Application of Feto-Placental-Maternal Physiologically-based Pharmacokinetic Model to Predict Tenofovir Concentration during Pregnancy

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Background

Tenofovir is a drug used in combination with other anti-HIV drugs to treat patients with HIV-1 infection. It is used during pregnancy to reduce the risk of HIV transmission to the child. The aim of this work is to use a Physiologically-Based Pharmacokinetic (PBPK) model for prediction of maternal and fetal tenofovir concentration at birth.

Methods

A full Feto-Placental-Maternal PBPK model (see Fig 1) that includes placenta as a 3-comparment permeability limited organ and 14 compartments for different fetal organs was developed using physiological [1,2] and drug specific parameters [3] to predict tenofovir concentration in 50 virtual pregnant mothers at term after single administration of 600 mg of tenofovir disoproxil fumarate (272 mg tenofovir). The mechanistic model was implemented using the Simcyp Lua interface within the Simcyp Simulator. Fetal as well as maternal tissue to plasma ratio values were predicted using the Rodgers & Rowland method with a Kp scalar of 1.5. Predictions of tenofovir maternal and fetal plasma concentration were compared to reported observations [4].

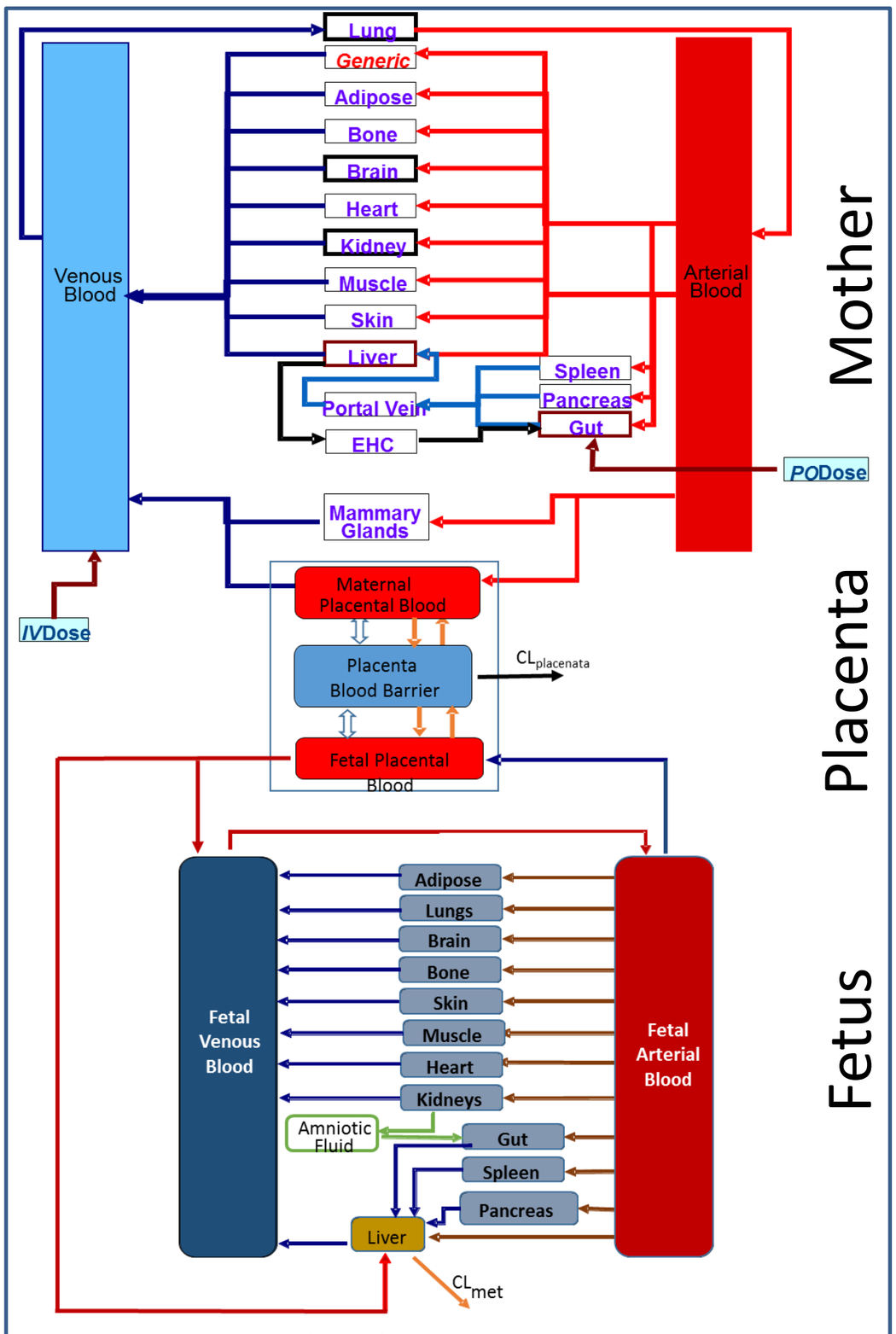

Figure 1. Structure of the full Maternal-Placental-Fetal Model

Results

All model parameters were calculated using the bottom-up approach except the placenta transfer by cotyledon was changed to 10 times higher the mean reported value from the perfusion experiments [5].

In spite of the large variability in the observed data, the model adequately replicated the maternal as well as fetal clinical observations [4]. The maternal predicted-to-observed ratio for AUC24hr and Cmax were 1.13 and 1.08, respectively. The predicted fetal exposure was well predicted within the 5th and 95th percentiles and was 0.51 of maternal exposure (AUC24h), the reported value is 0.60 [4].

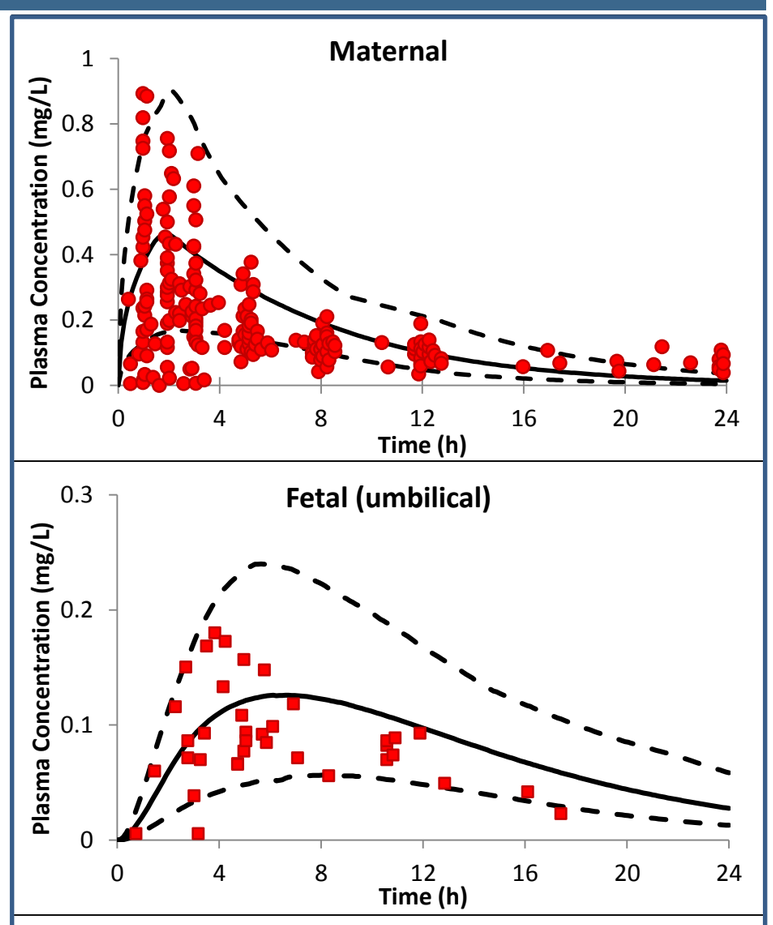

Figure 2. Predicted tenofovir concentration in maternal (upper) and fetal (lower) plasma. Solid line represents mean and dashed lines represent 5 -95 percentiles. Dots represent observations [4].

