Revision of CYP2D6 Activity During Pregnancy in the Simcyp Pregnancy PBPK Model

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Background

The activity of CYP2D6 during pregnancy within the current Simcyp Simulator is based on Dextromethorphan/Dextrorphan metabolic ratio [1], this indicates a 35% increase in the activity of CYP2D6 towards term. A more recent report investigated the activity of CYP2D6 in subjects with different phenotypes and suggested more than 2-fold higher activity towards the end of pregnancy [2]. The current study seeks to identify the optimal CYP2D6 activity profile during pregnancy.

Aims

The aim of this study is to use the PBPK approach to investigate the temporal increase in CYP2D6 activity during pregnancy and to compare the prediction of two CYP2D6 pregnancy activity functions using Metoprolol as a probe compound.

Methods

Simcyp V17R1 was used in all simulations. The compound file SV-Metoprolol and the sim-Pregnancy population were selected from the library. The ADAM absorption model was used to describe the absorption phase, while the full PBPK model (Vss prediction using Rodgers & Rowland's method) and the IVIVE enzyme kinetics to describe the elimination of metoprolol in an extensive metaboliser group.

A simulation was run for gestational week (GW) zero (non-pregnant population) to ensure the compound file described the PK in a non-pregnant population. Simulations comprising of 10 trials and 10 subjects within each trial, to match the clinical study [3], were used to predict metoprolol kinetics. In these simulations, the original CYP2D6 pregnancy activity profile (V17R1) and the updated activity profile of CYP2D6 were used. The updated profile uses a gestational age dependent function based on Ryu et al [2] for the extensive CYP2D6 metabolizers; CYP2D6 (fold change in activity) =1*(1+ 0.0163 *GW + 0.0009 * GW^2). The new function was then used to predict Propranolol PK during pregnancy.

A compound file was developed for propranolol with first order absorption, a full PBPK distribution model and enzyme kinetic elimination mediated by CYP2D6 and CYP1A2.

The model was used to predict propranolol PK in 6 trials of 6 healthy non-pregnant women aged between 20 – 40 years), after 10mg intravenous infusion over 10 minutes or 120 mg oral administration [4]. The new verified model was then used to predict propranolol kinetics in 6 trials of 6 pregnant women between 32 and 36 weeks gestation given the same doses (simulation was done for 34 weeks).

Results / Discussion

The previous CYP2D6 function under-predicted metoprolol clearance and showed over prediction for the exposure during pregnancy. The new function showed an improvement in metoprolol exposure prediction (Figure 1).

Simulations were performed for propranolol using the original function and the results also indicated over prediction of the concentration time profile during pregnancy. When the new function was applied, adequate description of the drug during pregnancy can be visually seen within the 5th and 95th predictive intervals (Figure 2).

Results

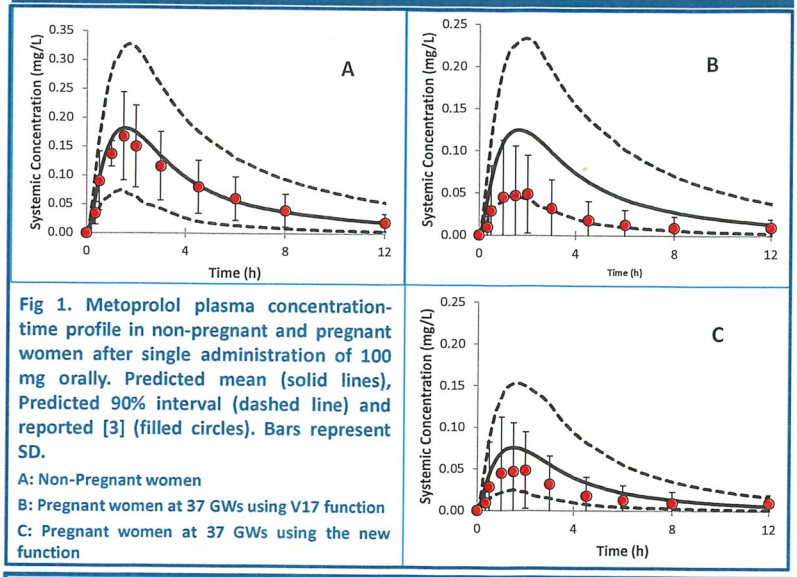

Fig 1. Metoprolol plasma concentration-time profile in non-pregnant and pregnant women after single administration of 100 mg orally. Predicted mean (solid lines), Predicted 90% interval (dashed line) and reported [3] (filled circles). Bars represent SD.

A: Non-Pregnant women

B: Pregnant women at 37 GWs using V17 function

C: Pregnant women at 37 GWs using the new function

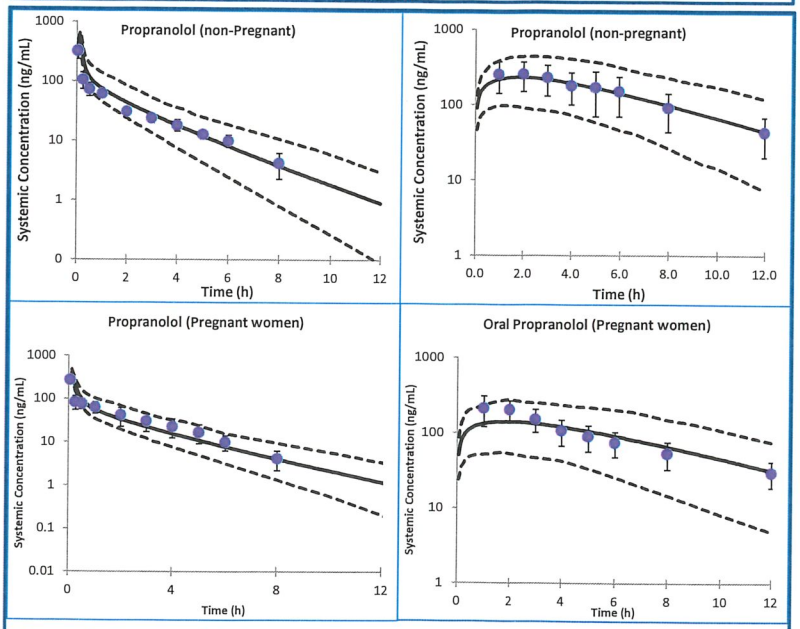

Figure 2. Propranolol plasma concentration-time profile in non-pregnant (top panel) and pregnant women (bottom panel) after single dose administration of 10 mg i.v. infusion (left) and 120 mg oral (right). Predicted mean (solid lines), Predicted 90% interval (dashed line) and reported [4] (filled circles and squares).

Conclusions

The new function showed better prediction and will be implemented in Simcyp V18 for the Sim-Pregnancy Population.

References

[1] Tracy et al 2005. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy.Am J Obstet Gynecol. 2005;192(2):633-9.

[2] Ryu et al., 2016. Pharmacokinetics of metoprolol during pregnancy and lactation. J Clin Pharmacol. 2016;56(5):581-9.

[3] Högstedt et al., Pregnancy-induced increase in metoprolol metabolism. Clin Pharmacol Ther. 1985 ;37(6):688-92.

[4] O'Hare et al., Pharmacokinetics of propranolol during pregnancy. Eur J Clin Pharmacol. 1984;27(5):583-7