Journal of Pharmacokinetics and Pharmacodynamics (2025) 52:31
https://doi.org/10.1007/s10928-025-09975-6

ORIGINAL PAPER

Beyond the linear model in concentration-QT analysis

Géraldine Cellière[1] · Andreas Krause[1] · Guillaume Bonnefois[1] · Jonathan Chauvin[1]

Received: 27 February 2025 / Accepted: 15 April 2025

Abstract
The white-paper regression model is the standard method for assessing QT liability of drugs. The quantity of interest, placebo-corrected QTc change from baseline (ΔΔQTc) with corresponding confidence interval (CI), is derived from the difference in model-estimated ΔQTc for active compound and placebo in a linear model. Model assumptions include linearity and no time delay between change in concentration and change in ΔQTc. Alternative models are commonly not considered unless there is a clear indication of inappropriateness of the assumptions. This work introduces several extensions for concentration-QT modeling in a pharmacometric context. The model is formulated as linear drug-effect model with treatment, nominal time, and centered baseline as covariates on the intercept. This approach enables straightforward use of other concentration-ΔQTc relationships, including loglinear, E_{max}, and indirect-effects models. In addition, the setup allows for the use of pharmacometric model assessments for ΔQTc and ΔΔQTc, including visual predictive checks and quantitative model comparison based on the Bayesian information criterion. The proposed approach is applied to several compounds from a previously published QTc study. The results suggest that a nonlinear mixed-effects model for ΔΔQTc and comparing a set of candidate models quantitatively can be a more powerful approach than fitting only the white-paper regression model. A semi-automated approach that compares nonlinear and hysteresis models to the linear model enables a reliable choice of the best model and determination of the degree of prolongation at the concentration of interest. Standard pharmacometric tools can assess the appropriateness of the models and the potential extent of hysteresis.

Keywords Concentration-QT · Hysteresis · Population PK/PD · QT interval · TQT

Introduction

The white-paper regression model [1] is the de facto standard modeling method for assessment of the QT liability of a drug. One of the aims of the suggested model is to enable QT effect characterization from entry-into-man studies and not necessarily from more complex thorough QT (TQT) studies. While TQT studies typically follow a cross-over design with placebo administration, single- and multiple-ascending dose studies common in entry-into-man studies are usually not cross-over studies and frequently do not have placebo administration, e.g., in oncology.

Modeling change from baseline in QTc (ΔQTc) can be applied to data with and without placebo data, and if placebo data are available, the white-paper model allows for the derivation of the placebo-corrected change from baseline in QTc (ΔΔQTc). A mixed-effects linear regression model is suggested to relate ΔQTc to drug concentration. The quantity of interest, ΔΔQTc, is derived from the difference of the ΔQTc regression model fits for active drug and placebo with corresponding confidence interval (CI). Key assumptions, suggested to be verified, include linearity of the concentration-effect relationship and a direct effect (change in concentration immediately results in change in effect, i.e.., ΔQTc, without any delay). Unless visual diagnostics suggest that these assumptions might not hold, the linear direct-effect model is employed for all further inferences. Nonlinear concentration-QT relationships [2–5] and delayed effects (hysteresis) [5–7] occur in practice, suggesting that a systematic evaluation of alternative models can improve the model fit. Population pharmacokinetic/pharmacodynamic (PK/PD) models provide an alternative to the statistical regression model [2, 8].

✉ Géraldine Cellière
geraldine.celliere@simulations-plus.com

[1] Clinical Pharmacology and Pharmacometrics, Simulations Plus, Inc., PO Box 12317, Research Triangle Park, NC 27709, USA

Published online: 10 May 2025

This work derives a pharmacometric modeling approach to investigate all candidate models in an integrated fashion. The model is reformulated as a pharmacometric model. On one hand, the structural model (i.e.. drug-effect model) describes ΔQTc by an intercept and a slope on concentration. On the other hand, the statistical model defines the inter-individual variability including random effects and covariate effects (nominal time, treatment, and centered baseline on the intercept). This model reformulation allows for straightforward implementation of a wide class of models in a pharmacometric context, including linear, loglinear, maximum pharmacologic effect (E_{max}), and indirect-effect models. The models differ only in the structural model. This approach facilitates quantitative model comparison between, eg, a linear and an E_{max} model or a direct-effect and an indirect-effect model, using pharmacometric tools such as the visual predictive check (VPC) [9] and the Bayesian information criterion (BIC) [10]. Based on this model formulation, different models are fitted for ΔQTc and for ΔΔQTc directly and compared with respect to parameter estimates and upper limits of the 2-sided 90% CIs (equivalent to one-sided 95% CIs).

A general workflow is suggested, consisting of: (1) fitting of a set of candidate models, (2) determination of the best-fitting model based on the corrected Bayesian information criterion (BICc), (3) hysteresis assessment, and (4) goodness-of-fit assessment based on VPCs for ΔQTc versus time as well as ΔQTc versus drug concentration. The methods are developed and illustrated with applications to four datasets with different characteristics. An R package to apply these steps in an automated fashion and generate a report is provided as supplementary material.

Methods

The following section defines the model as a structural model and a statistical model with covariates to subsequently introduce other structural models with direct and indirect effect.

Pharmacometric modeling

Standard model for ΔQTc

The white-paper model is defined as:

with i denoting the subject, j the treatment (j = 1 for active or j = 0 for placebo), k the nominal time, Θ_0 the population mean intercept at concentrations of 0, Θ_1 the treatment effect ($TRT_j = 0$ indicates placebo and $TRT_j = 1$ active drug), Θ_2 the population average slope of the linear association between concentration and ΔQTc, $C_{i,j,k}$ the concentration for subject i in treatment j at time k, $\Theta_{3,k}$ the fixed effects associated with each nominal time (as categorical variables), Θ_4 the fixed effect associated with the centered baseline, $QTc_{i,j,k=0} - \text{mean}(QTc_{i,j,k=0})$ the baseline centered by the mean over all individuals i and treatments j, and $\eta_{0,i}$ and $\eta_{2,i}$ the inter-individual variabilities (random effects) associated with intercept (Θ_0) and slope (Θ_2), respectively [1].

The baseline-corrected QTc (ΔQTc) interval duration can be derived in many ways from the QTc observations depending on the study design. The baseline may be a single measurement of QTc prior to start of treatment. However, because of known circadian variation in electrocardiogram (ECG) parameters, a common approach is to collect a full 24-h cycle of QTc measurements prior to treatment start and subsequently derive time-matched changes from baseline within each study participant. If 24-h profiles were not collected and a placebo group exists, time matching with 24-h average placebo QTc may be considered.

Pharmacometric formulation of the standard model for ΔQTc

The white-paper model can be rewritten to have two components, the structural model (i.e.. the drug effect model) and the statistical model (i.e.. inter-interindividual variability with random effects and covariate effects). The structural linear model defines the ΔQTc prediction from the individual parameters that comprise the intercept $\Theta_{0,i}$ (ie, the effect at drug concentrations of 0) and the slope $\Theta_{2,i}$ (ie, the change in ΔQTc with a change of 1 concentration unit).

$$\textit{Structural model}: \Delta QTc_{i,j,k} = \Theta_{0,i} + \Theta_{2,i} * C_{i,j,k} \quad (1)$$

Intercept $\Theta_{0,i}$ and slope $\Theta_{2,i}$ vary between individuals and are assumed to follow a normal distribution within the population. In addition, treatment (TRT_j), time ($TIME_k$), and centered baseline ($BL_{cent,i,j} = (QTc_{i,j,k=0} - \text{mean}(QTc_{i,j,k=0}))$) are formulated as covariates on the intercept. The covariates are

$$\Delta QTc_{i,j,k} = \left(\Theta_0 + \eta_{0,i}\right) + \Theta_1 * TRT_j + \left(\Theta_2 + \eta_{2,i}\right) * C_{i,j,k} + \Theta_{3,k} * TIME_k + \Theta_4 * \left(QTc_{i,j,k=0} - \text{mean}\left(QTc_{i,j,k=0}\right)\right)$$

contained in the dataset. TRT_j is an indicator variable with values 0 for placebo and 1 for active treatment (any dose). $TIME_k$ is a categorical covariate (i.e.. factor) for each nominal time. The $BL_{cent,i,j}$ is derived from the baseline measurements per subject and treatment.

Statistical model:

$$\Theta_{0,i} = \Theta_{0,pop} + \eta_{0,i} + \Theta_1 * TRT_j + \Theta_4 * BL_{cent,i,j} + \Theta_{3,T1} * I(TIME = T1) + \Theta_{3,T2} * I(TIME = T2) + \ldots \quad (2)$$

$$\Theta_{2,i} = \Theta_{2,pop} + \eta_{2,i} \quad (3)$$

$\Theta_{0,pop}$ and $\Theta_{2,pop}$ denote the typical values of intercept and slope in the population of individuals, $\eta_{0,i}$ and $\eta_{2,i}$ denote the random effects, ie, the inter-individual variability (IIV). Θ_1 denotes the treatment effect, Θ_4 the baseline effect, and $\Theta_{3,k}$ the effect of each nominal time (the first nominal time, T0, is excluded, representing the reference factor level). The function I(.) denotes the indicator function that is 1 if the condition (.) is true and 0 otherwise.

