Using mechanistic PBPK models to assess prenatal drug exposure: thalidomide vs efavirenz as case studies

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INTRODUCTION

- Pharmacokinetics are not fully characterised in pregnancy and drug can penetrate the placenta resulting in foetal exposure.
- The correlation between foetal exposure to maternal drugs and reported toxicity or safety has not been fully elucidated.
- With thalidomide and efavirenz as case studies, we evaluated the extent of foetal exposure to maternal drugs during different stages of pregnancy, using physiologically-based pharmacokinetic (PBPK) modelling approach.

METHODS

- The maternofoetal PBPK (mf-PBPK) model, built using Simbiology® (MATLAB® 2017b, Mathworks Inc., US), is composed of a female adult model integrated with a foetal sub-model as recently reported (1).
- Pregnancy-induced changes in system parameters were defined using ordinary differential equations with gestational age (1,2). Key drug-specific parameters were obtained from literature (3,4).
- Drug clearance by CYP450 enzymes was used to estimate the metabolism of efavirenz in the foetal liver, maternal intestine and liver with *in vitro* to *in vivo* scaling technique. Clearance of thalidomide by *CYP2C19* and through hydrolysis in the liver and plasma respectively were also simulated.
- Transplacental drug transfer was modelled as bi-directional passive diffusion using an adaptation of Fick's Law of diffusion (6).
- Virtual populations of non-pregnant adults (n = 100) were simulated using the adult PBPK model to predict the pharmacokinetics (PK) of 600 mg efavirenz and 200 mg thalidomide in adults at steady-state and to validate the models.
- Additionally, virtual pregnant women (n = 100) were simulated with the mf-PBPK model to predict the PK of 600 mg efavirenz and 200 mg thalidomide in pregnant women and the extent of foetal exposure to each drug.

RESULTS

Fig 1: Predicted time profile of cord-to-maternal blood concentration (C:M) and foetal-to-maternal blood concentration (F:M) ratios across the dosing interval with maternal dose of 600 mg efavirenz during second and third trimesters. Data presented as mean (SD).

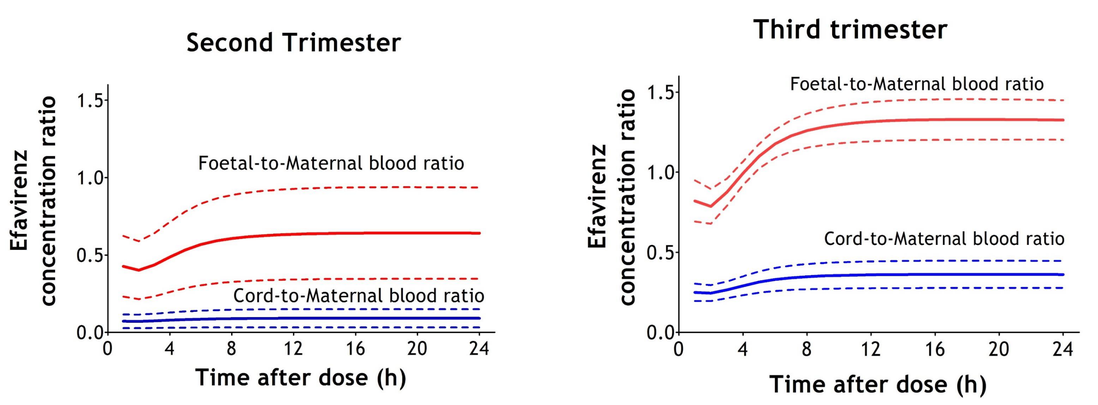

Figure 2: Predicted time profile of cord-to-maternal blood concentration (C:M) and foetal-to-maternal blood concentration (F:M) ratios across the dosing interval with maternal dose of 200 mg thalidomide during second and third trimesters. Data presented as mean (SD).

