



Pharmacokinetic (PK) and Pharmacodynamic (PD) Implications of Diurnal Variation of Gastric Emptying and Small Intestinal Transit Time for Quinidine Mechanistic Simulation

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INTRODUCTION

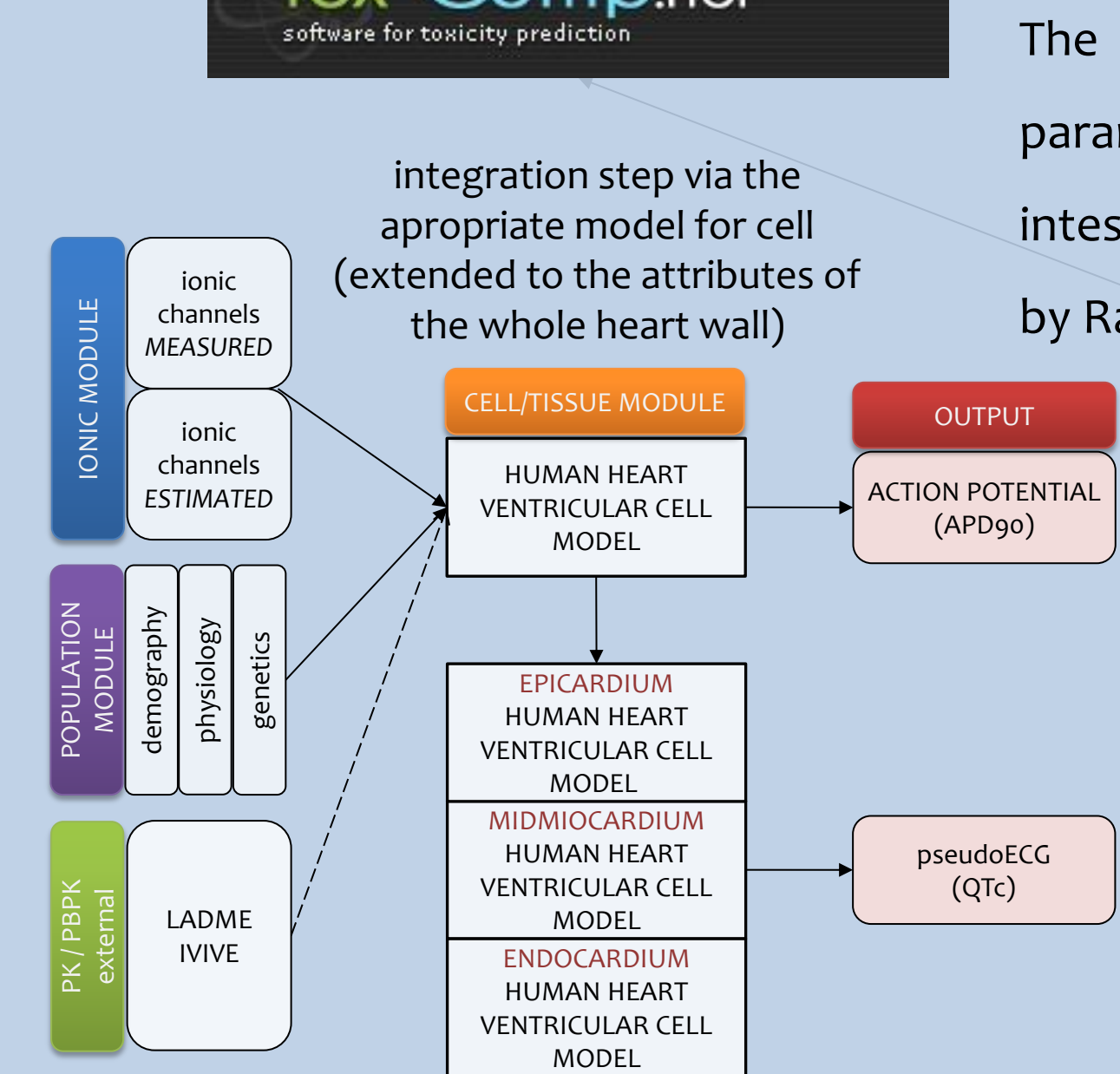
Chronopharmacology may play an important role for drugs with narrow therapeutic window particularly for patients predisposed to safety issues due to the genetic factors. There are several reports pointing out the influence of the circadian dependence in drugs pharmacokinetics and pharmacodynamics including diazepam, dextromethamphetamine, rabeprazole, nifedipine [1,2,3,4]. Despite the impact of circadian variability on drugs activity and safety, clinical studies are not common to test the diurnal variation in PK and/or PD effects. Modelling and simulations could help to fill this gap in clinical assessment and/or help in decision making of whether or not to carry out clinical study.

