Predictive performance of Pregnancy Physiologically based Pharmacokinetic (PBPK) model for Cefazolin in Pregnant and Non-Pregnant Women

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Background

Cefazolin is commonly used as prophylaxis during surgical interventions, including cesarean sections. Extensive and progressive gestation-induced physiological alterations during pregnancy are likely to influence the drug pharmacokinetics (PK) [1]. Since cefazolin is mainly excreted unchanged via glomerular filtration and because the glomerular filtration rate (GFR) increases during pregnancy, it is expected that the PK of cefazolin will change in parallel [2].

Methods

The pharmacokinetics of Cefazolin was investigated in a pregnant and non-pregnant women after intravenous administration using the Sim-Pregnancy population within Simcyp Simulator V17.

Cefazolin compound file was generated using drug related parameters collated from the literature. Full PBPK distribution model using Rodgers & Rowland method was used to calculate the drug partition between tissues and plasma, while the elimination was represented by in vivo clearance (CL_{iv}) of 4.2 L/h of which renal clearance (CL_R) was 3.63 L/h from non-pregnant population [3]. Cefazolin PBPK model performance was first verified against Healthy volunteer populations.

To replicate the clinical study [1], total 120 virtual subjects, grouped into 20 trials aged 20-45 years were used in the simulations. Two different simulations were performed, one for non-pregnant women and another for pregnant women at 25 weeks gestation following administration of 500 mg cefazolin. Predictive performance of the PBPK model was evaluated by comparing the simulated to the clinical results for both concentration-time profiles and PK parameters in pregnant vs non-pregnant.

Results

Simulated concentration profiles were in good agreement with the clinical observations in both pregnant and non-pregnant women (Figure 1). The ratios of predicted vs observed mean area under the curve (AUC_{inf}) and total clearance (CL) were within 0.8-1.25 range (25% error) for both pregnant and non-pregnant women (Table 1). In non-pregnant women half-life was slightly shorter for the predicted vs reported value (1.2 vs 1.7 h), which is most probably due to involvement of some active reabsorption components.

Predicted and observed individual AUC_{inf} and CL for pregnant and non-pregnant women were represented in Figure 2. Overall, 80-100% of observed individual data were well within the prediction range for the population studied. The simulated profiles for the intravenous dose indicated a lower mean AUC_{inf} for the pregnant compared with the non-pregnant women which corresponds to 22% difference between the two groups. Predicted mean clearance was 1.3 fold higher in pregnant women vs non-pregnant women, which could be the result of increase in either renal blood flow or glomerular filtration during pregnancy. (Table 1 and Figure 2)

Conclusions

A pregnancy PBPK model that accounts for inter-individual variability and gestational age dependent physiology provided a good prediction of Cefazolin PK. This approach can be applied to predict maternal drug disposition throughout pregnancy and in designing clinical PK studies.

Results(cont.)

