Optimal design and QT-prolongation detection in oncology studies

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Introduction

QT interval prolongation is considered as a biomarker of *torsade de pointe* (TdP) in cardiac safety assessment in drug development. While specific QT/QTc studies are usually performed in healthy volunteers, allowing an accurate estimation of such noisy data as QT interval length, those approaches are not feasible in the specific context of oncology, where patients only can receive the drug. A model-based strategy, including population approach may help the description of PKPD relationship while taking into account all sources of variability but the clinical constraints of phase I/II studies in oncology limit electrocardiogram (ECG) schedules.

Objective

Our aim is to propose a cardiac safety assessment method, based on both optimal sampling design and population PKPD modelling. The ultimate goal is to estimate the power of detection of any potential effect of an anticancer drug on QT interval length.

Methods

Model Building

Baseline poly-cosine QT model :

- Built on a thorough QT/QTc study data (62 + 87 healthy volunteers) :
- Exponential inter-individual variability (IIV) on every parameter.
- Additive residual error model.

$$QT(t) = QT_M(t) \cdot \left(1 + \sum_{n\in\{1,2,3\}} QTA_n \cdot \cos\left(\frac{t - T_{L_n}}{24/2^{n-1}}\right)\right)$$

Drug effect is assumed linear on Mesor :

- Inter-individual variability on slope parameter γ.

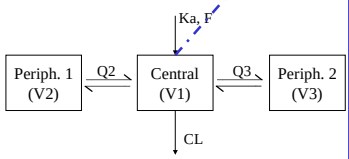
$$QT_M(t) = QT_{M_0} \cdot (1 + \gamma \cdot C(t))$$

PK model :

The chosen PK model was a 3-compartments model, with first order absorption and elimination. Inter-Individual Variability (IIV) on every parameter except inter-compartment constants and 2nd peripherical volume.

The model was built from the data of 2 phase 1 studies :

- 14 patients, administered IV multiple doses and oral single dose
- 35 patients administered oral multiple doses



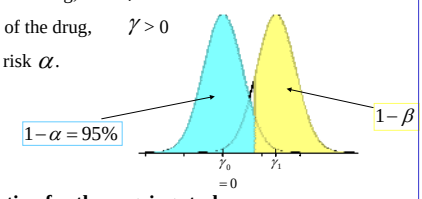
Design Study

Power of detection of a drug effect :

The model described above was then used in order to evaluate an ECG measurement schedule. The Fisher Information Matrix (FIM) relative to a known design was computed using PopDes 3.0, thus giving the precision of estimation of the model parameters. The resulting distribution of drug effect parameter was then used to assess the power (1 - β, with β the 2nd order risk) of the design.

- *Null hypothesis* H_0 *:* no QT effect of the drug, $\gamma = 0$
- *Alternate hypothesis* H_1 *:* QT effect of the drug, $\gamma > 0$

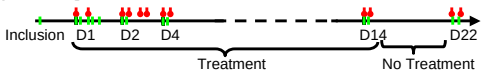
H_0 will be rejected with a 5 % first order risk α. The power of detection was computed for $\gamma \in [10^{-3};5]$ which corresponds to clinically relevant values of QT prolongation ($[5\,ms;150\,ms]$).



ECG Measurement Schedule Evaluation for the ongoing study

The evaluated study had 100 subjects and 14 ECG sampling times per patient (see below, green marks correspond to an ECG measurement and red marks correspond to dose events.

Individual PK profiles were assumed to be known, as ECG sampling is not linked to PK sampling. All the parameters of the QT model were considered estimated.



ECG Measurement Schedule Optimization

The optimal ECG measurement schedule was computed by maximizing the determinant of the FIM (D-Optimal Design), using a Fedorov exchange algorithm, as it is implemented in PopDes 3.0 under MATLAB.

Results

Model Building

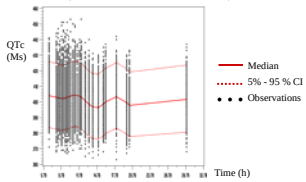
Baseline poly-cosine QT model :

Parameter values and relative standard error (RSE)

	QTM_0 (ms)	QTA1	QTL1 (hour)	QTA2	QTL2 (hour)	QTA3	QTL3 (hour)	Erra (ms)
Estimates	400	0.0112	12	0.0103	7.66	0.00732	5.73	5.35
(RSE %)	(0.214)	(12)	(1.98)	(7.75)	(1.04)	(3.8)	(0.609)	(2.5)
IIV	0.000766	0.0838	2.4	0.0287	0.488	0.047	0.0908	.
(RSE %)	(10.7)	(32.3)	(24.3)	(43.2)	(26.2)	(40.9)	(23.7)	

