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A PBPK/PD model using free quinidine heart concentrations to simulate QT prolongation in Caucasian and Asian females

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PURPOSE

Quinidine, a class 1 antiarrhythmic agent that is also used in the treatment of severe malaria, is known to cause lengthening of the QT interval in the electrocardiogram (ECG), with greater potential for QT prolongation in females [1-3]. Ethnic differences in QT prolongation have also been demonstrated [3]. Lengthening of the QT interval corrected for heart rate (QTc) that is > 500ms is believed to be a contributory factor to the life-threatening side effect of Torsades de pointes observed with some drugs [4]. Pharmacokinetic/pharmacodynamic (PK/PD) models linking plasma concentrations to QT changes in Caucasians and Asians have suggested higher Emax (the maximum value of QTc changes) values in Caucasians with similar EC_{50} (concentration of quinidine required to produce 50% of the maximum response) values in both ethnic groups, suggesting similar sensitivity to quinidine concentrations in the two groups [3]. Physiologically based pharmacokinetic /pharmacodynamic (PBPK/PD) modelling using concentrations of quinidine that may be more relevant to the QT prolongation effect (ie heart concentrations) of the drug may have a greater potential to provide an understanding of the ethnic differences in the observed QT prolongation.

METHODS

Data from the study by Shin and coworkers [3] were used to develop the PBPK/PD model, using the Simcyp Population Based Simulator.

- Populations : Caucasian Healthy Volunteers (HV) and Chinese HV (to represent Korean/Asian)
- Quinidine dose: 4 mg/kg given as a 20 minute infusion
- **PK model**
  - * Full PBPK model with First order absorption
  - * Clearance of quinidine of 19.4 (CV 38%) L/h in Caucasians and 18.16L/h (34%) in Asians
- **PD model**
  - * Measured mean baseline QTc of 443 ms for Asians and 445 ms for Caucasians [3] were used
  - * Input to PD model was predicted free heart concentrations
  - * Fitting was used to estimate ΔEmax and EC_{50}. EC_{50} was used as a marker of sensitivity and compared in the two groups of virtual subjects.

RESULTS

1. Cardiac concentration profiles in Caucasian and Asian females

Predicted free heart concentrations of quinidine in the two study groups were not significantly different (Figure 1).

2. Parameter estimation

The estimated values for the simple Emax models were significantly different with respect to the ΔEmax values (190.0 vs 175.19 ms) and EC_{50} (1.53 vs 1.8 μM) in Caucasian and Asian females respectively.

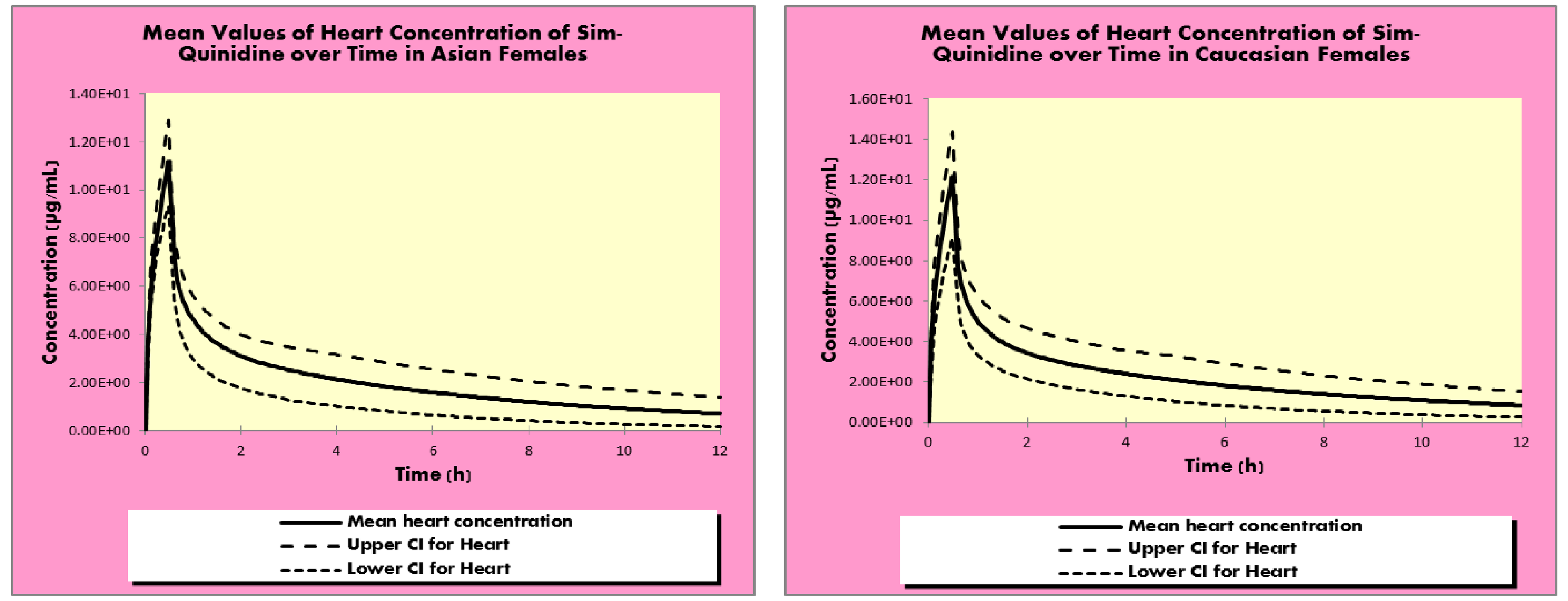

Figure 1. Mean predicted (solid lines) heart concentration – time profiles in Asian and Caucasian females. The dotted lines represent the 90% CI of the predictions.

