

Identifying the translational gap in the evaluation of drug-induced QTc interval prolongation

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Introduction

Assessment of the propensity of new drugs in prolonging QT/QTc interval is critical for the progression of compounds into clinical development. Given the similarities in QTc response between dogs and humans, dogs are often used in pre-clinical CV safety studies. However, it is unclear how the changes in QTc interval in dogs can be translated into risk of QTc interval prolongation in humans

Objectives

The objective of our investigation was to assess the predictive performance of a model-based approach for the evaluation of interspecies differences in drug-induced QTc prolongation.

Methods

PK and PD data from typical CV safety studies in conscious dogs and first time in human trials in healthy subjects were used to evaluate the effects of GSK945237, SB237376 and GSK618334, three new compounds in development. First, drug concentrations at the time of each QT measurement were derived. Concentration-QT interval data were then analysed using a hierarchical PKPD model previously implemented and tested with positive controls, namely moxifloxacin, sotalol and cisapride. A threshold of 10 msec was used to explore the probability of QTc interval prolongation at the relevant therapeutic range. Results were compared using model-derived PC₅₀ estimates, i.e., the concentration associated with a probability of 50% increase in QTc interval ≥10msec. Modelling was performed using WinBUGS v1.4.3., whilst R was used for data manipulation, graphical and statistical summaries.

The PKPD model

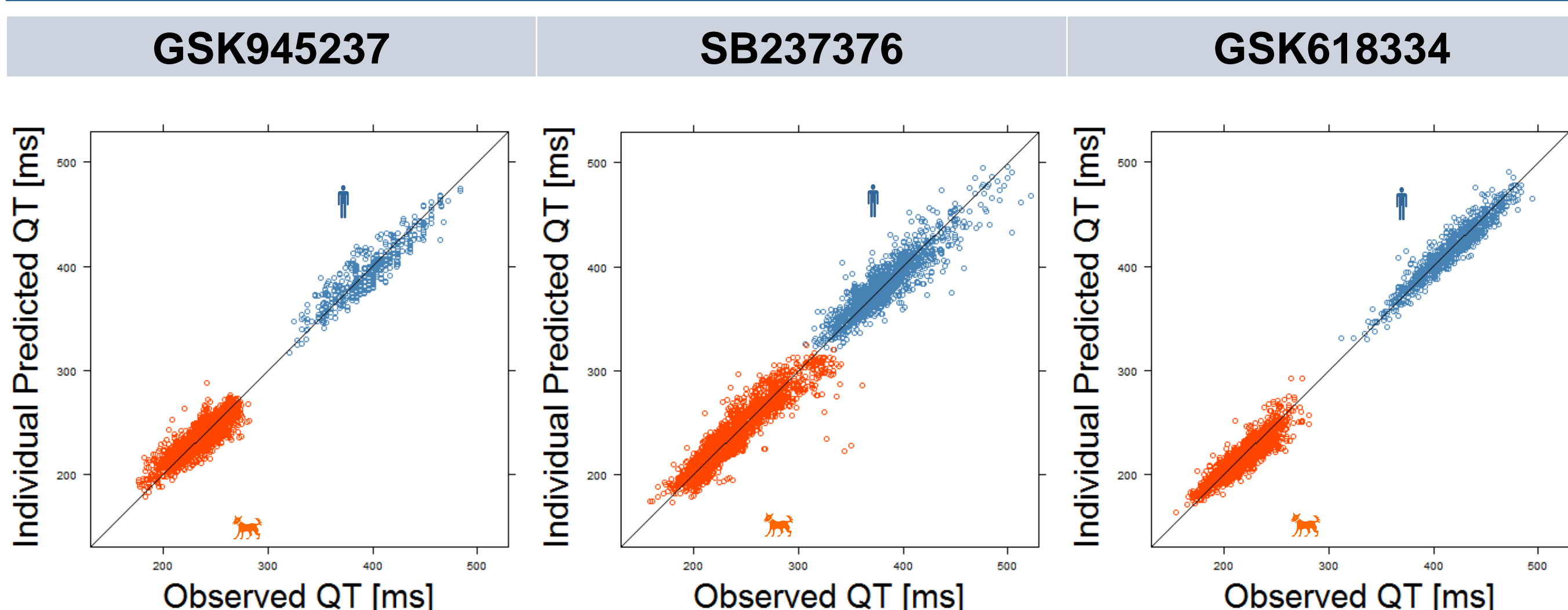
$$QT = QT_{c0} \cdot RR^{\alpha} + A \cdot \cos \left[\frac{2\pi}{24} (t - \varphi) \right] + Slope \cdot C$$

QT_{c0}, α, A and φ are system-specific parameters indicating the baseline RR corrected QT, the RR-correction factor, the amplitude of the circadian rhythm and the phase of the circadian rhythm, respectively. Slope is the drug-specific parameter and hence the one that quantifies the propensity for QTc interval prolongation.

