Mechanistic modeling of placental drug transfer and fetal-neonatal drug exposure

22/10/2021 / André Dallmann
Conflicts of interest / disclaimer

• I am an employee of Bayer AG
• I use Open Systems Pharmacology (OSP) software, tools, and models in my professional role
Maternal-fetal PBPK modeling: Where do we stand?

Despite impressive progress much work is still left

- Model validation for the 1st trimester of pregnancy
- Drug absorption from the gastrointestinal tract
- Disease-effect on top of pregnancy-induced physiological changes
- Fully mechanistic model structure for the fetus
- Mechanistic description of placental drug transfer
- Coupling prenatal and postnatal PBPK models to enable simulating transition from maternal-fetal pharmacokinetics to postpartum and neonatal pharmacokinetics
- PBPK models for large molecules and new modalities (proteins, siRNA etc.)
- …
Fetal protein binding is often omitted in PBPK models

The Significance of Plasma Protein Binding on the Fetal/Maternal Distribution of Drugs at Steady-State

Martin D. Hill and Fred P. Abramson

George Washington University, School of Medicine and Health Sciences, Department of Pharmacology, Washington

Maternal and fetal plasma differ in their concentrations of the important drug binding plasma proteins, albumin and α1-acid glycoprotein, with albumin being slightly more concentrated in fetal plasma, and α1-acid glycoprotein being only 37% of the maternal concentration at term. In general, these differences relate linearly to the bound to free concentration ratio of drugs associated with these proteins. Although only the free concentration is generally considered to be the pharmacologically active form, these differences can dramatically affect the total concentration and relative distribution of drugs between maternal and fetal plasma.
Different unbound drug fractions in mother and fetus affect the maternal-fetal concentration ratio

Only valid at pseudo-equilibrium!

\[ [\text{Albumin}_{\text{fetus}}] < [\text{Albumin}_{\text{mother}}] \]
→ lower fetal protein binding
Fetal fu: 0.77

\[ [\text{Albumin}_{\text{fetus}}] = [\text{Albumin}_{\text{mother}}] \]
→ equal fu in mother and fetus
Fetal fu: 0.4

\[ [\text{Albumin}_{\text{fetus}}] > [\text{Albumin}_{\text{mother}}] \]
→ higher fetal protein binding
Fetal fu: 0.33

Fetal-maternal ratio: 0.82

Fetal-maternal ratio: 1.0

Fetal-maternal ratio: 1.5
Different unbound drug fractions in mother and fetus affect the maternal-fetal concentration ratio

Fetal: Maternal concentration ratio (FM) = \( K_{\text{plasma, fetus:plasma,mother}} \)

= \( \frac{K_{\text{cell,fetus:plasma,mother}}}{K_{\text{cell,fetus:plasma,fetus}}} \)

= \( \frac{f_{u,\text{mother}}}{K_{\text{cell,fetus:water}} \times K_{\text{cell,fetus:water}} f_{u,\text{fetus}}} \)

= \( \frac{f_{u,\text{mother}} f_{u,\text{fetus}}}{K_{\text{cell,fetus:water}} f_{u,\text{fetus}}} \)
Open Systems Pharmacology (OSP) software as open-source tool for PBPK modeling

- The Open Systems Pharmacology (OSP) software includes the PBPK tool PK-Sim® and the systems biology tool MoBi®
- **Open-source freeware** under GNU Public License v2.0 released on GitHub
- Fully transparent development of scientific content and qualification approaches on GitHub
- Inclusion of a pregnancy module for population PBPK modeling in PK-Sim®
Modeling differential protein binding in mother and fetus

Maternal and fetal $f_u$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fraction unbound in non-pregnant subjects</th>
<th>Maternal fraction unbound</th>
<th>Fetal fraction unbound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>0.85 (15)</td>
<td>0.88</td>
<td>0.88</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.67 (16)</td>
<td>0.73</td>
<td>0.68</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.020 (17)</td>
<td>0.027</td>
<td>0.021</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>0.0070 (18)</td>
<td>0.0088</td>
<td>0.0080</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>0.96 (15)</td>
<td>0.97</td>
<td>0.98</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.89 (17)</td>
<td>0.92</td>
<td>0.89</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.27 (17)</td>
<td>0.33</td>
<td>0.28</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>0.17 (15)</td>
<td>0.24</td>
<td>0.23</td>
</tr>
</tbody>
</table>

