Accounting for sex effects on QT prolongation by quinidine: A simulation study using PBPK linked with PD

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Background

Quinidine is a class 1 antiarrhythmic agent that is also used in the treatment of severe malaria. It 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. Proposed postulations to account for the sex 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 effects on the potential risk of significant QT prolongation using a PBPK/PD model.

Methods

The Simcyp Population Based Simulator (version 12 release 1) was used to simulate the plasma concentration-time profiles of quinidine in virtual male and female Caucasian healthy volunteers with a full PBPK model and a systemic clearance of quinidine of 20.59 (CV 38%) L/h [5]. The virtual healthy male and female subjects were aged between 18 and 35 years and received a single standard dose of 4mg/kg of quinidine, which was similar to the study by Shin and coworkers [3]. Each simulation consisted of 3 trials with 10 subjects. Simulated plasma concentration profiles in males and females were compared with clinical data. Cardiac concentrations of quinidine were also generated and compared in males and females, although clinical data was not available for comparison.

Clinically observed changes in QT prolongation corrected for heart rate (QTc) were used to develop the Emax models with differences in baseline QTc values between males and females obtained from the literature [3]. Parameter estimation was used to determine the ΔEmax (the maximum value of ΔQTc) and the concentration of quinidine required to produce 50% of the maximum response (EC_{50}). A comparison of the EC_{50} values between males and females was used to determine sex differences in sensitivity to QTc prolongation. Plasma concentrations were used for the PD model.

Following evaluation of the developed models to predict clinically observed data, the models were used to simulate PD profiles in 500 males and females respectively. The proportion of subjects of each sex who showed QTc >500ms and hence probably carried a greater risk of experiencing torsade de pointes [5] was then estimated.

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).

Simulation of the heart concentrations of quinidine suggested that sex differences may not exist in these profiles (Figure 2).

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).

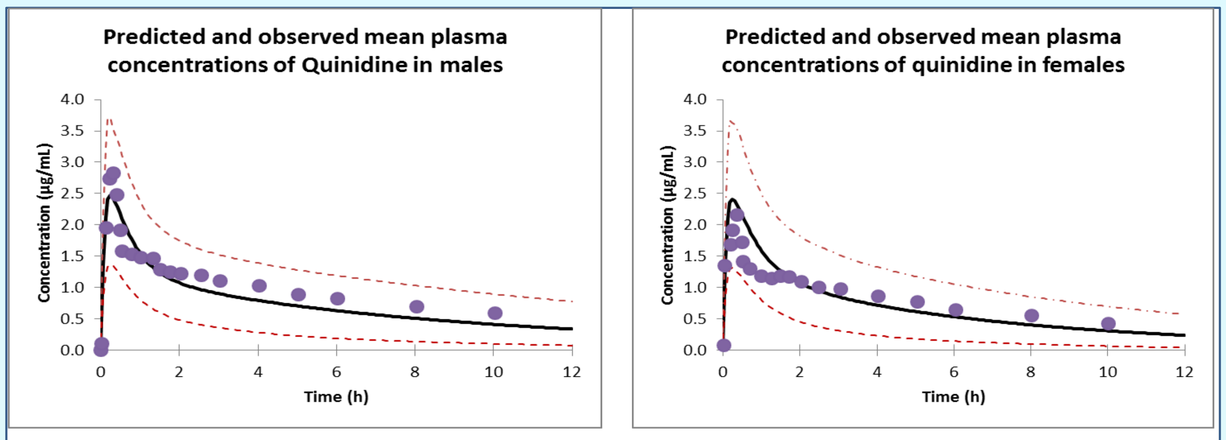

Figure 1. **Mean predicted (solid lines) and observed (filled circles) [3] plasma concentration – time profiles in Caucasian males and females. The dotted lines represent the 90% CI of the predictions.**