Results

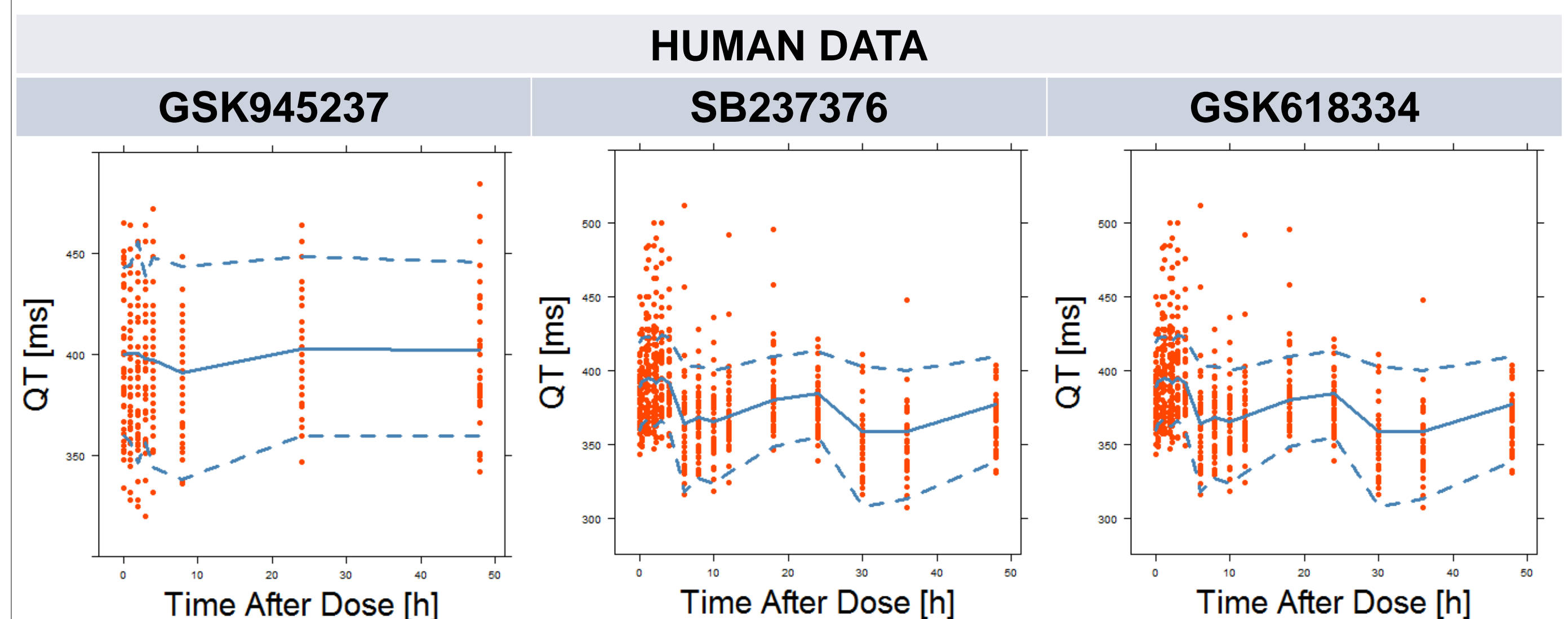
Goodness-of-fit plots show comparable model performance for both dog (orange dots) and human (blue dots) data.

Goodness of fit



Our analysis showed that GSK945237 does not prolong QTc interval neither in humans nor in dogs, whilst SB237376 shows a weak effect in both species, but does not reach the 10ms threshold at the expected therapeutic range. In contrast to the other two compounds, GSK618334 was found to cause QTc-interval prolongation ≥ 10 msec. These results differed from typically reported results in telemetered dogs, which are often based on non-parametric methods and statistical summaries of the data.