→ Diazepam: $\frac{f_{u,mother}}{f_{u,fetus}} = 1.29$

→ Dolutegravir: $\frac{f_{u,mother}}{f_{u,fetus}} = 1.10$

Maternal plasma concentrations

Protein binding differences between mother and fetus are small at term delivery

Maternal and fetal AUC\textsubscript{tlast}

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC\textsubscript{tlast} predicted in umbilical cord plasma with equal maternal and fetal fraction unbound (µg h/mL)</th>
<th>AUC\textsubscript{tlast} predicted in umbilical cord plasma with different maternal and fetal fraction unbound (µg h/mL)</th>
<th>Difference (％)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>1.9</td>
<td>2.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>38.5</td>
<td>38.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.87</td>
<td>0.85</td>
<td>28.9</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>15.0</td>
<td>16.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>10.2</td>
<td>10.1</td>
<td>-0.98</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>12.3</td>
<td>12.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.024</td>
<td>0.028</td>
<td>18.7</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3.0</td>
<td>3.2</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Umbilical cord plasma concentrations

Diazepam

- Observed data
- Predicted geometric mean (equal fraction unbound in mother and fetus)
- Predicted 5 - 95th percentile range (equal fraction unbound in mother and fetus)

Dolutegravir

- Observed data
- Predicted geometric mean (different fraction unbound in mother and fetus)
- Predicted 5 - 95th percentile range (different fraction unbound in mother and fetus)

Different influx and efflux rates at both apical and basolateral membrane need to be considered

Variation in influx or efflux transport across the apical (maternal-facing) membrane of the trophoblasts

Variation in both influx and efflux transport across the basolateral (fetal-facing) membrane of the trophoblasts

→ Drug transporters expressed in the apical membrane of the trophoblasts significantly modulate placental transfer

→ Transport rate across the basolateral membrane seems not to be rate-limiting step for diazepam and dolutegravir, but appears to be so for other compounds (e.g. cefuroxime)

Predicting fetal-neonatal drug exposure by coupling prenatal and postnatal PBPK models

**Emtricitabine**
Delivery (at 33 – 42 weeks of gestation)

**Dolutegravir**
Delivery (at 36 – 40 weeks of gestation)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean delivery time (relative to last dose) [h]</th>
<th>Mean drug amount in fetal compartments [µmol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emtricitabine</td>
<td>4.9</td>
<td>9.58</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>11.8</td>
<td>4.89</td>
</tr>
</tbody>
</table>

Maternal-fetal-neonatal PBPK modeling in action: Postnatal PK of transplacentally acquired drugs

Emtricitabine
Postnatal washout kinetics in neonates

Assumed OCT2 activity: 30% of adult level

Dolutegravir
Postnatal washout kinetics in neonates

Assumed UGT1A1 activity: 60% of adult level

In postnatal week 1, the activity of OCT2 and UGT1A1 may be ~10% and ~30% of that in adults, respectively.

**Emtricitabine**
Postnatal washout kinetics in neonates

- Sensitivity analyses results suggest that the specific activity of OCT2 in neonates with a postnatal age of <2.5 days is ~10% of that in adults.

**Dolutegravir**
Postnatal washout kinetics in neonates

- Sensitivity analyses results suggest that the specific activity of UGT1A1 in neonates with a postnatal age of <7 days is ~30% of that in adults.

Conclusions

In view of the limited participation of pregnant individuals in clinical trials, PBPK modeling can complement the PK understanding in cases where clinical data are sparse, missing or conflicting.

More drug examples are needed to build confidence in maternal-fetal PBPK models.

Model structures for the placenta and fetal compartments need to be mechanistically refined to enable predictions at earlier stages of gestation.

New PBPK modeling frameworks need to be developed for:

- The use of new modalities (proteins, siRNA etc) in pregnant individuals
- Simulating drug pharmacokinetics smoothly along the prenatal-peripartum-postpartum axis

Collaboration between different stakeholders/research institutions is key to advance the field.
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Thank you!

Bye-Bye