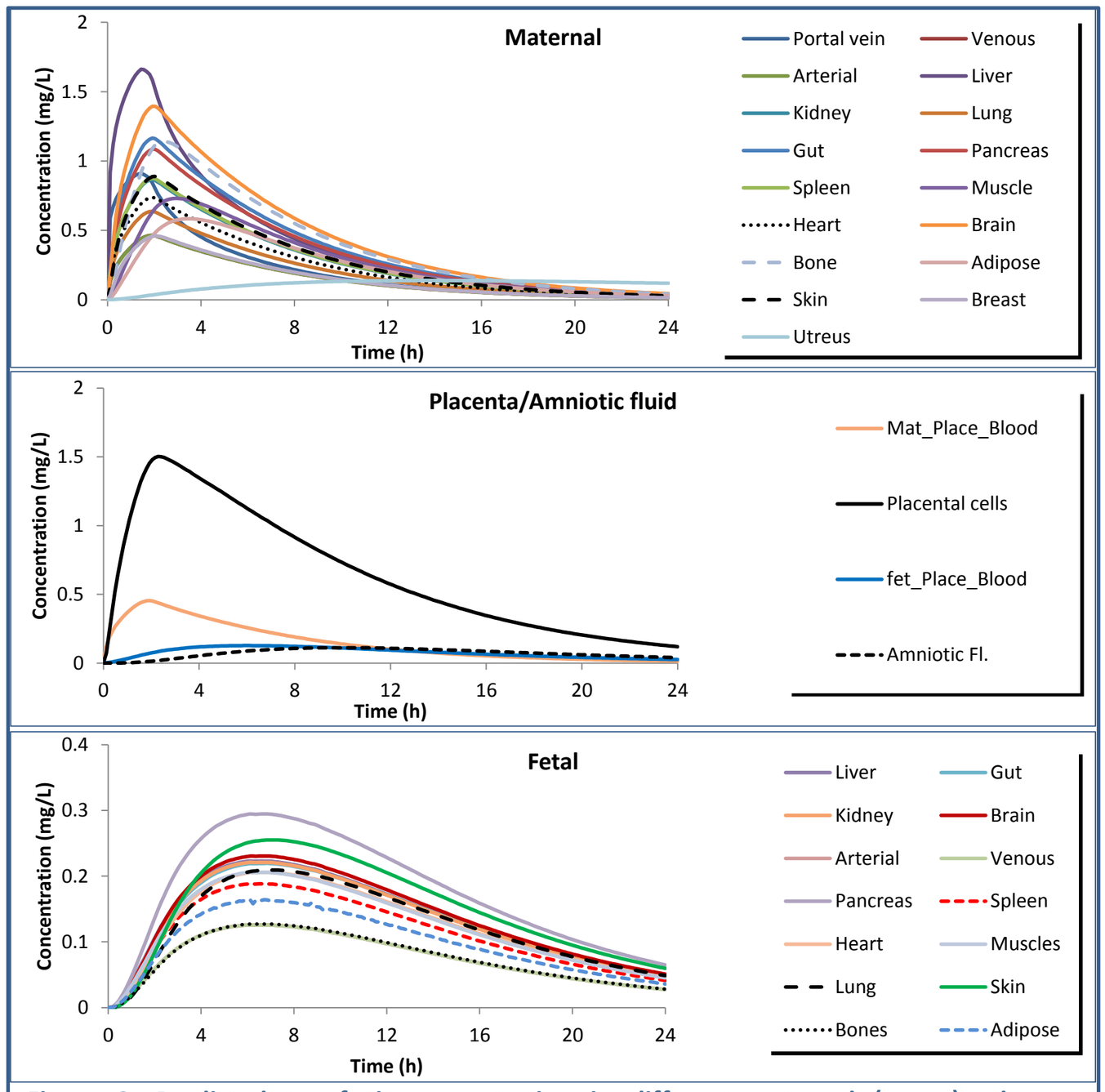

Figure 3. Predicted tenofovir concentration in different maternal (upper), placenta (middle) and fetal (lower) tissue compartments.

Conclusions

The developed feto-placental-maternal PBPK models can be used to predict drug exposure in fetal organs during in utero growth. The average and inter-subject variability can be predicted incorporating both the drug physicochemical properties and system (placental, maternal and fetal) parameters.

References

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