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 CYP 2A6, 2B6, 2C19, 2E1, and/or 3A4/5.

Methods

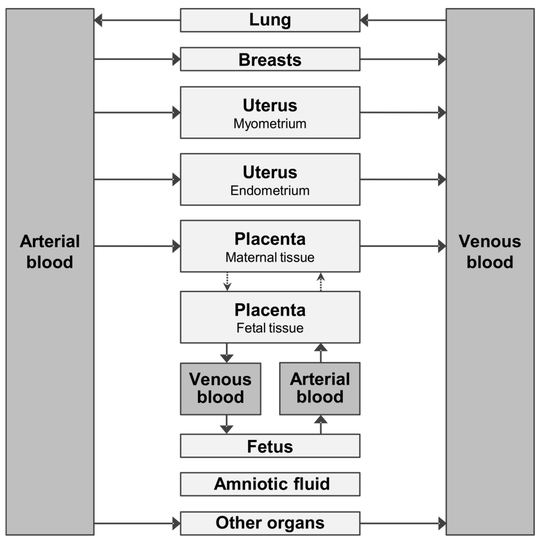

Fig. 1: Structure of the pregnancy PBPK model. The pregnancy PBPK model structure includes all 18 compartments of the standard structure implemented in PK-Sim® (15 of which are not explicitely shown but grouped together as "Other organs") and *nine additional compartments* specifically relevant in pregnancy (in particular, the breasts, endometrium, myometrium, maternal and fetal placental tissue, fetus, amniotic fluid and the arterial and venous blood pool of the umbilical cord).
Solid arrows represent drug transport pathways via blood flow and dotted arrows via passive diffusion.
The structure and parametrization of the pregnancy PBPK model are described in detail elsewhere [1,2].

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 CYP 2A6, 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 CYP 3A4/5), metronidazole (substrate of CYP 2A6, 2E1 and 3A4/5), and diazepam (substrate of CYP 2B6, 2C19 and 3A4/5) in the third trimester of pregnancy. The PBPK models were developed in PK-Sim® and MoBi® 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].

Tab. 1: Changes in apparent enzyme activity in the 3rd trimester collected from the literature

Enzyme	Probe substrate/technique for deriving change in enzyme activity	Change in activity relative to non-pregnant level [%]	Reference
CYP 2A6	Nicotine; paraxanthine	82%	[3,4]
CYP 2B6	In vitro to in vivo extrapolation	90%	[5]
CYP 2C19	Proguanil	−68%	[5]
CYP 2E1	Paracetamol	80%	[6]
CYP 3A4/5	Cholesterol; clorazepate; midazolam	60%	[7,8,9]

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).

