Predicting the pharmacokinetic changes in fluoxetine during pregnancy

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Introduction

Mood changes during pregnancy may necessitate the use of drugs such as fluoxetine, although little is known about the appropriate doses. One clinical study on 11 mothers showed that plasma concentrations of fluoxetine were on average 35% lower during the third trimester of pregnancy, following a daily oral dose of 20 mg or 40 mg of the drug.[1] Models to predict such changes will be useful since ethical constraints prevent adequate clinical testing. The aim of this project was to construct a PBPK model to predict the changes in fluoxetine pharmacokinetics (PK) associated with the changes in the body composition, physiology and biochemistry that occur during pregnancy.

Methods

Simcyp Simulator V15 R1

Pregnancy PBPK model [2]

Model accounts for maternal changes in:

* body mass
* fat mass
* cardiac output
* haematocrit
* plasma volume
* glomerular filtration rate
* renal blood flow
* CYP3A4 induction
* CYP2D6 induction
* CYP1A2 inhibition

Fluoxetine Model

Full PBPK model

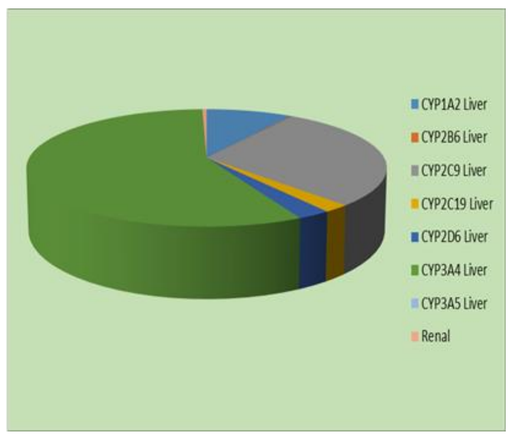
First order absorption

fa=1

ka =0.97 1/h

Fraction unbound: 0.079

Elimination



Study Design

Fluoxetine 40mg daily for 5 days in 3rd trimester of pregnancy and in non-pregnant females

10 trials of 11 females 25yrs to 43yrs

Based on clinical study[1]

Prediction of PK profiles and parameters in pregnant (3rd trimester) and non-pregnant populations.

Comparison of PK profiles and parameters in the two groups.

Predicted results vs clinical data.

Results

Predictions of PK profiles and PK parameters in the pregnant and non-pregnant subjects are compared in Figure 1 and Table 1. An increase in fluoxetine clearance (CL) and a corresponding decrease in maximum plasma concentrations (Cmax) and area under the plasma-concentration curve (AUC) is seen in pregnant subjects. The mean ratio of trough concentrations (Cmin) in pregnant vs non-pregnant subjects for the 10 trials was 0.74 (0.60-1.01).

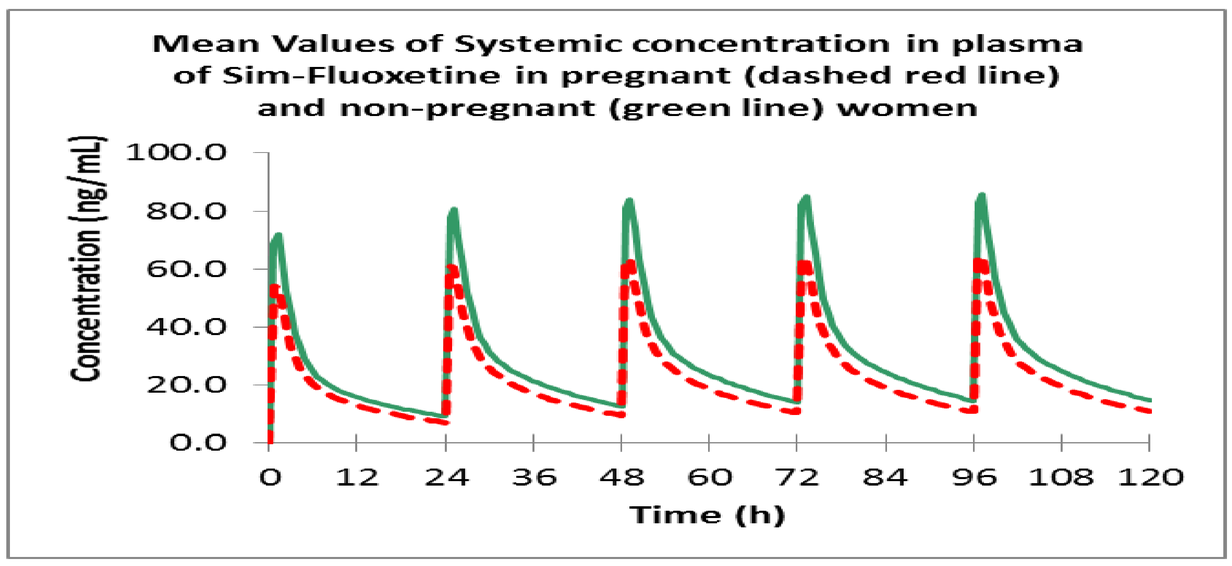


Figure 1: PK profiles of fluoxetine in pregnant and non-pregnant women

Table 1: PK parameters in pregnant and non-pregnant women

Parameter	Pregnant Subjects (Geometric Mean; Confidence Interval)	Non-Pregnant Subjects (Geometric Mean; Confidence Interval)	Ratio (Pregnant: non-pregnant)
Cmax (ng/mL)	63.7; 59.7-68.0	84.2; 79.0 – 89.7	0.76
AUC (ng/mL.h)	521.2; 474.8 – 572.3	667.9; 619.0 – 742.3	0.77
CL (L/h)	76.7; 69.9 – 84.3	59.0; 53.9 – 64.6	1.3

Conclusions

The PBPK model recovers the increased clearance and reduced plasma concentrations observed in the clinical study as seen in Figure 1 and Table 1. The predicted Cmin ratio in pregnant vs non-pregnant subjects is 0.74 (0.60 – 1.01) while the clinically observed mean ratio[1] is 0.65. These results suggest that PBPK models can be useful tools for predicting PK changes in drugs due to changes in body composition, physiology and metabolism during pregnancy.

References : 1. Heikkinen T. et al (2003) CPT; 2. Abduljalil K. et al (2012) Clin PK.