Application of Feto-Maternal Physiologically-Based Pharmacokinetic model To Predict Emtricitabine Concentration during Pregnancy

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Abstract

Emtricitabine (ETC) is a drug used to treat HIV or to prevent its multiplication. It has been shown that a single dose of ETC during delivery (in combination with tenofovir) reduces the resistance mutations developed against tenofovir. ETC has good placental transfer (about 80%) after maternal administration. Its PK have been studied in clinical and experimental settings using trans-placental perfusion experiments. The objective of this work is to build a detailed maternal-placental-fetal full PBPK model to allow integration of the physiological changes. This includes the growth of the feto-placental unit and drug dependent parameters obtained from trans-placental experiments, to predict the drug concentration in different maternal, placental and fetal tissues simultaneously. Emtricitabine was used as a drug model and the predicted concentration profiles in maternal as well as fetal plasma were compared to the available clinical observations.

Background

To use a Physiologically-Based Pharmacokinetic (PBPK) model for prediction of Emtricitabine concentration in pregnant women and to compare the predictions with observed data [3].

Methods

A full Feto-Maternal PBPK model was developed using Lua interface within the Simcyp Simulator V17. The model incorporates physiological [1-3] and drug specific parameters to predict Emtricitabine concentration in 100 virtual pregnant term mothers after single administration of 400 mg. Trans-placental kinetics was obtained from an experimental perfusion model [5]. Predictions of ETC maternal and fetal plasma concentration were performed and compared to reported observations [4].

Results

In spite of the large variability in the observed data, the model adequately replicated the maternal as well as fetal clinical observations [3,4] (see Figure 1). The maternal observed vs predicted median AUC_{24} hr was 14.3 vs 13.4 mg/L*h, while the median Cmax was 1.7 vs 2.7 mg/L and the mean CL_{po} was 39.9 vs 31 L/h. The fetal observed vs predicted median AUC_{24} hr was 9.33 vs 11.3 mg/L*h and the median Cmax was 0.72 vs 0.95 mg/L.

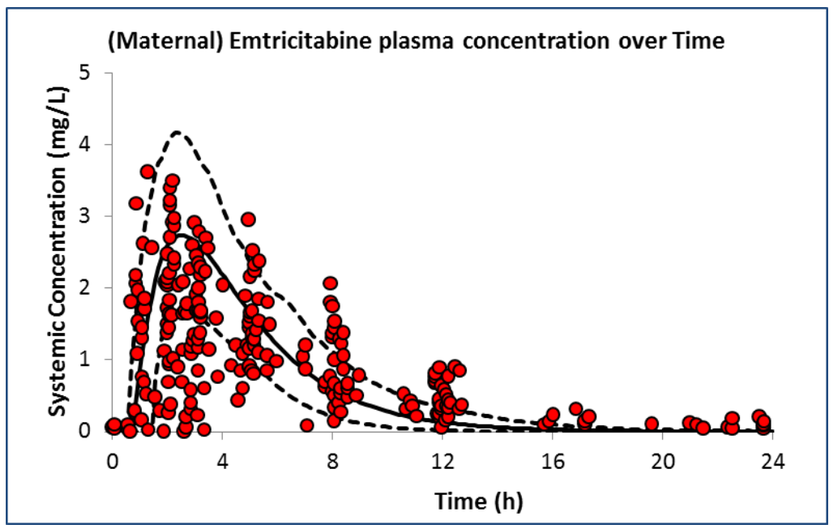

Figure 1. Predicted (dark line shows mean and dashed lines show 5-95 percentiles) vs observed (red dots) Profiles of Emtricitabine in maternal (left) and fetal (right) plasma.

Conclusion

The results show the developed feto-maternal PBPK models can adequately predict observed data for ETC. Hence, the model can be used to predict drug exposure in inaccessible fetal organs during utero growth and can be used to assess potential toxicity. The inter-subject variability can be predicted incorporating both the drug physicochemical properties and system (maternal and fetal) parameters.

