

Population PK/PD modelling of QT-interval prolongation in awake dogs and humans

E. Marostica¹, K. Van Ammel², A. Teisman², J. Van Bocxlaer¹, K. Boussey¹, F. De Ridder³, A. Vermeulen^{1,3}, D. J. Gallacher²

Laboratory of Medical Biochemistry and Clinical Analysis, Ghent University, Belgium¹,
Global Safety Pharmacology² and Model Based Drug Development³, Janssen R&D, Beerse, Belgium



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Introduction

- Drug-induced Torsades de Pointes (TdP) and consequent sudden cardiac death are positively correlated with QT-interval prolongation.
- Conversely, not all "QT-prolonging drugs" induce TdP.
- Nevertheless, the early risk biomarker QT-interval prolongation is frequently used to deselect drugs.
- An improved understanding of it is needed.

Objectives

- To develop a pharmacokinetic/pharmacodynamic (PK/PD) model to describe "QT data" in awake beagle dogs and humans receiving drugs that are known to affect the QT interval (see Table 1).
- To determine the unbound concentration needed to reach 50% probability (CP_{50}) of QT interval prolongation/shortening greater than 10 ms.
- To assess the translational opportunities of the approach between species.

Materials

Compound	Awake dogs	Humans
Moxifloxacin	# Dogs: 2 (PK), 6, and 10 (vehicle only) Doses: placebo, 10, 30, and 100 mg/kg	# Subjects: 33 Doses: placebo and 400 mg
C1	# Dogs: 6 Doses: placebo, 15, 30, and 60 mg/kg	# Subjects: 37 Doses: placebo, 250, 500, and 750 mg
C2	# Dogs: 4 + 4 (vehicle only) Doses: placebo and 10 mg/kg	# Subjects: 42 Doses: placebo and 750 mg
C3	# Dogs: 6 Doses: placebo and 20 mg/kg	# Subjects: 71 Doses: placebo, 4, 8, 20, 40, 60, 90, 150, 225, 300, 350, and 400 mg

Table 1: For each compound, the number of dogs and humans as well as the doses are indicated.

Methods

- Different PK models were implemented in NONMEM 7.1 to describe plasma concentration-time profiles of moxifloxacin, C1, C2, and C3 in both species.
- Log-normal distributions and a constant CV error model were assumed. Log-transform-both-sides approach and the FOCE method were used for parameter estimation.
- The QT interval was modelled as [1]:

$$QT = QT_0 \left(\frac{RR}{RR_{ref}} \right)^\alpha + A \cos \left(\frac{2\pi}{24} (t - \varphi) \right) + E(t) \quad (1)$$

$$E(t) = \text{slope} C \quad \text{Hill} \quad E(t) = \frac{E_{max} C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

- QT_0 : intercept of the QT-RR relationship; α : individual heart rate correction factor; A and φ : amplitude and phase of the circadian rhythm, respectively.
- The best model was selected according to the lowest objective function value provided by NONMEM and then implemented within a fully Bayesian framework using WinBUGS 1.4.3.
- The probability of QT-interval prolongation/shortening greater than 10 ms was assessed for all the compounds.
- Based on the posterior distributions of the parameter estimates, the probability curves of the typical and the new subject/dog were calculated. The corresponding unbound CP_{50} was evaluated.
- The estimated $slope$ values in both species were then compared and a regression curve was estimated:

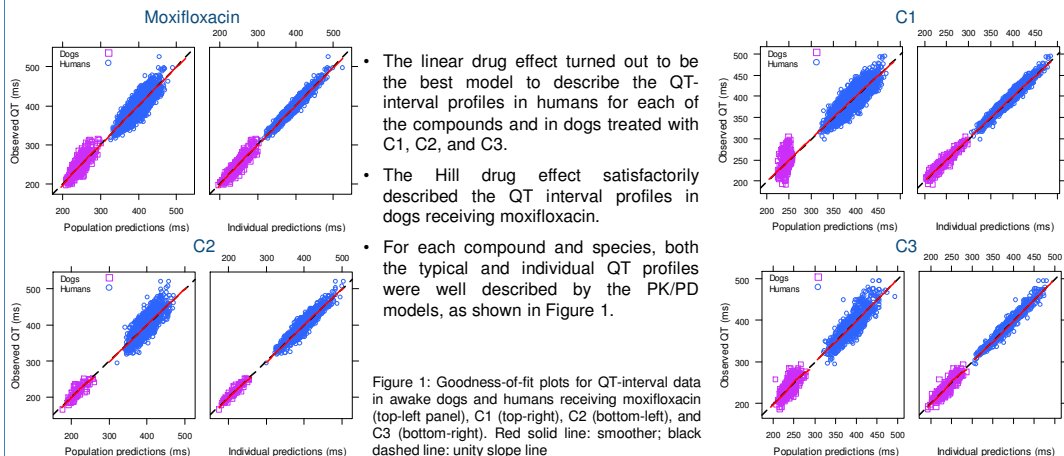
$$slope_{humans} = a_0 + a_1 slope_{dogs}$$

- where a_0 is the intercept of the regression curve and a_1 is the translational scaling factor.
- When the Hill model was identified, the corresponding $slope$ value was calculated considering the sigmoid drug effect between 20% and 80%.