AIM

The objective of this study was to establish and validate methodology allowing for simulation of QT change for an orally taken drug with use of mechanistic methods accounting for population variability.

MATERIALS & METHODS

The PK simulations for quinidine and its 3-hydroxy metabolite were carried out using Simcyp platform (V12) and its compound library files in virtual healthy Caucasians. It was assumed that the morning/night differences in PK are predominantly caused by the differences in absorption and bioavailability.



The known chronological variations in gastric emptying time (h) and small intestinal transit time (h) can influence these parameters as suggested in the literature [4]. Gastric emptying half-life in fasted state was set to 0.4 and 2 h and corresponding intestinal transit times were 3.5 and 7 h [5,6] for 10am and 10pm respectively. Virtual patients mimicked the clinical study reported by Rao [7] (8 males, 18-26 years old). ToxCmp platform in version 1.2 (www.tox-comp.net) was used and the ten Tuscher human

Table 2. ToxCmp input data (in vitro ionic currents inhibition).

Ionic current	Quinidine [IC ₅₀]/n	3-OH quinidine [IC ₅₀]/n
I _{Kr}	0.82/1	1.19/1*
I _{Ks}	44/1	39.67/1*
I _{Ca}	10/1	26.38/1*
I _{Na}	16.6/1	-

* ToxCmp built-in QSAR model predictions

cardiomyocyte model was applied. 1D string simulation Epi/M/Endo cell - 20/30/50% respectively was used to mimic left ventricular heart wall. PD endpoint was ΔQTcF derived from the pseudoECG simulated by the ToxCmp system based on the in vitro currents inhibition and the Simcyp predicted free plasma concentrations separately for all individuals [8]. Quinidine and its main, active metabolite (3-OH quinidine) were considered during ECG simulation. Circadian changes to baseline and drug effects on QT were accounted for by applying the diurnal changes to heart rate and K⁺, Na⁺, Ca²⁺ ions in plasma.

RESULTS

Observed study reported prolongation of T_{max} (1.29 fold), no change in C_{max} (0.97 fold) and 1.13 fold increase in AUC for the pm administration. Simulated diurnal changes in C_{max} (0.98 fold) and AUC (1.13 fold) were consistent with observations. Simulated prolongation of T_{max} (1.61 fold) appeared to be more than the observed magnitude. Predicted ΔQTcF values were concentration dependent and followed circadian rhythm. Maximum population ΔQTcF for 10pm and 10am scenarios were 38 (3 am) and 43 (1 pm) ms respectively.