Substituting Eqs. (2) and (3) into (1), the full model is given as:

$$\begin{aligned}\Delta QTc_{i,j,k} = {} & (\Theta_{0,pop} + \eta_{0,i}) + (\Theta_{2,pop} + \eta_{2,i}) * C_{i,j,k} \\ & + \Theta_1 * TRT_j + \Theta_{3,T1} * I(TIME = T1) \\ & + \Theta_{3,T2} * I(TIME = T2)... + \ldots + \Theta_4 * BL_{cent,i,j}\end{aligned}$$

Confidence interval derivation

The quantity of interest is the estimated mean ΔΔQTc (calculated as $\Delta\Delta QTc = \Delta QTc_{i,j=1,k} - \Delta QTc_{i,j=0,k} = \Theta_1 + \Theta_{2,pop} * C$) at concentrations of interest, such as the maximum concentration (C_{max}) at steady state with the anticipated therapeutic dose. Confidence intervals for the linear model can be derived in closed form using the standard errors of the estimated Θ_1 and $\Theta_{2,pop}$ parameters [1]. For nonlinear structural models, confidence intervals for ΔΔQTc can be derived by sampling population parameters (eg, Θ_1 and $\Theta_{2,pop}$) from their uncertainty distribution given by the standard errors and the correlation matrix of the estimates (or equivalently the variance–covariance matrix). For each set of sampled values and concentration of interest, the corresponding ΔΔQTc is calculated. The confidence interval limits are estimated using the 5th and 95th percentiles of the model-predicted ΔΔQTc for each concentration, i.e., pointwise.

Modeling ΔΔQTc

Instead of modeling ΔQTc and deriving ΔΔQTc from ΔQTc for active and ΔQTc for placebo, ΔΔQTc can be modeled directly if placebo data are available. ΔΔQTc is defined as $\Delta\Delta QTc = \Delta QTc_{i,j=1,k} - \Delta QTc_{i,j=0,k.}$ With the intercept ($\Theta_{0,pop} + \eta_{0,i}$) and nominal time terms, $\Theta_{3,T1}$*I(TIME = T1) + $\Theta_{3,T2}$*I(TIME = T2) + …, being identical for active and placebo treatment, these terms cancel out. With TRT = 1 for active and TRT = 0 for placebo, the parameter Θ_1 denoting the treatment effect for ΔQTc becomes the intercept for ΔΔQTc (without random effects). For the centered baseline covariate, the difference between centered baselines of the treatment and the placebo group can be regrouped into a single term with a new covariate: $BL_{cent,AdjPl,i} = BL_{cent,i,j=1} - BL_{cent,i,j=0}$.

The full model is:

$$\begin{aligned}\Delta\Delta QTc_{i,k} = {} & \Theta_{1,pop} + (\Theta_{2,pop} + \eta_{2,i}) * C_{i,k} \\ & + \Theta_4 * BL_{cent,AdjP1,i}\end{aligned}$$

The full model can be decomposed into:

Structural model:

$$\Delta\Delta QTc_{i,k} = \Theta_{1,i} + \Theta_{2,i,} * C_{i,k}$$

Statistical model:

$$\Theta_{1,i} = \Theta_{1,pop} + \Theta_4 * BL_{cent,AdjP1,i}$$

$$\Theta_{2,i} = \Theta_{2,pop} + \eta_{2,i}$$

It can be noted that the structural model formulation is the same for ΔQTc and ΔΔQTc, while the statistical model and the interpretation of the parameters are different.

Alternative structural models for (Δ)ΔQTc

Considering that the structural model is expressed as a simple function of the concentration, other models are specified by defining the transformation of the concentration, $f(C_{i,j,k})$:

$$General\ structural\ model: (\Delta)\Delta QTc_{i,j,k} = \Theta_{0,i} + f(C_{i,j,k})$$

The formula applies to both ΔQTc and ΔΔQTc. The other model components remain unchanged: for ΔQTc, covariates TRT, TIME, and BL_{cent} are added on the intercept. For ΔΔQTc, the covariate $BL_{cent,AdjPl}$ is added on the intercept.

A selection of structural models and their definitions is given in Table 1. All model parameters can be associated with IIV. Higher model complexity, ie, more individual parameters, generally leads to better individual fits. Other structural models may be explored, too, and the BIC_c comparison may help in the determination of the best model.

τ_0 characteristic time of appearance of effect, γ steepness parameter (Hill coefficient), *Cc* drug concentration in the central compartment, *Ce* hypothesized concentration in the

Table 1 Structural model alternatives

Model	Structural model[a]	Parameters
No effect	$f(Cc) = 0$	
Linear	$f(Cc) = slope*Cc$	slope
Loglinear	$f(Cc) = p_1*\log(1 + Cc/p_2)$	p_1, p_2
E_{max}	$f(Cc) = E_{max}*Cc/(Cc + EC_{50})$	E_{max}, EC_{50}
E_{max} with sigmoidicity	$f(Cc) = E_{max}*Cc^{\gamma}/(Cc^{\gamma} + EC_{50}{}^{\gamma})$	E_{max}, EC_{50}, γ
Effect compartment (hysteresis)	$d/dt(Ce) = (1/\tau_0)*(Cc\text{-}Ce)$ $f(Ce) = slope*Ce$	τ_0, slope

[a](Placebo-corrected) change from baseline is modeled as $(\Delta)\Delta QTc_{i,j,k} = \Theta_{0,i} + f(C_{i,j,k})$

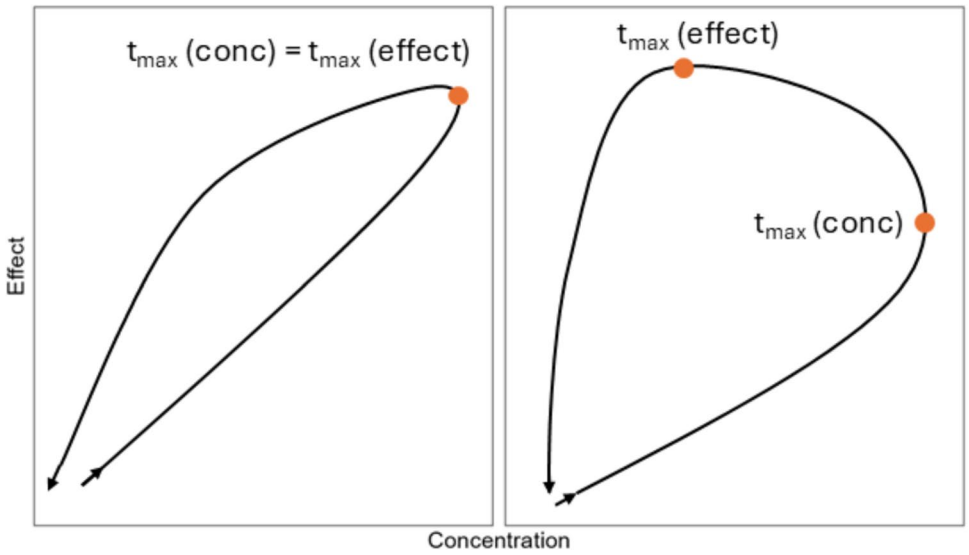

Fig. 1 Two different shapes indicating hysteresis. Left: no difference between time of maximum concentration and time of maximum effect; right: substantial difference. Lines: concentration-effect in timely sequence (arrows indicate direction); orange bullets: times of maximum concentration and/or maximum effect; conc: concentration; t_{max} (conc/effect): time of maximum drug concentration/effect

effect compartment, EC_{50} concentration at which half the maximum drug effect is achieved, E_{max} maximum drug effect for large concentrations, *p1, p2* scale and shape parameters.

Hysteresis modeling

Presence of hysteresis, ie, a delay in change in ΔQTc versus change in concentration, is commonly assessed by visual inspection of ΔQTc versus concentration. Observations are interconnected by directional arrows indicating the time sequence [6, 7]. If the effect is direct, i.e.., immediate, ΔQTc increases with increasing concentrations and decreases with lower concentrations on the same path. This implies that a given concentration has a similar effect independent of whether the concentration occurs in the absorption or the elimination phase.

With hysteresis, effect on QTc increases more slowly than the concentration and remains after the drug concentration decreases. Hysteresis patterns may have very different shapes (Fig. 1). The directional pattern shows a counterclockwise relationship [11]. Identical concentrations have larger effects in the late phase compared to the early phase after drug administration.

Models such as the linear model assume a direct and immediate effect of the concentration on QTc interval duration and can, therefore, not be used if hysteresis is present because it violates the model assumptions. Of particular importance is the possibility that the time of maximum concentration may be substantially different from the time of maximum effect. Diagnosis of hysteresis can be based on population averages or individual ΔQTc versus concentration plots, as depicted in Fig. 1.