Results

Compound	Awake dogs	Humans
Moxifloxacin	1-comp model with first order absorption. Each dose was characterized by a different F1.	1-comp model with first order absorption. A mixture distribution was assumed for ALAG1. IOV on k_{el} was estimated.
C1	1-comp model with sequential zero-first order absorption. IOV on k_{el} was estimated as well as ALAG1.	1-comp model with sequential zero-first order absorption. A different F1 was estimated for the different dose levels.
C2	1-comp model with first order absorption.	2-comp model with first order absorption.
C3	1-comp model with first order absorption.	2-comp model with sequential zero-first order absorption. Different ALAG1 was estimated for each of the formulations.

Table 2: PK models identified to describe the plasma concentration-time profiles of each compound in awake dogs and humans. First order elimination was considered in all cases. F1: relative bioavailability; IOV: inter-occasion variability; ALAG1: delay of the absorption process; k_{el} : absorption rate constant



- The linear drug effect turned out to be the best model to describe the QT-interval profiles in humans for each of the compounds and in dogs treated with C1, C2, and C3.
- The Hill drug effect satisfactorily described the QT interval profiles in dogs receiving moxifloxacin.
- For each compound and species, both the typical and individual QT profiles were well described by the PK/PD models, as shown in Figure 1.

Figure 1: Goodness-of-fit plots for QT-interval data in awake dogs and humans receiving moxifloxacin (top-left panel), C1 (top-right), C2 (bottom-left), and C3 (bottom-right). Red solid line: smoother; black dashed line: unity slope line

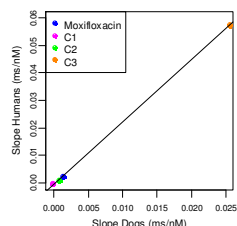


Figure 2: Comparison of estimated slope values across all the compounds and between species

- Figures 2 (all compounds) and 3 (no C3) show the $slope$ values estimated for dogs and humans.
- Low concentrations were available in dogs receiving C3. Through extrapolation towards higher concentrations, outside the observed range, a prolongation effect could be seen.
- The translational scaling factor was found to be 2.3 when all the compounds were considered (Figure 2) and 1.5 in the case C3 was removed (Figure 3).

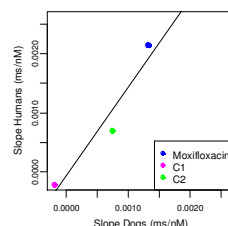


Figure 3: Comparison of estimated slope values across three compounds and between species

- The probability curves for the typical and the new subject/dog are shown in Figure 4.
- Table 3 shows that similar unbound concentrations (CP_{50}) of moxifloxacin, C1, and C2 are needed in dogs and humans to reach the same prolongation/shortening effect. A greater difference in CP_{50} values was found when dogs and humans received C3.

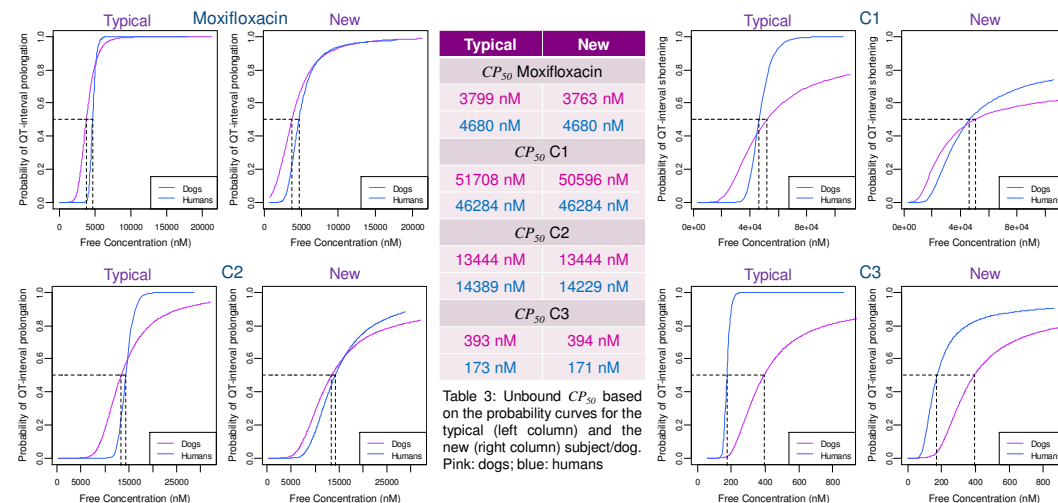


Figure 4: Probability of QT-interval prolongation/shortening greater than 10 ms in awake dogs and humans receiving moxifloxacin (top-left panel), C1 (top-right), C2 (bottom-left), and C3 (bottom-right). The probability curves for the typical subject/dog (left hand side of each panel) as well as for a new subject/dog (right hand side of each panel) are reported for each compound.

Conclusions

- The PK/PD model was able to describe both QT-interval prolongation and shortening.
- The knowledge of the translational scaling factor can provide an insight into the possible effect that a new compound may have on the QT interval in humans, based on the drug effect observed in dogs.
- The inclusion of more compounds will definitely refine our understanding of the relationship between dogs and humans by improving the estimate of the translational scaling factor.

Reference: [1] Anne S.Y. Chain, Vincent F.S. Dubois et al, Identifying the translational gap in the evaluation of drug-induced QTc interval prolongation, Br J Clin Pharmacol 76, pp. 708-724, 2013