References

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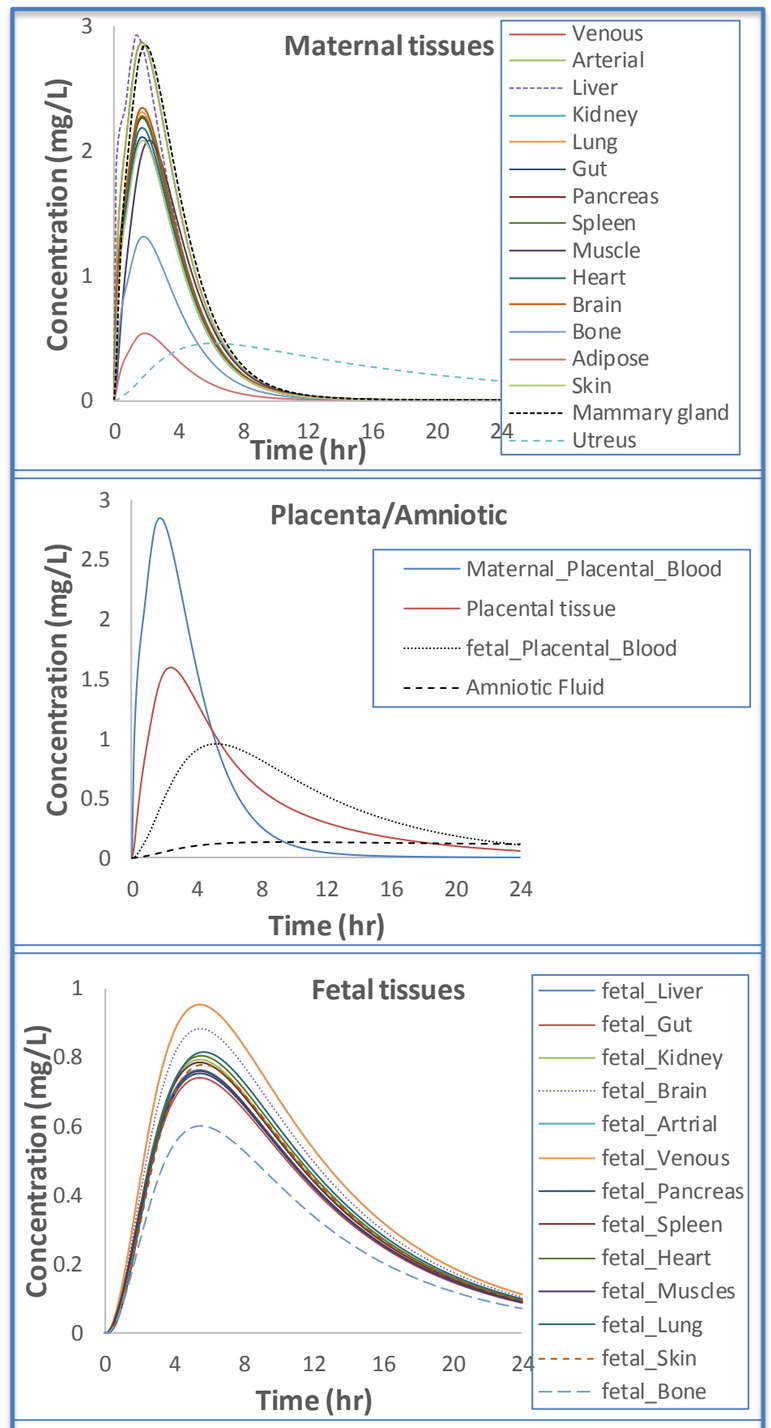

Fig 2. Predicted concentration time profiles of Emtricitabine in different maternal and fetal tissues

Tissue Compartment	Cmax (mg/L)	Tmax (hr)	AUC_{24hr} (mg/L*hr)
Portal vein Conc	4.574	1.320	17.978
Venous Conc	2.872	1.680	12.472
Arterial Conc	2.872	1.680	12.475
Liver Conc	2.929	1.440	11.808
Kidney Conc	2.264	1.680	9.840
Lung Conc	2.313	1.680	10.045
Gut Conc	2.112	1.680	9.185
Pancreas Conc	2.267	1.800	9.865
Spleen Conc	2.281	1.680	9.916
Muscle Conc	2.087	2.160	9.468
Heart Conc	2.187	1.680	9.506
Brain Conc	2.345	1.680	10.204
Bone Conc	1.315	1.800	5.731
Adipose Conc	0.540	1.920	2.367
Skin Conc	2.084	1.800	9.069
Mammary gland	2.848	1.920	12.483
Utreus	0.459	6.240	7.125
Maternal_Placental_Blood	2.844	1.680	12.465
Placental tissue	1.594	2.400	11.769
Fetal Placental Blood	0.955	5.280	11.373
Amniotic Fluid	0.133	9.360	2.700
fetal Liver	0.763	5.400	9.094
fetal Gut	0.740	5.520	8.817
fetal Kidney	0.793	5.520	9.446
fetal Brain	0.883	5.520	10.512
fetal Arterial	0.952	5.520	11.345
fetal Venous	0.952	5.520	11.346
fetal Pancreas	0.753	5.520	8.970
fetal Spleen	0.785	5.520	9.349
fetal Heart	0.804	5.520	9.575
fetal Muscles	0.759	5.520	9.049
fetal Lung	0.815	5.760	9.701
fetal Skin	0.778	5.640	9.267
fetal Bone	0.601	5.520	7.153

Table 1. Mean PK parameters of predicted concentration time profiles of Emtricitabine in different maternal and fetal tissues