Physiologically-Based Pharmacokinetic Modeling to Predict Changes in Drug Exposure during Pregnancy Using the Simcyp Simulator

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**Purpose**

Purpose: 1. To utilize physiologically-based pharmacokinetic (PBPK) modeling with the Simcyp Simulator to predict changes in drug disposition and systemic exposure during pregnancy for four probe compounds; and 2) To evaluate the Simcyp predictions of changes in systemic exposure as pregnancy matures to published data using GastroPlus.

**Methods**

PBPK modeling was performed using Simcyp Simulator Version 14.0.93.0. Modeling was used to predict systemic exposure in pregnant women as pregnancy progresses (i.e., across trimesters), based on physiologic changes during pregnancy that can impact ADME pathways. Four probe compounds were studied: caffeine, lopinavir, metformin and tacrolimus. Plasma concentration-time profiles were then simulated for each compound across four populations (non-pregnant women, 1st, 2nd, and 3rd trimester pregnant women) using Simcyp virtual populations of healthy and pregnant women. The predicted systemic exposure metrics (Cmax, AUC) were compared to published clinical data \(^{1,2,3,4}\) and the fold error (FE, ratio of observed and predicted data) was calculated. Simcyp predictions were compared to the results from a previous study using GastroPlus \(^5\).

**Results**

The Simcyp-simulated pharmacokinetic profiles for test compounds were in agreement with observed clinical data for the changes in exposure (AUC and Cmax) during pregnancy (Table 1). The ratio of observed and predicted values ranged 0.39 to 1.13, indicating that the PBPK modeling approach was useful in predicting drug pharmacokinetics in pregnant women during each trimester. The predictive performance of Simcyp was comparable to GastroPlus.

**Conclusion**

Two-thirds of women take at least one medication during pregnancy, and 5% or pregnant women require medication to treat a chronic condition. Therefore, pregnancy-associated changes in pharmacokinetics can influence the delivery of safe and effective medication to this special population. The findings of this study demonstrate that the Simcyp Simulator represents a potential tool to help establish dosing guidelines for pregnant patients and to predict potential changes in systemic exposure in pregnant women for compounds undergoing clinical development.

**References:**


