Clinical QT Assessment: A Case Study in Assessing QT as Part of a DDI Study: Handling Competing Heart Rate Effects

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Michael A. Tortorici, PharmD, PhD
Pfizer, Clinical Pharmacology
Agenda

- Regulatory Position: Review the ICH-E14 Guidance Document
- Review the use of alternative designs (eg, DDI study) as dedicated QT study
- Discuss the importance of the choice of appropriate correction factor when a drug has an effect on heart rate
- Case Study
  - Review handling of ketoconazole as a metabolic inhibitor in a dedicated QT study
- Conclusions
- Q&A
Outline an approach to evaluating drug effects on QT/QTc interval

Due to the inverse relationship to heart rate, the measured QT interval is corrected to a less heart rate dependent value: QTc

“Thorough QT/QTc Study”

- Adequate, well-controlled study with mechanisms to deal with potential bias including:
  - Randomization and blinding
  - Concurrent placebo control group

- Use of a positive control to establish assay sensitivity
  - Mean 5 msec increase in QT/QTc interval

- Conduct of study at therapeutic and supratherapeutic concentrations of the test drug
  - Ensure dose-response and concentration-response relationship
    - Can be assessed by testing more than 1 dose in TQT study
    - Alternatively, can be assessed with increased concentrations with metabolic inhibition during DDI
Supratherapeutic exposures can be achieved through the use of high dose or metabolic inhibition

ICH-E14 Guidance - Analysis

- **Central tendency analysis:**
  - Captures the largest time-based population effect that a drug caused on the QT interval

- **Categorical analysis:**
  - QTc >450, >480, >500 msec
  - Largest $\Delta$QTc of $\geq 30$, $\geq 60$ msec

**Assay sensitivity:**
- Positive control: Mean placebo corrected change from baseline $\sim 5$ msec (i.e. the lower bound of the 95% CI $> 0$ msec)

**Negative study is defined as:**
- The upper bound of the 95% confidence interval must be $< 10$ msec

Concentration-QT analysis

- Concentration-QT analysis:
  - Regulatory reviews typically include characterization of the conc-QT relationship
  - Examples provided of the role of conc-QT analysis in the interpretation of the TQT study
    - Ex. 1: Predict QTc at lower doses not included in the TQT study
    - Ex. 2: Support an argument for no effect on QTc when the study was nominally positive
    - Ex. 3: Assess assay sensitivity for the positive control
  - Determine potential for QTc prolongation when a TQT cannot be performed

Alternative Approaches to a TQT Study: Oncology

Table 1. Thorough QT Study design considerations for anticancer drugs

<table>
<thead>
<tr>
<th>TQT feature per E14</th>
<th>Oncology study feature</th>
<th>Implication for QT risk evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVs</td>
<td>Genotoxin; tolerability</td>
<td>No HVs</td>
</tr>
<tr>
<td>Supratherapeutic exposure required</td>
<td>Presumed therapeutic exposure at maximum tolerated dose</td>
<td>No supratherapeutic exposure</td>
</tr>
<tr>
<td>Positive control drug</td>
<td>Advanced refractory cancer populations</td>
<td>Consider 5 HT-3 inhibitor as positive control or no positive control as appropriate</td>
</tr>
<tr>
<td>Time-matched ECGs; use of placebo and washout period without active treatment</td>
<td>Advanced refractory cancer populations</td>
<td>Extended placebo dosing and washout not acceptable</td>
</tr>
</tbody>
</table>

Use of a DDI as an Alternative to a TQT – Points of Considerations

- Underlying assumption is that the metabolic inhibitor does not have an effect on the QT interval
- Primary endpoint of the study is the difference in baseline adjusted QTc interval between the test drug plus inhibitor and placebo plus inhibitor
- Known inhibitors that do effect the QT interval include:
  - Fluvoxamine (CYP1A2)
  - Fluconazole & amiodarone (CYP2C9)
  - Quinidine (CYP2D6)
  - Ketoconazole (CYP3A4)
- If the metabolic inhibitor has an effect on QT, following the E14 recommended method, the estimate at supratherapeutic concentrations may be biased
  - Presents a PKPD model to describe the concentration-QT relationship

