

Application of Physiologically-based Pharmacokinetic model to Predict Nifedipine Pharmacokinetics of Different oral Formulation in Pregnant Women

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Introduction: Nifedipine is used for the treatment of hypertension during pregnancy, the longer-acting formulations are generally recommended because of improved tolerability and patient compliance with therapy [1]. Pregnancy is characterized by myriad of physiological changes that can alter pharmacokinetic [2] dependent on drug parameters and the route of administration.

Objectives: To assess the performance of physiologically based pharmacokinetic (PBPK) model to predict clinical data following administration of two different formulations of nifedipine in pregnant women.

Methods: 'Sim-Pregnancy' population within the Simcyp Simulator V19R1 was used to replicate the clinical studies for immediate release (IR) [3] and controlled release (CR) formulations [4] of nifedipine in pregnant women under fasted conditions. The default Sim-Nifedipine file settings within the Simcyp Simulator was used. The Advanced Dissolution, Absorption and Metabolism (ADAM) model was used to describe the absorption via formulation specific predictions. Drug distribution was defined using a full PBPK model, method 3 (Rodgers et al [5] with ion membrane permeability) and elimination by enzyme kinetics (mainly CYP3A4). The trial design for IR formulation was set up as 10 trials of 15 females aged 20-35 years at 32 gestational weeks, receiving 10mg of nifedipine every 6 hours for total of 9 doses (54 hours study duration). The trial design for the CR formulation was set up as 10 trials with 12 females aged 20-40 years at 36 gestational weeks, receiving 20mg of nifedipine every 12 hours for 6 day. Gastrointestinal changes during pregnancy were not considered in the model as there are limited existing data for relevant gastrointestinal parameters.[2] The absorption of the IR formulation was predicted using the diffusion layer model with default input data while for the CR an in vitro dissolution profile [6] was incorporated. Predictive performance of the PBPK model was evaluated by comparing the simulated to the clinical results for both concentration-time profiles and pharmacokinetic parameters at steady state in pregnant women.

Results: The predicted mean oral plasma concentration profiles of nifedipine IR and CR formulations were in good agreement with the clinical observations. Observed mean values were within the 95% confidence interval for the predictions. The ratios of predicted vs observed mean of the key pharmacokinetic parameters C_{max} , T_{max} and AUC_{0-t} at steady state in pregnant women were 1.2, 1.1, 1.2 for IR formulation and 1.1, 1.2, 0.7 for CR formulation, respectively. There was significant inter-subject variability in the observed data for both IR and CR studies, especially around C_{max} . Sensitivity analysis around relevant gastrointestinal parameters for nifedipine i.e. Small intestine mean residence time for CR and gastric pH, gastric volume and Jejunal bile salt concentration for IR formulation showed no significant difference in AUC and C_{max} , indicating these changes have little influence on predictions for the simulated studies of Nifedipine.

Conclusions: A pregnancy PBPK model that includes gestational age dependent physiology and inter-individual variability consideration within the model framework, provided good prediction of nifedipine pharmacokinetics for oral IR and CR formulations. A similar approach can be applied in

combination with appropriate in vitro formulation-specific data to predict maternal drug pharmacokinetics throughout pregnancy. The model can be used to predict nifedipine exposure during the different trimesters and in exploring different scenarios such as drug-drug interaction or optimizing the maternal dose.

References:

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