Prediction of Tolerance to Caffeine Pressor Effect during Pregnancy using Physiologically Based PK-PD Modelling

K. Abduljalil[1], R. Rose[1], T.N. Johnson[1], T. Cain[1], L. Gaohua[1], D. Edwards[1], M. Jamei[1], A. Rostami-Hodjegan[1,2]

k.abduljalil@Simcyp.com

1-Simcyp (a Certara company), Blades Enterprise Centre, John St, Sheffield, S2 4SU, UK
2-School of Pharmacy and Pharmaceutical Sciences, Manchester University, Manchester, UK

Background

Pregnancy is associated with a variety of anatomical, physiological and biochemical changes that can alter maternal drug disposition [1]. Although the application of physiologically based pharmacokinetic (PBPK) models is becoming a popular approach to anticipate and understand the drug disposition, adjusting the drug dose during pregnancy requires incorporation of pharmacological effects and its population variability. Thus, linking pharmacodynamic (PD) models to the PBPK models of pregnancy would be of interest [2].

Objectives

To demonstrate application of PBPK-PD linked model in simulating the concentration-response of caffeine after 150mg daily dose, in a virtual healthy pregnant population using the Simcyp Simulator.

Methods

Gestational age-dependent PBPK parameters [1], including CYP1A2 activity, were incorporated into the Simcyp V12 Release 2 Simulator and added to prior *in vitro* information on the metabolism and kinetics of caffeine available in Simcyp. The absorption phase was predicted based on the physicochemical properties of the drug and the full PBPK model was used to describe the drug distribution.

The change in mean arterial pressure (MAP) was used as the PD marker of the pressor effect of caffeine. The PK-PD relationship was represented by an empirical tolerance model, as adopted by Shi *et al.,* 1993 [4]. The tolerance model was defined in Simcyp using the PD custom scripting module, which was then linked to the systemic concentration of the full PBPK model (Figure 1). Simulated PBPK-PD profiles were compared to the reported observed values [3, 4].

Results

Predicted caffeine plasma levels and response for different doses and routes of administration were in agreement with the clinical observations (Figure 2).

Predicted PBPK-PD time profiles for non-pregnant and pregnant women are presented in Figure 3. The predicted total area under the concentration curve, $AUC_{0\text{-}72h}$, was 2.2-fold higher in pregnant compared to non-pregnant women (78 vs 35 mg/L·h). The corresponding free AUC, $fAUC_{0\text{-}72h}$ and free maximum concentration, Cu_{max} were 58 and 24 mg/L·h and 3.73 and 4.30 mg/L for pregnant and non-pregnant women, respectively.

Similarly, the predicted area under the effect curve, based on total concentration in plasma, $AUEC_{0\text{-}72h}$, was 1.84-fold higher in pregnant women compared to the non-pregnant women (311 vs 169 mmHg·h).

Non-pregnant women did not show a marked tolerance effect, based on a daily dose of 150mg caffeine; however, tolerance to the pressor effect is still substantial in pregnant women using the same dosing regimen (Figure 4).

Conclusions

The link between PD and PBPK, combined with *in vitro-in vivo* extrapolation, offers an extension of the success of PBPK in drug development [2]. In this case study, the implemented approach allowed successful simulation of the tolerance to the pressor effect of caffeine observed in clinical studies [4] and offers prediction of the response in a pregnant population. The decreased activity of CYP1A2 during pregnancy results in the reduction of drug elimination and prolongation of the effect. The custom PD module facilitates the linkage of more flexible user defined PD models to the Simcyp PBPK models, thus extending the simulator capabilities.

