

POWER OF PHARMACOKINETIC-PHARMACODYNAMIC (PKPD) ANALYSIS TO DETECT QTc EFFECT IN PRECLINICAL SETTING

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Background

- The QT interval is a surrogate marker for pro-arrhythmic risk and is regularly assessed in preclinical cardiovascular safety studies (CVS)
- A QT prolongation of 2-5 ms in the dog can lead to a relevant 10 ms effect in human^{1,2}
- PKPD analysis is not regularly used in preclinical CVS but could ease translation to humans

Objectives

- To investigate the power of population PKPD analysis to detect different magnitudes of QT-prolongation in the conscious telemetered dog
- To compare the power and estimated drug effects with conventional statistical analysis (analysis of covariance, ANCOVA)³⁻⁵

Results

- Power:** PKPD analysis had a power of ~80% to detect a Δ QTc of 4 ms, ANCOVA only ~50% (Fig-2, left)
- False-positive rate:** higher by ANCOVA (40%) than by PKPD (< 5%).
- Dose-effect relationship:** similar estimates from PKPD analysis and ANCOVA

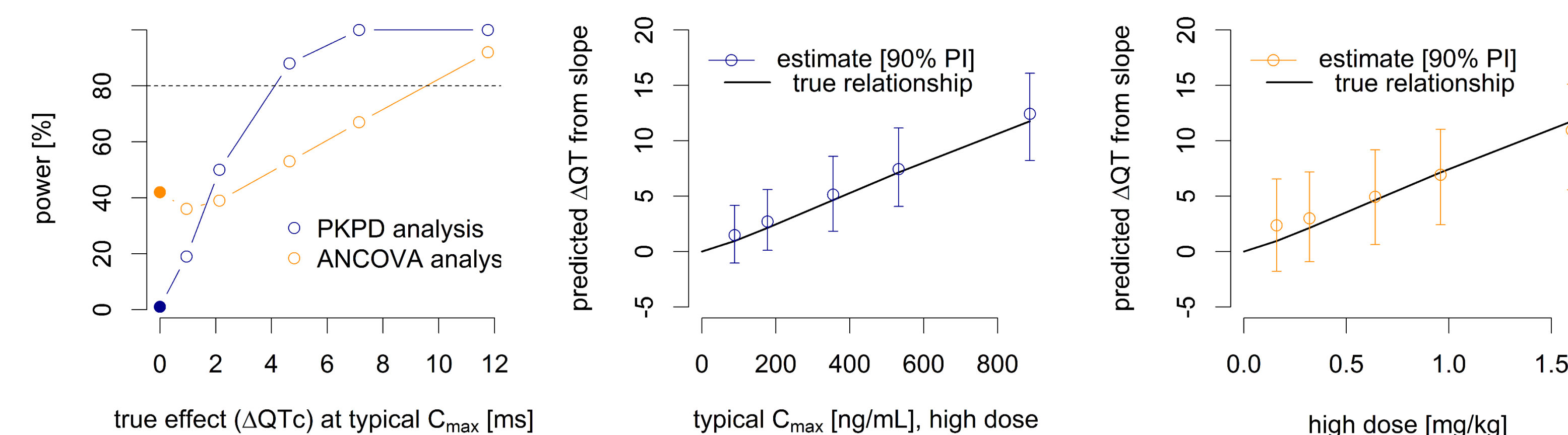


Fig-2: Left: Power estimates (open circles) and false positive rate (filled circles). Middle: predicted drug-induced Δ QTc from slope estimate by PKPD analysis or ANCOVA (Right). 90% PI: 90% prediction intervals.

Conclusions

- PKPD analysis showed very good power to detect small magnitudes of QTc prolongation in a typical preclinical setting. Compared to traditional ANCOVA superior power was observed.
- These results underscore the its value in preclinical safety testing. Sensitivity of estimates to PK profiles, number of PD sampling times / individuals should be tested.

Methods

- A realistic “true” PKPD model (Tab-1) was developed using data from vehicle arms of 28 CV studies and a sotalol study (positive control)
- QTc = individual heart rate corrected QT interval
- $QT_c(t) = BL + A \cdot \cos\left(\frac{2\pi}{24} \cdot (t - \varphi)\right) + \frac{E_{max} \cdot C(t)^\gamma}{EC_{50}^\gamma + C(t)^\gamma}$

Parameter	Typical value	BSV/IOV (CV%)
Baseline QTc, BL [ms]	254	5.6%/1.4%
Amplitude A [ms]	1.7	±1.7 ms
Shift φ [h]	19	11%
E_{max} [ms]	50	27%
EC_{50} [ng/mL]	2370	43%
Hill coefficient, γ	1.2	29%

