Prediction of Differences in Pharmacokinetics between Chinese and Caucasian Populations using a Mechanistic Physiologically-Based Pharmacokinetic Model

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BACKGROUND

- ICH guidelines emphasise the need for a better understanding of the influence of ethnicity on drug response to minimise duplication of clinical studies, thereby expediting drug approval.
- We have developed a Chinese data base for the 'bottom-up' prediction of differences in the population pharmacokinetics of drugs mainly metabolised by cytochromes P450 (CYPs) relative to Caucasian populations.
- Such predictions should help to inform the need for duplication of *in vivo* PK studies in the two ethnic groups and the design of such studies.

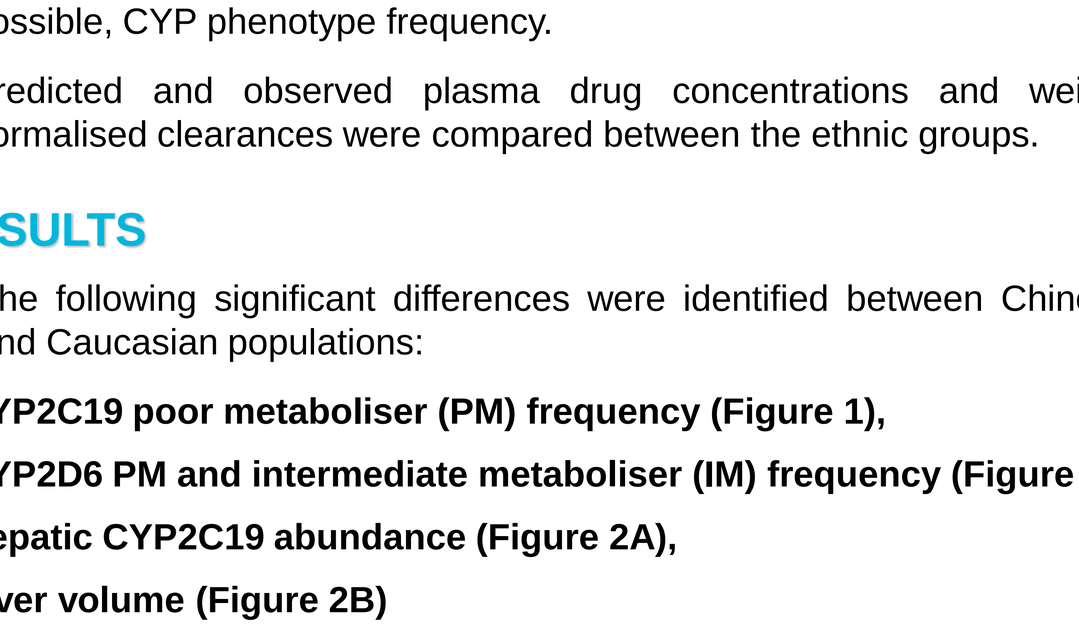
METHODS

- Demographic and physiological data for Chinese, along with information on CYP abundances and the frequencies of associated genetic polymorphisms in Chinese were collated from literature sources and incorporated within the Simcyp Population-based Simulator® (v10.0).
- Default Simcyp parameter values for a virtual Caucasian population and for model compounds metabolised principally by specific CYPs were used.
- The drugs and the main CYP involved in their metabolism were desipramine (CYP2D6), tolbutamide (CYP2C9), omeprazole (CYP2C19) and midazolam (CYP3A).
- Observed plasma drug concentration – time profiles after oral administration were obtained from published *in vivo* studies in both Chinese and Caucasian subjects.
- Virtual subjects generated within Simcyp were matched to the subjects used in the *in vivo* studies with respect to age, sex, dosage and, where possible, CYP phenotype frequency.
- Predicted and observed plasma drug concentrations and weight normalised clearances were compared between the ethnic groups.

RESULTS

- The following significant differences were identified between Chinese and Caucasian populations:
  - **CYP2C19 poor metaboliser (PM) frequency (Figure 1),**
  - **CYP2D6 PM and intermediate metaboliser (IM) frequency (Figure 1),**
  - **Hepatic CYP2C19 abundance (Figure 2A),**
  - **Liver volume (Figure 2B)**
- Reported hepatic abundances per gram of liver of CYP2C9 and CYP3A4 are similar in Chinese and Caucasians. However, a lower liver weight propagates 30% lower net levels of these enzymes in Chinese.
- No data on the hepatic abundance of CYP2D6 in Chinese were available. A mean value of 5 pmol/mg determined from Japanese livers was assumed (c.f. 8 pmol/mg for Caucasian livers).

Figure 1 Differences in CYP phenotype frequency between Chinese and Caucasian populations



UM - Ultra rapid Metaboliser; EM - Extensive Metaboliser; IM – Intermediate Metaboliser; PM – Poor Metaboliser

RESULTS

- The observed plasma drug concentration-time profiles and weight normalised clearances were predicted accurately (within 2-fold of observed) for all substrates in both ethnic groups (Table 1).
- Predicted and observed clearances of desipramine, omeprazole and midazolam clearances were lower in Chinese than Caucasians (Table 1). Differences in the predicted and observed exposure of desipramine between the ethnic groups are shown in Figure 3 as an example.
- Predicted and observed clearances of tolbutamide were similar for both Chinese and Caucasians (Table 1) indicating relative insensitivity to the differences in hepatic CYP2C9 levels.