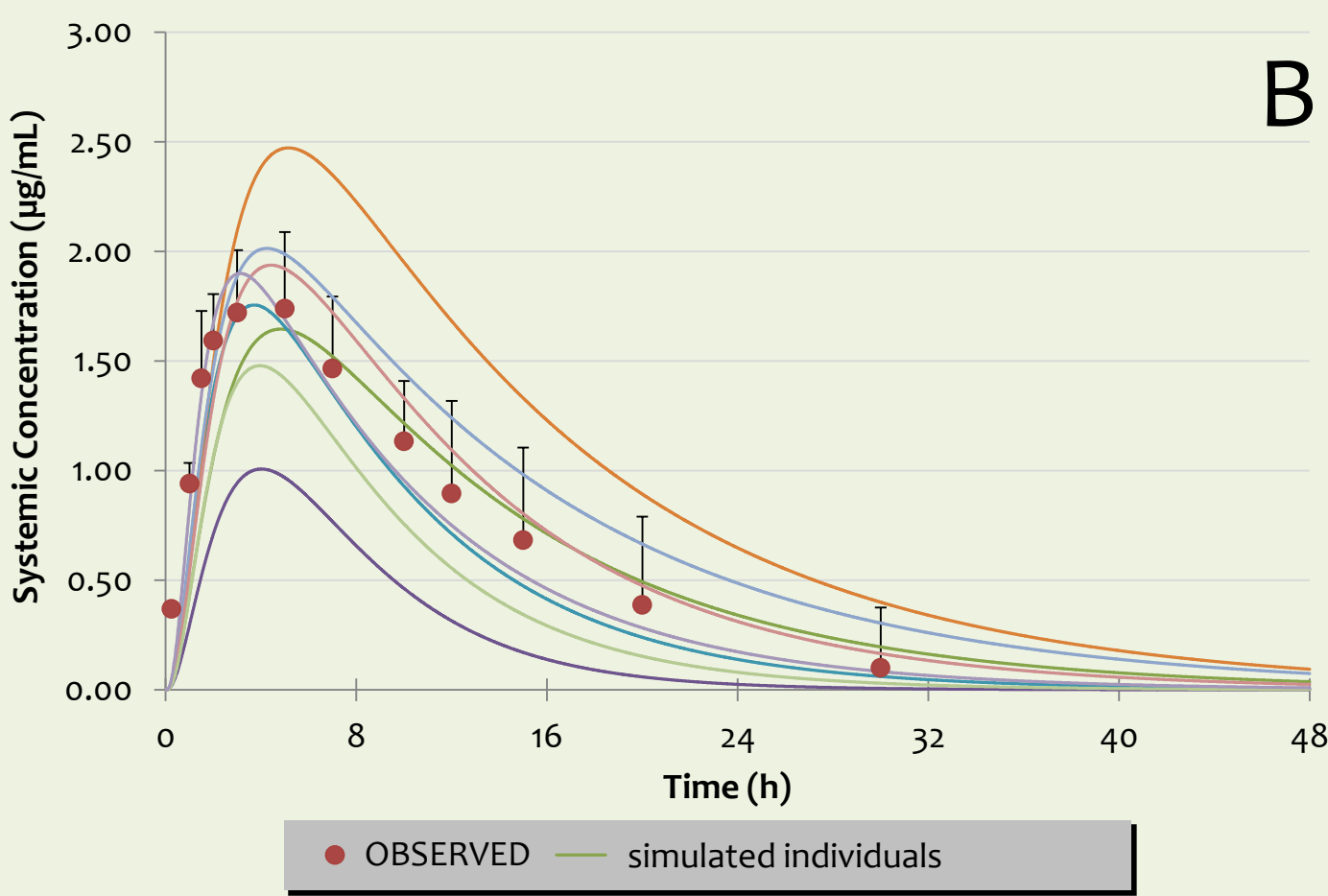
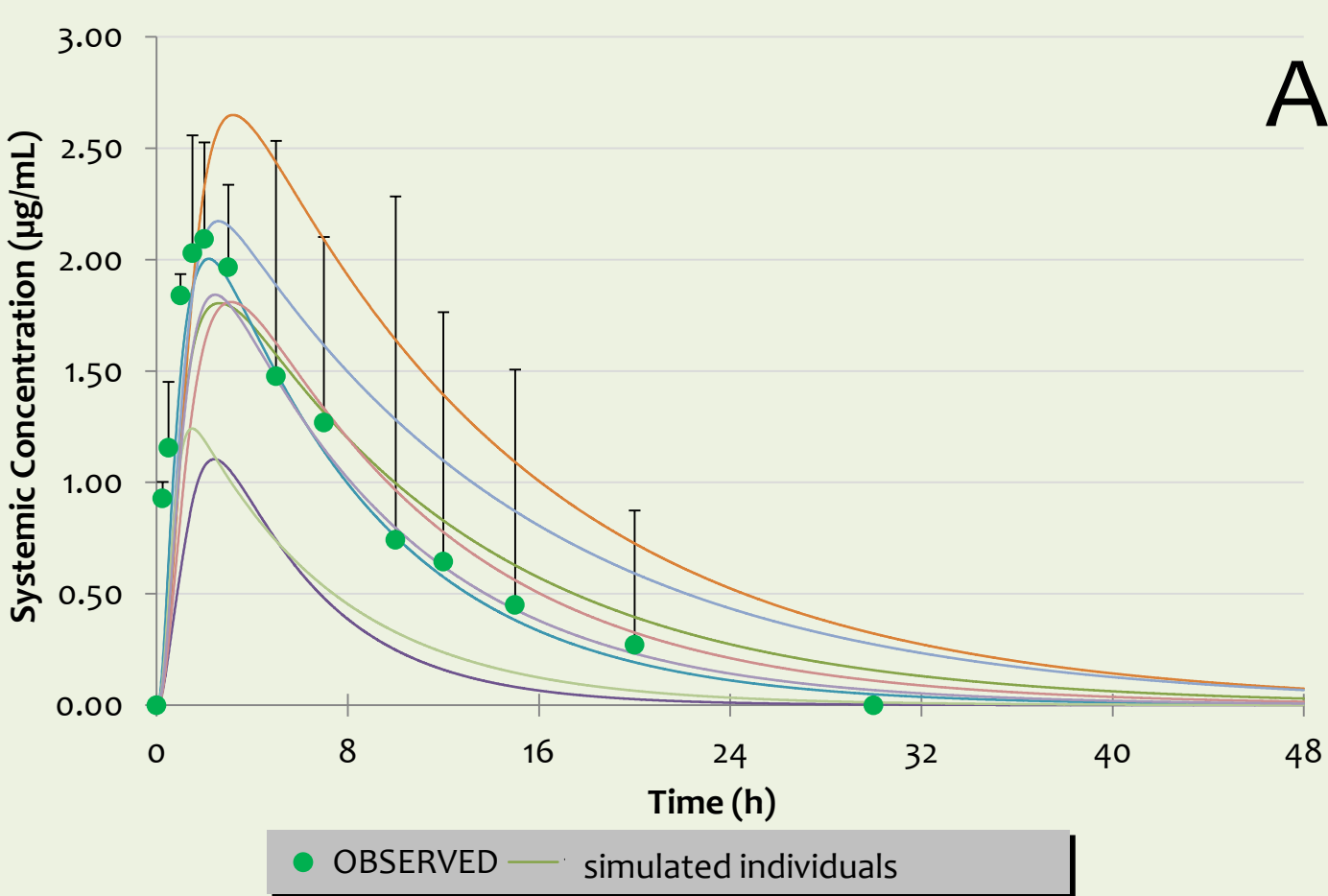