Ketoconazole as an Inhibitor in a DDI QT study

- Ketoconazole is widely used in DDI studies as a potential inhibitor of CYP3A4
- Non-clinical data demonstrates that ketoconazole blocks the hERG channel
- Ketoconazole increases heart rate > 6 bpm
- Clinical data not consistent when assessing the effect of ketoconazole on QT interval:
  - Chaikin et al demonstrated a ~ 7 msec increase in QTc
  - Other reports have conflicting results
    - Robert M et al demonstrated ΔΔQTcB of 2.65 msec
    - Koslogou T et al demonstrate mean change from baseline in QTcB of -1.65 msec

1 Domaine et al. J Clin Pharmacol 2005
3 Chaikin P et al Br J Clin Pharmacol 2005
4 Robert M et al Drug Metab Dispo 2007
Choice of Correction Factor: Standard Approaches

- For drugs that do not affect the heart rate: Commonly used heart rate correction factors (fixed-corrections) using “off-drug” study period data:
  - Fridericia's: $QTc_F = \frac{QT}{RR^\beta}$: where $\beta = 0.33$
  - Bazett's: $QTc_B = \frac{QT}{RR^\beta}$: where $\beta = 0.5$
  - Study Specific correction (QTcS) = $\frac{QT}{RR^\beta}$: where $\beta = \theta$
  - Individual subject specific correction: $\frac{QT}{RR^\beta}$: where $\beta = \theta + \eta$
Choice of Correction Factor: Haloperidol Example

- Haloperidol administered as single 10-mg dose to 16 HV.
- Data was corrected using Bazett’s, Fridericia’s, and Individual Specific methods using placebo period only.
- Haloperidol caused ~7 bpm increase in HR compared to placebo and caused QTc prolongation using three correction methods at 10 hr time point.
- The magnitude of the mean QTc prolongation varied between the three methods used.

**Figure 1: Corrected QT vs RR interval Using Off Drug Data**

**Figure 2: QTc vs Time**

Approaches to Assess QT for Drugs with an Effect on Heart Rate

• Simultaneous Analysis of QT, RR, and Concentration; One-stage approach
  • Based on all ECG readings (“off-drug” and “on-drug”)
  • Can account for drug-induced changes in RR
  • Recommended method when significant effect of test drug on heart rate is observed

• Many other methods
Consequence of Selecting an Inappropriate Correction Factor – Sibenadet Example

- Dual $\beta_2$-adrenoceptor/D$_2$ dopamine receptor agonist
- Mechanistically increases HR

**Objective:** Examine the difference in using the ICH E14 recommended statistical method and PKPD modeling approach

Consequence of Selecting an Inappropriate Correction Factor – Sibenadet Example

• Fixed Correction Factors
  • Corrected QT interval using QTcB, QTcF, QTcS and QTcI
  • Analyzed the data according to the recommended method in the E14 guidance at multiple time-points

• Simultaneous Analysis of QT, RR, and Concentration; One-stage approach
  • Based on all ECG readings (“off-drug” and “on-drug”)
Consequence of Selecting an Inappropriate Correction Factor – Sibenadet Example

Fixed Correction QTcF

ICH E14 statistical method showed a positive QTc prolongation regardless the baseline QTc and correction method selected in the analysis.

Consequence of Selecting an Inappropriate Correction Factor – Sibenadet Example

PK/PD Modeling: Simultaneous Analysis of QT, RR and Conc

Population PK/PD modeling approach allowing the correction factor to change between placebo and active treatments demonstrated no QTc prolongation for sibenadet, consistent with the mechanism of its action and the findings from extensive pre-clinical studies.

