Can Bayes prevent QTC-interval prolongation? A challenge beyond random effects.

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Introduction

Early in the course of clinical development, it is important to be able to assess the propensity of non-antiarrhythmic drugs to prolong the QT/QTc interval. The current regulatory guidelines suggest using the largest time-matched mean difference between drug and placebo (baseline-adjusted) over the sampling interval, thereby neglecting any exposure-effect (PKPD) relationship and nonlinearity in the physiological fluctuation of QT interval. This leads to major issues in terms of data analysis: high rate of false positives and low statistical power. We propose the use of a parametric Bayesian approach to characterise the exposure-effect relationship and optimise the design of QT/QTc specific studies.

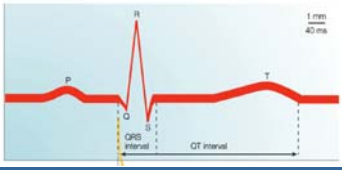


Figure 1. ECG trace showing the QT interval

Objectives

- To use a Bayesian hierarchical modelling approach to characterise the time course and variability in QT interval and to establish the PKPD relationship of three compounds known to cause QT/QTc interval prolongation.
- To estimate the rate of false positives/negatives of the proposed Bayesian approach relative to the regulatory 'double-delta' method.

Methods

Clinical database

Data from single dose, randomised placebo-controlled crossover studies were extracted from GlaxoSmithKline's clinical data repository:

1. **Sotalol** (160 mg)**:** n= 29 subjects
2. **Grepafloxacin** (600 mg): n= 31 subjects
3. **Moxifloxacin** (400 mg): n= 137 subjects

Pharmacodynamic Model of QT/QTc Prolongation

The QT interval was described as a function of heart rate, clock time and concentration by the following equation:

$$QT = QT_0 \cdot RR^{\alpha} + A \cdot \cos\left(\frac{2\pi}{24}(t-\phi)\right) + slope \cdot C$$

where,
QT_0 (ms) – intercept of QT-RR relationship (sex was included as a covariate for this parameter)
RR (s) – interval between successive R waves
α – individual heart rate correction factor
A (ms) – amplitude of circadian rhythm
t – clock time
Φ (h) - phase
Slope – (ms/concentration) – linear pharmacodynamic relationship
C – predicted concentration of drug at time of QT measurements

Bayesian Hierarchical Models

The k^{th} observed QT measurement for the j^{th} occasion for the i^{th} (QT_{ijk}) individual was assumed to be normally distributed around the individual predicted QT measurement f_{ijk} with an unknown precision τ:

$$QT_{ijk} \sim N(f_{ijk}, \tau), \quad \tau = \frac{1}{c^2}$$

Non-informative priors were specified as:

$$\theta \sim MVN(\vec{\mu}, \Sigma^{-1}), \quad \vec{\mu} = \begin{bmatrix} QT_0 \\ \alpha \\ A \\ \phi \\ Slope \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \Sigma^{-1} = 0.0001 \cdot I_5$$

where θ is a vector of population mean parameter estimates, $\vec{\mu}$ is the prior of the population means, Σ^{-1} is the precision of the prior for the population mean parameter values and *I* is the identity matrix. The inverse of the between subject variance, Ω^{-1}, arises from a Wishart distribution: $\Omega^{-1} \sim W(\rho\Omega,\rho)$ with ρ=5 degrees of freedom, where Ω represents our prior guess at the order of magnitude of the covariance matrix. Finally, non-informative Gamma(0.001,0.001) priors were assumed for measurement precision and interoccasion variability of QT_0.

A monitor was set to calculate the probability of an effect greater than 10 ms at a concentration of C_{max} by counting the proportion of values in the posterior sample of Slope·C_{max} which are greater than 10 ms.

WinBUGS version 1.4 was used to fit the QT data. Two MCMC chains were run for 25,000 samples and pooled to provide parameter estimates.

Results

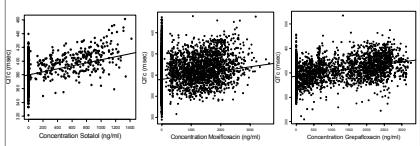


Figure 2. QTc vs. Concentration with Model Population Prediction for the Three Studies