Tab-1. Parameters from “true” PKPD model used for study simulations. BSV/IOV: between-subject/inter-occasion variability. Residual: ±6.2 ms

- The “true” PKPD model was used to simulated repeatedly (100x) CVS with decreasing dose intensities producing typical drug-induced Δ QTc at high-dose C_{max} : 0-12 ms (Fig-1)
- Each simulated study was analysed for drug effects using both PKPD and ANCOVA analysis and power was calculated (Fig 1):

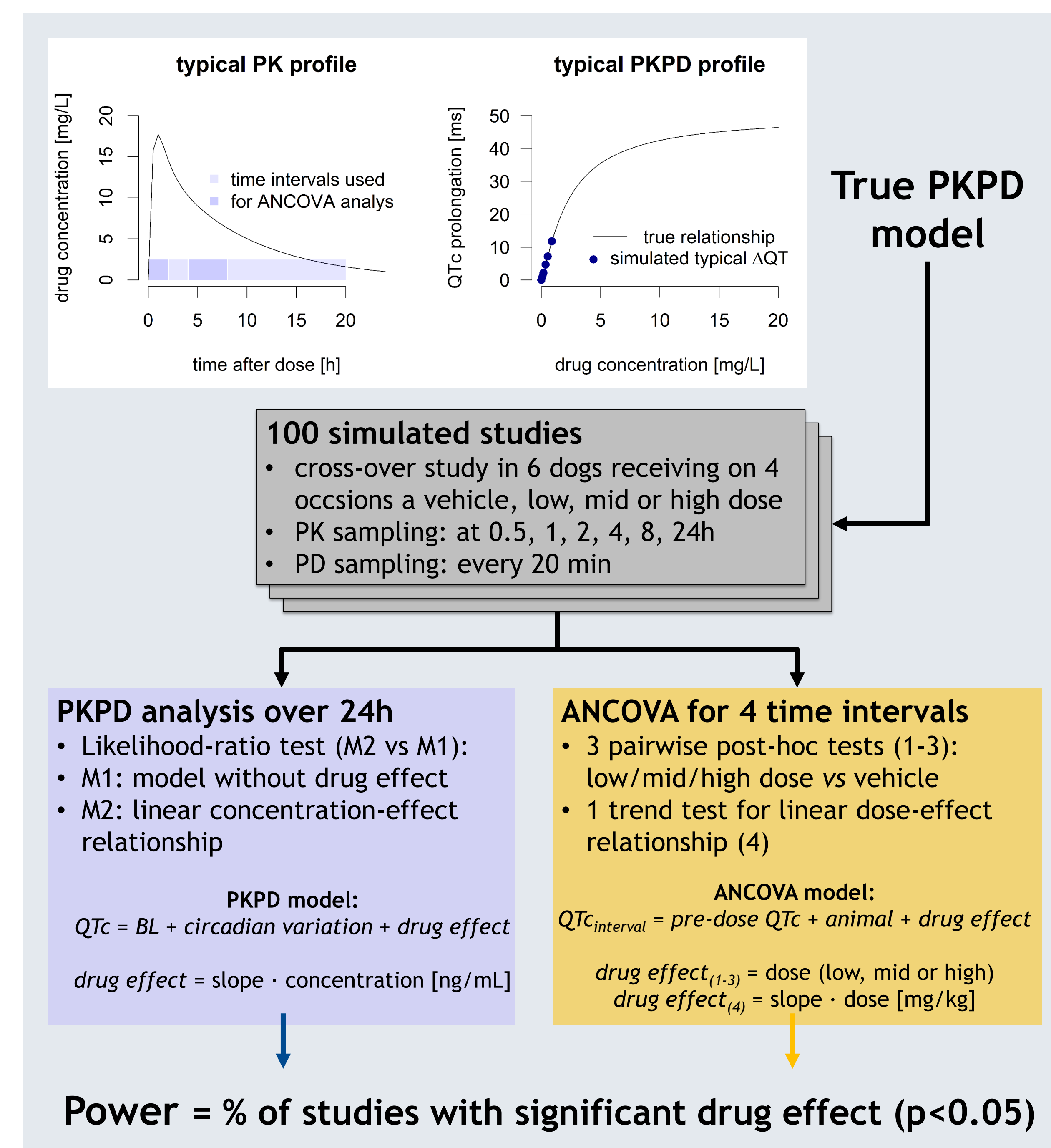


Fig-1. Illustration of study simulation and power calculation.

References

- Chain A et al., Br J Clin Pharmacol 2013
- Leishman DJ et al., J Pharmacol Toxicol Methods 2012
- Aylott M et al., Pharm Stat 2010
- Chiang A et al., J Pharmacol Toxicol Methods 2007
- Sivarajah A et al., J Pharmacol Toxicol Methods 2010

