**Dosing for Two: Placental Transfer of Darunavir and Fetal Exposure**

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Abstract # 753

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 dosing regimens in terms of fetal exposure relative to the EC50 for resistant virus (0.55 mg/L).

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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Hct</td>
<td>50%</td>
<td>(Abduljalil, 2012)</td>
</tr>
<tr>
<td>FM perf</td>
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<td>(Abduljalil, 2012)</td>
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<tr>
<td>AF perf</td>
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<td>(Smith, 2002)</td>
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<td>(Smith, 2002)</td>
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<tr>
<td>Ncot</td>
<td>30</td>
<td>(Wang, 2016)</td>
</tr>
<tr>
<td>CL cot</td>
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<td>Derivative</td>
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</table>

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.

4. CONCLUSIONS

• We demonstrated that data obtained from ex vivo cotyledon perfusions can be integrated in a p-PBPK model to simulate fetal darunavir exposure (Figure 2b, 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 3).

Acknowledgments

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