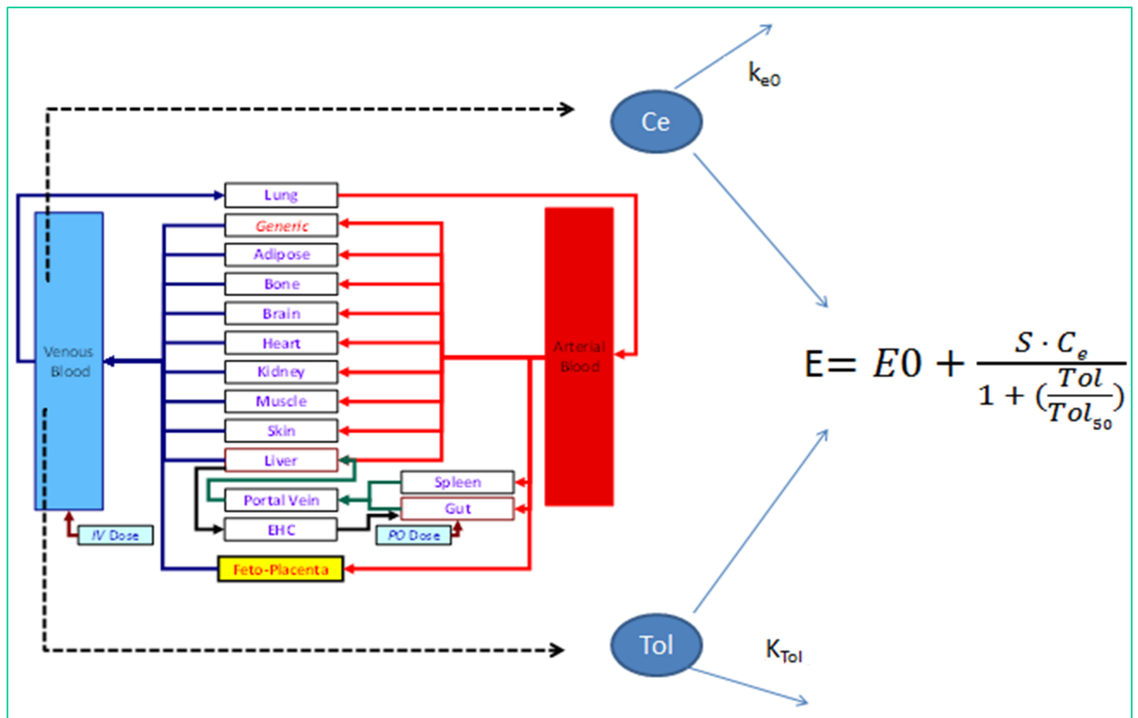

Figure1. Linked Maternal PBPK-PD model

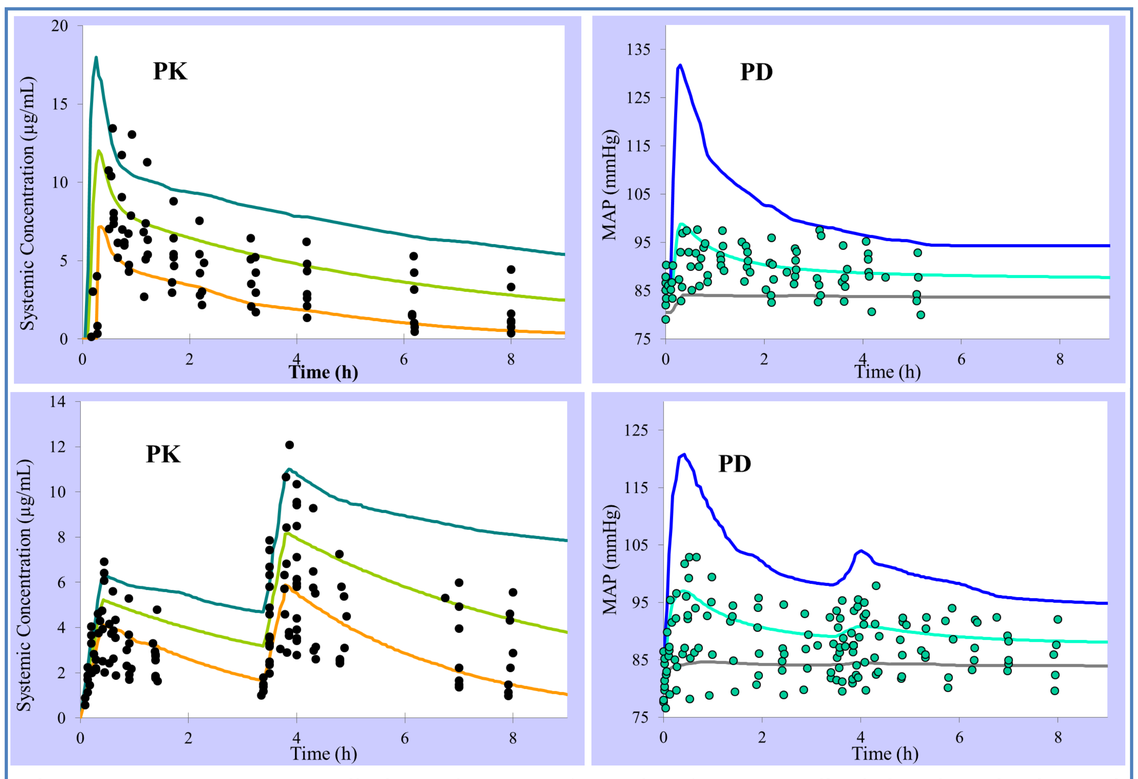

Figure 2. PBPK-PD Predictions (mean, 5th and 95th percentiles) for the single oral dose 4mg/kg (upper panel) and after two i.v. infusion doses of 2mg/kg (lower panel) in healthy male subjects. Solid dots are clinical data from Shi *et al.*, 1993 [4]

