Physiologically Based Pharmacokinetic Model for Pregnant Women to Predict the Pharmacokinetics of Drugs Metabolized Via Several Enzymatic Pathways

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Supplemental Digital Content

Fig. 1: Observed and predicted plasma concentration-time profiles of midazolam and nifedipine for different scenarios of CYP 3A4/5 activity induction in pregnancy

The figure shows observed (symbols) and predicted (lines) mean plasma concentration-time profiles of midazolam (A) and nifedipine (B) in pregnant women. The green solid line represents the predicted mean pharmacokinetic (PK) profile assuming 60% induction in CYP 3A4/5 activity in all tissues as proposed in this study. The black dashed line represents the predicted mean PK profile assuming 100% induction in hepatic CYP 3A4/5 activity and no change in intestinal CYP 3A4/5 activity as it has been previously suggested [37]. Error bars indicate the standard deviation. A semi-log plot of each PK profile is shown in the top right corner. (A) Midazolam mean PK profile in pregnant women with a mean GA of 30 weeks after oral administration of 2 mg. Observed data (mean values) taken from [16]. (B) Nifedipine mean PK profile in pregnant women with a mean GA of 32 weeks after oral administration of 10 mg or 20 mg in steady state. Concentrations are dose-normalized to 20 mg. Observed data (mean values) taken from [57].

conc: concentration; MDZ: midazolam; NIF: nifedipine
Fig. 2: Sensitive analysis on the fraction metabolized via CYP 1A2, 3A4, and 2D6 for ondansetron. 4 mg ondansetron were intravenously administered to pregnant women at term. Observed data taken from [61].

cnc: concentration; fm: fraction metabolized; OND: ondansetron;