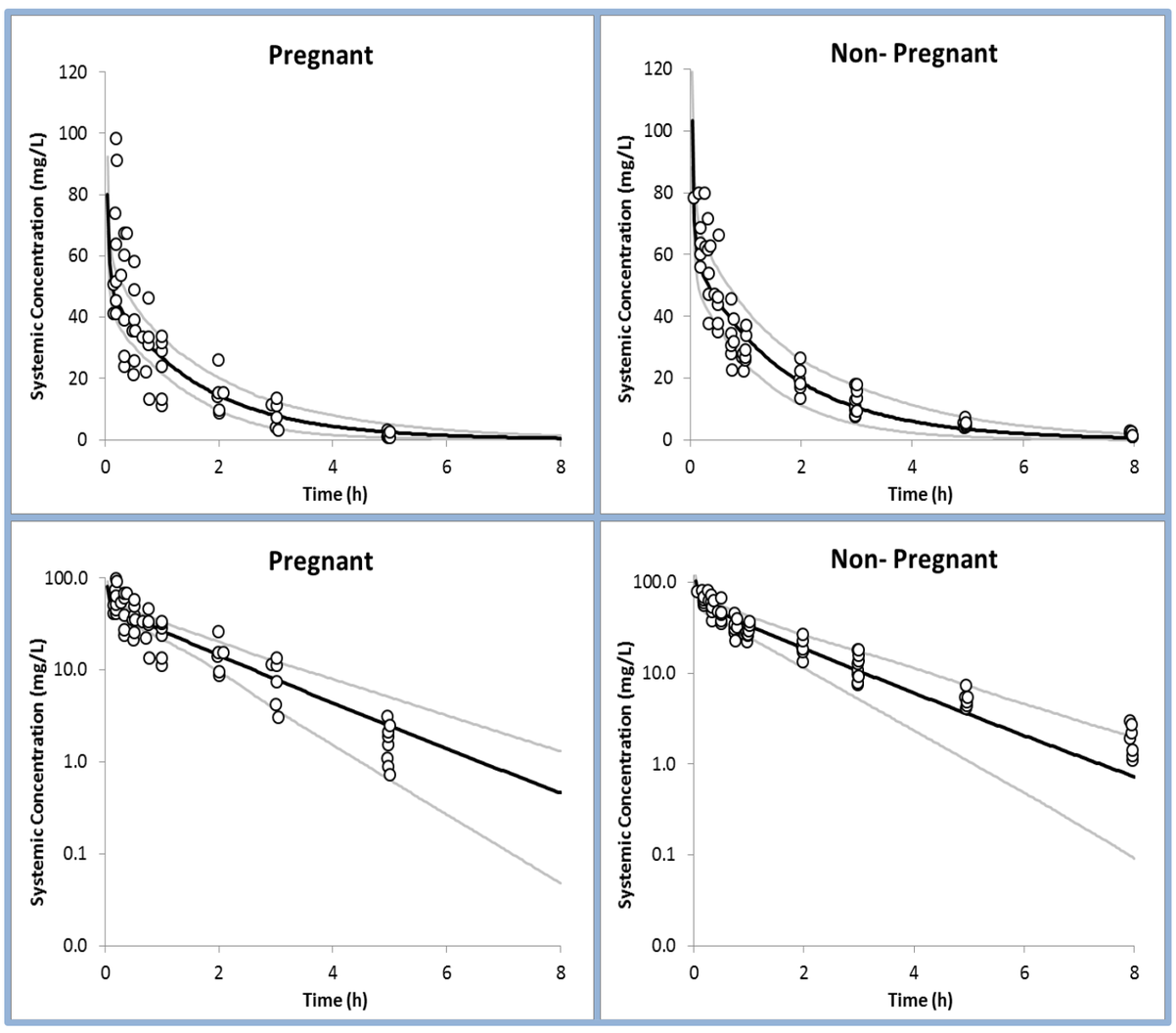

Figure 1. Cefazolin plasma concentration-time profile (Top figure) and log plasma concentration-time profile (bottom figures) in Pregnant (left) and Non-Pregnant (right) women following 500 mg intravenous administration. Predicted mean (Black lines), Predicted 5th and 95th percentiles (Gray lines) and Observed data [1] (Open circles).

PK Parameters	Pregnant			Non-Pregnant		
	Predicted	Observed	Ratio	Predicted	Observed	Ratio
AUC_{inf} (mg/L.h)	83.8	75.7	1.1	107.6	110.0	1.0
CL (L/h)	6.2	7.3	0.8	4.9	4.7	1.0
CL/BW (L/h/kg)	0.08	0.11	0.8	0.07	0.08	1.0
Half-life (h)	1.1	1.1	1.0	1.2	1.7	0.7

Table 1. Predicted and Observed pharmacokinetic parameters of Cefazolin in Pregnant and Non-Pregnant women.

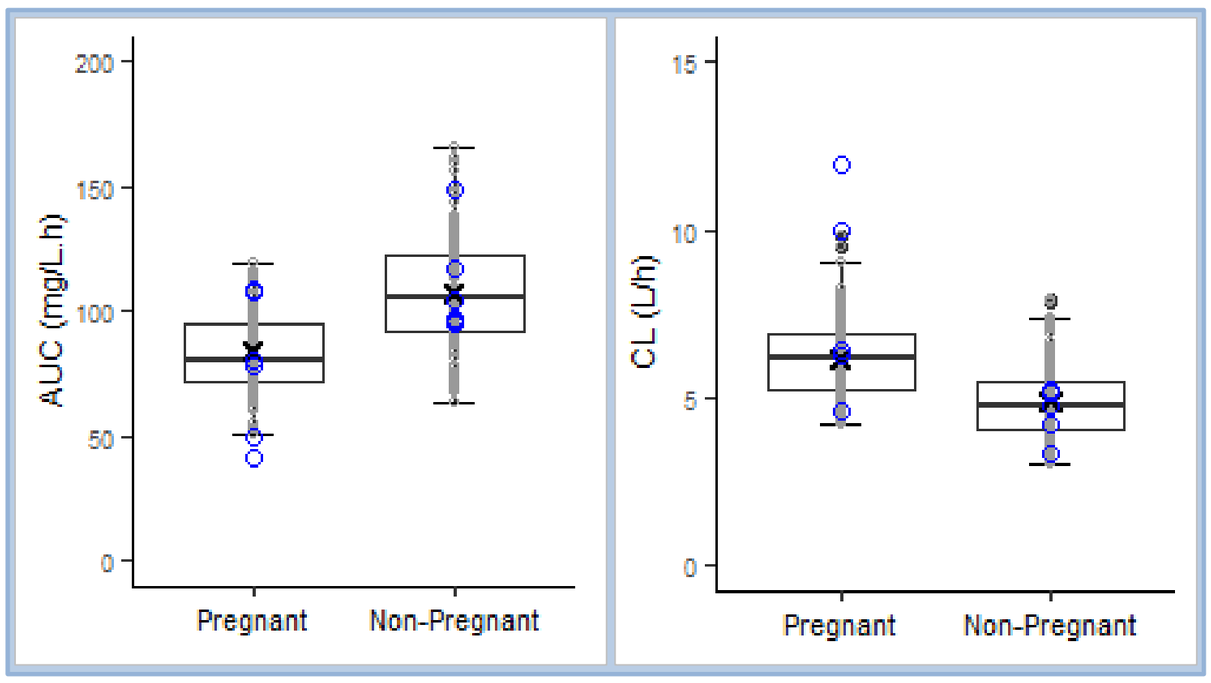

Figure 2. Box and whisker plot with predicted individual (gray open circles) and mean (cross markers) AUC and Clearance of Cefazolin in Pregnant and Non-Pregnant women. Observed individual data [1] (blue open circles) are overlaid.

References

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[3] Smyth RD, Pfeffer M, Donald AG, Van Harken R, Hottendorf GH. Clinical pharmacokinetics and safety of high doses of ceforanide (BL-S786R) and cefazolin. Antimicrobial agents and chemotherapy, 1979. 16(5): p. 615-621.