Individual QT/RR Relationship as a Tool for QT Correction in the Primate

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The assessment of QT prolongation in animal models is now a mandatory element of Safety Pharmacology investigations (CPMP/468/96 point to consider and ICH STB draft guideline). As drug effects can result in modifications of heart rate and QT duration is sensitive to these changes, different correction formulas have been used. None of them is recognized as fully reliable. The principle of individual correction based on QT/RR relation for each animal has already been used in dogs, but not in primates. Indeed, the quality of the signal obtained in conscious primates limits the use of computer-assisted detection of ECG marks.

Therefore, this study aimed to answer three questions:
1) What is the best formula to fit the QT/RR relation in primates?
2) What is the impact of averaging cycles on the QT/RR relation?
3) How to use this QT/RR relation to assess QT prolongation?

**Material**

ECG recordings were performed on 14 cynomolgus monkeys (Noveprim, Mauritius) previously implanted with telemetric transmitters (DSI Data Sciences International). ECG signals were sampled at 500 Hz by means of a computerized system (HEM v 3.5, Notocord system and DSI link v 2.2). Q, R, and T waves were identified off-line, using a Microsoft Excel template and automation macros. All marks were checked by the operator, who adjusted them manually when necessary.

The end of the T wave was defined as the intersection of the ECG baseline (50 ms period preceding the Q wave) and either:
1) the ECG waveform
2) the most negative tangent to the T wave

**Part 1: Assessment of the best fit**

Methods

RR and QT were obtained from 14 monkeys during acclimation or placebo experiments. The recording period lasted between 8 and 14 hours, including at least one hour of “night”. Twenty cycles were measured every 5 or 15 minutes, leading to 1000 to 2000 QT/RR pairs for each animal. Data were sorted by RR interval and the median for QT was obtained for each 20 ms RR step to plot the QT/RR pairs for each animal. Data were sorted by RR interval assessed by the following six formulas:

- **LN1**: \( a \times \ln RR + b \)
- **LN2**: \( a \times \ln (RR - b) \)
- **POW**: \( a \times RR^b \)
- **EXP1**: \( a \times (1 + e^{-b \times RR}) \)
- **EXP2**: \( a \times e^{-b \times RR} + c \)

The coefficient of correlation (R2) and standard error from the estimate (SEE) were evaluated for each individual and reported as mean ± SD.

**Results**

<table>
<thead>
<tr>
<th>Formula</th>
<th>R2</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIN</td>
<td>0.955 ± 0.022</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>POW</td>
<td>0.953 ± 0.025</td>
<td>7.71 ± 3.36</td>
</tr>
<tr>
<td>LN1</td>
<td>0.948 ± 0.028</td>
<td>8.04 ± 3.71</td>
</tr>
<tr>
<td>LN2</td>
<td>0.851 ± 0.115</td>
<td>14.11 ± 9.22</td>
</tr>
<tr>
<td>EXP1</td>
<td>0.950 ± 0.027</td>
<td>7.82 ± 3.48</td>
</tr>
<tr>
<td>EXP2</td>
<td>0.950 ± 0.028</td>
<td>8.02 ± 3.27</td>
</tr>
</tbody>
</table>

**Conclusion 1**: the best fit to use for individual correction is linear regression.

**Comparison to fixed formulas**

Based on these results, the corrected QT was defined as:

\[
QT_i = QT + a \times (1000 - RR)
\]

The efficiency of this formula was demonstrated in comparison to the usual fixed formulas used in the literature: Bazett (QTb), Fridericia (QTf) and Van de Water (QTv).

As presented in the graph below, QTi resulted in the flattest QT/RR plot.

**Reproducibility**

Using linear regression, the same approach was performed for each animal. The slopes and intercepts of linear fits obtained with the two methods were compared (paired t-test).

**Conclusion 2**: the individual QR/RR relation is often stable with time, but the quality of the signal obtained in conscious primates limits the use of computer-assisted detection of ECG marks.

**Part 2: QT/RR relation with mean cycles**

**Aim**

As the primate ECG signal is often noisy, the use of averaged cycles has been suggested and tested. The main advantage is to improve automated ECG analysis, but this approach does not take into account the impact of abrupt changes in RR or QT variation.

We investigated the impact of averaging the cycles in the use of individual QT/RR relations, as previously described.

**Methods**

RR and QT were obtained from 11 monkeys (same experiments and duration as in part 1). Ten consecutive cycles were averaged every minute, leading to 450 to 720 QT/RR pairs for each animal. Individual RR/QT relations were obtained as previously.

The slopes and intercepts of linear fits obtained with the two methods were compared (paired t-test).

**Results**

The linear parameters were not different using the two methods, and correlated well for all animals.

**Conclusion 3**: if the ECG signal is noisy and hard to analyze, the use of averaged improves the waves’ detection, but does not modify the parameters of the QT/RR relationship.

**Part 3: How to use QT/RR relation fits**

**Aim**

The use of individual QT/RR relation to correct QT for heart rate takes place in safety pharmacology studies, along with or instead of classic formulas.

**Methods**

Six female cynomolgus monkeys were administered orally with Astemizole (10 mg/kg), a reference QT prolongation inducer, or the vehicle (methylcellulose).

**Results**

As presented in the graph below, QTi resulted in the flattest QT/RR plot.

**Conclusion**: In order to be used efficiently, the individual QR/RR relation must be obtained from long recording periods, so that QT duration can be extrapolated from all RR intervals.

The linear regression fits well with the QT/RR relation in primates and makes its use easier than in dogs.

Although often reproducible, the individual QT/RR relation should be checked once per study, before the administration of the drugs.

**Asteromizole increased the slope of the QT/RR relationship**

**Asteromizole prolonged QT and QT300 when compared to the vehicle.** U waves were present as soon as 30 minutes and up to 10 hours after Astemizole administration.