Simulation Study on a Method for PK-QT Analyses When Several Active Compounds or Metabolites Are Present

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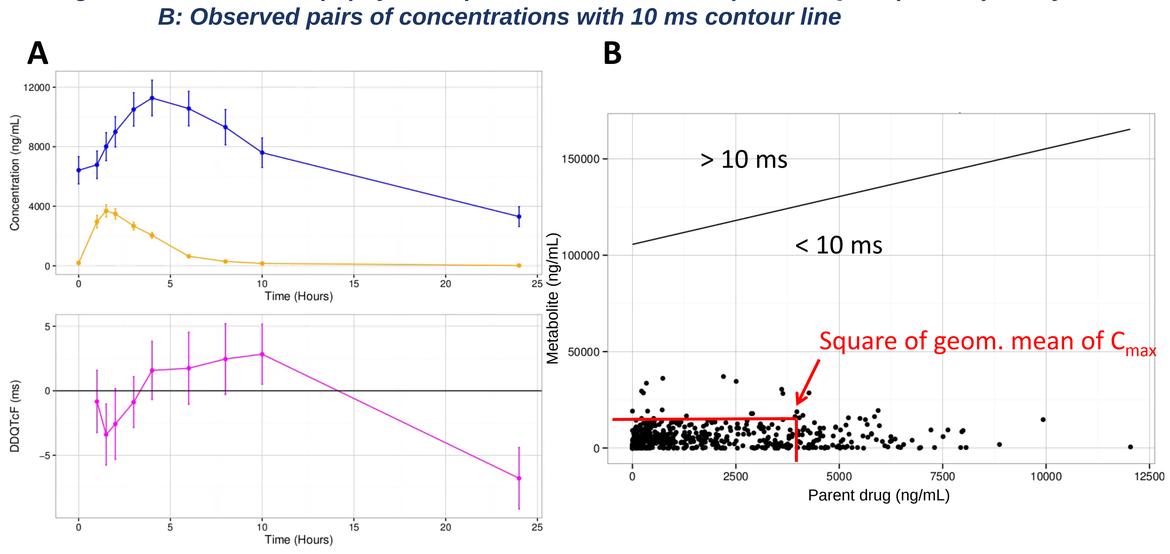
Motivating Example

- QT study: single sequence and single dose with placebo on day -1 and study drug on days 1 to 8 (= steady state of parent drug).
- ΔΔQTcF interval increased by 3-5 ms between days 8 and 1
- Initial plan: separate exposure-response analyses for parent and metabolite.
- Exploratory data analysis showed that maximum QT effect occurred several hours after t_{max} for parent (2h) and metabolite (8h, see Figure 1A). At the same time there was drop in QT effect at t_{max} of parent.
- A different approach to characterize exposure-response is needed.

Objectives

- Characterize QT-response as joint function of parent and metabolite concentration.
- Develop a statistically sound method (including type I error control) for PK-QT analysis when jointly modeling the impact of several active compounds.
- Conduct simulation to understand the operating characteristics of the proposed procedure

Figure 1. ***A: Mean conc.(top; yellow=parent, blue=metabolite) and ΔΔQTcF (bottom) at day 8***
B: Observed pairs of concentrations with 10 ms contour line



Methods

Statistical model

- Primary endpoint "change from time-matched" baseline (ΔΔQTc) includes linear term for each compound and random subject effect:

$$\Delta\Delta QTc_{lkt} = \vartheta_1 C_{1,dkt} + \vartheta_2 C_{2,dkt} + U_{kt} + \epsilon_{dkt}$$

d = day 1 or day 8, k = subject, t = time point, $C_{i,lkt}$ = concentration of compound i = 1,2 for subject k on day d at time point t, ϑ_i = slope parameters, U_{kt} = random effect for subject k at time point t, ϵ_{lkt} = residual noise.

- When using endpoint "change from mean baseline" (ΔQTc) and placebo group, a term p_t for the diurnal variation would need to be added.
- Other factors or interaction terms can be added as well.

Basic Statistical Analysis

- A drug is considered "safe" if the QT effect is < 10 ms for (pairs of) concentrations which are smaller than the respective C_{max} values $C_{1,max}$ and $C_{2,max}$ for the two compounds (Figure 1B).
- Graphically summarized by the estimated contour lines $x = \hat{\vartheta}_1 C_1 + \hat{\vartheta}_2 C_2$: corresponding to our model the contour lines corresponding to values $x \geq 10\ ms$ should be outside the square defined by respective C_{max} values (see Figure 1B)
- The estimates $\hat{\vartheta}_1$ or $\hat{\vartheta}_2$ for the unknown parameters ϑ_1 and ϑ_2 were obtained using the lme() function from R (version 3.0.2)
- A formal statistical test involves the null-hypothesis

$$H_0: max_{C_1 \leq C_{1,max}, C_2 \leq C_{2,max}} (\vartheta_1 C_1 + \vartheta_2 C_2) \geq 10$$

A Bootstrap Hypothesis Test

- Generate boostrap copies of the data by randomly drawing the observations of entire subjects (concentrations $C_{1,lkt}$, $C_{2,lkt}$, and $\Delta\Delta QTc_{lkt}$)
- Obtain bootstrap copies $\hat{\vartheta}_j^{[b]}$ of the slope estimates and bootstrap copies $\hat{C}_{j,max}^{[b]}$ of the estimated C_{max} values for both compounds (j = 1,2)
- For each boostrap copy b=1, ..., B check if 10 ms boostrap contour line crosses/touches the estimated null-hypothesis space :

