Accounting for ethnic and sex differences in QTc prolongation using heart drug concentrations with physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) models.

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Background

Quinidine is known to cause lengthening of the QT interval in the electrocardiogram (ECG), with greater potential for QT prolongation in females [1-3]. 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]. The reason for the greater prolongation of QTc in females despite no observed sex differences in plasma concentrations of quinidine is unclear. Similarly, the differences in QTc prolongation between Asians and Caucasians is poorly understood. Proposed postulations to account for the sex and ethnic differences include greater intrinsic sensitivity to the effects of quinidine on cardiac repolarisation as well as the possibility of higher cardiac concentrations of quinidine in females [2]. While a modicum of evidence exists for the former postulation, measurement of cardiac concentrations of quinidine in patients is challenging. Physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) modelling may be useful in testing such hypotheses.

Objectives

To evaluate the sex and ethnic effects on the potential risk of significant QT prolongation using a PBPK/PD model.

Methods

The PBPK model was constructed using the Simcyp Population Based Simulator.

- Populations : Male and female Caucasian Healthy Volunteers (HV) and female Chinese HV (to represent Korean/Asian)
- Quinidine dose: 4 mg/kg given as a 20 minute infusion[3]
- **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 [3]
- **PD model**
  - * Measured mean baseline QTc of 443 ms for Asians, 445 ms for Caucasian females and 408 ms for males [3] were used
  - * Input to PD model was predicted free heart concentrations
  - * Parameter estimation 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. Plasma and cardiac concentration profiles in males and females

Visual predictive checks suggested that the PBPK model recovered the clinical plasma PK profiles adequately and there was no significant difference between the PK profiles in males and females. (Figure 1). The PBPK model also predicted concentration-time profiles in Asian females adequately.

Simulation of the free heart concentrations of quinidine over time suggested that sex and ethnic differences may not exist in these profiles.

2. Parameter estimation

The estimated parameters for the simple Emax models were not significantly different with respect to the Δ Emax values in males and females (128.9 ms and 130.8 ms respectively) but differed in the values for EC_{50} (6.28 µM for females and 7.01 µM for males). 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.

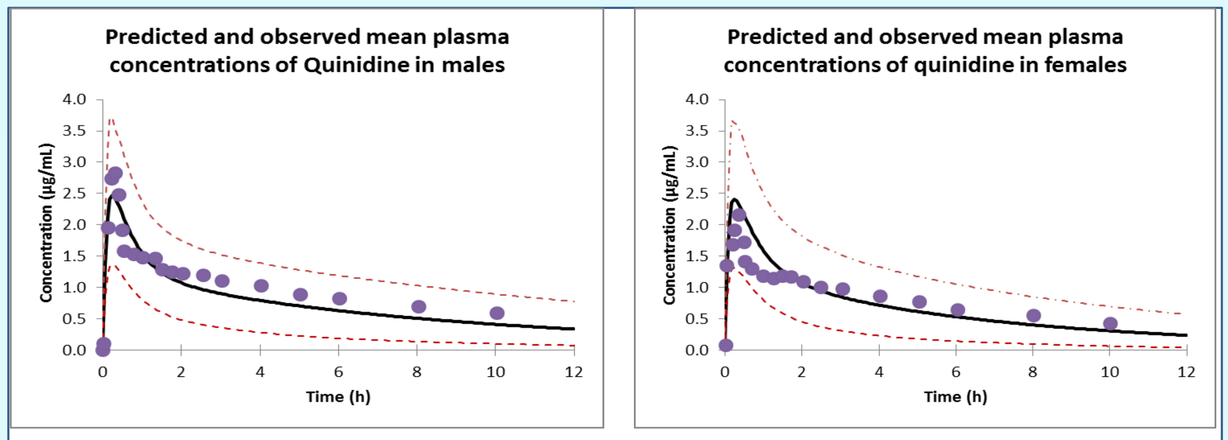

Figure 1. **Mean predicted (solid lines) and observed (filled circles) [3] plasma concentration – time profiles in Caucasian males and females. The dotted lines represent the 90% CI of the predictions.**

3. Comparison of QTc between sexes and ethnic groups

Predicted 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 and a female:male ratio of 0.89.

