

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 (CIT) is a racemic mixture of an R-enantiomer (R-CT) and an S-enantiomer (S-CT), the latter is escitalopram (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 USA 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), pharmacometricians [2,3,4] 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 placebo-adjusted change from baseline QTc to observed plasma concentrations (favored 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 dosage and a supratherapeutic dosage compared with placebo and an active control (single 400 mg oral dose of moxifloxacin). Individual serial time-matched ECGs of QT/QTc intervals were extracted from Holter data which was collected for 24 hours after dosing on dedicated ECG days. PK sampling was performed for each subject at each ECG timepoint for S-CT, R-CT, and their respective inactive metabolites, S-demethyl-citalopram (S-DCT) and R-demethyl-citalopram (R-DCT).

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

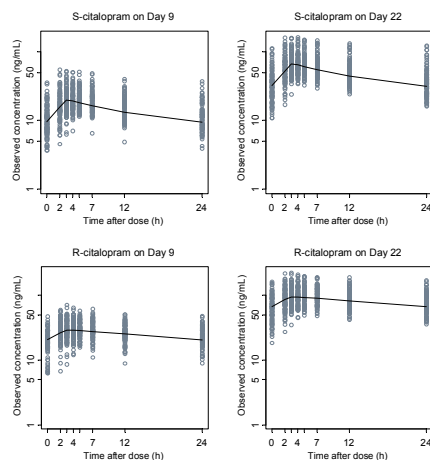
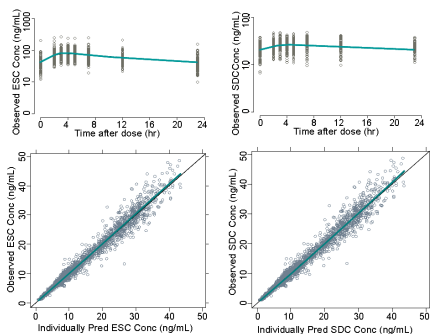


Figure 2. ESC TQT Study: Observed concentrations with overlaid model-typical lines (Day 22-supratherapeutic dose) [top]; model diagnostic plots for the population PK model [bottom]



METHODS

The method 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,

$$QT = a_i + b_i \times RR + \text{error},$$

where a_i is the intercept and b_i is the slope

2. The estimated subject-specific slope b_i , serving as the individual correction parameter, was used in calculating QTcNi as follows:

$$QTcNi_j = QT + b_i (1 - RR)$$

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

$$\Delta\Delta QTc = \text{intercept} + \text{slope} \times C_{p,obs} + \text{error}; \text{ OR}$$

$$\Delta\Delta QTc = \text{intercept} + \text{slope} \times \log(C_{p,obs}) + \text{error}$$

Options – based on AIC 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

Drug Effect Model Method #2 - "covariate" model

Population PK

The goal of the PPK modeling was to predict individual plasma concentration levels of S-CT, R-CT, S-DCT, and R-DCT at the times the ECG measurements were taken. The PPK analyses for all four compounds followed similar steps: an exploratory analysis of model relationships was followed by the selection of an appropriate structural model (1-, 2-, and 3-compartment structural models), followed by the addition of significant covariates to the structural model. When appropriate, exponential error models were used to estimate intersubject variability on PK parameters. Additive, proportional, or a combination of the 2 error models were used to model the residual variability. The FOCE estimation method with interaction in NONMEM™ (version VI) was used to build the population PK models.

For S-DCT and R-DCT, the metabolites' concentrations were each modeled using a disposition model, parameterized with clearances and volumes of distribution, with first order absorption. The doses for S-DCT and R-DCT were set to typical values of 0.3 and 0.5 times of the dose of S-CT and R-CT, respectively, based on the ratio between the mean steady state concentrations of parent and metabolite observed in this study. Inter-occasion variability was included on these ratios.

