# 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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- Circadian variability influences the pharmacokinetics (PK) and pharmacodynamics (PD) of certain drugs [1-4].
- Our objective was to validate methodology simulating a QT change for orally administered quinidine using mechanistic methods - Simcyp Simulator for PK and Cardiac Safety Simulator (CSS) for PD - accounting for circadian variability.

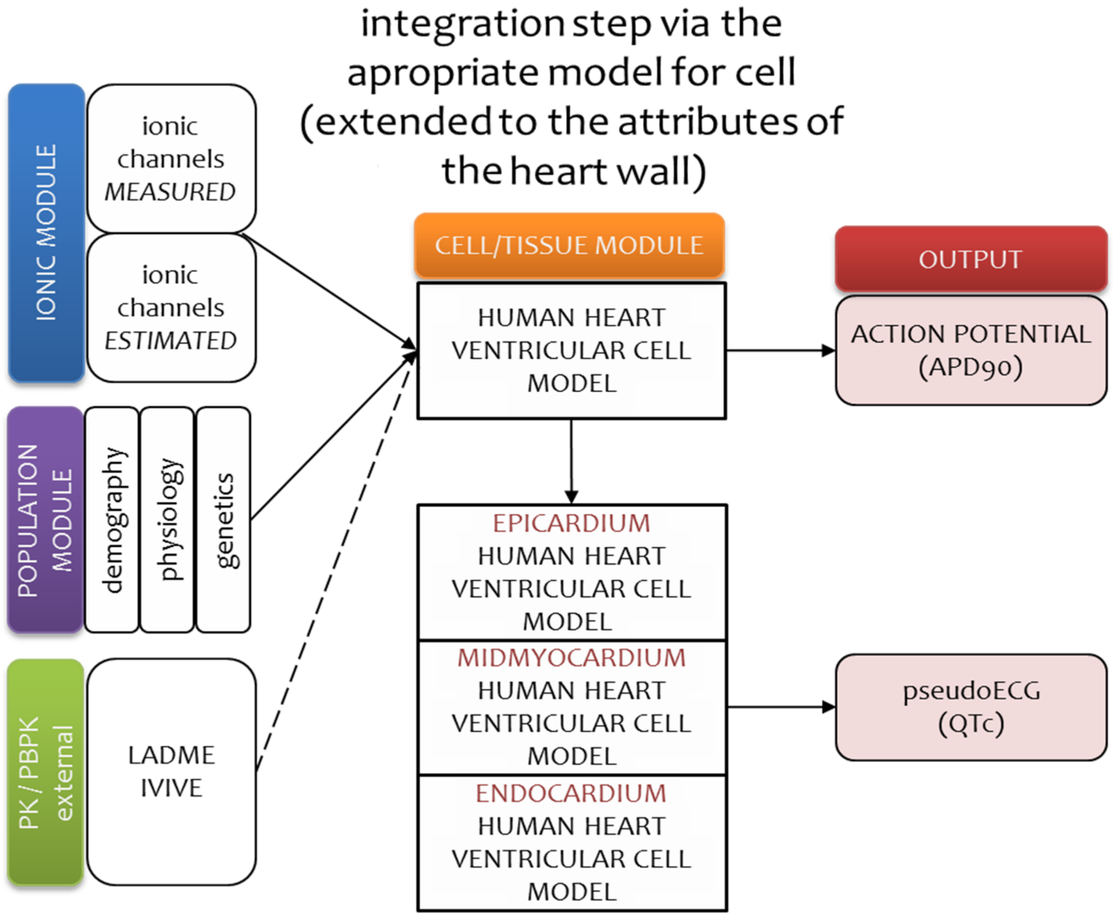


**Table 2.** Cardiac Safety Simulator (CSS) input data (*in vitro* ionic currents inhibition).

| 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 | - |

* ToxComp built-in QSAR model predictions

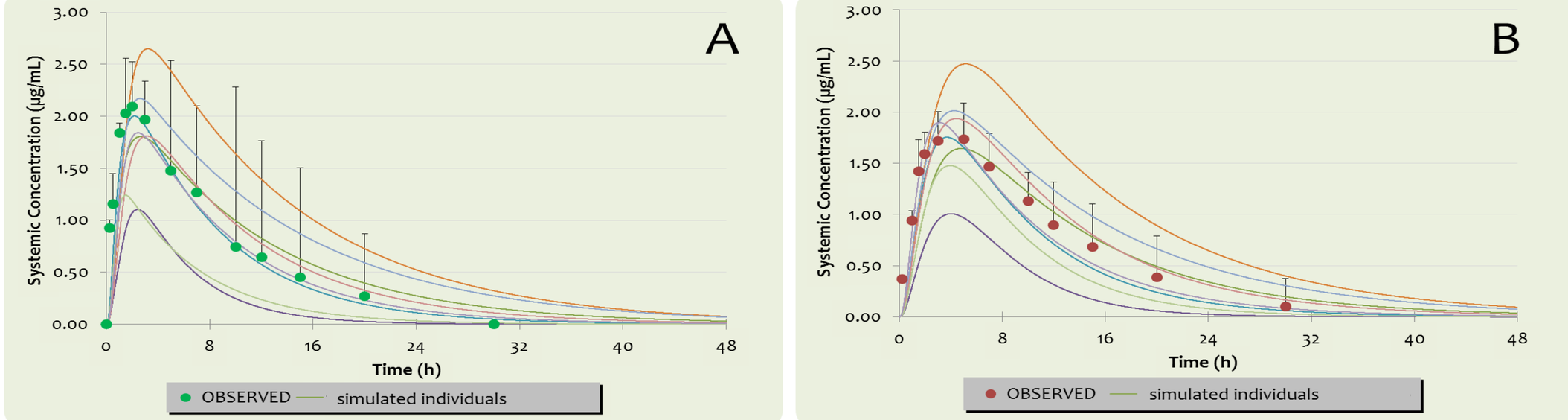