	Grepafloxacin (n=29)	Sotalol (n=30)	Moxifloxacin (n=137)
QT_0 (ms)	393 (388 – 398)	380 (375 – 383)	396 (394 – 398)
Sex Effect (ms)	-	17 (7 – 27)	8 (5 – 12)
α	0.29 (0.25 – 0.32)	0.28 (0.25 – 0.31)	0.41 (0.40 – 0.43)
A (ms)	5.1 (3.9 – 6.1)	3.4 (2.7 – 4.1)	2.7 (2.2 – 3.0)
φ (h)	5.8 (4.6 – 7.1)	6.4 (5.4 – 7.4)	9.5 (7.7 – 11.1)
Slope (ms/conc)	0.0098 (0.0069 – 0.013)	0.022 (0.018 – 0.026)	0.0040 (0.0033 – 0.0046)
IOV (QT_0) %	2.5 (2.0– 3.4)	1.3 (1.1 – 1.7)	0.65 (0.54 – 0.79)
BSV (QT_0) %	2.3 (1.6 – 3.4)	2.2 (1.6 – 3.1)	1.9 (1.5 -2.3)
BSV (α) %	21 (15 – 31)	18 (13 – 26)	15 (11 – 19)
BSV (A) %	2.4 (1.5 – 9.5)	3.6 (2.2 – 9.2)	4.4 (2.9 – 9.6)
BSV (φ) %	16 (8 – 42)	12 (7 – 28)	14 (7 – 39)
BSV (Slope) %	65 (52 – 87)	34 (26 – 47)	83 (73 – 96)
Residual Error (ms)	15.0 (14.7 – 15.4)	5.9 (5.7 – 6.18)	5.3 (5.2 – 5.4)
Probability Effect >10 ms at C_{max}	1.0	1.0	1.0

Table 1. Parameter Estimates. Mean (95% Credible Interval)

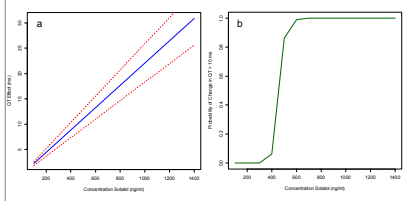


Figure 3: a) Estimate (95% CI) of QT prolongation *vs.* sotalol concentrations and b) Probability of QT prolongation > 10ms *vs.* sotalol concentration range

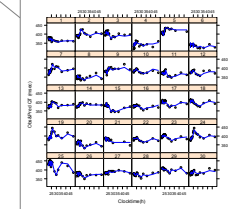


Figure 4. Individual QT time course after administration of sotalol

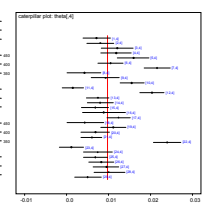


Figure 5. Individual slope parameters with 95% CI's for grepafloxacin

Simulations

Simulations were designed to replicate a three-period crossover study in 10, 20 or 30 subjects receiving single doses of placebo, a positive control (moxifloxacin) and study drug. A one compartment model with population parameters k_a = 0.75 h^{-1}, k_{el} = 0.125 h^{-1}, V = 100L and Dose = 100 mg was used to simulate study drug concentrations. QT measurements were made at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours post-dose. 250 simulated populations were used to estimate false positive/negative rates using the two following methods:

1. Double Delta – The change from baseline in QTcF (Fridericia correction α=0.33) for study drug minus the change from baseline for placebo at each post-dose sampling time was analysed using a repeated measures model. If the 90% CI at each time point exclude an effect of 10ms or greater, the study was considered to be negative

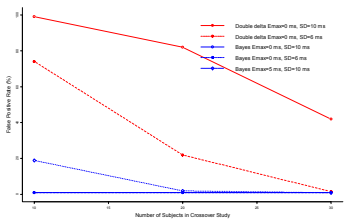
2. Bayesian hierarchical model – A study was considered to be negative if the probability of an effect greater than 10 ms at C_{max} was less than 5%.

False negatives. The maximum effect was assumed to be either 10 or 20 ms, and σ was set to 10 ms.

	E_{max} = 10 ms		E_{max} = 20 ms	
Subjects	Double Delta	Bayesian	Double Delta	Bayesian
10	<1%	1.2%	<1%	<1%
20	<1%	1.2%	<1%	<1%
30	<1%	1.6%	<1%	<1%

Table 2. False negative rates.

False positives. We considered cases where σ=10 ms or σ=6 ms and the true maximum effect effect was either 0 or 5 ms.



Conclusions

- An integrated hierarchical Bayesian modelling approach can be used to accurately describe the variation in QT measurements due to heart rate, circadian rhythm and drug effect.
- The double-delta method yields unacceptable high levels of false positives (Type I error). This is overcome by the proposed methodology.
- In addition to higher accuracy in the estimates of drug effect, the Bayesian approach enables easy translation of findings into clinically relevant measures.

References

- ICH Guidance for Industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.
- Piotrovsky V. *AAPS Journal* 7(3):E609-24, 2005.

Acknowledgements

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