With circadian variation in QTc, ΔQTc based on a single baseline measurement may lead to false conclusions about hysteresis, ie, ΔQTc varying with the time of day [13]. Such limitations can be overcome with time-matched baseline data, i.e., 24-h QTc measurements at the same nominal times prior to treatment start. In such cases, ΔQTc is defined as the time-matched change from baseline, the difference between QTc after treatment start and QTc at baseline at the same time of day. Obviously, hysteresis can only be present in subjects on active treatment. Alternatively, presence of hysteresis can be assessed by comparing the goodness of fit for a direct-effect model to a model with effect compartment.

If hysteresis is present, it might be caused by an active metabolite that exerts an effect on QTc such that the time

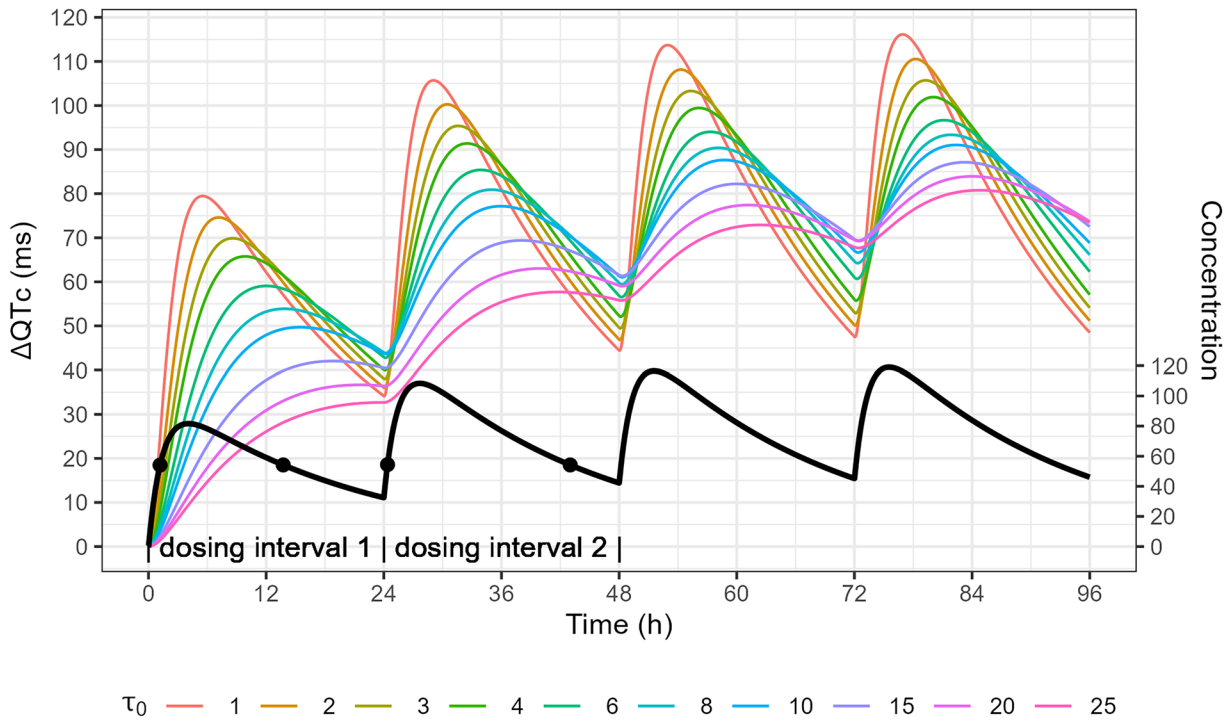

Fig. 2 Hysteresis visualization: delayed ΔQTc (colors) and concentration (black) versus time for different values of τ_0. The pharmacokinetic model was a 1-compartment model with $k_a = 0.7$/h, $k_{el} = 0.05$/h, V = 1L, and once-daily doses of 100 mg. Bullets indicate 4 different nominal times with identical concentrations, corresponding to the bullets in Fig. 3

delay between parent concentration and effect change actually describes the metabolism from parent drug to metabolite with the effect originating from the metabolite. With metabolite concentration data, a metabolite-QT model with direct effect can be fitted and compared to a hysteresis model built on only parent concentration. Alternatively, a model where both compounds exert a direct effect on the QT interval can be fitted and the contributions of both compounds to the effect be assessed [2, 4]

In absence of such knowledge or data, hysteresis can be described by an effect-compartment model for the parent compound concentration. The effect compartment serves as the delay descriptor and the time delay is driven by the rate parameter that builds up the effect (Table 1).

The effect-compartment model is implemented as:

$$d/dt(Ce) = (1/\tau_0) * (Cc - Ce)$$

$$\Delta QTc = \Theta_0 + slope * Ce$$

with τ_0 denoting the time with which the (virtual) concentration in the effect compartment, Ce, follows drug concentration in the central compartment, Cc [14, 15]; τ_0 has time units whereby larger values of τ_0 yield larger delays between concentration and effect change. The effect, ΔQTc, is described by an intercept, Θ_0, and a slope for the relation between effect and concentration *in the effect compartment*, Ce. The statistical model for Θ_0 and slope remains the same.

An example illustrates the role of the parameter τ_0. In a 1-compartment linear PK model with $k_a = 0.7$/h, $k_{el} = 0.05$/h, V = 1L, and once-daily doses of 100 mg, the delay between change in concentration and change in effect, ΔQTc, increases with larger τ_0. The time of maximum concentration after the first dose is 4.1 h. The times of maximum effect range from 5.5 h for $\tau_0 = 1$ to 23.8 h for $\tau_0 = 25$ over the first dosing interval to 29.1 h and 41.8 h (5.1 h and 17.8 h after dosing) for the second dosing interval (Fig. 2). The visualization of repeated doses shows that times of maximum effect after last dosing decrease with repeated doses (for all values of τ_0).

The shapes of the hysteresis plots differ visibly, depending on the values of τ_0. Furthermore, shapes and locations differ between first and subsequent doses (Fig. 3).

Model comparison

Common practice is to fit the linear regression model and inspect data and modeling results for violations of the model assumptions. Linearity is largely assessed visually, e.g, by inspecting a visualization of ΔQTc versus concentration or, post-hoc, residuals versus concentration supported by, e.g,

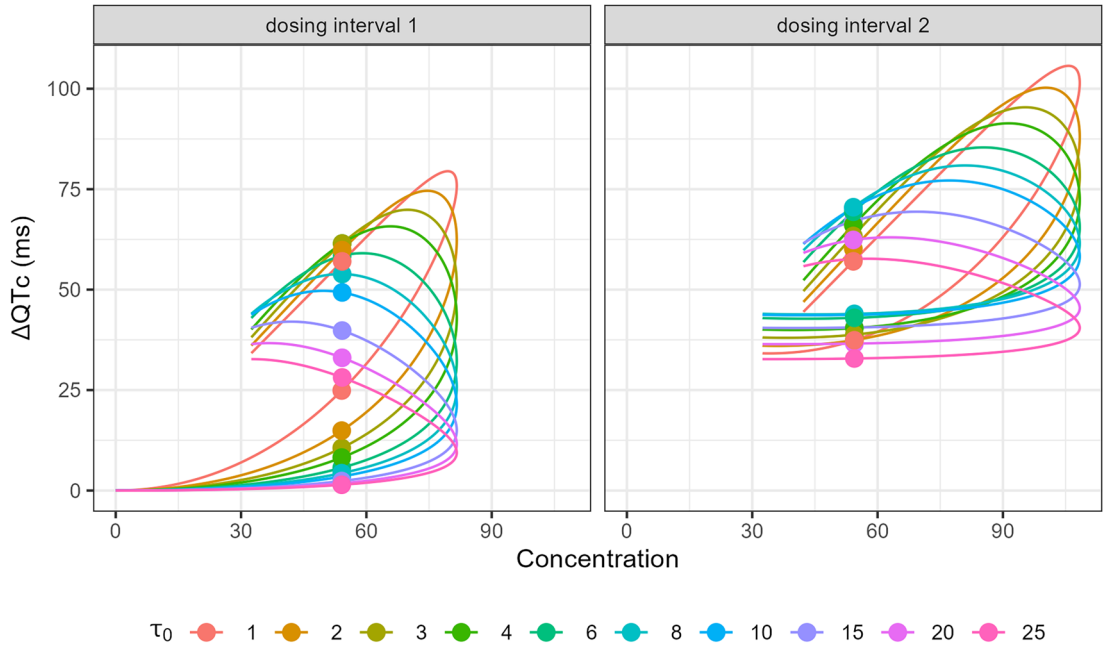

Fig. 3 Hysteresis plots for different values of τ_0. Bullets indicate different nominal times with identical concentrations, corresponding to the bullets in Fig. 2

a polynomial fit or a locally weighted scatterplot smoother [16, 17].