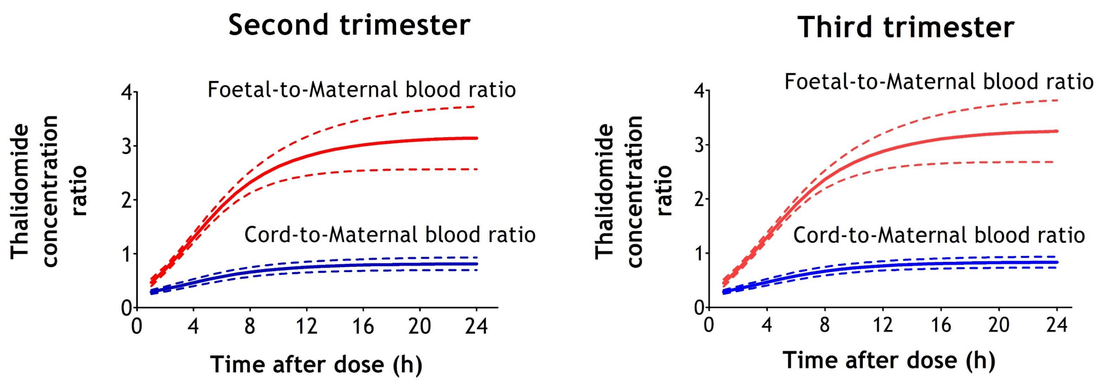

Table 1. Predicted foetal exposure following 600 mg efavirenz and 200 mg thalidomide in the foetal plasma and umbilical cord during pregnancy. Data presented as median (range).

PK Parameter (Units)	2nd Trimester n = 100	3rd Trimester n = 100	2nd Trimester n = 100	3rd Trimester n = 100
	600 mg Efavirenz		200 mg Thalidomide	
Foetal Plasma				
Drug conc. (mg/L)	1.28 (0.264-8.50)	2.11 (0.984-8.35)	1.12 (0.739-1.84)	2.10 (1.43-3.11)
AUC_{0-24} (mg.h/L)	29.9 (6.12-196)	49.1 (23.0-193)	26.7 (17.6-43.6)	49.8 (33.9-73.9)
Foetal : Maternal	0.62 (0.12-1.01)	1.24 (1.02-1.41)	2.36 (1.94-3.74)	2.42 (2.03-3.71)
Umbilical Vein				
Drug conc. (mg/L)	0.192 (0.019-1.50)	0.540 (0.242-2.03)	0.351 (0.21-0.655)	0.679 (0.467-1.14)
AUC_{0-24} (mg.h/L)	4.47 (0.44-34.6)	12.6 (5.65-46.8)	8.29 (4.95-15.5)	16.0 (11.0-26.8)
Cord : Maternal	0.08 (0.01-0.19)	0.34 (0.21-0.47)	0.69 (0.44-0.90)	0.70 (0.51-0.95)

DISCUSSION

- This is the first report showing the extent of prenatal exposure to efavirenz and thalidomide during pregnancy *via* PBPK modelling.
- The foetal-to-maternal blood concentration (F:M) ratio can represent a useful predictor of drug accumulation in the foetus and may be more suitable to assess prenatal exposure than the cord-to-maternal blood concentration (C:M) ratio.
- F:M and C:M ratios were independent of changes in the maternal dose (data not shown) likely due to the first-order nature of the modelled transplacental transport. This may be extrapolated to other doses of maternal drugs.
- A single time-point determination of C:M and F:M ratios near delivery may be insufficient to estimate fetal exposure as both F:M and C:M ratios vary within each dosing interval (Fig 1 & 2).
- Unlike thalidomide, the averaged F:M and C:M ratios across the dosing interval increases with gestational age for efavirenz. The foetus may be most exposed to efavirenz at delivery when pre-exposure prophylaxis is most vital.
- The average foetal plasma concentration of thalidomide was estimated to be over 200% of the maternal concentration compared with 61% and 124% of the maternal plasma concentration for efavirenz in the second and third trimesters, respectively (Table 1).
- Few data on the extent of fetal exposure to most drugs exists which prevents evidence-based guidance on risk-benefit assessment of drug use during pregnancy.
- Predicted foetal PK of efavirenz before delivery and thalidomide before and after delivery were not validated due to lack of relevant clinical data.
- Availability of more data defining the anatomical and physiological parameters of the foetus at the first trimester may facilitate the prediction of *in utero* exposure when embryogenesis occurs.
- Activity of drug transporters and metabolising enzymes at the placenta were not utilised due to scarce data. Incorporating the influence of pregnancy on these drug disposition enzymes may improve the accuracy of the model predictions.
- A safety threshold may be established with this approach by comparing data on the extent of foetal exposure to 'safe' drugs with exposure to known teratogens. This may be employed as a potential strategy to predict the likelihood of fetotoxicity.
- With the need to manage chronic ailments such as hypertension, diabetes and HIV in pregnant women, drug administration in pregnancy cannot be circumvented.
- The developed pregnancy mf-PBPK model may play a significant role in assessing drug safety through prediction of prenatal exposure during pregnancy. However, there is still a need to validate this approach with additional drugs and their corresponding clinical data during pregnancy and upon delivery.

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