Visual Predictive Checks, 10°- 90° percentile

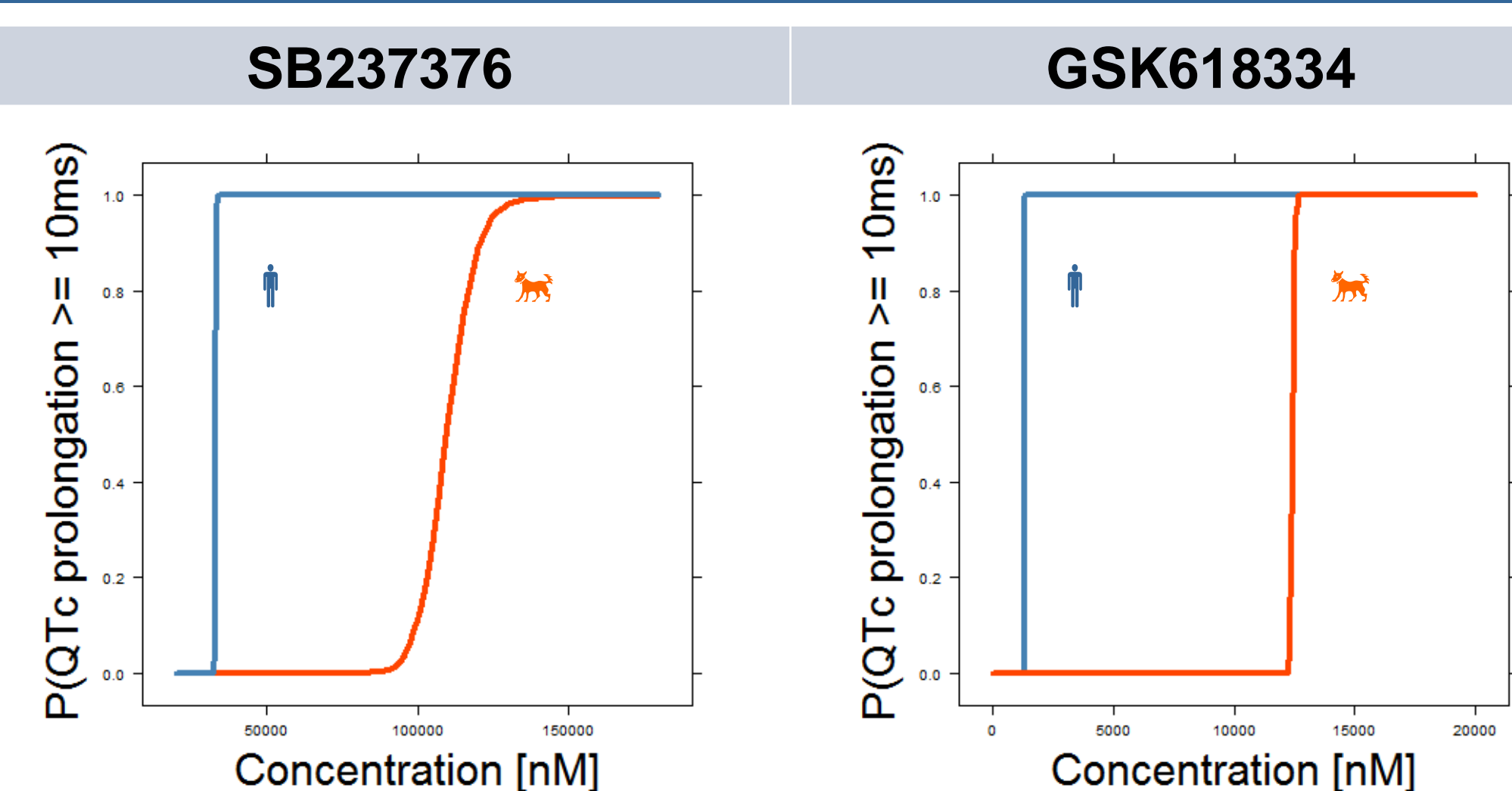


Drug-specific parameter estimates

	GSK945237	SB237376	GSK618334
DOG			
Slope [s/M]	9.76 (-12.4, 32.3)	91.88 (74.32, 108)	804.3 (793.9, 814.6)
PC₅₀* [nM]	5000000	109500	12440
C_{max} [nM]	62936.18	24660.21	16698.98
HUMAN			
Slope [s/M]	11.4 (7.58, 17.1)	301 (297, 304)	7558 (7554, 7561)
PC₅₀* [nM]	4005000	33275	1323.25
C_{max} [nM]	13096.86	329.17	4295

*Concentration associated with a P(QTc increase ≥ 10ms) = 50%

Probability of a QTc prolongation ≥ 10 ms



Overall our findings suggest interspecies differences in drug potency, as indicated by the derived PC₅₀ estimates, i.e., the concentration corresponding to a 50% probability of QTc prolongation ≥10 msec.

Conclusions

Although no QTc-prolonging effects were observed for GSK945237, the results from the analysis of SB237376 and GSK618334 illustrate the importance of a quantitative approach to characterise drug effects in early drug development. Furthermore, our analysis highlights the need for suitable pharmacokinetic sampling and some understanding of expected therapeutic exposure to accurately interpret pre-clinical findings in preclinical species.

Based on the evidence obtained so far from 6 compounds, dogs appear to be a suitable, but less sensitive species to the pro-arrhythmic effects of drugs, as compared to humans.