Comparison of Analysis Methods for Population Exposure-Response in Thorough QT Studies

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OBJECTIVE
To compare two approaches for evaluating the relationship between drug concentrations and QTc interval.

INTRODUCTION
Citalopram (CT) is a racemic mixture of an R-enantiomer (R-CT) and an S-enantiomer (S-CT), the latter is oxidocitalopram (ESC). ESC is responsible for the highly selective serotonin reuptake inhibition associated with CIT. ESC is an approved medication (Lexapro®) for the treatment of major depressive disorders. Both CIT and ESC have been approved and marketed in the US and EU for the treatment of depression. The work described herein focuses on the analyses of thorough QT (TQT) studies for CIT and ESC conducted in accordance with the ICH E14 guidance. While the Union-Intersection Test (UIT) [1] (a hypothesis-test approach to inference) remains the primary endpoint in TQT studies, (including the studies shown here), pharmacometrics [2-5] have demonstrated the multiple comparison bias and inefficiency of the UIT approach in contrast to a population modeling-exposure-response approach. Two approaches to exposure-response analysis are commonly used for concentration-QTc data:

- "Method #1" - Relating the derived plasmo-adjusted change from baseline QTc to observed plasma concentrations (favorable by US FDA IRT-QT)[3]
- "Method #2" - Relating the QTc to plasma concentrations predicted from a population PK (PPK) model, with additional terms for baseline, placebo effect, and covariates [5]

Both approaches have been applied independently for the TQT studies of CIT [6] and ESC. The details of these two studies are previously published [7,8].

DATA
Both studies had the same design: a multicenter, randomized (stratified by sex), double-blind, placebo-controlled, crossover, multiple dose study in normal adult volunteers to assess the effects on cardiac repolarization following a therapeutic treatment of depression. Both studies had the same design: a multicenter, randomized (stratified by sex), double-blind, placebo-controlled, crossover, multiple dose study in normal adult volunteers to assess the effects on cardiac repolarization following a therapeutic treatment of depression. For CIT and ESC conducted in accordance with the ICH E14 guidance. Figure 1. CIT TQT Study: Observed concentrations with PK model [bottom] and diagnostic plots for the population PK model [top].

METHODS
The methods for individual correction was pre-specified in the study protocol and therefore not part of the exposure-response analysis. QTcNi was calculated using the following 2 steps:
1. For each subject, all predose QT and RR data were fitted to the linear regression model:
   \[ QTCi = a + b \times \log (\text{Cmax}) \]
   where \( a \) is the intercept and \( b \) is the slope.
2. The estimated subject-specific slope \( \beta \) serving as the individual correction parameter, was used to calculating QTcNi as follows:
   \[ \text{QTcNi} = QTCi - \beta \times \log (\text{Cmax}) \]

Drug Effect Model Method #1 - "delta-delta" model

\[ \Delta QTC = \frac{\text{QTc predicted} - \text{baseline QTc}}{\text{QTc predicted} + \text{baseline QTc}} \]

\[ \Delta QTC = \text{intercept} + \text{slope} \times \log (\text{Cmax}) + \text{error} \]

Options - based on AUC and BIC criteria:
- Intercept estimated at population and individual level
- Population typical value of intercept fixed to zero
- No intercept at population or individual level

Drugs Effect Model Method #2 - "covariate" model

\[ \text{QTc} = \text{intercept} + \text{slope} \times \log (\text{Cmax}) + \text{error} \]

Population PK

The goal of the PPK modeling was to predict individual plasma concentration levels in order to simulate the population-typical value of intercept fixed to zero (90% CI) QTc change of 6.6 ms (5.3, 7.9) [6], but the covariate approach estimated 8.3 ms (7.5, 9.2). For both studies, the "delta-delta" method utilized log concentrations as the predictor, with a model form that included an intercept estimated at the population and individual level (9). For both studies, the delta-delta method provided a QTc prolongation. At a 20 mg dose, the delta-delta approach estimated a mean (90% CI) QTc change of 6.4 ms [5, 7, 9], but the covariate approach estimated 8.3 ms (7.5, 9.2).

RESULTS

Population PK

<table>
<thead>
<tr>
<th>CITrazoline (20 mg)</th>
<th>Citalopram (60 mg)</th>
<th>Citeopram+R-Citeopram (20 mg)</th>
<th>Citeopram+R-Citeopram (60 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcNi (ms)</td>
<td>7.8 (6.2, 9.3)</td>
<td>8.2 (6.5, 10.4)</td>
<td>8.5 (6.2, 10.8)</td>
</tr>
<tr>
<td>CITrazoline (40 mg)</td>
<td>12.6 (10.9, 14.3)</td>
<td>12.5 (10.3, 15.6)</td>
<td>Not possible</td>
</tr>
<tr>
<td>CITrazoline (60 mg)</td>
<td>18.0 (16.4, 19.7)</td>
<td>18.5 (16.9, 20.3)</td>
<td>Not possible</td>
</tr>
</tbody>
</table>

For both studies, the "covariate" method found an Emax model appropriately described the exposure-response relationship (the pattern in Figure 5 was confirmed by a statistically significant improvement in model fit seen with an Emax model versus a linear model). No additional improvement in the fit was found via incorporation of the metabolite data (Figure 4). For both the CIT study, both approaches gave similar mean predictions of drug-related prolongation, but with different confidence intervals (Table 1). For the ESC study, the two approaches gave different predictions of drug-related prolongation (Figure 4).

Conclusions:

- Both exposure-response approaches gave a basis for (a) showing the additional prolongation expected from CIT relative to ESC and (b) estimating the prolongation expected at intermediate dose, but the approaches were not in full agreement.

Modeling QTc directly using the covariate approach may provide a more physiologically relevant model for predictions across the full concentration range, whereas the delta-delta method provided an estimate of reduced QTcNi at zero concentrations of CIT that is not physiologically meaningful. In contrast, the delta-delta approach may be computationally less intensive. While both approaches avoid the multiple comparison bias and inefficiency of the Intersection Union Test commonly used in I14-standard TQT studies, they may provide different results. Additional validation work is recommended in comparing the relative merits of each CIT-QT approach.

REFERENCES


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Figure 1. CIT TQT Study: Observed concentrations with overlaid model-typical lines (Day 9 is therapeutic dose, Day 22 is supratherapeutic dose)

Figure 2. ESC TQT Study: Observed concentrations with overlaid model-typical lines (Day 9 is therapeutic dose, Day 22 is supratherapeutic dose)

Figure 3. CIT TQT Study: Observed concentrations with overlaid model-typical lines (Day 9 is therapeutic dose, Day 22 is supratherapeutic dose)

Figure 4. CIT TQT Study: Observed concentrations with overlaid model-typical lines (Day 9 is therapeutic dose, Day 22 is supratherapeutic dose) (top); model diagnostic plots for the population PK model (bottom)

Figure 5. Change in QTc Interval Due to Additive Effects of S-CT and R-CT in CIT TQT Study Compared to S-CT Alone in S-CT TQT Study

CONCLUSIONS
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