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Application of Physiologically Based Pharmacokinetic (PBPK) Models in Predicting Drug Pharmacokinetics for Different Ethnic Groups

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2017 AAPS ANNUAL MEETING & EXPOSITION

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PURPOSE

The purpose of this study was to evaluate the ability of PBPK models to predict the pharmacokinetics (PK) of different compounds in two ethnic groups, Caucasian and Chinese. The test set included compounds that have different clearance mechanisms. The population difference was captured by the built-in physiologies provided in GastroPlus™ (Simulations Plus, Inc.), which accounted for the differences in tissue sizes, blood flow rates, enzyme expression levels, glomerular filtration rates, plasma protein binding, and other factors in the two population groups.

METHOD(S)

The PBPKPlus™ module in GastroPlus was used to model the PK for multiple drug compounds, which have different enzymatic clearance (Table 1) and varying fractions of renal secretion. The Advanced Compartmental Absorption and Transit (ACAT™) model was used to describe the intestinal dissolution, precipitation, absorption, and intestinal metabolism (where applicable) after oral (p.o.) administration. The default dissolution model was used for most of the compounds. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™ module. The Chinese physiology model is based on multiple publications and the weight and height data is based on the China Health and Nutrition survey data (CHNS). The organ sizes are calculated as functions of age, weight and height (and/or other parameters such as bioimpedance, BSA).

Tissue/plasma partition coefficients for most compounds were calculated by the default Lukacova algorithm (some used measured Kp values for a few tissues) based on tissue composition and *in vitro* and *in silico* physicochemical properties. Physicochemical and biopharmaceutical properties for all compounds (and metabolites, where applicable) were either obtained from literature or predicted by ADMET Predictor™ (Simulations Plus, Inc.). Metabolic reactions were modelled by Michaelis-Menten kinetics with built-in expression levels of each particular enzyme in gut and liver for the corresponding populations. Enzyme kinetic parameters (Km and Vmax) were used as reported in literature from *in vitro* experiments or fitted against *in vivo* plasma concentration-time (Cp-time) profiles in Caucasian populations only.

Table 1. Modeling details for the list of compounds

Compound	Theophylline	Ketoconazole	Atomoxetine	Fluconazole
BCS Class	I	II	I	I
Main Clearance Pathway	CYP 1A2	CYP 3A4	CYP 2D6 CYP 2C19	Renal
Num of Data Sets	8	7	7	10
Dosage Forms	IV, Tab	Tab	Cap	IV, Cap, Tab

Compound	Gemfibrozil	Midazolam	Rifampicin	Tolbutamide
BCS Class	II	I	II	II
Main Clearance Pathway	CYP 3A4 UGT 2B7	CYP 3A4	Esterase, CYP 3A4, Renal	CYP 2C9
Num of Data Sets	9	10	5	7
Dosage Forms	Tab, Cap	IV, Tab, Sol	Cap, Tab	IV, Tab

RESULT(S)

The model accurately described the mean Cp-time profiles for the listed compounds and their metabolites (where applicable) for different doses and formulations in both populations and explained inter-ethnic differences in the PK of specific compounds. The detailed information of each compound is given in Table 1. The overall prediction errors for Cmax and AUC averaged across all compounds/studies are both less than 20%: 15.9% for Cmax and 17.1% for AUC. Some compounds exhibit more pronounced population differences, such as midazolam (AUC difference > 70%), and some compounds have only minimal effects, such as rifampicin (AUC difference < 20%). Predictions of representative studies for 5 of the 8 test compounds are shown in Figures 1-5, where we presented those with most distinct clearance pathways. Studies with similar dose amounts and formulations in Chinese and Caucasian subjects were selected to show for an easy comparison of inter-ethnic differences.

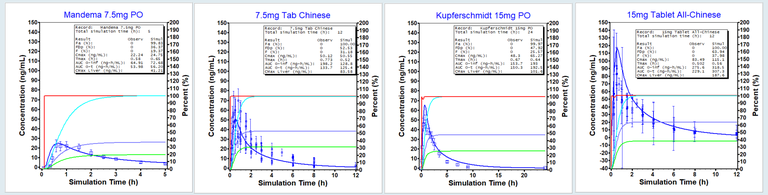

Figure 1: Simulated and observed midazolam Cp-time profiles after administration of midazolam tablet in fasted Caucasian and Chinese adults. A. 7.5 mg midazolam in a 22-year-old, 69 kg Caucasian male. **B.** 7.5 mg midazolam in a 23-year-old, 63.6 kg Chinese male. **C.** 15 mg midazolam in a 25-year-old, 70 kg Caucasian male **D.** 15 mg midazolam in a 40-year-old, 67.3 kg Chinese male. Km and Vmax values for 3A4 were from [Paine 1997].