**Figure 1.** Observed (average ± SD) and Simcyp predicted (8 individuals) quinidine plasma concentration after 10 :00(A) and 22:00 (B) single oral dose.

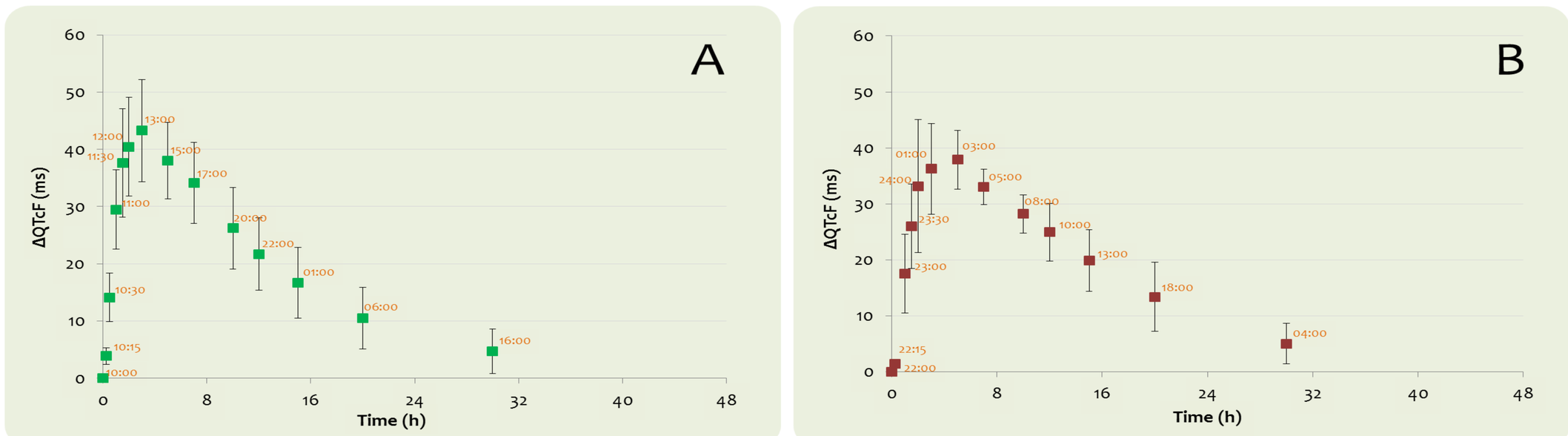


**Figure 2.** Cardiac Safety Simulator predicted (average ± SD) quinidine triggered QTc change after 10 am (A) and 10 pm (B) single oral dose.

- Predicted ΔQTcF values were concentration dependent, followed circadian rhythms and maximum population values for 22:00 and 10:00 scenarios were 38 (03:00) and 43 (13:00) ms respectively.
- Mechanistic in vitro-in vivo extrapolation (IVIVE) incorporates knowledge determining circadian PK / PD variability using *in vitro* data on drugs and may assist in clinical study design for drugs affected by chronobiology.

[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.