Case Study
Drug X: Background

- Under development for the treatment of solid tumors

- Lack of effect on hERG potassium channel current in HEK293 cells
  - >3000-fold safety margin compared to free Cmax achieved at the human starting dose
    - Drug X: 50% inhibition not achieved at the highest concentration tested (i.e., IC_{50} > 1159 ng/mL)
    - Metabolite 1: 50% inhibition for hERG inhibition not achieved (i.e., IC_{50} > 17,000 ng/mL)
    - Metabolite 2: binding affinity (Ki) > 32000 ng/mL indicating lack of binding

- Single-dose dog cardiovascular study
  - No dysrhythmia or change in waveform morphology up to doses of 30 mg/kg
  - No changes in PR interval or QRS interval, or any indication of QT or QTc prolongation
Case Study: Clinical QT Assessment

- “Alternative” to a TQT Study
  - Randomized, 2-way crossover study in healthy volunteers
  - 35 subjects were randomized to receive:
    - Treatment A: Drug X, 5 mg single oral dose on Day 1
    - Treatment B: Ketoconazole, 400 mg oral dose on Days 1-7, with a single oral dose of Drug X 5 mg on Day 4.
  - Triplicate, time-matched ECG assessments were collected 1, 2, and 3 hours post-dose.
  - Patient were randomized as follows:

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Screen Baseline Rand
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<table>
<thead>
<tr>
<th>Placebo</th>
<th>Drug X</th>
<th>Drug X + Keto</th>
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<tbody>
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</table>
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**QT Interval Correction**

Correlation between Corrected Baseline and Placebo Period QT Interval versus RR Interval

**Baseline and placebo “off drug” assessment**

- **Bazett:**
  \[ QT_{cB} = \frac{QT}{(RR/1000)^{0.50}} \]

- **Fridericia:**
  \[ QT_{cF} = \frac{QT}{(RR/1000)^{0.33}} \]

- **Study Specific:**
  \[ QT_{cS} = \frac{QT}{(RR/1000)^{0.44}} \]

Fridericia’s (QTcF) and Bazett’s (QTcB) correction methods did not appear to adequately correct the observed correlation between QT interval and RR interval. QTcF undercorrected, and QTcB slightly overcorrected.

Study-Specific correction factor (QTcS) eliminated the correlation between QT and RR interval.
Standard Methodology: Highest Mean Placebo-Corrected Change from Baseline Using Fixed Correction Factors

<table>
<thead>
<tr>
<th>Correction</th>
<th>Value</th>
<th>Drug X Alone</th>
<th>Ketoconazole Alone</th>
<th>Drug X with keto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fridercia’s (QTcF)</td>
<td>0.33</td>
<td>6.1 (1.8, 10.5)</td>
<td>-5.7 (-8.7, -2.7)</td>
<td>9.1 (6.7, 11.5)</td>
</tr>
<tr>
<td>Bazett’s (QTcB)</td>
<td>0.50</td>
<td>-0.7 (-4.2, 2.8)</td>
<td>4.2 (1.3, 7.1)</td>
<td>4.4 (1.9, 6.9)</td>
</tr>
<tr>
<td>Study-Specific (QTcS)</td>
<td>0.44</td>
<td>2.2 (-1.9, 5.4)</td>
<td>0.7 (-2.2, 3.5)</td>
<td>6.1 (3.7, 6.4)</td>
</tr>
</tbody>
</table>
Concentration-QT Analysis: Traditional Two-Stage Analysis vs. Simultaneous Approach

Fixed Correction Factors

\[ QTcX_{ij} = \theta_1 + (\theta_2 \cdot \text{SEX}) + \eta_i^{(1)} + (\theta_3 + \eta_i^{(2)})\text{CONC}_{ij} + \epsilon_{ij} \]

Simultaneous analysis of QT, RR and concentration:

\[ \Delta\Delta QT_{ij} = (\theta_{\text{slope}} + \eta_i^{(1)}) \cdot \text{CONC}_{ij} \cdot ((RR/1000)^{\theta_\beta} + \eta_i^{(2)}) + \epsilon_{ij} \]
Concentration-QT Analysis: Traditional Two-Stage Approach

Drug X Alone:
Slope: 0.0008 (-0.06, 0.076)

Drug X alone + Drug X in presence of Ketoconazole
Slope: 0.0427 (0.017, 0.069)
Assessment of the Ketoconazole Effect on Heart Rate

- Used ketoconazole parameter estimates (with variability) reported in literature; based on analysis from 5 studies involving oral administration of single and multiple doses (100-800 mg).
- A 3-compartment model with first order absorption used to simulate ketoconazole concentrations at 1, 2, and 3 hr post dose to match ECG collections on ketoconazole alone treatment.