Figure 2 Comparison of A) hepatic CYP abundance and B) liver volume in Chinese and Caucasian populations

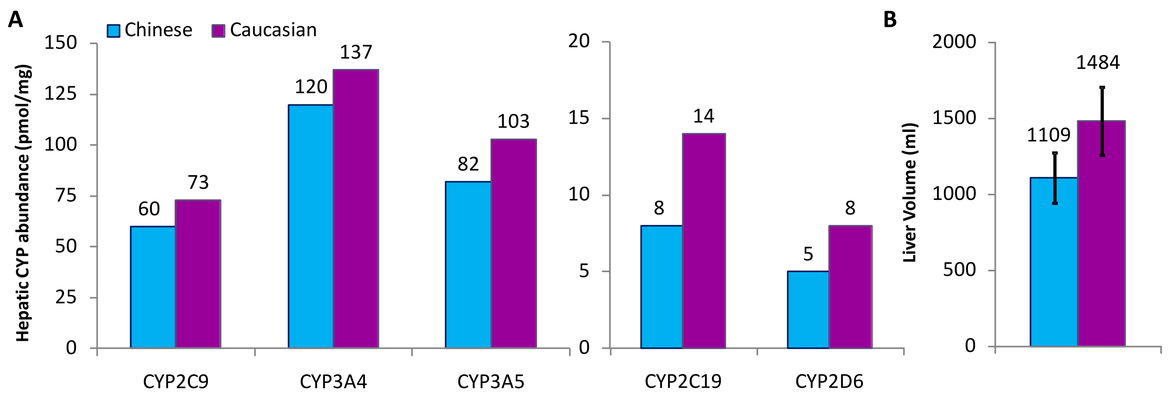
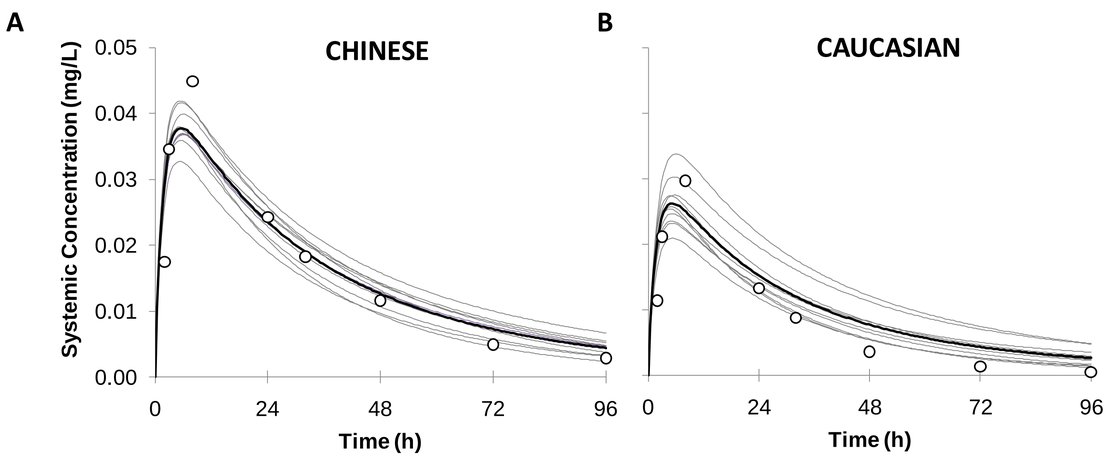


Table 1 Predicted and observed mean weight normalized clearances in Caucasian and Chinese populations

Drug	OBSERVED CLEARANCE (L/h/kg)			PREDICTED CLEARANCE (L/h/kg)		
	Chinese	Caucasian	% Difference Chinese *cf.* Cauc.	Chinese	Caucasian	% Difference Chinese *cf.* Cauc.
Desipramine[1]	1.27 (0.59)	1.78 (0.96)	-29	1.57	2.16	-27
Omeprazole[*2,3]	0.21 (0.13)	0.47	-55	0.30	0.94	-68
Midazolam[#4-9]	0.53 (0.09)	1.08 (0.71)	-51	0.82	1.08	-24
Tolbutamide[10,11]	0.014 (0.003)	0.013 (0.007)	+8	0.012	0.014	-14

[*]Population of CYP2C19 Extensive Metabolisers; [#]Population of CYP3A5 Poor Metabolisers
Standard Deviations of the observed data are provided in brackets.

Figure 3 Plasma concentrations of desipramine after a single oral dose of 100mg to healthy A) Caucasian subjects and B) Chinese subjects. Predicted profiles are indicated by the grey lines representing the outcome of 10 individual trials (n = 14); the solid black line is the mean prediction of the 10 x 14 trial simulations. The data points are the observed mean values from Rudorfer *et al* (1984).



CONCLUSIONS

- The results of this study indicate the value of simulation based on a mechanistic PBPK model in anticipating the likely extent of any differences in the kinetics of CYP substrates in Chinese and Caucasian populations arising from demographic, physiological and genetic differences.
- Extension of this to predict the impact of such differences on the handling of drugs by transporters is indicated.

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