Abstract # 753

Dosing for Two: Placental Transfer of Darunavir and Fetal Exposure

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1. BACKGROUND

- Fetal antiretroviral exposure is usually derived from the cord-to-maternal (ctm) concentration ratio. This static parameter does not provide information on the pharmacokinetics in utero, limiting the assessment of a fetal exposure-effect relationship.
- Pregnancy physiologically-based pharmacokinetic (p-PBPK) modeling could provide a solution. It can be used to simulate and predict fetal exposure during pregnancy. However, incorporating placental drug transfer in p-PBPK models remains a challenge to overcome.

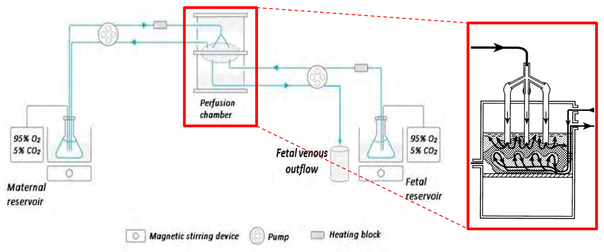
Objective

We aimed to include placental transfer parameters derived from an *ex vivo* human cotyledon perfusion model into a p-PBPK model to quantitatively simulate fetal exposure to the antiretroviral agent darunavir, co-administered with ritonavir, at term.

2. METHODS

- Using Berkeley Madonna as a modeling platform, an existing p-PBPK model of darunavir/ritonavir was used to simulate maternal darunavir exposure.
- Subsequently, *ex vivo*, human placental cotyledons were perfused with clinically relevant darunavir concentrations and placental transfer parameters were determined (Figure 1).
- Maternal-to-fetal (mtf) and fetal-to-maternal (ftm) clearance values were used to incorporate and parameterize a feto-placental unit in the maternal p-PBPK model (Figure 2).
- Fetal and maternal pharmacokinetic profiles were simulated and compared with observed clinical data.
- For illustration of model functionality, we simulated and explored several different DRV/r dosing regimens in terms of fetal exposure relative to the EC_{50} for resistant virus (0.55 mg/L).

Figure 1: Schematic overview of experimental placenta perfusion system. To obtain clearance parameters three perfusion were conducted in mtf direction and three in ftm direction.



3. RESULTS

Figure 2: Darunavir concentration-time and mass-balance profiles from the ex vivo placenta perfusion experiments. Ftm and mtf clearances were determined based on linear regression of natural log-transformed darunavir concentrations in the closed reservoir from 60 minutes onwards.

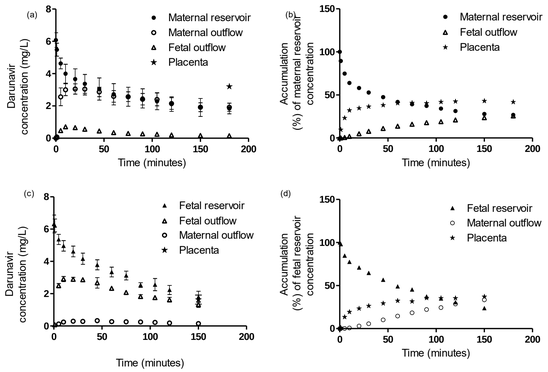


Table 1: In vitro and physiological parameters used to parameterize the feto-placental unit. Ftm and mtf cotyledon clearances were scaled to whole-organ placental clearance based on number of cotyledons and corrected for protein binding.

