Optimal design of QTc interval measurements for circadian rhythm determination

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Introduction

Several classes of non antiarrhythmic drugs induce lengthening of the QT interval which is a biomarker of Torsade de pointe. QT/QTc studies are required by authorities for non antiarrhythmic drugs [1]. QTc interval is known to vary during the day (circadian rhythm) [2]. Badly designed studies can miss this rhythmicity and lead to wrong conclusions concerning the cardiotoxic effects if not taken into account. It is thus important to reveal this phenomenon. As the number of ECG is often limited, it could be useful to determine the minimum number and the location of ECG records by an optimal design approach.

Objectives: to determine optimal ECG's record times which allow the best estimation of the parameters describing the circadian rhythm

Method: Population Model and Optimal Design

-Dataset: 160 patients, two phase I studies, 10 records per perior and per subject. 24h-ECG Baselines are under placebo.

-Population PD model:

Model building : Likelihood Ratio Test, using NONMEM (version 5) with FOCE interaction method.

Model evaluation: Visual Predictive Check (500 simulations)

-Optimal design:

Optimisation of ECG's record times.

Optimisation for only one group of 100 subjects.

Design domain between 6 and 24h o'clock to save sleep period.

Optimal record times were estimated by D-optimal design approach in PopDes (version 3.0). [3]

Algorithm: Modified Fedorov exchange algorithm. [4]

Option: LOCAL, POPULATION, FIXED TIMES.

Population Model Results

-Model structure: 3 cosine model, with periods of 24, 12 and 6h.

7 fixed parameters

$QT=QTM.(1+ QTA1.\cos[2\pi/24.(t-QTL1)] + QTA2.\cos[2\pi/12.(t-QTL2)] + QTA3.\cos[2\pi/6.(t-QTL3)])$

-Inter-individual variability: IIV_QTM, IIV_QTA1 and IIV_QTL2

Residual variability: multiplicative error model.

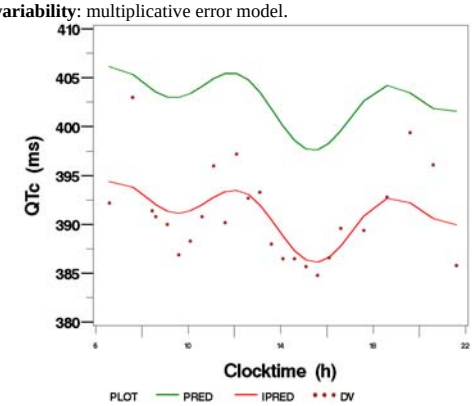

Fig1. Population prediction, individual prediction and observations of QTc for a typical subject between 6 and 22h o'clock.

Table1. Population parameter estimates and Relative standard error (RSE%) associated to parameter estimates.

	QTM ms	QTA1	QTL1 h	QTA2	QTL2 h	QTA3	QTL3 h	PROP %
Mean	403	0.0238	6.69	0.00495	9.39	0.00597	18.3	1.3
(RSE %)	(0.2)	(26)	(15)	(12)	(2.1)	(7.3)	(0.3)	(3.1)
SQRT %	**IIV_QTM**	**IIV_QTA1**			**IIV_QTL2**			
(RSE %)	2.9 (12)	92 (30)			132 (32)			

Good precision of estimation for the fixed effects (<20%) except for the amplitude of the first cosine term (QTA1)

Model Validation: Predictive Check

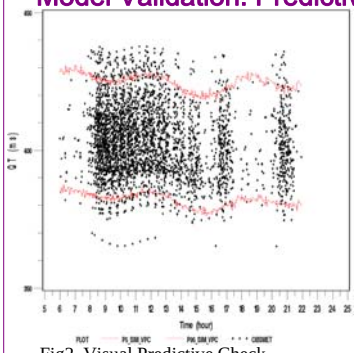

Fig2. Visual Predictive Check

Visual Predictive Check:

9.08% of the observations are out of the 90% prediction interval

→ This model predicts well the evolution of the QTc interval versus time

Optimal Record Times Results

7 optimal records times: at 8:30, 13:00, 16:30, 19:30, 21:00, 23:15, 23:45

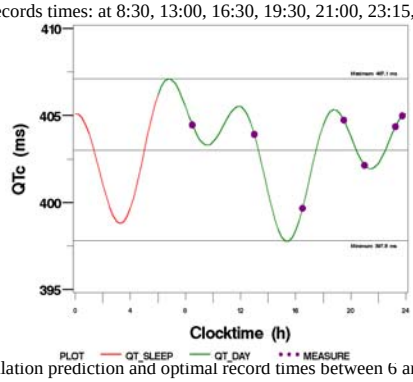

Fig3. Population prediction and optimal record times between 6 and 24h o'clock

Simulation and Efficiency Evaluation

The D-optimal record time design was evaluated by simulation (500 datasets with 100 patients) and re-estimation using NONMEM with FOCE interaction method, by computing the empirical relative standard error (RSE) and the relative root mean square error (RMSE).

PopDes vs Simulation Results

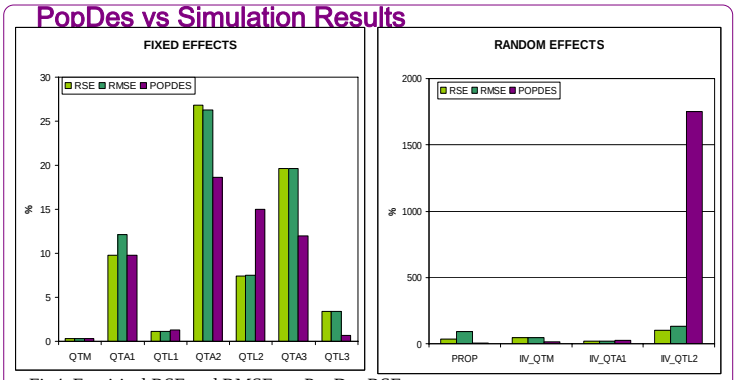

Fig4. Empirical RSE and RMSE vs. PopDes RSE

The expected RSEs obtained from the Population Fisher Information Matrix given by PopDes provided the same trend as that obtained after simulation of 500 datasets with the Optimal record time design, for the fixed effect parameters. Design satisfying because smaller than 20% (except for QTA2).

Concerning the parameters measuring the intersubject variability, RSE for IIV_QTL2 was different between PFIM and simulations.

Conclusion

A design with 7 ECG's records leads to a good estimation of circadian QTc rhythm parameters.

This ECG record time design could be applied in regular QTc studies when data are analyzed by population PK/PD modeling in addition of ECG record times relative to the PKPD model of the tested drug.

Next step: Optimal ECG record time design for parameter estimation of PKPD models of positive controls.

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2. Piotrovsky, V. « Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. » APPSJ 7.3 (2005):E609-E624

3. I. Georgueva, K. Ogungbenro, G. Graham, S. Glatt, and L. Aarons. A program for individual and population optimal design for univariate and multivariate response pharmacokinetic and pharmacodynamic models. *Comput. Methods Programs Biomed.* **86**(1): 51-61 (2007).

4. K.Ogungbenro, I. Gueorgueva, G. Grahams, and L. Aarons. The use of a modified Fedorov Exchange Algorithm in Optimising Sampling Times for Population Pharmacokinetic Experiments. *Comp. Meth. Prog. Biomed.* 80(2): 115-125 (2005).