While a linear model frequently describes the concentration-QT data reasonably well, alternatives are generally not considered unless there is sufficient evidence that an assumption does not hold. On the opposite, pharmacometric analyses commonly compare model alternatives by visual assessments of predicted versus observed data and VPCs [9, 18] as well as by numerical measures of goodness of fit. Numerical assessments are based on likelihood comparisons. The likelihood expresses numerically the proximity of the model predictions to the observed data and generally increases with higher model complexity (number of parameters). To gauge if higher model complexity is warranted, the likelihood is counterbalanced by a penalty term for the number of parameters, leading to information criteria such as Akaike's information criterion (AIC) [19], the BIC [20], and the BIC_c [10]. If the increase in likelihood is marginal compared to the higher model complexity, the simpler model is preferred, ie, the model with lower information criteria.

Decisions for model selection tend to be similar between AIC, BIC, and BICc. In the following, BIC_c is employed for model comparison because of its specificity for mixed-effects models with different penalty terms for fixed and random effects.

Dataset characteristics

The QT interval is known to exhibit diurnal variation, i.e., repeating patterns over the course of a day [21, 22]. Baseline-corrected QTc, i.e., ΔQTc, can be derived in several ways. Ideally, the analyses are based on time-matched ΔQTc with baseline data available as 24-h QTc profiles prior to drug administration. Change from baseline in QTc is derived by subtracting the time-matched baseline measurement from the QTc measurement after drug administration. This, on average, eliminates the circadian variation in ΔQTc.

If only a single baseline measurement is available, circadian variation can be modeled, e.g, as a cosine curve with parameters time shift and amplitude. Alternatively, a time component with time as a categorical covariate may be included into the model (as done in the white paper model), adjusting for each nominal time individually instead of employing a continuous curve. With circadian variation in ΔQTc, it can be expected that some corresponding nominal time parameters are different from 0. The placebo correction in ΔΔQTc removes the time component again.

In a study setup where placebo and active drug are administered to different subjects, e.g, in entry-into-man or parallel-group studies, baseline correction may be conducted based on the average placebo response per nominal time.

Overall, the definition of the change from baseline (single baseline value or time-matched change from baseline on the individual level or on the aggregate level using average placebo values) as well as the centered baseline affects the

data set preparation from the raw data but not the modeling process as such.

Implementation

Mixed-effects regression models (linear and nonlinear) were employed for all analyses. Model parameters were estimated using the stochastic approximation expectation–maximization (SAEM) algorithm. All models were implemented in Monolix 2024R1 [23]. Calculations of CIs were performed using Simulx 2024R1 [24]. Monolix and Simulx were used through the lixoftConnectors package [25], which provides an application programming interface (API) from R for the MonolixSuite. R version 4.4.2 [26] was used, and an R quarto script [27] (quarto version 1.5.57) served as a wrapper to create the output as Word files. The Monolix models can be fitted from the GUI version, too, by opening the corresponding mlxtran files.

The R functions allowing to (1) format an input dataset for analysis, (2) generate Monolix projects to run a conc-QTC analysis using the standard linear model as well as alternative non-linear models and (3) generate a report as Word document can be downloaded from https://monolixsuite.slp-software.com/r-functions/?contextKey=package-conc-qtc. Example of usage and results for the 4 compounds in Johannesen et al. [28] are also provided on the webpage.

Applications

The proposed workflow is applied to the data in Johannesen et al. [28], comprising the 4 compounds dofetilide, quinidine, ranolazine, and verapamil. The clinical 5-way crossover study administered single doses of 500 µg (dofetilide), 400 mg (quinidine sulfate), 1500 mg (ranolazine), 120 mg (verapamil hydrochloride), or placebo to 22 healthy subjects. PK and QT data were collected at 16 matching nominal times over 24 h after dose administration. The data are available for download [29]. The data used for the analyses shown here are slightly reformatted and available for download from the appendix. There is one dataset per compound, including the compound itself and the placebo period. They contain columns for ΔQTc or ΔΔQTc, the drug concentration Cc, and the covariates TRT, TIME, and $BL_{cent,AdjP1}$ or BL_{cent}. The drugs and the study design are described in Johannesen et al. [28].

In this cross-over study, each study participant received each of the active drugs as well as placebo. In this specific setup, ΔΔQTc can be calculated as the difference in change from baseline on active drug and change from baseline on placebo for each subject individually.

In the following, these compounds serve as illustration of the methods discussed, the aim is not to provide complete analyses. The nomenclature QTc is used to indicate that the application is not restricted to QTcF, however, the heart rate correct is the Fridericia correction, ie, QTcF, in all applications.

The R scripts provided include an automated procedure to fit many different model alternatives to a dataset. A report containing all figures suggested in Garnet et al. [1] is generated, including a comparison of the different models. The functions provided are generic and can be reused on other datasets.

Results

The methods discussed in the previous section were applied to all 4 datasets in Johannesen et al. [28]. All results are available from https://monolixsuite.slp-software.com/r-functions/?contextKey=package-conc-qtc. The focus is on the methods, not on the data, such that only selected results relevant to the methods under consideration are shown in the following.

The extensions of the linear model comprise:

- modeling of ΔQTc and ΔΔQTc, investigating if they lead to similar results and conclusions;
- modeling of nonlinear concentration-QT relationships with related goodness-of-fit assessments and comparison of the results versus the linear model; and
- hysteresis modeling, i.e., capturing time-delayed effects and therefore different times of maximum concentration and maximum effect.

Modeling ΔQTc versus ΔΔQTc

While modeling of ΔQTc is the standard approach proposed by the white paper, modeling of ΔΔQTc has the advantage of being much simpler with fewer parameters to estimate and fewer covariates (if placebo data are available).

For each of the 4 datasets, 2 approaches were employed to characterize the data:

- Fitting a model for ΔQTc for active drug and placebo and deriving ΔΔQTc as the difference between ΔQTc (active drug) and ΔQTc (placebo), i.e., the white-paper approach; and
- Fitting a model for ΔΔQTc directly.

The key parameters affecting model-predicted ΔΔQTc, the treatment effect (Θ_1) and the effect of concentration, the slope (Θ_2), are summarized in Table 2. Full results are provided in the supplementary material.

The ΔQTc model includes much more factors (in particular one factor per time point) than the ΔΔQTc model.

Table 2 Parameter estimates for ΔQTc and ΔΔQTc regression models

Compound	Population parameter	ΔQTc model			ΔΔQTc model		
		Estimate	RSE (%)	95% CI	Estimate	RSE (%)	95% CI
Dofetilide	Treatment/ Intercept (Θ_1)	0.002	80,761%	(− 2.575, 2.579)	− 3.326	38%	(− 5.784, − 0.869)
	Concentration (Θ_2)	0.026	6%	(0.023, 0.029)	0.028	5%	(0.025, 0.031)
Quinidine	Treatment/ Intercept (Θ_1)	4.607	33%	(1.65, 7.563)	3.128	47%	(0.243, 6.012)
	Concentration (Θ_2)	0.042	7%	(0.036, 0.047)	0.043	7%	(0.038, 0.049)
Ranolazine	Treatment/ Intercept (Θ_1)	2.108	41%	(0.43, 3.785)	2.441	33%	(0.874, 4.008)
	Concentration (Θ_2)	0.005	17%	(0.003, 0.006)	0.004	22%	(0.002, 0.006)
Verapamil	Treatment/ Intercept (Θ_1)	1.997	32%	(0.752, 3.242)	2.236	25%	(1.151, 3.321)
Verapamil	Treatment/ Intercept (Θ_1)	1.997	32%	(0.752, 3.242)	2.236	25%	(1.151, 3.321)
	Concentration (Θ_2)	0.021	80%	(− 0.012, 0.055)	0.017	102%	(− 0.017, 0.052)

Θ1 denotes the parameter treatment in the ΔQTc model and the parameter intercept in the ΔΔQTc model. *Θ2* denotes the slope parameter in both models. The linear model was not the best-fitting model in all cases

ΔΔQTc placebo-corrected change from baseline in QTc interval duration, *ΔQTc* change from baseline in QTc interval duration, *CI* confidence interval, *RSE* relative standard error

Consequently, the parameter estimates are more uncertain in the ΔQTc model. Overall, slope parameter estimates were numerically similar while intercept parameters (based on the intercept parameter in the ΔΔQTc model and the treatment parameter in the ΔQTc model) differed, in particular, for dofetilide and quinidine. These were, however, associated with large uncertainties as expressed by relative standard errors (RSEs). Slope parameter estimates were generally associated with lower RSEs than intercept parameter estimates with the exception of verapamil (where both CIs contained 0).

A visualization of the concentration-ΔΔQTc linear regression model fits showed that the model-predicted ΔΔQTc were similar for all compounds in the range of observed drug concentrations (Fig. 4).

The key results, the estimated upper limits of the 2-sided 90% CIs at geometric mean maximum concentrations and the estimated concentrations at which the upper limits exceed 10 ms, show limited differences (Table 3). Further comparisons of ΔQTc and ΔΔQTc models are provided in the supplementary material (Figs. S1, S2, S3 and S4).