Exposure-Response

$$QTc = \text{baseline} + \text{placebo effect} + \text{drug effect} + \text{error}$$

Model building proceeded stepwise:

- Develop a model for baseline data in order to assess the influence of subjects' demographics and circadian rhythm (time using "truncated Fourier series",

$$\text{Amplitude} \times \cos\left(\left[\text{time} + \text{acrophase}\right] / (2 \times \pi \times 24/n)\right),$$

where, $n = 1, 2, \dots$ as supported by the data

- Add placebo data and investigate the presence of additional circadian rhythm on the placebo effect,

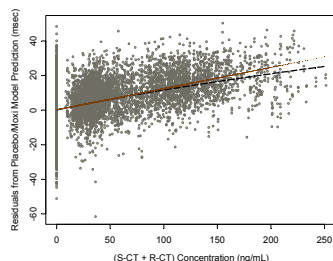
- Incorporate treatment data into the model to assess the drug effect :

$$\text{Drug Effect} = b \times C_p; \text{ OR}$$

$$\text{Drug Effect} = E_{\max} \times C_p / (EC_{50} + C_p),$$

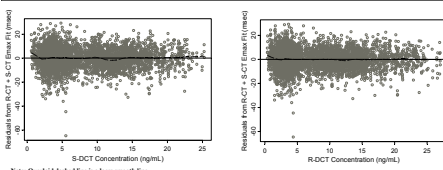
- A possible delay or hysteresis between plasma drug concentrations and QTcNi drug effect was assessed, as well as any residual signal associated with metabolite levels independent of parent.

Figure 3. Covariate Model: Plotting citalopram (S-CT + R-CT) concentrations vs. residuals from a model prior to the addition of a citalopram term showed a sublinear trend for the C-QTc relationship



Note: Solid line is a simple linear fit with zero-intercept. Overlaid dashed line is a bessel smooth line.

Figure 4. Residuals from applying Covariate Model relating QTcNi to R-CT + S-CT concentrations do not correlate with metabolite concentrations (S-DCT and R-DCT)



Note: Overlaid dashed line is a bessel smooth line.

RESULTS

Population PK

Observed concentrations for each study are shown in Figures 1 and 2. The population PK models for all compounds performed adequately, with clear concordance between observed data and individual model predictions (Figure 2, bottom, shows results for ESC study). A full presentation of the population PK results has been published previously. [7,8]

Exposure-Response

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 [6]. For both studies, the delta-delta analysis approach yielded models with population median intercepts that excluded zero [9] (e.g., -19.6 ms for CIT), which would be physiologically unlikely (i.e., indicate QTc shortening at low concentrations).

For both studies, the "covariate" method found an Emax model appropriately described the exposure-response relationship (the pattern in Figure 3 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 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 (mean and 90% CI) of drug-related QTc prolongation. At a 20 mg dose, the delta-delta approach estimated a mean (90% CI) QTc change of 6.6 ms (5.3, 7.9)[6], but the covariate approach estimated 8.3 ms (7.3, 9.2).

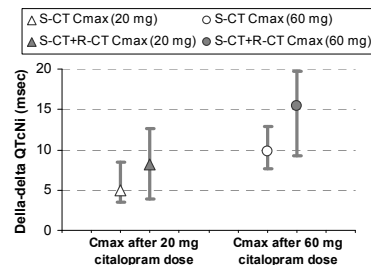
Table 1. Max Mean QTcNi Change (ms, 90% CI), CIT Study

Citalopram Dose	Delta-delta Method [6]	Covariate Method	ICH E14 Analysis [6]
20 mg	7.8 (6.2, 9.3)	8.2 (6.5, 10.4)	8.5 (6.2, 10.8)
40 mg	12.6 (10.9, 14.3)	12.5 (10.1, 15.6)	Not possible
60 mg	16.0 (14.0, 18.1)	15.5 (12.2, 19.7)	18.5 (16.0, 21.0)

Note: QTcNi change estimates are from simulation at Cmax. Typical Cmax for delta-delta was the observed median individual Cmax for each dose, with linear interpolation for 40 mg.

The additional model-estimated prolongation observed in the CIT study versus the ESC study, at equivalent concentrations of S-CT, is postulated to be related to R-CT (Figure 5). Since the pharmacologic effect of CIT in depression is primarily due to S-CT, the outcome of this study suggests a higher risk of QTc prolongation with CIT treatment compared with S-CT without additional clinical benefit.

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

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 an 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 E14-standard TQT studies, they may provide different results. Additional validation work is recommended in comparing the relative merits of each C-QT approach.

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