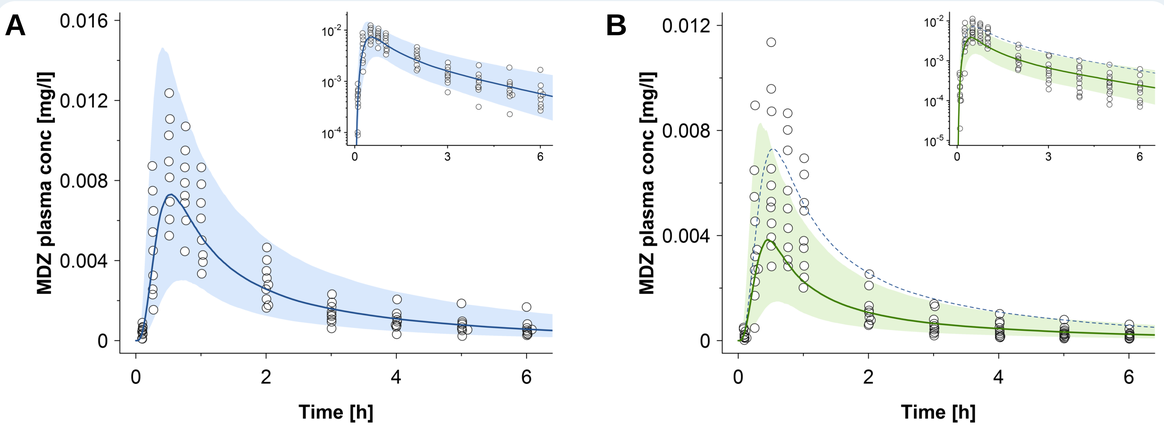

Fig. 2: PK profiles of midazolam in populations of non-pregnant (A) and pregnant women (B) after oral administration of 2 mg. Solid lines represent predicted median plasma concentration and the shaded areas predicted 5th – 95th percentile range. In (B), the dotted line shows the predicted median plasma concentration in non-pregnant women. Mean gestational age of pregnant women is 30 weeks. Symbols represent observed data [9]. Semi-log scale figure in top right corner.