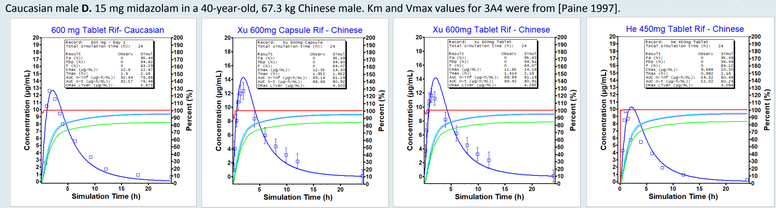

Figure 2: Simulated and observed rifampicin Cp-time profiles after rifampicin administration in fasted Caucasian and Chinese adults. A. 600 mg rifampicin tablet in a 30-year-old, 70kg Caucasian male. **B.** 600 mg rifampicin capsule in a 21-year-old, 62.8 kg Chinese male. **C.** 600 mg rifampicin tablet in a 21-year-old, 62.8 kg Chinese male. **D.** 450 mg rifampicin tablet in a 22-year-old, 65.5 kg Chinese male. Esterase and renal clearance were derived from [Lau 2007]. Km for 3A4 was from [Kajosaari 2005] and Vmax value was estimated from [Lau 2007].

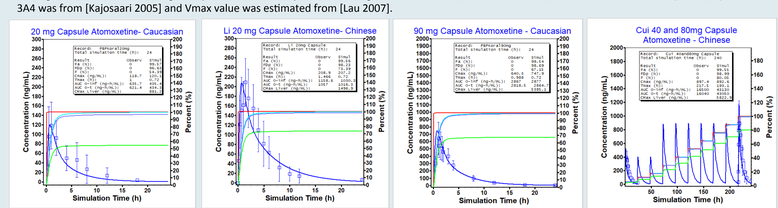

Figure 3: Simulated and observed atomoxetine Cp-time profiles after administration of atomoxetine capsule in fasted Caucasian and Chinese adults. A. 20 mg atomoxetine in a 52-year-old, 81 kg Caucasian male. **B.** 20 mg atomoxetine in a 24-year-old, 59 kg Chinese male. **C.** 90 mg atomoxetine in a 30-year-old, 74 kg Caucasian male. **D.** 40 and 80 mg atomoxetine (40 mg once daily (qd) for 3 days (days 1, 2 and 3), followed by atomoxetine 80 mg qd for 7 days (days 4–10)) in a 30-year-old, 62 kg Chinese male of 62 kg. Km values were from [Ring 2002] and Vmax values were fitted.

NOTE: In all plots, the dark blue colored lines and data points represent plasma concentrations (shown on the left Y-axis). The red, cyan, light blue and green colored lines are cumulative percents of the dose dissolved, absorbed, entering portal vein and entering systemic circulation, respectively (shown on the right Y-axis). The observed data are from multiple publications listed in the references and the subject weight and age are averages of the subjects in these studies.

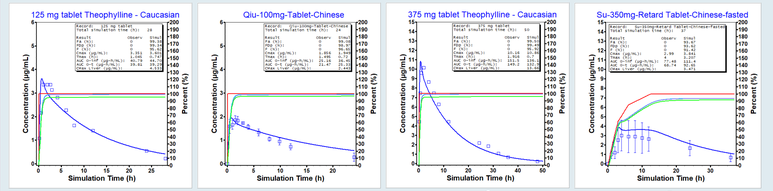

Figure 4: Simulated and observed theophylline Cp-time profiles after administration of theophylline tablet in fasted Caucasian and Chinese adults. A. 125 mg theophylline in a 30-year-old, 62 kg Caucasian male. **B.** 100 mg theophylline in a 30-year-old, 69 kg Chinese male. **C.** 375 mg theophylline in a 30-year-old, 62 kg Caucasian male. **D.** 350 mg theophylline (as modified release tablet) in a 25-year-old, 63 kg Chinese male. The controlled released profile used in the GastroPlus simulation was from published *in vitro* dissolution data. Km for 1A2 was from [Tjia, 1996] and Vmax value was fitted.

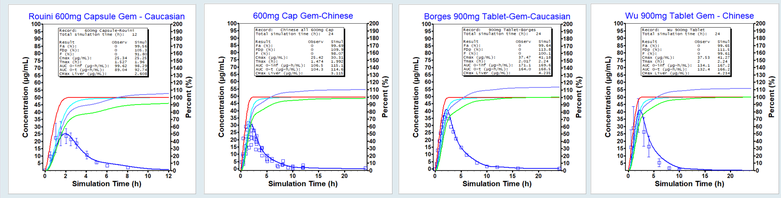

Figure 6: Simulated and observed gemfibrozil Cp-time profiles after gemfibrozil administration in Caucasian and Chinese adults. A. 600 mg gemfibrozil in a 30-year-old, 70 kg Caucasian male. **B.** 600 mg gemfibrozil in a 21-year-old, 59.8 kg Chinese male. **C.** 900 mg gemfibrozil in a 30-year-old, 65 kg Caucasian male. **D.** 900mg gemfibrozil in a 25-year-old, 65.5 kg Chinse male. The percent entered portal vein is over 100%, which is caused by the conversion of the glucuronide metabolite back to the parent compound in the intestine. Km for UGT2B7 was from [Mano 2007] and Vmax value was fitted.

CONCLUSION(S)

The work described the use the mechanistic absorption model/ physiologically based pharmacokinetic MAM/PBPK approach for drug development and demonstrates the ability to predict inter-ethnic differences in PK over a range of compounds. The current approach helps to quantify dose regimens for different ethnic groups; hence, it will be very useful in a number of areas including drug safety, pharmacodynamics, and drug-drug interactions. The MAM/PBPK approach incorporates all of the relevant processes in drug absorption, distribution, metabolism, and elimination, and facilitates prediction of PK for different dosage forms and study designs.

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*note, this is only a selected list

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