Chien JY et al Drug Disp Metab 2006
Effect of Drug X and Ketoconazole on Heart Rate

- Drug X decreases HR; max 5 bpm, which is consistent with nonclinical evaluations.
- Ketoconazole alone increases HR; (max 11 bpm), consistent with previous reports.

### Linear mixed effect modeling of RR vs Concentration

<table>
<thead>
<tr>
<th>Period</th>
<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X Alone</td>
<td>Slope (msec/ng/mL)</td>
<td>2.28</td>
<td>(1.46, 3.10)</td>
</tr>
<tr>
<td>Ketoconazole Alone</td>
<td>Slope (msec/ug/mL)</td>
<td>-16.2</td>
<td>(-19.6, -12.8)</td>
</tr>
<tr>
<td>Drug X plus Ketoconazole</td>
<td>Slope (msec/moles)</td>
<td>1.14</td>
<td>(0.715, 1.57)</td>
</tr>
</tbody>
</table>
Placebo-Corrected QTc Interval versus Concentration

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<th>Parameter</th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug X Alone</td>
<td>Slope (msec/ng/mL)</td>
<td>-0.0314</td>
<td>-0.068, 0.005</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>0.472</td>
<td>0.421, 0.523</td>
</tr>
<tr>
<td>Ketoconazole Alone</td>
<td>Slope (msec/ng/mL)</td>
<td>-0.331</td>
<td>-0.860, 0.198</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>0.401</td>
<td>0.362, 0.440</td>
</tr>
<tr>
<td>Drug X + Ketoconazole</td>
<td>Slope (msec/ng/mL)</td>
<td>0.0725</td>
<td>0.045, 0.101</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>0.425</td>
<td>0.385, 0.465</td>
</tr>
</tbody>
</table>

- Lack of effect of Drug X concentrations on the QT interval for Drug X alone treatment arm
- When Drug X was administered in the presence of ketoconazole, the slope of the line was different from zero
Comparison of Fixed Correction vs. Simultaneous Modeling of RR, QT and Conc–Simulation of Drug X (at the mean Cmax)

QTcB

Median -2.5 msec

QTcF

Median 1.61 msec

QTcS

Median 0.46 msec

Simultaneous

Median -1.58 msec
Comparison of Fixed Correction vs. Simultaneous Modeling of RR, QT and Conc – Simulation of Ketoconazole (at the mean Cmax)

**QTcB**

- Median 2.67 msec

**QTcF**

- Median -6.46 msec
- Observed Mean: -5.7

**QTcS**

- Median 2.69 msec

**Simultaneous**

- Median -2.49 msec
- Observed: -2.76
Comparison of Fixed Correction vs. Simultaneous Modeling of RR, QT and Conc – Drug X + Ketoconazole (at the mean Cmax)

- **QTcB**: Median 3.06 msec
- **QTcF**: Median 8.19 msec
- **QTcS**: Median 1.60 msec
- **Simultaneous**: Median 5.70 msec

Observed values:
- **QTcB**: 4.4 msec
- **QTcF**: 9.1 msec
- **QTcS**: 6.1 msec
- **Simultaneous**: 6.46 msec
Conclusions

- Drug interaction studies can be used in a dedicated QT study to achieve supratherapeutic concentrations.
- An understanding of the effects of the metabolic inhibitor on both QT and RR intervals is critical to accurately interpret the data.
- Consider collecting time-matched concentrations of the metabolic inhibitor.
- Many methods to correct the QT interval when the drug has an effect on heart rate.
  - Special consideration in the design of the study will allow for ease of implementation of these methods.
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  • Ana Ruiz-Garcia, PharmD, PhD
  • Brett Houk, PhD
  • Yazdi Pithavala, PhD
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