Results II: PBPK models for diazepam and metronidazole

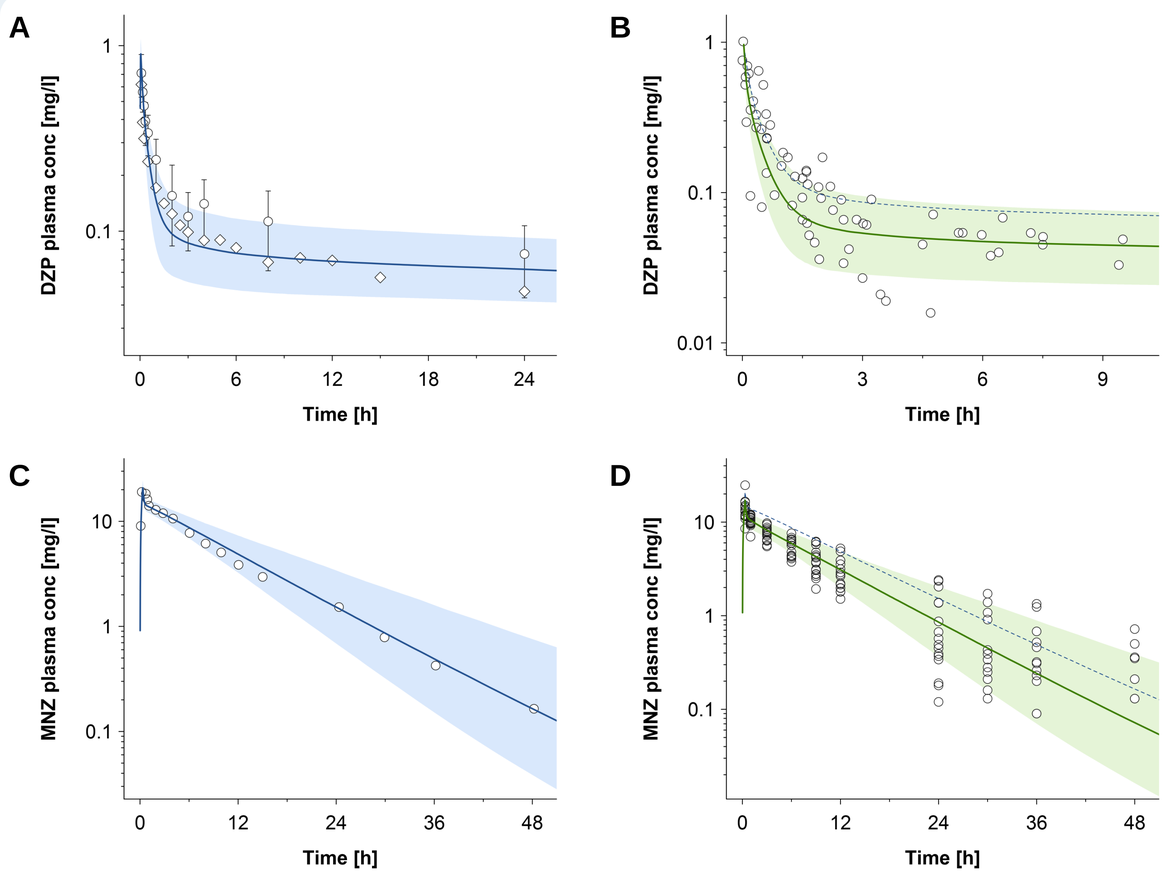

Fig. 3: PK profiles of diazepam (upper panel) and metronidazole (lower panel) in populations of non-pregnant subjects (left panel) and pregnant women (right panel).
Solid lines represent the predicted median plasma concentration; the shaded area the predicted 5th – 95th percentile range; and symbols the observed *in vivo* data. In the right panel, the dotted lines show the simulated median plasma concentration in non-pregnant subjects. (**A**) Diazepam PK profile in non-pregnant subjects after IV administration of 10 mg (circles) and 0.15 mg/kg (diamonds). Observed data (mean ± SD) from [10] (10 mg) and [11] (0.15 mg/kg). Concentrations dose-normalized to 10 mg. (**B**) Diazepam PK profile in pregnant women at term after IV administration of 5 or 10 mg. Observed data (individual values) from [12–14]. Concentrations dose-normalized to 10 mg. (**C**) Metronidazole PK profile in of non-pregnant women after IV administration of 500 mg. Observed data (mean values) from [15]. (**D**) Metronidazole PK profile in pregnant women at term after IV administration of 500 mg. Observed data (individual values) taken from [16].

The pregnancy population PBPK models for diazpeam 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).

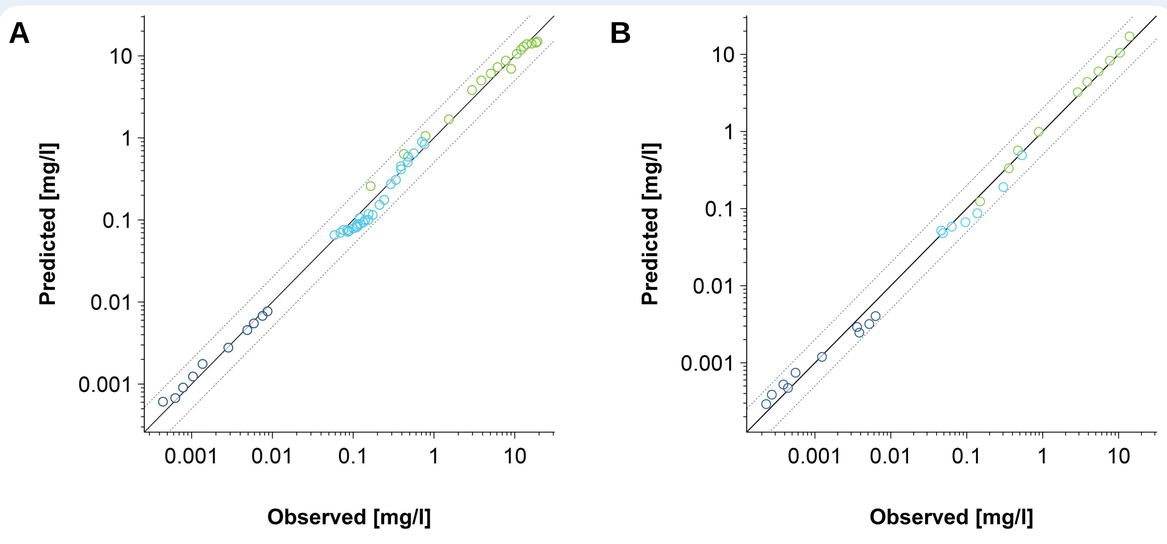

Fig. 4: Goodness-of-fit plots. The figure shows a goodness-of-fit plot for predicted mean plasma concentrations of midazolam (dark blue circles), diazepam (light blue circles), and metronidazole (green circles) in non-pregnant subjects (**A**) and pregnant women (**B**). Observed individual concentrations combined to mean values at corresponding time points.

Conclusions

We successfully developed and verified a pregnancy population PBPK model for drugs metabolized via CYP 2A6, 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.

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