PBPK modeling of drugs metabolized via several CYP enzymes in populations of pregnant women

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Objectives

The aim of this study is to verify a physiologically-based pharmacokinetic (PBPK) model for the prediction of pharmacokinetics (PK) of drugs metabolized via several cytochrome P450 (CYP) enzymes in populations of pregnant women.

Introduction

Pregnant women represent a special population with respect to drug therapy. As they are generally excluded from clinical trials, there is scant information on the PK. PBPK modeling is considered as a promising approach to predict the PK in pregnancy. Hence, we set out to extend a newly developed pregnancy PBPK model for renally cleared drugs [1] by quantitative information on pregnancy-induced changes in CYP enzymes and to verify it exemplary for three drugs metabolized via CYP2A6, 2B6, and/or 3A4/5.

Methods

A recently developed pregnancy PBPK model (Fig. 1) [1], verified for renally cleared drugs [2], was extended to predict the disposition of drugs metabolized via CYP2A6, 2B6, 2C19, 2E1 and/or 3A4/5 in the third trimester of pregnancy. Therefore, the literature was screened for quantitative information on pregnancy-dependent changes in the apparent activity of these CYP enzymes. The reported changes were pooled to overall mean values for the third trimester of pregnancy (Tab. 1) and used to scale the clearance via each enzymatic pathway from non-pregnant to pregnant women.

Subsequently, pregnancy PBPK models were built to predict the PK of midazolam (substrate of CYP3A4/5), metronidazole (substrate of CYP2A6, 2E1 and 3A4/5), and diazepam (substrate of CYP2B6, 2C19 and 3A4/5) in the third trimester of pregnancy. The PBPK models were developed in PK-Sim® and ModEl® as part of the Open Systems Pharmacology Suite (www.open-systems-pharmacology.org). PK predictions were evaluated by comparing them with experimentally observed in vivo PK data taken from the literature [9–16].

Results I: Midazolam PBPK model

The pregnancy population PBPK model successfully predicted the PK of midazolam. Predicted plasma concentrations were in adequate agreement with the observed in vivo data (Fig. 2). All predicted mean plasma concentrations in pregnant women were within a 2-fold error range and 70% within a 1.5-fold error range (Fig. 4).

Results II: PBPK models for diazepam and metronidazole

The pregnancy population PBPK models for diazepam and metronidazole adequately predicted the in vivo PK in pregnant women. Variability in plasma concentrations was reasonably well predicted (Fig. 3). For both drugs, all predicted mean plasma concentrations in pregnant women fell within a 2-fold error range and 88% within a 1.5-fold error range (Fig. 4).

Conclusions

We successfully developed and verified a pregnancy population PBPK model for drugs metabolized via CYP2A6, 2B6, 2C19, 2E1, and/or 3A4/5. Ultimately, this model can be applied to investigate in silico the PK of drugs undergoing metabolism in pregnancy and help design dosages e.g. for clinical trials in this vulnerable special population.

References