PBPK/PD approach to discern potential sex and ethnic differences in the time course of QT prolongation following quinidine administration: Caucasian vs Korean healthy populations

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Background and Objective:

- A randomised, double-blind, cross over study in 24 Korean and 13 Caucasian subjects was conducted by Shin *et al.* (2006) to assess the time course of QT prolongation following an intravenous infusion of quinidine [1].

- The objective of the current work was to conduct a virtual clinical trial replicating the above study but using prior systems and drug information to drive the expected QT prolongation within a physiologically based pharmacokinetic (PBPK) model linked with pharmacodynamics (PD).

Methods:

- Data representing the mean time course of plasma concentration of quinidine and mean time course of QT values in male and female Caucasian and Korean populations were extracted from Shin *et al.*

- A PKPD analysis was conducted using the PBPK/PD models in Simcyp (V11.2). In the first stage of the analysis the most appropriate distribution model was selected. PK profiles for male Caucasians aged between 20 and 30 years were simulated using a minimal PBPK, minimal PBPK model with single adjusting compartment (SAC) and a full PBPK model and compared with the observed PK profile from the Shin *et al.* study.

- Parameter values for SAC viz Kin, Kout and Vsac were estimated using the Simcyp Parameter Estimation (PE) module with the Nelder – Mead minimisation method. SAC parameters were estimated for female Caucasians and male and female Koreans (note: a Simcyp Japanese population was used instead of Korean population based on the similarities between the two populations).

- PK/PD profiles were simulated in the 4 groups using the Simcyp simulator. An Emax model with additive baseline was used. The parameters in the PD model were from Shin *et al.* with and without covariate (model without covariate effect on E0 and ΔEmax). The PK models were evaluated using a Visual Predictive Check (VPC). For the PD data, the mean 5th and 95th percentiles of model predictions were overlaid on the mean observed QT and visually compared.

Results:

- A minimal PBPK model with SAC compartment provided the best fit to the PK data.

- The Kin (h^{-1}), Kout (h^{-1}) and Vsac (L/Kg) for the Caucasian males were 0.652, 0.960, 0.17, Caucasian female were 1.97, 1.52, 1.96, Korean male were1.15, 0.92, 0.37 and Korean female were 14.17 , 5.49, 0.80.

- Neither sex nor ethnicity influenced the PK of quinidine

- The observed PD data fell within the 95th percentile range of simulated values.

- Caucasian females were most susceptible to QT prolongation following quinidine dosing followed by Korean females, Caucasian males and Korean females.

- The visual predicted check for female Caucasian and male Korean are shown in figures 1 and 2.

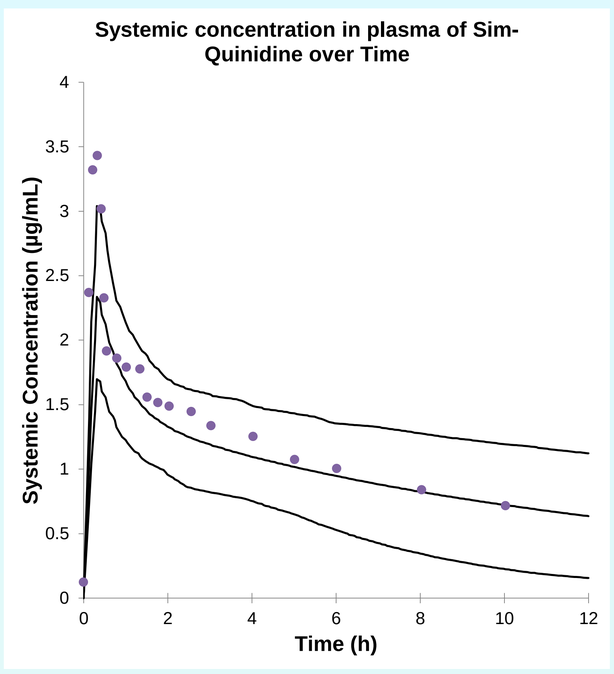

Figure 1: VPC showing the observed individual quinidine concentrations in plasma (▪) mean, 5th and 95th percentile of model predictions (-) in Caucasian females

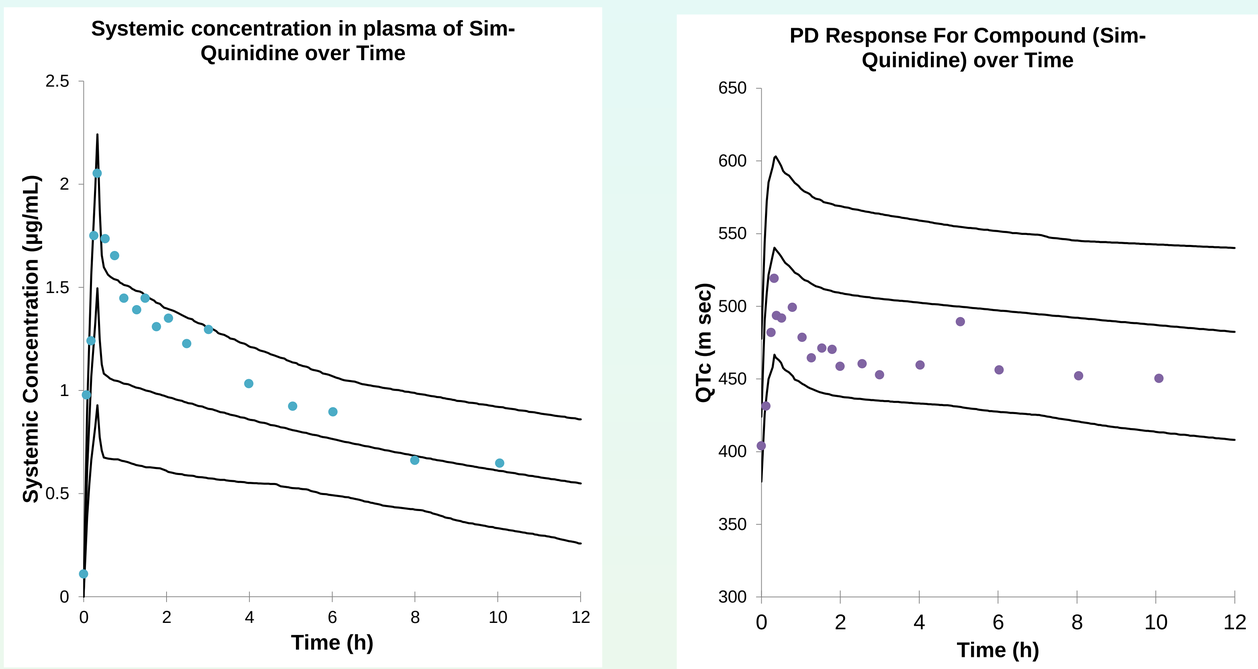

Figure 2: VPC showing the observed individual quinidine concentrations in plasma (▪) mean, 5th and 95th percentile of model predictions (-) in Korean males

Discussion and conclusion:

- Simulations indicated that Caucasian females were most susceptible to QT prolongation following quinidine and Korean males the least.

- The impact of metabolite was not considered in the current simulation

- Combining PBPK/PD modelling with prior systems and drug data allowed successful prediction of observed clinical data but also suggested that the source of variable susceptibility does not relate to pharmacokinetics.

References:

1. Shin *et al.,* British Journal of Clinical Pharmacology, 2006, 63(2), 206-215