Concentration-QTc Analysis Following Dofetilide Administration in Telemetered Beagle Dogs

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Figure 1. PK data following dofetilide (0.03 mg/kg) ± SD

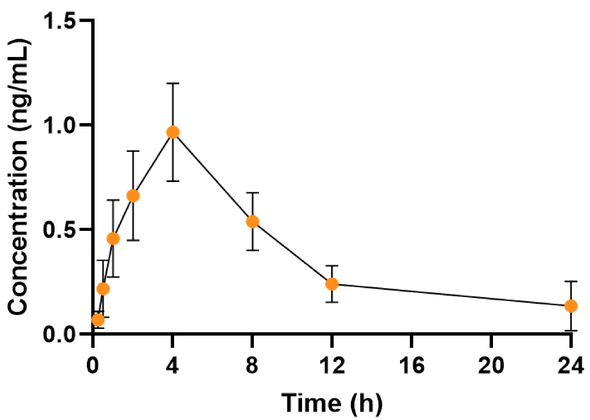


Figure 2. QTc prolongation following dofetilide (0.03 mg/kg) ± CI

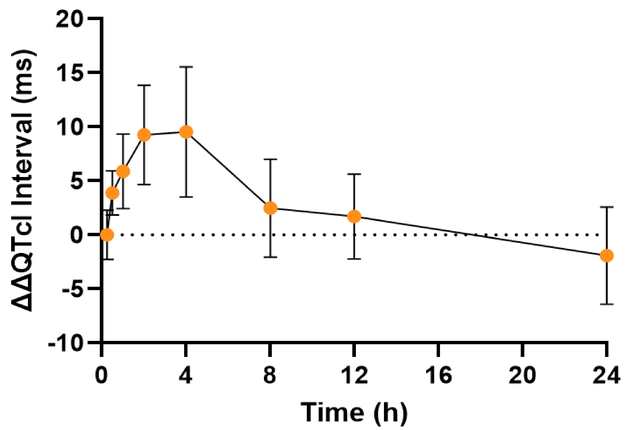


Figure 3. Concentration-QTc analysis (± 90% CI) with individual points

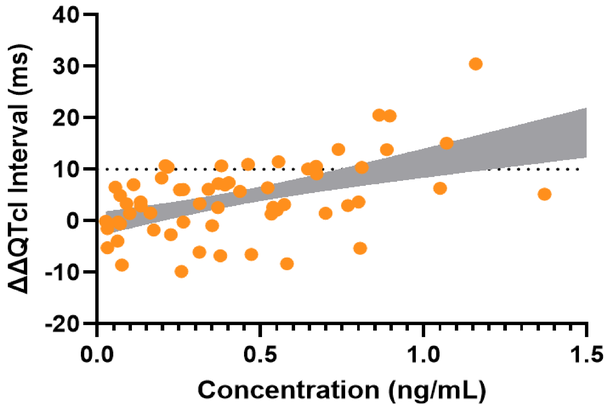


Figure 4. Concentration-QTc analysis (± 90% CI) with deciles

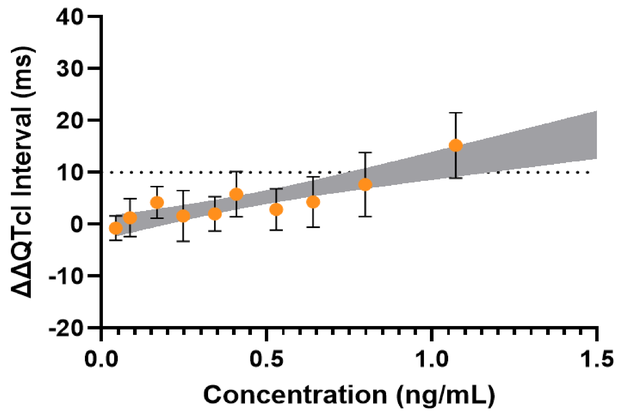


Figure 5. Concentration-QTc analysis with literature comparison

Study	Slope (ms/ng/mL) (90% CI)	Intercept (ms)	Cmax (ng/mL)	Estimate at Cmax (ms) ± 90% CI	Concentration (ng/mL) needed to detect a 10 ms increase in QTcI
Current Study (Inotiv, 2021)	11.9 (7.6 to 16.2)	-0.7227	0.967	10.8 (8.1 to 13.5)	0.739
Komatsu et. al 2019 – J-ICET	11.3 (9.5 to 13.0)	-1.12	1.09	11.1 (9.4 to 12.9)	0.850

Background

The ICH S7B guidance describes conduct of the in vivo QTc assay, where agents are evaluated at and above therapeutic plasma concentrations. Traditional analysis techniques utilize a by-time-point analysis where treatment groups are statistically compared to a vehicle group. While this approach can demonstrate adequate sensitivity to detect a clinically relevant increase in the QTc interval, it fails to account for observed plasma exposures. Exposure-response (ER) analysis can utilize pharmacokinetic data collected from the same animals to determine the relationship between exposure and QTc interval prolongation.