Figure 1. Observed (average ± SD) and Simcyp predicted (8 individuals) quinidine plasma concentration after 10 am (A) and 10 pm (B) single oral dose.

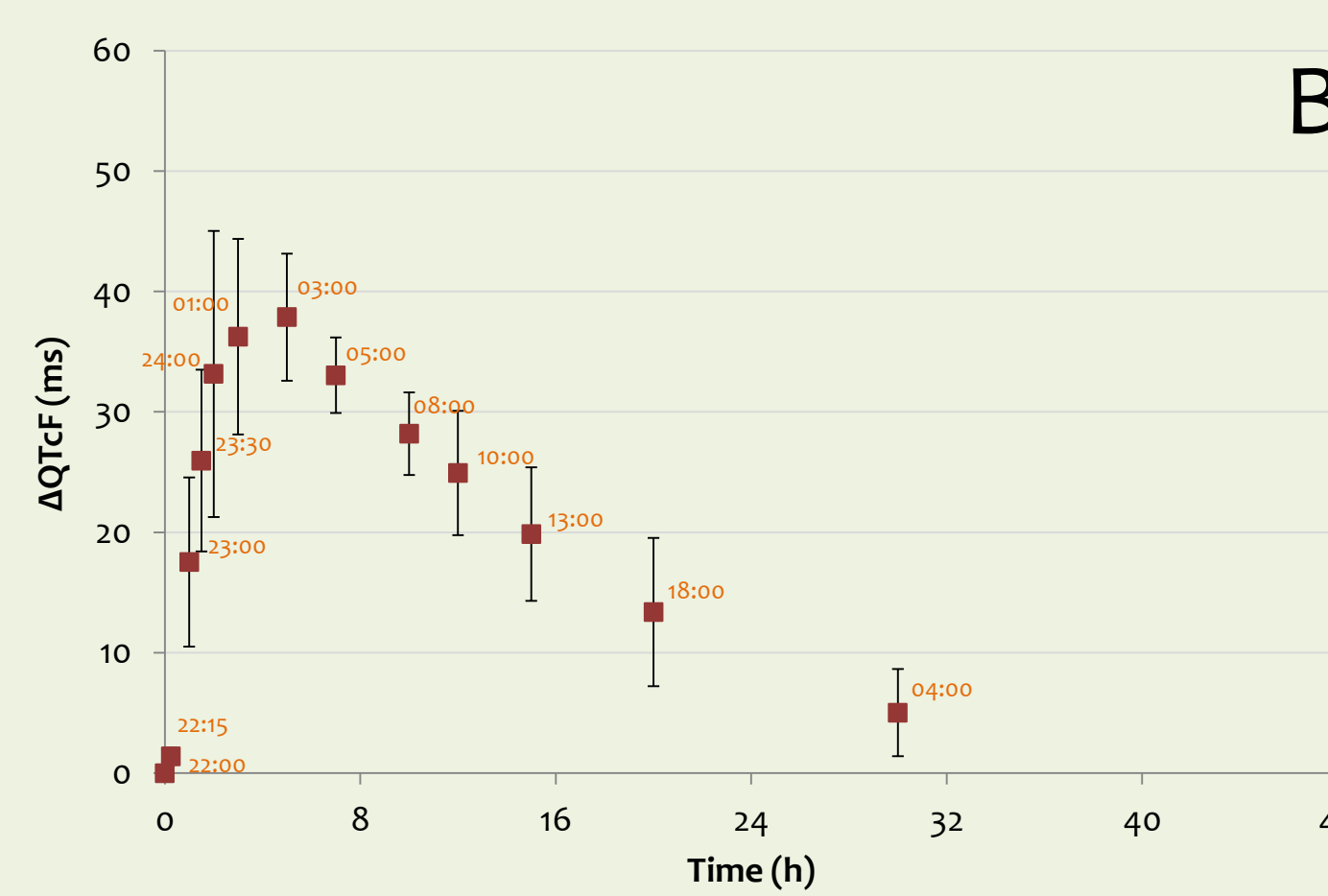
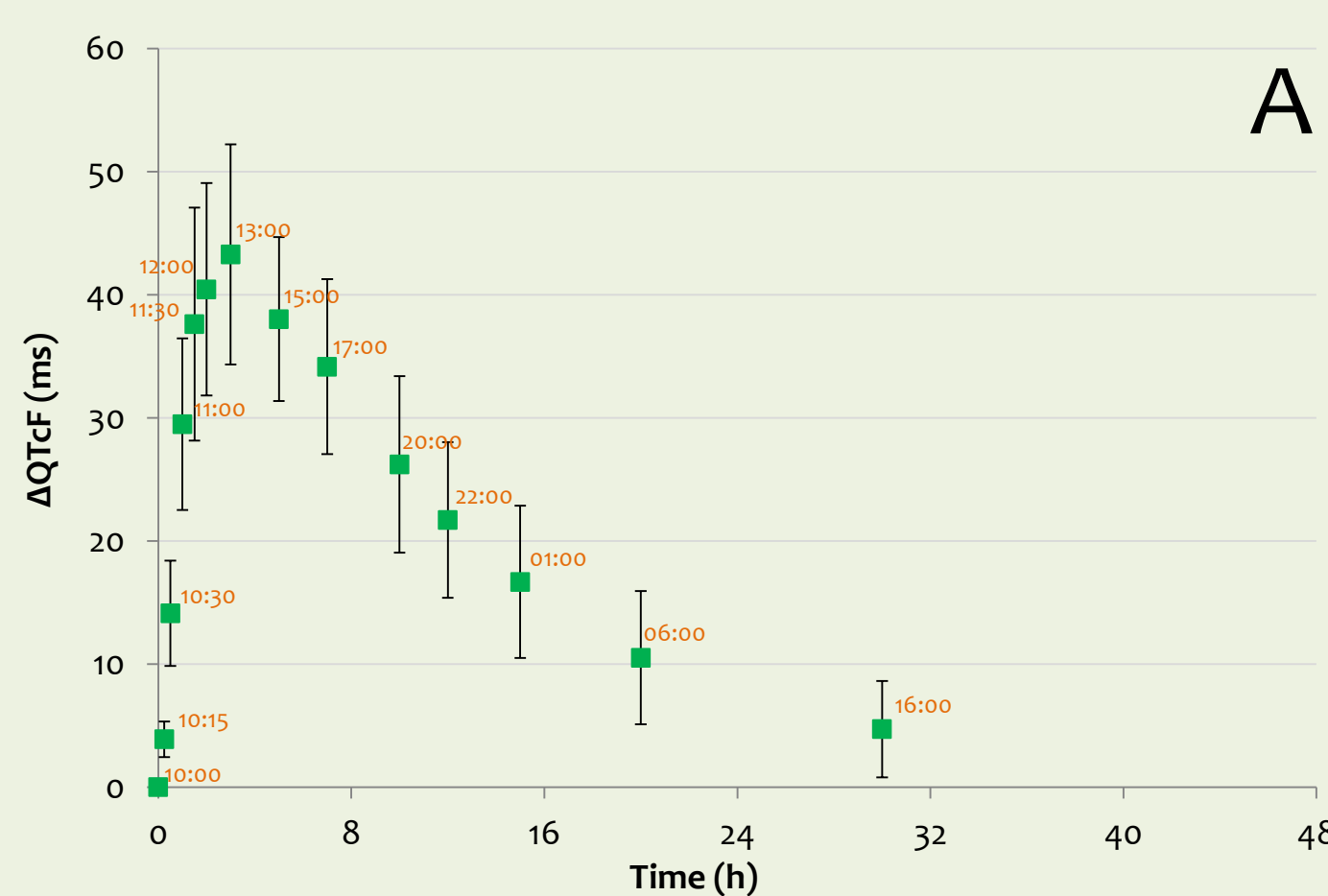


