 1). Each regression model has two parameters: α and β. Once they are estimated, they can then be converted to generic heart rate correction formulæ (Table 1).

Randomised Clinical Trial Data (Example 1)

This example is from 4 thorough QT trials conducted between 2007 and 2008. The ECG databases were derived from the collection of 12-lead surface ECGs performed during the trials.

Mean values of various measurements of QT correction performance from 225 subjects by six selected models with their correction parameters and the mean absolute regression slopes of QTc-RR are shown in Table 2.

• In conclusion, the golden section approach always finds the correction factor that makes QTc totally independent of RR for all six correction formulæ.

Randomised Clinical Trial Data (Example 1)

These values were statistically significantly different from 0 (P=0.001). Therefore, the mixed model failed to make QTc values independent of RR values.

Simulation Study (Example 2)

In this example, a dataset was simulated for individual QT-RR patterns according to a proposed strategy [7]. The aim of the simulation was to get a range of possible performances. The simulation results were generally in agreement with those observed for Example 1 (Table 2).

Two observations are particularly worth commenting on. The golden section procedure generated QTc values that were totally uncorrelated to RR for all six formulæ (mean values of the estimated absolute individual correlation coefficients and regression slopes were always equal to zero). The parabolic QT correction formulæ produced QT intervals with the smallest mean variation when QTc intervals were uncorrelated to RR intervals.

4-way Crossover Study (Example 3)

This example is different from Example 1 in that it contains off-drug ECGs and on-drug ECGs, e.g. here we simulate the evaluation of various QT correction formulæ under the real-life scenario of a thorough QT study.

The results were consistent with those observed from Example 1 and 2. However, there was a marked difference in means of absolute correlation coefficients between the golden section approach and two regression approaches. The mean values of p generated by the golden section approach were zero for all six correction formulæ but the mean values of p generated by the least square regression model and mixed model were statistically significantly different from zero (P=0.001) for all six correction formulæ.

Discussion

The results from 225 individual off-drug QT-RR profiles from the 4 clinical trials (Example 1) demonstrated that the golden section approach always provides the best correction factor for all six correction formulæ in terms of QTc-RR relationship. The mean absolute values of correlation coefficients and slopes for the 225 subjects were equal to zero meaning that the golden section approach generated QTc values that were invariant of heart rate regardless of correction formulæ.

The results from the simulated ECG data (Example 2) confirmed the above observation. Even for the on-drug ECG dataset (Example 3), the golden section approach also yielded zero correlation coefficient and near zero slope for all six correction formulæ.

The parabolic model (Model 3) produces QTc intervals which are independent of RR and with the smallest variation in terms of standard deviation and range - smallest mean range of QTc from the golden section (37.915 msec), largest mean range of QTc for the hyperbolic model (39.073 msec).

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• It is therefore recommended that parabolic correction formulæ should be used to correct QT for heart rate in clinical studies and that its correction factor (α) should be estimated using the golden section approach.

• In contrast, least square regression model and mixed model may use a correction formulæ that fails to make the QTc independent of RR and should be avoided when defining the best correction factor.