Numerical and visual predictive checks

Observed Values compared to Simulated Confidence Interval			
CI	**Obs below CI (%)**	**Obs in CI (%)**	**Obs above CI (%)**
MEDIAN	49.2	.	50.8
[P1-P99]	0.6	97.6	1.8
[P5-P95]	3.8	90.6	5.6
[P10-P90]	9.4	80.6	10
[P25-P75]	23.3	51.9	24.8

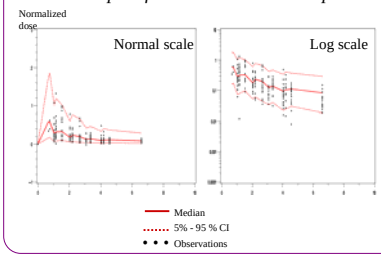


PK model

Parameter values and relative standard error (RSE)

	CL	Ka	F	V1	V2	V3	Q2	Q3	ErrA	Errp
Estimates	54	0.74	0.30	45	630	61	12	35	0.0092	0.31
(RSE %)	(10.1)	(12)	(10.3)	(14.6)	(28.8)	(11.7)	(12.8)	(12.8)	(32.2)	(6.36)
IIV	0.114	0.342	0.277	0.202	.	0.143	.	.		
(RSE %)	(38.8)	(32.2)	(28)	(35.5)		(46.9)				

Example of Numerical and visual predictive checks (oral single dose)



Observed Values compared to Simulated Confidence Interval			
CI	**Obs below CI (%)**	**Obs in CI (%)**	**Obs above CI (%)**
MEDIAN	61.1	.	38.8
[P1-P99]	1.7	97.6	0
[P5-P95]	6.1	91.7	2.2
[P10-P90]	10.4	85.3	4.3
[P25-P75]	26.4	60.2	13.4

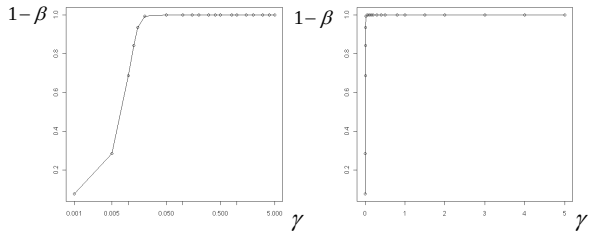
Design Study

Power of detection of drug effect :

QT prolongation is not a parameter of our model. Therefore, we have to evaluate the value of drug effect γ that may cause a QTc prolongation.

$\gamma = 0.02$ corresponds to a prolongation of 5 ms for a highly exposed patient.

$\gamma = 0.0125$ corresponds to a prolongation of 5 ms for a normally exposed patient.



Power vs. Drug effect. Power > 80 % for $\gamma > 0.0125$ and > 90 % for $\gamma > 0.02$

Schedule Evaluation and Comparison with optimal design

An optimal design was computed in order to see to what extent the ECG sampling schedule we used could be improved. The constraints on the timepoints were to keep the same daily structure (5 samples on D1, 2 samples on D2, 2 samples on D4, 2 samples on D14, 2 samples on D22). The precision of estimation is satisfactory for both designs, but this information may help for future studies.

Sampling times :	**D1**	**D2**	**D4**	**D14**	**D22**
Initial design	0, 1.5, 4, 5.5, 8 h	0, 1.5h	0, 1.5h	0, 1.5h	0, 1.5h
Optimized design	3.1, 7.2, 7.7, 9.5, 10h	0, 5h	0.9, 4.5h	2.9h, 5.7h	0, 1.6h

	QTM_0	Gamma	QTA1	QTL1	QTA2	QTL2	QTA3	QTL3	Erra
RSE % (Study Design)	0.4	24.3	27.1	5.9	8.5	13.7	10.9	2.9	4.73
RSE % (Opt. Design)	0.29	15.2	10.2	2.9	5.3	7.8	7.3	1.5	5.4

Conclusion

This work proposes a modelling and simulation based strategy in order to show QT prolongation risk is correctly assessed in the context of clinical trials in oncology.

The prelimiray results are very encouraging, as the power of detection of our sampling design is above 90% for clinically relevant values of drug effect. However, the assumptions underlying our approach will have to be challenged throughout clinical development.

References

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Ogungbenro K, Dokoumetzidis A, Aarons L. "Application of optimal design methodologies in clinical pharmacology experiments". Pharm Stat. (2009) Jul-Sep;8(3):239-52.