Parameter; Gestational age at 38 weeks	Value	Reference
Fetal cardiac output, Q_{fco} (L/hr)	85.5	(Kiserud, 2006)
Fetal weight (kg)	3.56	(Abduljalil, 2012)
Amniotic fluid volume (L)	0.86	(Abduljalil, 2012)
Fetal blood volume, $V_{bloodFetal}$ (L)	0.24	(Smith, 2002)
DRV CL_{af} (L/hr)	0.04	Estimated
DRV CL_{fa} (L/hr)	0.08	Estimated
DRV $CLcot_{mf}$ (mL/min)	0.91 ± 0.11	Determined
DRV $CLcot_{fm}$ (mL/min)	1.6 ± 0.31	Determined
Ncot	30	(Syme, 2004)
DRV fu_{perf}	0.16	Determined
Hct	50%	(vd Akker, 2008)

$CLcot_{mf}$, maternal-to-fetal cotyledon clearance; $CLcot_{fm}$, fetal-to-maternal cotyledon clearance; Hct, hematocrit; Ncot, average number of cotyledons per placenta; fu_{perf}, free fraction of darunavir in perfusion medium; CL_{af}, amniotic fluid-to-fetal blood clearance; CL_{fa}, fetal blood-to-amniotic fluid clearance.

3. RESULTS (continued)

Figure 3: Schematic representation of the darunavir/ritonavir p-PBPK model including the scaled placental clearances and a feto-placental unit.

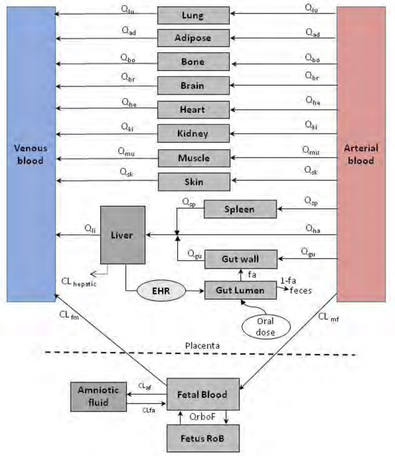
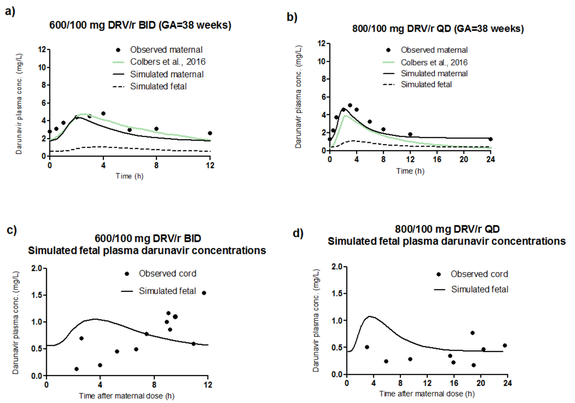
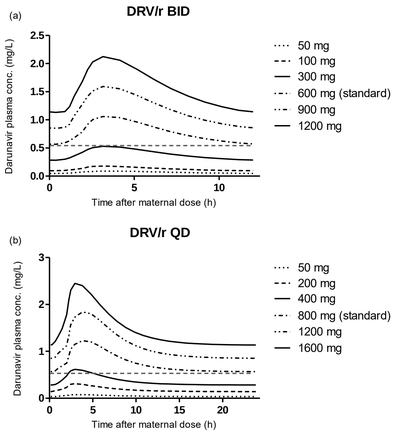


Figure 4: Predicted maternal and fetal darunavir concentration-time profiles following administration of two different dosing regimens, at term.



3. RESULTS (continued)

Figure 5: Predicted fetal darunavir concentration-time profiles for several darunavir dosing regimens, at term. The grey dashed lines represent the therapeutic target Ctrough (EC50 for resistant virus; 0.55 mg/L).



4. CONCLUSIONS

- We demonstrated that data obtained from *ex vivo* cotyledon perfusions can be integrated in p-PBPK models to simulate fetal darunavir exposure. (Figure 2&3; Table 1)
- The simulated fetal darunavir plasma concentrations (at term) were in the range of observed cord blood concentrations. (Figure 4)
- This advanced model provides a valuable tool in assessing the implications of new dosing regimens, optimizing the safety of maternal pharmacotherapy, and optimizing fetal antiretroviral treatment. (Figure 5)

Acknowledgements

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