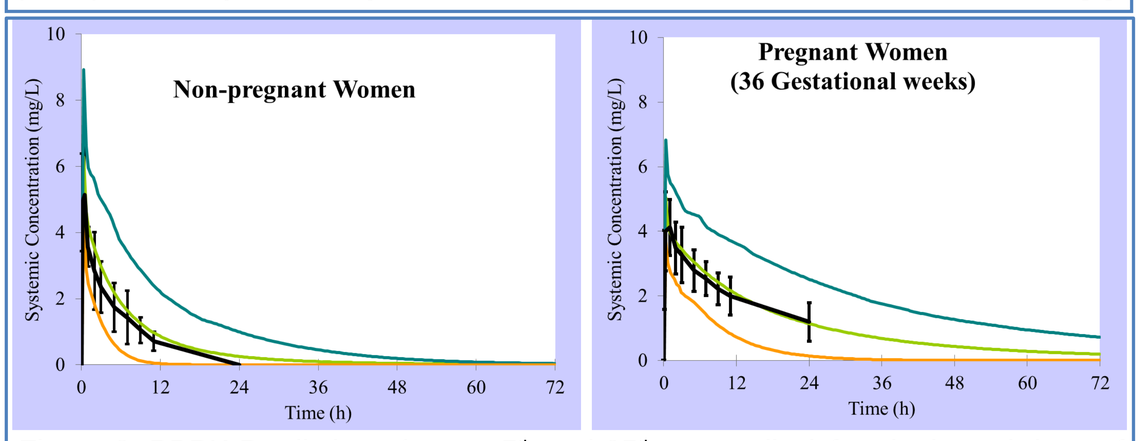

Figure 3. PBPK Predictions (mean, 5th and 95th percentiles) for single oral dose of 150mg in healthy non-pregnant and pregnant populations. Black lines and bars are clinical observations from Brazier et al., 1983 [3].

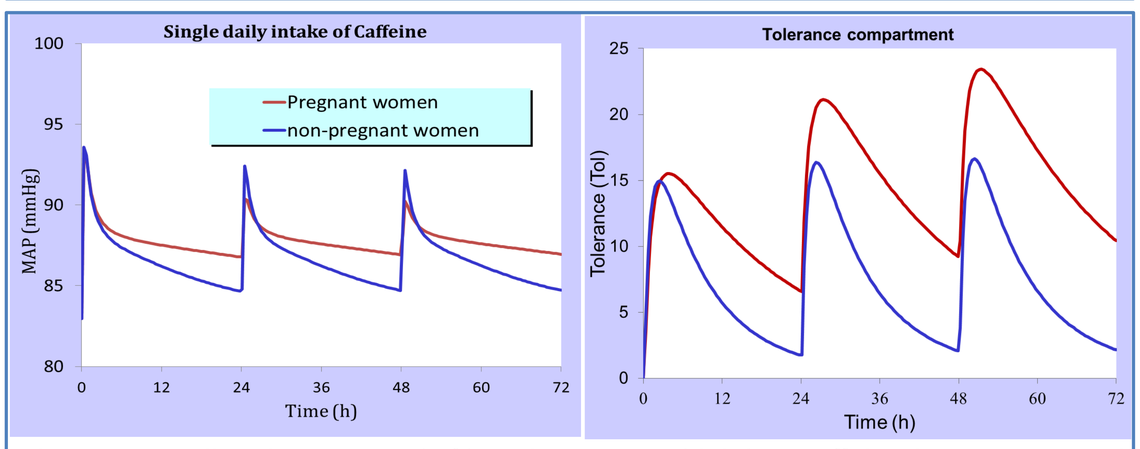

Figure 4. Predicted response (left) and tolerance (right) to caffeine in pregnant and non-pregnant virtual populations after oral daily intake of 150mg.

References

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