Figure 2. ToxCmp predicted (average ± SD) quinidine triggered QTc change after 10 am (A) and 10 pm (B) single oral dose.

REFERENCES

[1] Watanabe H et al. Jpn J Clin Pharmacol Ther, 1990;21(3):579-584. [2] Shappell et al. J Clin Pharmacol, 1996;36:1051-1063. [3] Pehlivanov et al. Alim Pharmacol Ther, 2003;18:883-890. [4] Lemmer et al. Chronobiol Int, 1991;8(6):485-494. [5] Goo RH et al. Gastroenterology 93:515-518, 1987. [6] Gorard DA et al. Gut, 1994;35:203-210. [7] Rao BR, Rambhau D. Arzneimittel-Forschung/Drug Research, 1995;45:681-683. [8] Polak S et al. Computing in Cardiology 39:789-793, 2012.

Table 2. Observed and simulated values for all four study phases.

	Dose time	TMax (h)	CMax (µg/mL)	AUC (µg/mL×h)
PREDICTED	10 am	2.60	1.79	21.45
	10 pm	4.18	1.75	24.30
	10pm/10am ratio	1.61	0.98	1.13
OBSERVED	10 am	2.00	2.17	22.13
	10 pm	2.57	2.10	24.90
	10pm/10am ratio	1.29	0.97	1.13

CONCLUSIONS

The results demonstrated the potentials of the mechanistic in vitro-in vivo extrapolation (IVIVE) for incorporating the knowledge of chronological variations in physiological system parameters leading to PK or PD variations. The simulations may assist with determining the PD variability occurring diurnally using the in vitro data on drugs and are suitable for designing studies which might be affected by the chronobiology of PK and/or PD.