Objectives

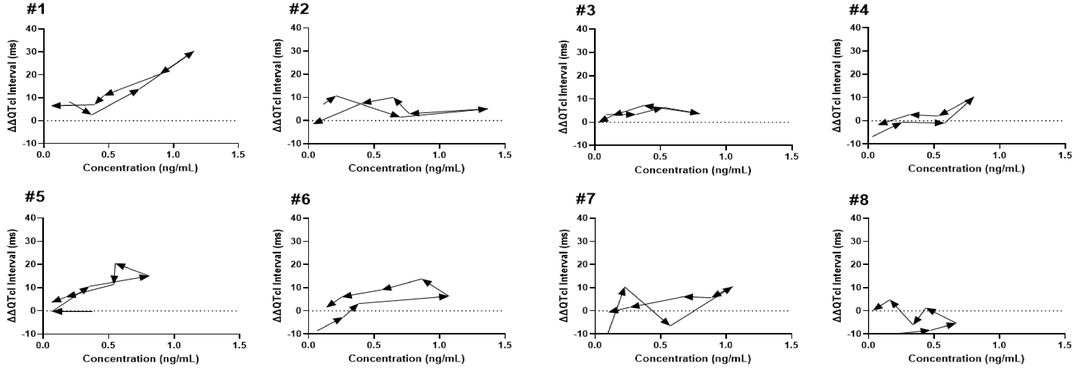
The goals of this study were to determine the ER relationship of dofetilide in beagle dogs and compare results to a by-time-point analysis.

Methods

Eight male beagles were dosed (PO) with 0.03 mg/kg of dofetilide with telemetry collected for 24 hours (CV Phase). Heart rate-corrected QT (QTcI) intervals were calculated with data organized into 15-minute segment averages. Individual baseline-adjusted changes from vehicle (ΔΔQTcI) were also calculated. The same animals were administered 0.03 mg/kg of dofetilide following a washout to determine plasma exposures at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours postdose (PK phase). Data from 0.25 to 24 hours postdose were included in the analysis. During model selection for the ER analysis, linear, log-linear, and nonlinear Emax models were compared. The best fit was determined using the corrected Akaike's Information Criterion (AICc). Individual ΔΔQTcI data points were matched with corresponding exposure measurements from the PK phase. ΔΔQTcI data points were the 15-minute segment average preceding the corresponding exposure timepoint. Matched pairs were pooled and analyzed to determine the concentration-QTc relationship. Calculations included slope, intercept, and 90% confidence intervals.

Results

Individual animal data were inspected for hysteresis. Significant hysteresis was not observed in any animal; therefore, adjustments were not made for the exposure-response modeling.



A linear model was the best fit for the data. The ER relationship (slope) was 11.9 ms per total ng/mL (90% CI: 7.557 to 16.22). The ER-predicted QTc change at Cmax (10.8 ms) was similar to the difference statistically detected using a by-time-point analysis (11.9 ms). Comparisons with previously published data suggests this analysis approach is reproducible between labs.

Conclusions

Our results suggest ER analysis can serve as an alternate approach to by-time-point comparisons while accounting for drug exposure. Inclusion of this data in regulatory submissions can increase confidence in data used to predict proarrhythmic risk.

References

Anonymous. ICH S7B: The non- clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals; 2005.

Chui, R.W., Baublits, J., Chandra, F.A., Jones, Z.W., Engwall, M.J., Vargas, H.M. (2021). Evaluation of moxifloxacin in canine and non-human primate telemetry assays: Comparison of QTc interval prolongation by timepoint and concentration-QTc analysis. *Clinical and translational Science*. Available online.

Komatsu, R., Mizuno, H., Ishizaka, T., Ito, A., Jikuzono, T., Kakoi, T,. Bando, M., Koga, T., Handa, J., Takashi, Y., Kanno, A., Ozaki, H., Chiba, K., for the Japan activity for Improvement of Cardiovascular Evaluation by Telemetry. (2018). Exposure- response analysis of drug-induced QT interval prolongation in telemetered monkeys for translational prediction to human. *Journal of Pharmacological and Toxicological Methods*, 99, 106606.