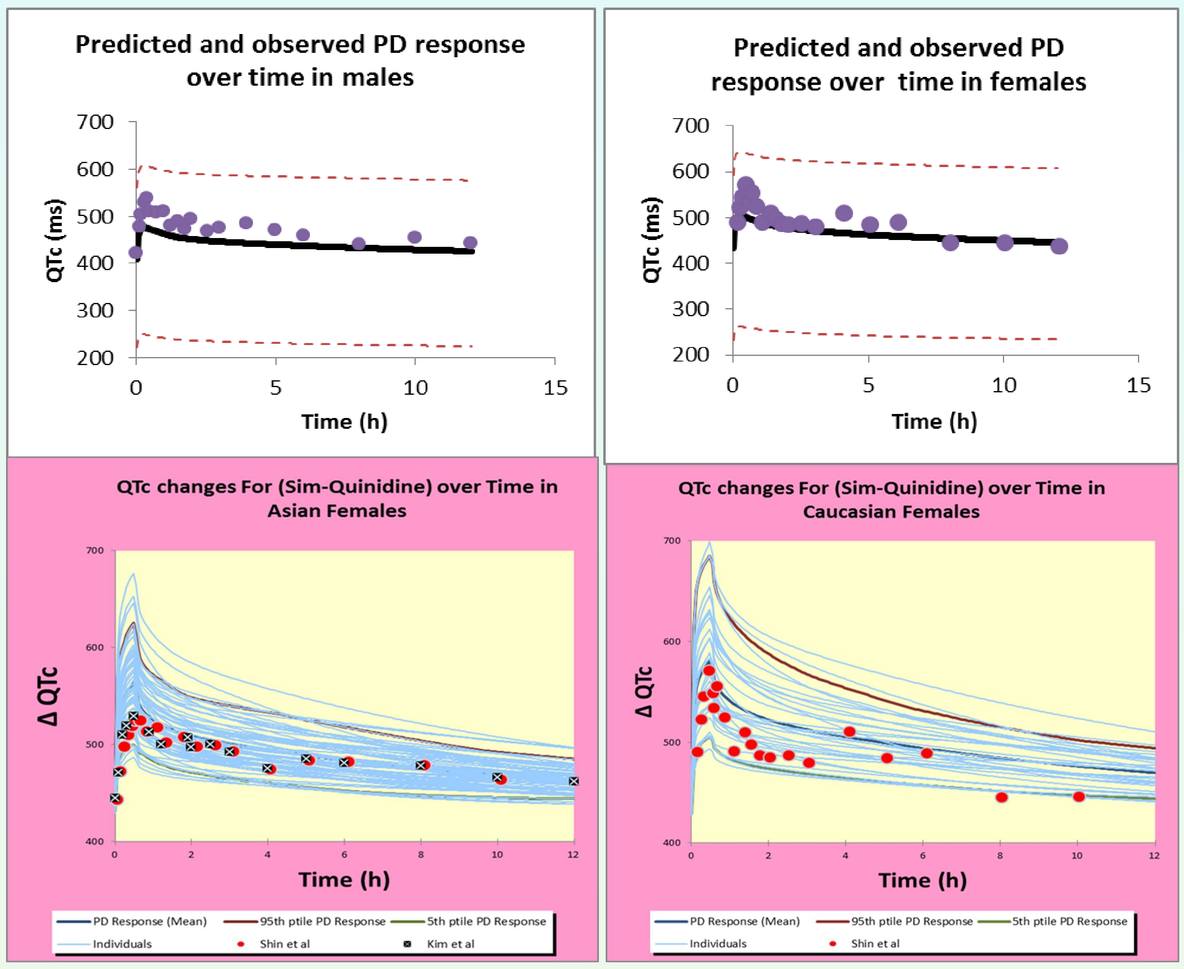

Figure 2. **Mean predicted (solid lines) and observed (filled circles) [3,5] PD profiles in Caucasian males and females. The dotted lines represent the 95% CI of the predictions.**

4. Relative risk of experiencing QTc > 500ms in males and females

Simulation of QTc in the sexes showed that 56% of females were likely to show maximum QTc > 500ms while the corresponding value for males was 43%.

Conclusions

The PBPK model predicted the observed plasma concentration profiles in males and females and no significant sex differences were observed. Predicted heart concentrations did not show sex or ethnic differences.

The PBPK/PD model effectively recovered the higher rate of QT prolongation reported in females and predicted a 1.3 times higher risk of significant QT prolongation in females on quinidine.

The estimated sensitivity parameter (EC_{50}) of the PD model suggests that females require lower heart concentrations for an equivalent QTc change in males. Clinical support for a higher sensitivity to QTc prolongation in Caucasian females comes from the study by Benton and coworkers who reported that a 'therapeutic' concentration of 3 µg/mL in women is likely to show a 38 ms greater increase in QTc change than in men [2]. This observation in this study is interesting since the rapid component of the delayed rectifier potassium current (I_{Kr}) in female rabbits is reported to be 0.83 times that of males and has been implicated in the mechanism of QT prolongation [6].

Future PBPK/PD models should include quinidines' active metabolite 3-hydroxyquinidine.

References

1.El-Eraky et al , Br J Clin Pharmacol 2003, 56: 198-204; 2.Benton et al, CPT 1994,67:413 ; 3. Shin et al, Br J Clin Pharmac 2006, 63(2):206; 4.Bednar et al, Prog Cardiovas Dis 2001, 43:1; 5.Kim et al, Korean Cir J2007;37:559-566; 6.Liu et al, J Pharmacol Exp Ther 1998, 285: 198-204.