

A Physiologically Based Pharmacokinetic (PBPK) Model of Sildenafil to Predict Exposure in Pregnant Females. What is missing?

**Background:** Sildenafil (S), a potent vasodilator, has recently been shown to reduce the incidence of operative delivery for intrapartum fetal compromise<sup>1</sup>, potentially leading to a new indication and more frequent administration to pregnant females. Pregnancy leads to profound changes in both body composition<sup>2</sup> and enzyme expression<sup>3</sup>, most likely requiring the revision of established dosing regimens for S, even for unchanged exposure targets. In order to assist dose finding for indications in the pregnant population, we developed a PBPK model of sildenafil in male adults, scaled it to pregnant females as described by Dallmann<sup>4</sup> and compared the predictions with sparse data from pregnant females having received 50mg capsule(s) of S during labor<sup>1</sup>.

**Material and methods:** A PBPK model of sildenafil was built in PK-Sim<sup>®</sup> (v 8.0)<sup>5</sup>. The compound specific physicochemical properties were retrieved from Drugbank<sup>6</sup> and Gobry<sup>7</sup>. Hepatic elimination (several CYP enzymes involved, fractions to metabolites poorly documented) was lumped into a single first order process (“dummy enzyme”). In order to describe the very rapid absorption of the drug in the fasted state, the dose was administered into the duodenum, with first order release kinetics. T<sub>1/2abs</sub> in the fasted and fed conditions, specific intestinal permeability, intrinsic clearance and LogP were fitted either sequentially or, when appropriate, simultaneously to digitized average concentration time courses retrieved from the literature (iv<sup>8</sup>, po capsule/tablet (fasted/fed)<sup>9</sup>). Thereafter, population simulations (n=500) with fixed parameters were performed and compared to digitized typical concentration time courses after single doses of S (25-200mg tablet, fasted)<sup>9</sup>. The model was then scaled to a pregnant population according to Dallmann<sup>4</sup>, increasing fraction not bound to albumin from 3.6 to 4.8%<sup>10</sup> and intrinsic clearance by 60% (CYP3A4/5 at term)<sup>3</sup>. A virtual population of full term pregnant females (n=500) was simulated and the predictions compared to sparse data (1 concentration/individual) from a subset of full term pregnant patients having received 50mg capsule(s) of S (n=32)<sup>1</sup>.

**Results:** The fit of the model to datasets was excellent. The parameter set optimally describing both iv and po (fasted and fed) concentration time courses was: LogP=2.43, Clint=1176L/h, specific intestinal permeability=2.85E-6 cm/min, t<sub>1/2abs</sub>(fasted)=0.13h, t<sub>1/2abs</sub>(fed)=0.68h, t<sub>lag</sub>(capsule)=0.25 h, F<sub>rel</sub> (capsule vs. tablet)=0.61, the latter finding highlighting the importance of formulation for dose selection. During validation in the male population, the typical concentration time courses of doses from 25-200mg (tablet, fasted) did not exceed the 90% boundaries of the population simulations, except for the very early and late time points in the 25mg cohort. The scaled pregnancy model yielded the expected decrease of dose normalized AUC and C<sub>max</sub> vs. non-pregnant females, but considerably overpredicted the concentrations of S in full term pregnant patients having received 50mg S capsule(s) (13/32, 41% of the observed concentrations below the 5<sup>th</sup> quantile of the simulated population, MedianPredictionError= -45%, MedianAbsolutePredictionError=57%<sup>11</sup>).

**Conclusion:** A PBPK model of S scaled to full term pregnant females using established procedures and concepts considerably overpredicted measured plasma concentrations of S in this population. Factors unaccounted for in the pregnancy module of MoBi<sup>®</sup>/PK-Sim<sup>®</sup> + albumin/enzyme content should be investigated. In addition, more complete and diverse PK datasets in this population are needed. We would like to caution against naively fitting the model to the available sparse PK, single source, full term pregnancy data, which may result in good descriptive, but poor predictive performance.

## References:

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