Nonlinear models

A visual analysis of the quinidine concentration-QT relationship might suggest an increase in ΔQTc up to concentrations of 750 ng/L and a slower increase at higher concentrations (Fig. 5). An E_{max} model with a maximum (saturable) effect might, therefore, be an alternative to describe the relationship.

Fitting all candidate models (no-effect, linear, loglinear, E_{max}, and E_{max} with sigmoidicity) to the quinidine data, the E_{max} model and the loglinear model were better fits than the linear model based on the BIC_c (Table 4, Table S1). The E_{max} model was the best-fitting model, supported by visual assessment (Fig. 6). The estimated effect at the geometric mean maximum concentration was similar between the models (86.6 ms with the linear and 80.3 ms with the E_{max} model). The concentrations at which the upper limit of the 90% CI reaches 10 ms showed a larger difference (105.5 vs 152.4 ng/mL, Table 5). The difference arises from the fact that these concentrations are in the low range of the concentration range (Fig. 6).

The VPCs of the E_{max} model assessing the goodness of fit of ΔΔQTc vs time and vs concentration suggest an adequate description of the ΔΔQTc time course and the relationship between ΔΔQTc and quinidine concentration (Fig. 7).

Hysteresis modeling

Hysteresis can be assessed using ΔQTc or ΔΔQTc. ΔΔQTc includes the placebo correction, such that circadian variations are accounted for and do not bias the visual hysteresis assessment. For ΔQTc, if the baseline data are time-matched with on-treatment data, circadian variation is corrected for

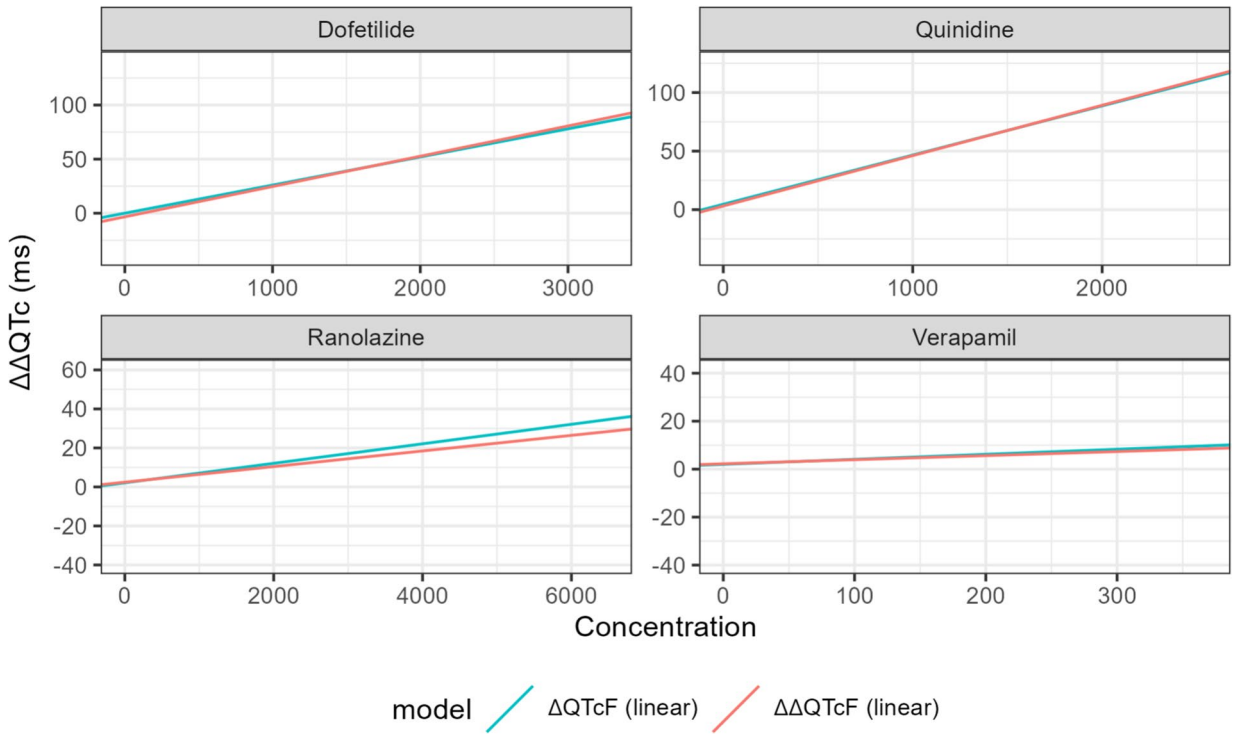

Fig. 4 Concentration-ΔΔQTc predictions for dofetilide, quinidine, ranolazine, and verapamil. Axis ranges correspond to data ranges

Table 3 Upper limits of the 90% confidence intervals for ΔQTc and ΔΔQTc with linear models

Compound	Geometric mean C_{max}	Upper limit of the 2-sided 90% CI (ΔQTc) (ms)	Upper limit of the 2-sided 90% CI (ΔΔQTc) (ms)	Concentration at which the upper limit of the 90% CI reaches 10 ms (ΔQTc model)	Concentration at which the upper limit of the 90% CI reaches 10 ms (ΔΔQTc model)
Dofetilide	2709.9 pg/mL	76.2	77.6	310.9 pg/mL	414.1 pg/mL
Quinidine	1754 ng/mL	85.0	86.6	74.9 ng/mL	105.5 ng/mL
Ranolazine	2043.2 ng/mL	13.9	13.8	1360.4 ng/mL	1379.7 ng/mL
Verapamil	113.6 ng/mL	7.0	7.0	180.4 ng/mL	184.4 ng/mL

The linear model was not the best-fitting model in all cases.

ΔΔQTc placebo-corrected change from baseline in QTc interval duration, *ΔQTc* change from baseline in QTc interval duration, *CI* confidence interval, C_{max} maximum concentration

too. If, however, the baseline consists of a single measurement, ΔQTc includes circadian variation in QT. In that case, ΔΔQTc might be preferable to assess hysteresis, if available. In the data set used here, the baseline measurement consists of a single measurement at the nominal time -0.5 h.

Practically, the differences between ΔQTc and ΔΔQTc hysteresis visualizations show only limited differences (Fig. 8). The display suggests that hysteresis might be present for dofetilide. The quinidine data shows a partial counterclockwise hysteresis or proteresis. Ranolazine does not show strong indications of hysteresis as the standard error bars mostly overlap, and verapamil assessment for hysteresis is prevented by having almost no data in the phase with increasing concentrations, reaching the maximum concentration rapidly (Fig. 8).

In absence of clear insight from the data visualization, both the linear and the hysteresis model (i.e. with effect compartment) were fitted to the dofetilide data. The hysteresis model captured the observed data better than the direct-effect model for both, ΔQTc and ΔΔQTc, with substantially lower BIC_c (Table 6). Accordingly, the τ_0 rate constants significantly differ from 0.

With hysteresis, the ΔΔQTc CI cannot be derived as before. Indeed, the effect will not solely depend on the current concentration anymore but on the entire past profile of the drug concentration. This can only be captured by a

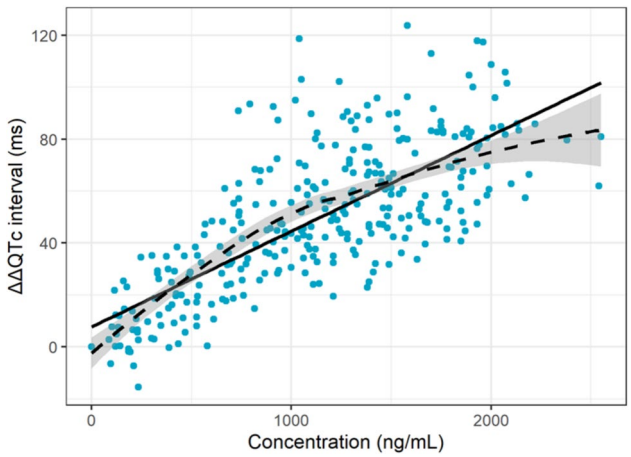

Fig. 5 Quinidine ΔΔQTc versus concentration. The solid black line indicates the linear regression fit. The dashed line indicates a nonlinear smoothing and the shaded area is the corresponding 90% confidence interval

Table 4 Goodness of fit for different models for quinidine ΔΔQTc

Model	BIC_c	ΔBIC_c
No-drug-effect model	3230.6	484.4
Linear model	2750.4	4.2
E_{max} model	2746.2	0.0
E_{max} model with sigmoidicity	2750.4	4.2
Log-linear model	2749.5	3.3

ΔBIC_c difference in BIC_c to the best model (lowest BICc), BIC_c corrected Bayesian information criterion, E_{max} maximum pharmacologic effect

population PK/PD model that models not only the effect of concentration on QTc, but also the shape of the concentration over time. Examples of such approaches are available in the literature [6]. With a population PK/PD model, the CI can be derived from a large number of simulations, estimating the CI from the empirical quantiles of the model fits.