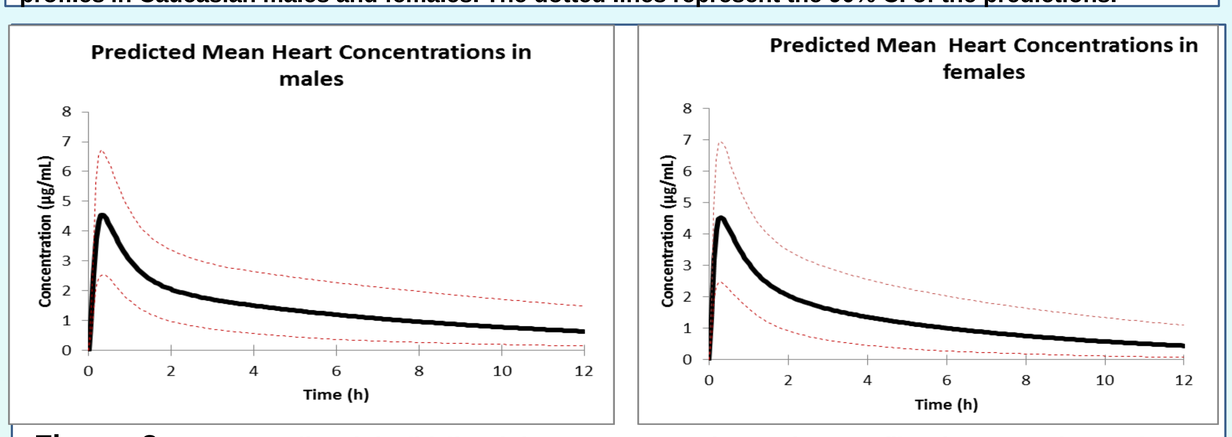

Figure 2. **Mean predicted (solid lines) heart concentration – time profiles in Caucasian males and females. The dotted lines represent the 90% CI of the predictions.**

3. PD models

Parameters used for the simple Emax models in males and females were: Emax: 128.9 ms (males) and 130.8 ms (females), EC_{50}: 7.01µM (males) and 6.28 µM (females), E_0: 408 ms (males) and 442 ms (females).

Predicted mean PD profiles together with observed data are shown in Figure 3.

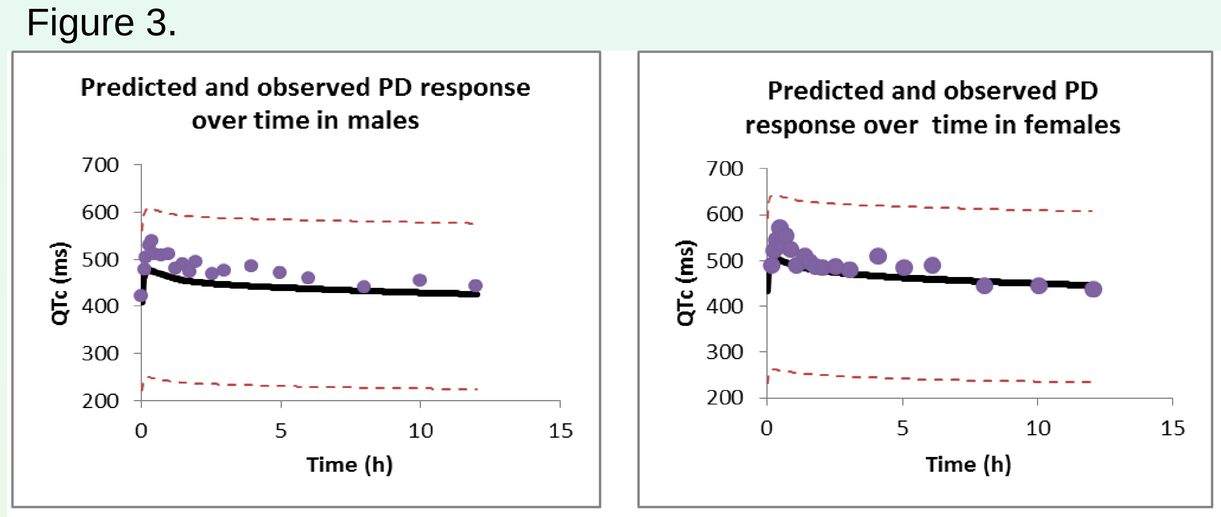

Figure 3. **Mean predicted (solid lines) and observed (filled circles) [3] PD profiles in Caucasian males and females. The dotted lines represent the 95% CI of the predictions.**

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 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 a female/male ratio of 0.89. 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

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