3. Comparison of QTc in the ethnic groups

Simulated mean PD profiles together with observed data are shown in Figure 2.The estimated sensitivity parameters (EC_{50}) showed a Caucasian:Asian ratio of 0.85.

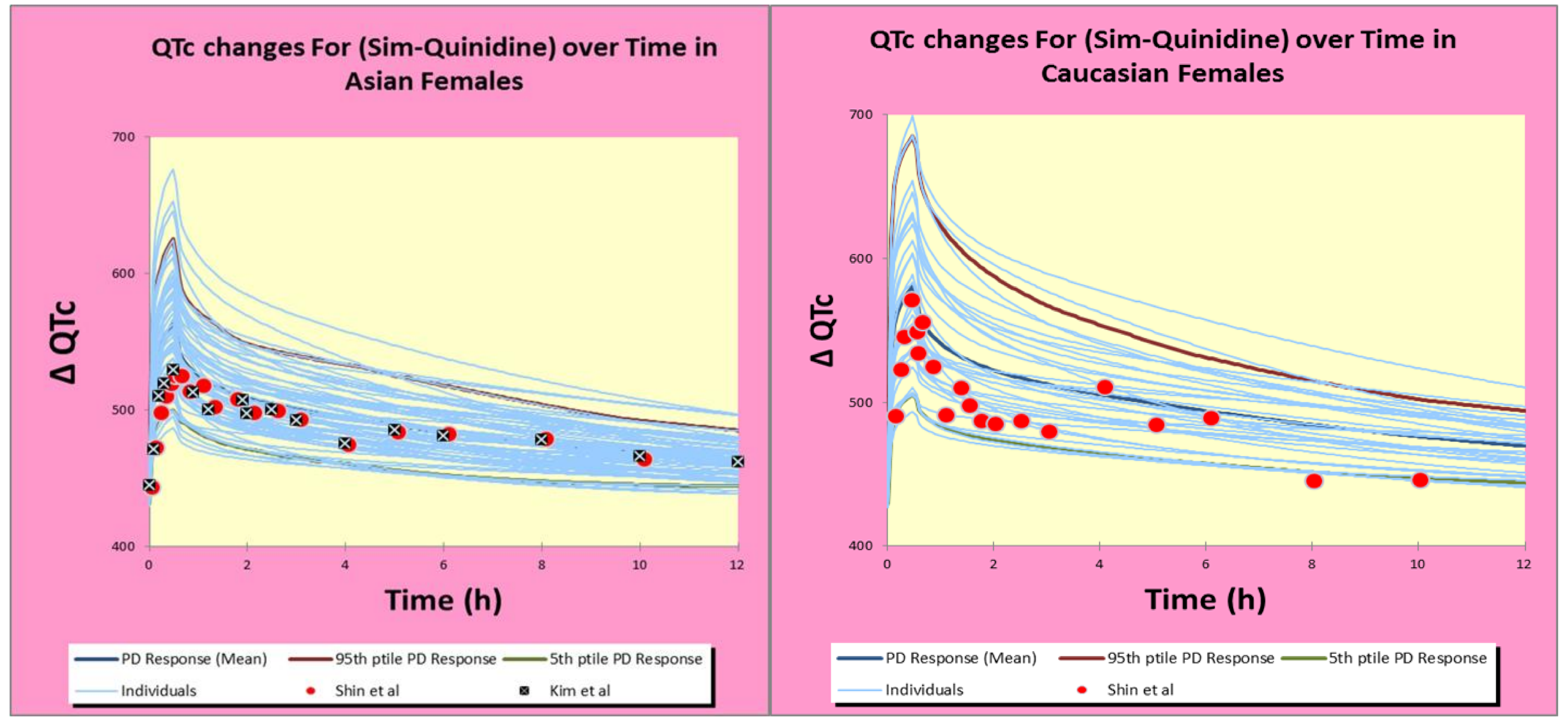

Figure 2. Mean predicted (solid lines) and observed (filled circles) [3,5] PD profiles in Asian and Caucasian females.

CONCLUSIONS

The PBPK/PD model driven by free quinidine heart concentrations adequately recovered the observed higher QTc in Caucasian females when compared to Asian females.

The higher EC_{50} in Asian females suggests that higher free concentrations of quinidine are required at the target site to produce an equivalent change in QTc prolongation.

REFERENCES

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