Discussion

The analyses in this manuscript highlighted that there are alternatives to applying the white-paper linear model to fit ΔQTc vs drug concentration and deriving the relationship between ΔΔQTc and drug concentration from the model-based difference between active-drug and placebo treatment [1].

Baseline definition

The baseline QTc interval duration can be characterized in different ways. In its simplest form, there is only a single value, QTc just prior to first dose administration. In crossover studies, a baseline measurement can be taken at the start of each period. It has become common to collect a full baseline day with the same nominal times points as on other profile days. This enables the derivation of time-matched change from baseline within each subject. The advantages are obvious: circadian variation in QT is corrected for by correcting with a measurement at the same time of day, and subject-specific components such as known sex or age differences are adjusted for, too. In such cases, it may be considered to drop the time components from the model for more robust estimation of the remaining model parameters.

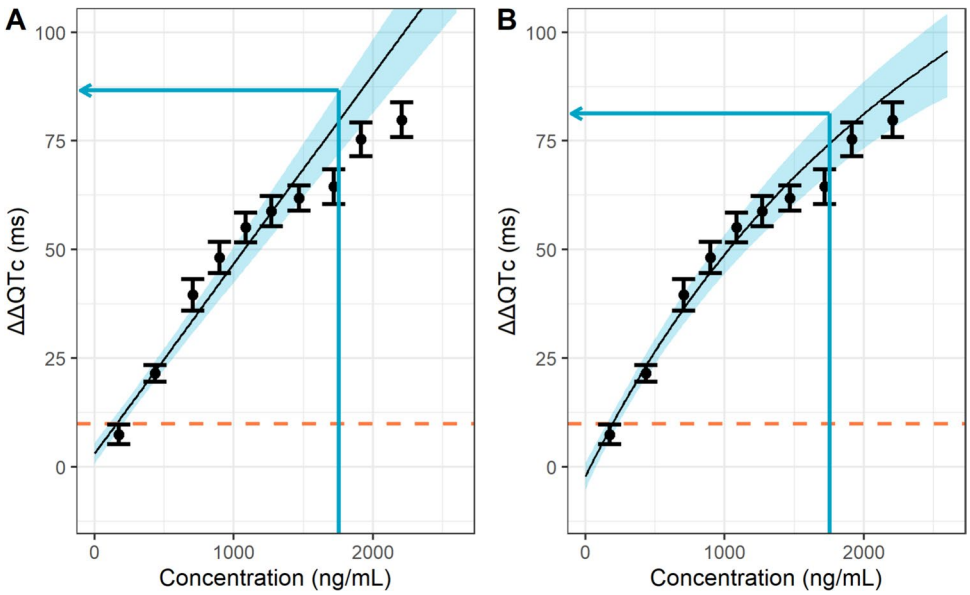

Fig. 6 Model fit and 90% confidence intervals overlaid with binned observed ΔΔQTc data for the linear model (**A**) and the E_{max} model (**B**) for the quinidine data

Table 5 Upper limits of the 90% confidence intervals for quinidine ΔΔQTc, linear and E_{max} model

Upper limit of the 2-sided 90% CI at the geometric mean C_{max} of 1754 ng/mL		Concentration at which the upper limit of the 90% CI reaches 10 ms	
Linear model	E_{max} model	Linear model	E_{max} model
86.6 ms	81.3 ms	105.5 ng/mL	152.4 ng/mL

ΔΔQTc placebo-corrected change from baseline in QTc interval duration, *CI* confidence interval, E_{max} maximum pharmacologic effect

If time-matched changes from baseline cannot be derived but multiple samples are available (eg, at different nominal times), the baseline can be defined as the average across all available baseline times. While this would correct for individual characteristics, it would not correct for circadian variation. This, however, is taken care of by the model formulation that includes time components.

Model reformulation

The mixed-effects regression model is commonly analyzed using statistical methodology such as analysis of residuals. The model formulation developed here (intercept and slope as structural model and treatment, nominal time, and centered baseline as covariates on the intercept) provides access to pharmacometric tools, i.e., fitting tools such as Monolix or NONMEM as well as model diagnostics, in particular VPCs.

In a subsequent step, creating simulations from the pharmacometric model allows for straightforward derivation of derived quantities such as estimation of the percentage of subjects expected to experience QT prolongations of more than 5 or 10 ms with different concentrations. Assessing at which concentration the upper limit of the 2-sided 90% CI exceeds 10 ms allows for derivation of a safety margin, ie, the difference between the concentration predicted to exceed 10 ms and the therapeutic concentration.

ΔQTc or ΔΔQTc as dependent variable

Overall, the case studies analyzed here showed that differences between modeling of ΔQTc or ΔΔQTc are limited. Using the linear regression model, the estimated upper limits of the two-sided 90% CIs at geometric mean C_{max} differed by less than 2% for all 4 compounds. The estimated concentrations at which the CIs reach 10 ms differed by 33, 41, 2 and 1% for dofetilide, quinidine, ranolazine, and verapamil, respectively. The conclusions however did not change. When exploring alternative concentration-(Δ)ΔQTc relationships, the structural model chosen are generally the same between ΔQTc and ΔΔQTc.

The ΔΔQTc model is simpler in structure because of some terms canceling out when deriving ΔΔQTc from ΔQTc. The intercepts as parameterized in the ΔQTc model and all nominal times cancel out. The treatment effect of the ΔQTc model becomes the intercept in the ΔΔQTc model and the centered baseline becomes the centered baseline on active treatment corrected by the centered baseline on placebo. In addition to a simpler model definition, this reduces the runtime and the risk of convergence failure.

Another advantage of using ΔΔQTc is that there is no necessity to model the circadian rhythm in QT interval duration, neither by using nominal time as covariate or by means of a trigonometric function, i.e., a cosine function, as the placebo-correction is assumed to correct for it.

There are situations though in which ΔΔQTc cannot be derived, e.g, if placebo data are not available (consider oncology studies where it might be unethical to administer toxic compounds to healthy subjects or placebo to patients with a life-threatening disease). If the data do not originate from a cross-over study but the participants on active treatment and placebo are different, the placebo correction in ΔΔQTc can only be derived based on the average placebo response.

Another alternative would be to model QTc and derive ΔQTc and ΔΔQTc and their respective confidence intervals from simulations. Modeling QTc, however, could necessitate modeling individual characteristics. For example, there are known sex differences in QT interval duration. The derivation of individual changes from baseline corrects for individual differences, eg, sex as covariate because the corresponding terms cancel out.

Alternative structural models

The pharmacometric formulation of the models allows to easily explore non-linear relationships between drug concentration and (Δ)ΔQTc. With relatively short runtimes for fitting the models, fitting all candidate models (no-effect, linear, loglinear, and E_{max}) provides a basis to choose from a set of standard models, and the BIC_c can serve as model selection criterion. More complex user-defined models can be implemented too, requiring changing a few lines of model code only.

The quinidine example shows that the exploratory data analysis displaying ΔQTc vs concentration does not reveal an obvious non-linearity, but that the E_{max} model provides a significantly better fit of the relationship compared to the standard linear model. Using an E_{max} rather than the linear model changes the concentration at which the 10 ms threshold is reached from 105.5 to 152.4 ng/mL (an increase of 40%).

Similarly, Garnett et al. [1] discuss a scenario with a simulated data set from an E_{max} concentration-ΔQTc model, concluding that identification of the misfit with a linear model can be difficult and must be based on careful review

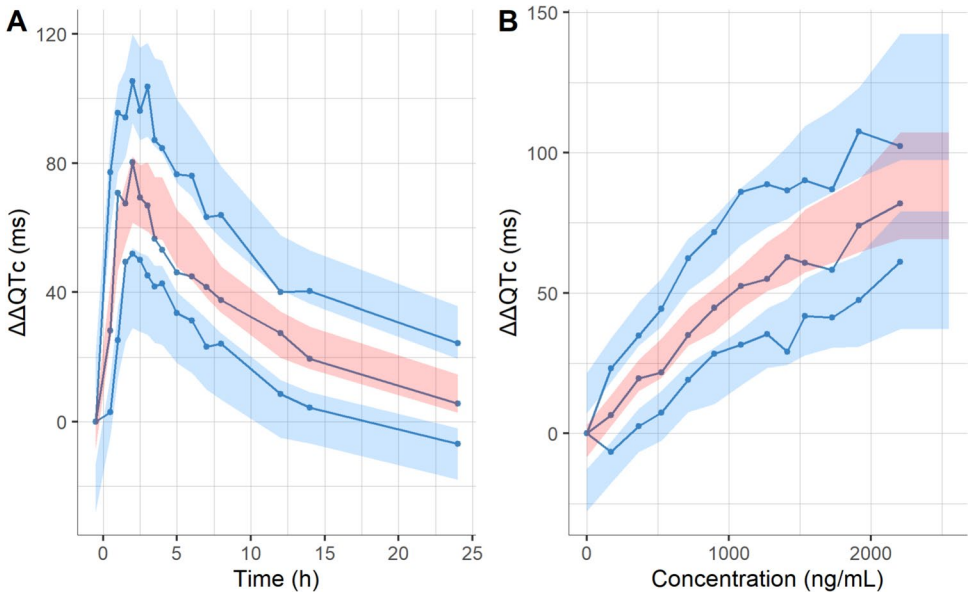

Fig. 7 Visual predictive checks for the quinidine E_{max} model: ΔΔQTc versus time (**A**) and versus concentration (**B**). Shaded areas = 90% confidence intervals for 5th and 95th percentiles (blue) and medians (pink); lines = corresponding medians and quantiles from data;

of model selection criteria (Garnett et al. supplementary material S3). Testing systematically several models has the advantage of avoiding the bias towards the linear model.