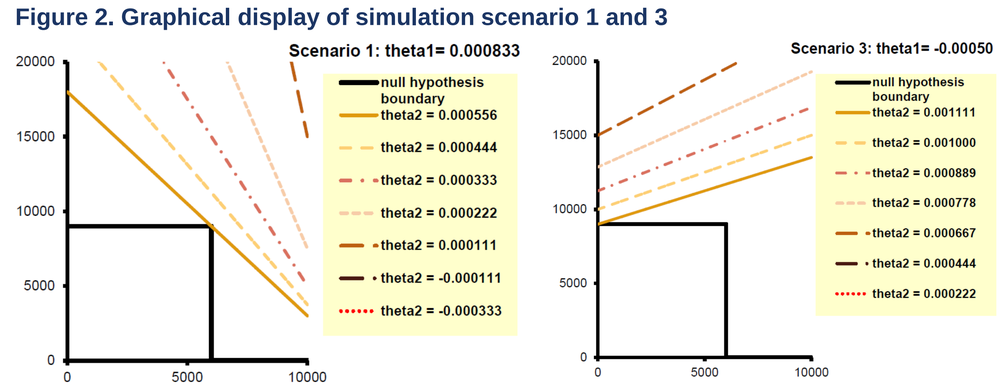
$$max_{C_1 \leq \hat{C}_{1,max}^{[b]},\ C_2 \leq \hat{C}_{2,max}^{[b]}} (\hat{\vartheta}_1^{[b]} C_1 + \hat{\vartheta}_2^{[b]} C_2) \geq 10$$

- Reject H_0 if this happens in less than 5% of the bootstrap copies.

Simulations

- Parallel group thorough QTc trials with placebo group (l=0) and two dose groups of the drug under test (l=1,2) were simulated; sample size per group varied between K = 20, K = 50, and K = 100 per group.
- Diurnal variation and mean concentrations for the two compounds used in the simulation study were taken from the real data example. The high dose group corresponded to a multilple (φ = 2 to 5) of the observed concentrations.
- Patient specific concentrations were generated by multiplying potentially correlated random subject effects and random noise to the time-dependent mean vectors of the two compounds.
- The mean concentrations of the two compounds also provided the "true" underlying C_{max} values (called $C_{j,max}$) for the simulations.
- A simulation scenario consisted of 7 pairs of slopes $(\vartheta_1, \vartheta_2)$. These pairs were selected to provide a maximum effect of 10 ms (9,8,7,6,5, and 2) on the concentration range defined by the "true" underlying C_{max} values $C_{j,max}$.(Figure 2)

Figure 2. Graphical display of simulation scenario 1 and 3

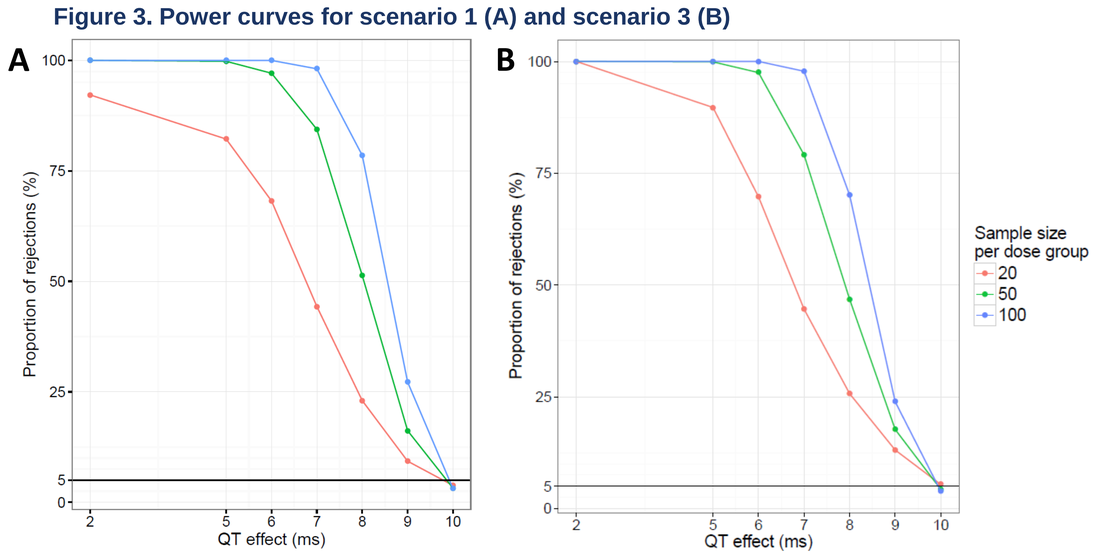


- The graphs show the 10 ms contour lines $(10 - \vartheta_1 C_1)/\vartheta_2$ for each subscenario
- The null hypothesis space is defined by the true underlying Cmax values
- The parameter values are calculated such that the maximum QT effect on the null hypothesis space equals 10, 9, 8, 7, 6, 5 and 2 ms

- QT effects were calculated using these parameters and the simulated concentrations, adding a further patient specific random effect and noise.
- For each scenario we conducted S = 1000 simulations with B = 1000 bootstrap runs. The results of the scenarios are summarized by power curves presenting the proportion of simulations which reject the null-hypothesis.

Results

Figure 3. Power curves for scenario 1 (A) and scenario 3 (B)



Conclusions

- The simulation study demonstrated that the type I error is adequately controlled in all tested scenarios (some of which are presented in Figure 3).
- As expected, power increases with sample size.
- For small sample sizes (as realistic for data pools of phase I trails), the power seems reasonable.

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