Diagnosis of hysteresis

Alternative structural models can facilitate the assessment of a potential effect delay. An effect-compartment model provides a flexible function form to capture hysteresis in the same modeling framework. Whether or not hysteresis is present in a dataset can be decided based on visual methods (visual detection of counterclockwise patterns in the concentration-ΔQTc relationship), but visual inspection is subjective. A quantitative approach such as comparison of BIC_c for alternative models provides an objective and reproducible measure. Alternative approaches to detect the presence of hysteresis have been proposed, such as the exposure-normalized Glomb-Ring Index (enGRI). This index has been rarely used in practice and experience on its effectiveness is limited [31]. Fitting an effect-compartment model, dofetilide exhibited a significant but small delay of around 0.28 h. If a pronounced delay is present and captured via an effect compartment, it is not possible to calculate a confidence interval for ΔΔQTc as a function of drug concentration because the ΔΔQTc effect depends not only on the current drug concentration but requires the knowledge of the entire past concentration profile. To circumvent this limitation, it is possible to use a population PK/PD approach to model the drug kinetics and link it to ΔQTc using an effect compartment.

Hysteresis modeling

If hysteresis is observed and metabolite data not available, an effect-compartment model provides a reasonable approach to model the time delay for the effect. If metabolite data are available, a direct-effect model with two effects, one for parent and one for metabolite concentration, can be fitted, ie, $\Delta QTc = \Delta QTc_0 + slope1*Cc + slope2*Cm$, where Cm denotes the metabolite concentration.

If two metabolites are hypothesized and no metabolite data are available, the model could include a direct effect for the parent compound and two effect compartments for the two metabolites, ie, $\Delta QTc = \Delta QTc_0 + slope1*Cc + slope2*Ce + slope3*Ce2$ with Ce2 and $\tau_{0,2}$ defined in analogy to Ce and τ_0. The model can subsequently be simplified if some of the effects appear negligible or if the data do not support the identification of all parameters.

Extensions to PK/PD modeling

One limitation of conc-QTc analysis is that the key findings are threshold concentrations (i.e., the concentration at which the 10-ms threshold is reached) while the clinician must decide about a dose. Doses can be linked to concentrations via a joint population PK-QTc model. Joint PK/PD models are common in pharmacometric modeling. They allow to simulate several doses and assess the resulting concentrations and PD effects, taking into account the interindividual variability in PK and PD. When applied to conc-QTc, this enables to characterize doses directly instead of concentrations.

Simulations from a population PK/QTc model would enable further quantitative assessments. Based on a large, simulated

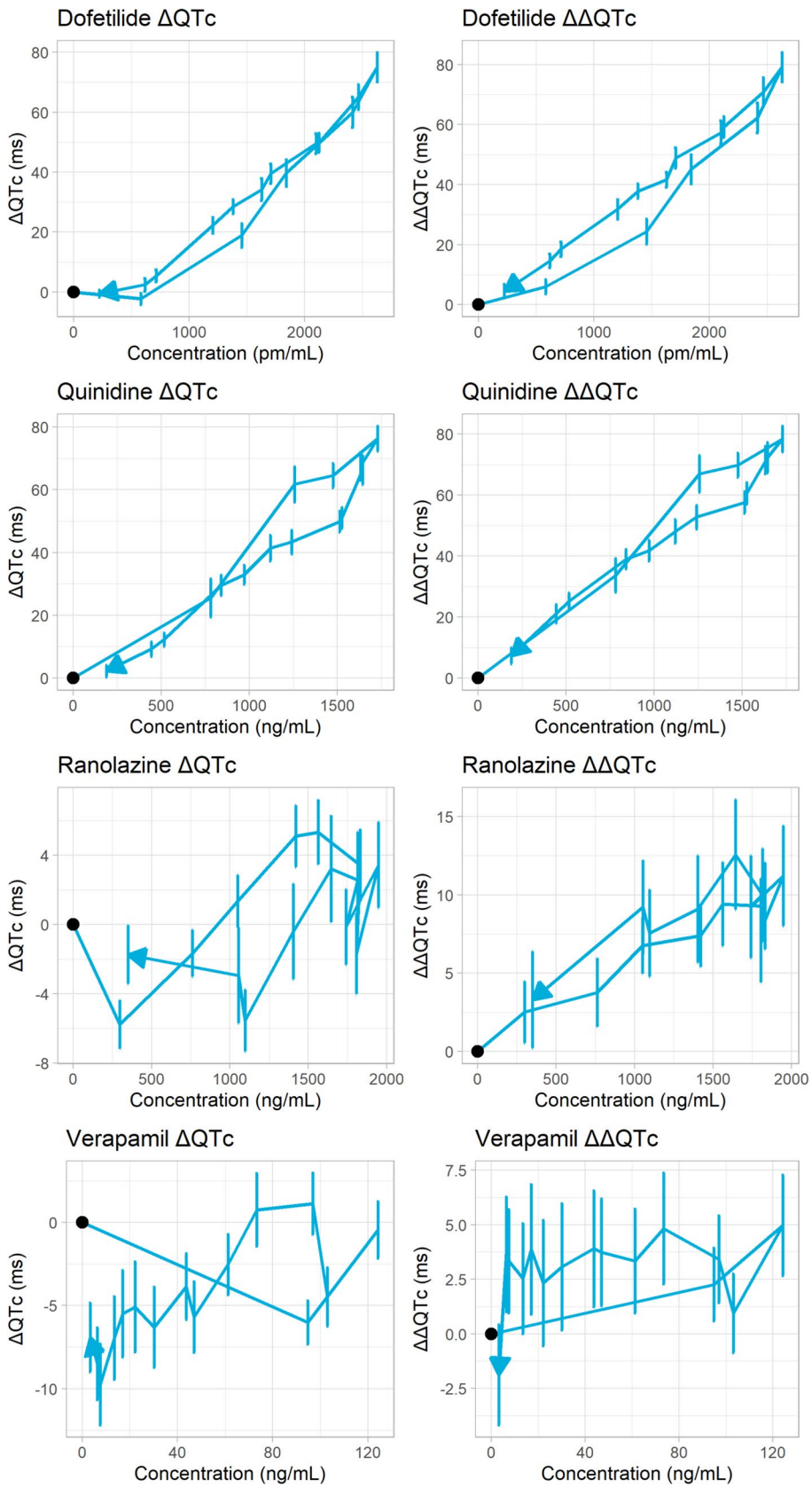

Fig. 8 Hysteresis assessment: ΔQTc (left) and ΔΔQTc (right) versus drug concentration for dofetilide, quinidine, ranolazine, and verapamil (rows, top to bottom). Lines: Arithmetic means per nominal time interconnected in temporal order. Black bullets: baseline observations and start of time series. Vertical intervals: standard errors in ΔQTc and ΔΔQTc per nominal time

Table 6 Goodness of fit for the direct- and indirect-effects models for dofetilide

Dependent variable	Model	BIC_c	ΔBIC_c	τ_0	Standard error (RSE%) (τ_0)	95% CI (τ_0)
ΔQTc	Linear, direct effect	5359.7				
ΔQTc	Linear with hysteresis	5250.1	-109.6	0.293	0.032 (11%)	(0.237, 0.362)
ΔΔQTc	Linear, direct effect	2813.8				
ΔΔQTc	Linear with hysteresis	2708.0	-105.8	0.271	0.029 (11%)	(0.220, 0.333)

ΔΔQTc placebo-corrected change from baseline in QTc interval duration, ΔBIC_c difference in BIC_c to the direct-effects model, *ΔQTc* change from baseline in QTc interval duration, τ_0 characteristic time parameter for time delay between change in concentration and change in effect, BIC_c corrected Bayesian information criterion, *CI* confidence interval, *RSE* relative standard error

population the percentage of subjects experiencing ΔΔQTc above thresholds such as 5 or 10 ms [32, 33] can be estimated for each dose, and the lowest *dose* exceeding 10 ms with its upper bound of the 2-sided 90% CI can be derived. This in turn can be used to assess a "safety margin," i.e., the ratio of the lowest safe dose and the therapeutic dose. Such assessments focus on dose again, complementing concentration-based assessments.

Conclusion

The standard linear mixed-effects model to fit ΔQTc has alternatives. Using a pharmacometric model formulation with a structural model and covariates on the intercept, nonlinear models (eg, loglinear, E_{max}, or effect-compartment models) can be fit and compared in a straightforward way.

The best-fitting structural model can be selected based on the Bayesian information criterion, BICc, and common pharmacometric diagnostic plots. Fitting several candidate models were shown to being able to detect hysteresis of low magnitude better than visual methods. Simulations provide accurate confidence intervals as well as estimates of drug concentrations at which the upper limit of the two-sided 90% confidence interval reaches 10 ms.

The results suggest that fitting ΔΔQTc with a simplified model is a viable alternative to fitting ΔQTc and deriving ΔΔQTc with associated confidence intervals. The generalized approach improves adequate capturing of the relationship between drug concentration and ΔΔQTc, even in situations where exploratory data visualization does not show evident violations of assumptions required to apply the standard linear model.

An automated solution can support fitting of a set of alternative candidate models and identification of the best model based on numerical criteria such as the BIC_c, including generation of the relevant goodness-of-fit assessments, numerical, and graphical results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10928-025-09975-6.

Acknowledgements The authors and contributors to the study of dofetilide, quinidine, ranolazine, and verapamil are acknowledged for study conduct, publication, and making the data set available [28, 29]. Peter Bonate (Astellas) is acknowledged for sharing the simulated data set from the supplementary material of the Garnett et al. paper. Julie Passarell (Simulations Plus) is acknowledged for discussions and helpful suggestions during the development of the concentration-QT R code.

Author Contribution AK, GC, and JC wrote the manuscript; JC conceptualized the software; JC and GC wrote the software; GC, GB, and AK tested the software; All authors reviewed the manuscript.

Funding No funds, grants, or other support were received.

Data availability The data sets analyzed in this manuscript were published by Johannesen et al. (2014). Proper attribution is provided in the manuscript and the references therein [28, 29].

Declarations

Conflict of interest All authors are employees and/or shareholders of Simulations Plus, Inc., the company developing and commercializing MonolixSuite. AK is a member of the editorial board of the Journal of Pharmacokinetics and Pharmacodynamics. The review process was conducted without his involvement.

References

1. Garnett C, Bonate PL, Dang Q et al (2018) Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn 45:383–397. https://doi.org/10.1007/s10928-017-9558-5

2. Briggs E, Chapel S, Zhang P, Palmisano M, Tran JQ (2021) Concentration-QTc modeling of Ozanimod's major active metabolites in adult healthy subjects. CPT Pharmacomet Syst Pharmacol 10:119–126. https://doi.org/10.1002/psp4.12580
3. Grosjean P, Urien S (2012) Moxifloxacin versus placebo modeling of the QT interval. J Pharmacokinet Pharmacodyn 39:205–215. https://doi.org/10.1007/s10928-012-9242-8
4. Kang D, Ludwig E, Jaworowicz D et al (2021) Concentration–QTc analysis of quizartinib in patients with relapsed/refractory acute myeloid leukemia. Cancer Chemother Pharmacol 87:513–523. https://doi.org/10.1007/s00280-020-04204-y
5. Tisdale JE, Overholser BR, Wroblewski HA et al (2012) Enhanced sensitivity to drug-induced QT interval lengthening in patients with heart failure due to left ventricular systolic dysfunction. J Clin Pharmacol 52:1296–1305. https://doi.org/10.1177/0091270011416939
6. Henrich A, Juif PE, Dingemanse J, Krause A (2021) PK/PD modeling of a clazosentan thorough QT study with hysteresis in concentration-QT and RR-QT. J Pharmacokinet Pharmacodyn 48:213–224
7. Anliker-Ort M, Hsin C-H, Krause A et al (2023) Modeling time-delayed concentration-QT effects with ACT-1014-6470, a novel oral complement factor 5a receptor 1 (C5a1 receptor) antagonist. Pharmacol Res Perspect 11:e01112. https://doi.org/10.1002/prp2.1112
8. Piotrovsky V (2005) Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. AAPS J 7:E609–E624. https://doi.org/10.1208/aapsj070363
9. Holford NHG, Karlsson MO (2008) A tutorial on visual predictive checks. 17th PAGE Meeting, Abstract 1434:1–17. http://www.page-meeting.org/?abstract=1434
10. Delattre M, Lavielle M, Poursat MA (2014) A note on BIC in mixed-effects models. Electron J Stat 8:456–475. https://doi.org/10.1214/14-EJS890
11. Ferber G, Darpo B, Garnett C et al (2020) Detection and impact of hysteresis when evaluating a drug's QTc effect using concentration-QTc analysis. J Pharmacokinet Pharmacodyn 48:187–202. https://doi.org/10.1007/s10928-020-09725-w
12. Girard P, Boissel JP (1989) Clockwise hysteresis or proteresis. J Pharmacokinet Biopharm 17:401–402. https://doi.org/10.1007/BF01061905
13. Minocha M, Li H, Chiu YL, Carter D, Othman AA (2019) Models of variability and circadian rhythm in heart rate, blood pressure, and QT interval for healthy subjects who received placebo in phase I trials. Clin Transl Sci 12:470–480. https://doi.org/10.1111/cts.12640
14. Upton RN, Mould DR (2014) Basic concepts in population modeling, simulation, and model-based drug development: part 3—introduction to pharmacodynamic modeling methods. CPT Pharmacomet Syst Pharmacol 3:e88. https://doi.org/10.1038/psp.2013.71
15. Kim Y, Kim A, Chung JY (2021) Population pharmacokinetic/pharmacodynamic modeling of delayed effect of escitalopram-induced QT prolongation. J Affect Disord 285:120–126. https://doi.org/10.1016/j.jad.2021.02.048
16. Cleveland WS (1979) Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 74:829–836. https://doi.org/10.1080/01621459.1979.10481038
17. Cleveland WS, Devlin SJ (1988) Locally weighted regression: an approach to regression analysis by local fitting. J Am Stat Assoc 83:596–610. https://doi.org/10.1080/01621459.1988.10478639
18. Holford NH (2012) An introduction to visual predictive checks. http://holford.fmhs.auckland.ac.nz/docs/vpc-tutorial-and-datatop.pdf
19. Akaike H (1974) A new look at the statistical model identification. IEEE Trans Autom Control 19:716–723. https://doi.org/10.1109/TAC.1974.1100705
20. Schwarz G (1978) Estimating the dimension of a model. Ann Statist 6:461–464. https://doi.org/10.1214/aos/1176344136
21. Singh I, Rabkin SW (2021) Circadian variation of the QT interval and heart rate variability and their interrelationship. J Electrocardiol 65:18–27. https://doi.org/10.1016/j.jelectrocard.2021.01.004
22. Sredniawa B, Musialik-Lydka A, Jarski P, Kalarus Z, Polonski L (2005) Circadian and sex-dependent QT dynamics. Pacing Clin Electrophysiol 28:S211–S216. https://doi.org/10.1111/j.1540-8159.2005.00006.x
23. Simulations Plus. Monolix User Guide. https://monolixsuite.slp-software.com/
24. Simulations Plus. Simulx User Guide. https://monolixsuite.slp-software.com/simulx/
25. Simulations Plus Lixoft connectors: R-package installation and initialization. https://monolix.lixoft.com/monolix-api/lixoftconnectors_installation/
26. R Core Team (2017) R: a language and environment for statistical computing. R Vienna, Austria: Foundation for Statistical Computing. https://www.R-project.org/
27. Allaire JJ, Teague C, Scheidegger C, Xie Y, Dervieux C (2024) Quarto. https://cran.r-project.org/web/packages/quarto/
28. Johannesen L, Vicente J, Mason JW et al (2014) Differentiating drug-induced multichannel block on the electrocardiogram: randomized study of dofetilide, quinidine, ranolazine, and verapamil. Clin Pharmacol Ther 96:549–558. https://doi.org/10.1038/clpt.2014.155
29. Johannesen L, Vicente J, Mason JW et al (2014) ECG Effects of Ranolazine, Dofetilide, Verapamil, and Quinidine 1.0.0. Data set to Johannesen et al (2014). https://physionet.org/content/ecgrdvq/1.0.0/SCR-002.Clinical.Data.csv
30. Mould DR, Upton RN (2013) Basic concepts in population modeling, simulation, and model-based drug development—part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacomet Syst Pharmacol 2:e38. https://doi.org/10.1038/psp.2013.14
31. Ferber G, Darpo B, Garnett C, Huang D et al (2020) Detection and impact of hysteresis when evaluating a drug's QTc effect using concentration-QTc analysis. J Pharmacokinet Pharmacodyn 48(2):187–202. https://doi.org/10.1007/s10928-020-09725-w
32. Simulations Plus. Vanoxerine C-QTc case study. https://monolix.lixoft.com/case-studies/vanoxerine-c-qtc-case-study/
33. Kümmel A, Bonate PL, Dingemanse J, Krause A (2018) Confidence and prediction intervals for pharmacometric models. CPT Pharmacomet Syst Pharmacol 7:360–373. https://doi.org/10.1002/psp4.12286