Drug Metabolism and Disposition

Supplementary Information

Development of A Novel Maternal-Fetal Physiologically Based Pharmacokinetic Model I: Insights into Factors that Determine Fetal Drug Exposure through Simulations and Sensitivity Analyses

Zufei Zhang, Marjorie Z. Imperial, Gabriela I. Patilea-Vrana, Janak Wedagedera, Lu Gaohua and Jashvant D. Unadkat

Department of Pharmaceutics, University of Washington, Seattle, WA (ZZ, MI, GP, and JU); Simcyp Limited (a Certara company), Sheffield, UK (JW and LG)

Merck Sharp & Dohme Corp., Kenilworth, New Jersey, USA (ZZ, current affiliation)

University of California San Francisco, Department of Bioengineering and Therapeutic Sciences (MI, current affiliation)
Figure Legends

Supplementary Figure S1: A three compartment model representing the maternal (M), placental (P), and fetal (F) compartments: 0- irreversible elimination. The remaining abbreviations are as in Figure 1. For simplicity, excretion of drugs from fetus into the amniotic fluid was assumed to be negligible.

Supplementary Figure S2: Changes in fetal renal clearance (fCL_R) or fetal amniotic fluid swallowing rate (fCL_reabsorp) affected drug concentrations in fetal plasma and amniotic fluid differently. Following a single oral dose of 400 mg drug X at week 40, fCL_R (0.196L/h) or fCL_reabsorp (0.024 L/h) of drug X was varied by 0.5-,1-,and 5-fold (red, green, and blue, respectively). Fetal plasma drug X concentrations remained independent of changes in either fCL_R (a) or in fCL_reabsorp (b), except when fCL_R was increased by 5-fold (but even in this case the AUC was not changed). In contrast, amniotic fluid drug X concentrations were quite sensitive to changes in these two pathways. Increasing fCL_R resulted in higher amniotic fluid drug concentrations (c), whereas increasing fCL_reabsorp reduced amniotic fluid drug X exposure (d). Increasing fCL_R from 0.098 L/h to 0.981 L/h proportionally increased amniotic fluid drug X AUC (solid bars) while fetal plasma AUC (hatched bars) remained constant (e). Similarly, increasing the magnitude of fCL_reabsorp from 0.01 L/h to 0.10 L/h proportionally decreased amniotic fluid AUC (solid bars) without affecting fetal plasma AUC (hatched bars)(f). Similar trends were observed with fetal:maternal (F:M) plasma AUC ratio (circles) and amniotic fluid:maternal plasma (AF:MP) AUC ratio (squares) (e and f, respectively). AF:MP and amniotic fluid:umbilical venous plasma (AF:UV) drug X concentration ratios also varied significantly when fCL_R (g and i,respectively) or fCL_reabsorp (h and j,
respectively) was altered. Increasing fCL\textsubscript{R} resulted in higher AF:MP and AF:UV ratios, while increasing fCL\textsubscript{reabsorp} reduced both ratios. See Table 2 for the clearance values used in these simulations.

**Supplementary Figure S3:** In this schematic, $X_c$ and $X_p$ denotes the amount of drug in the central compartment and the peripheral compartments, respectively; $k_{10}$ is the central compartment elimination rate constant, whereas $k_{12}$, and $k_{21}$ are the inter-compartmental distribution rate constants.
## Supplementary Table 1

<table>
<thead>
<tr>
<th>Figure</th>
<th>Dosing regimen</th>
<th>( CL_{m0} ) (L/h)</th>
<th>( CL_{PD} ) (L/h)</th>
<th>( CL_{MP} ) (L/h)</th>
<th>( CL_{PM} ) (L/h)</th>
<th>( CL_{p0} ) (L/h)</th>
<th>( fCL_{R} ) (L/h)</th>
<th>( fCL_{reabsorp} ) (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure S2</td>
<td>400mg single oral dose of drug X</td>
<td>45</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>0.90</td>
<td>0.1, 0.20, 0.98</td>
<td>0.021</td>
</tr>
<tr>
<td>a,c,e,g,i</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Figure S2</td>
<td>drug X at week 40</td>
<td>45</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>0.90</td>
<td>0.20</td>
<td>0.01, 0.02, 1.0</td>
</tr>
<tr>
<td>b,d,f,h,j</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( CL_{m0} \), maternal systemic clearance; \( CL_{PD} \), transplacental passive diffusion clearance; \( CL_{MP} \), placental efflux clearance; \( CL_{PM} \), placental apical uptake clearance; \( CL_{p0} \), placental metabolic clearance; \( fCL_{R} \), feal renal secretion clearance; \( fCL_{reabsorp} \), fetal swallowing of amniotic fluid.
Supplementary Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Can the unbound UV:MP ratio be used to indicate the unbound F:M AUC ratio</th>
<th>The extent of deviation of the unbound UV:MP ratio from the predicted unbound F:M AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous IV infusion</td>
<td>Yes at steady-state</td>
<td>None at steady-state</td>
</tr>
<tr>
<td>Single dose (IV or oral)</td>
<td>No</td>
<td>↑ as drug’s $t_{1/2}$ gets shorter or the drug becomes more polar; ↓ with increasing $t_{1/2}$ or lipophilicity of the drug</td>
</tr>
<tr>
<td>Multiple doses when $\tau &lt; \text{drug } t_{1/2}$</td>
<td>No</td>
<td>↑ as $\tau$ becomes shorter relative to drug $t_{1/2}$</td>
</tr>
<tr>
<td>Multiple doses when $\tau &gt;&gt; \text{drug } t_{1/2}$</td>
<td>Yes</td>
<td>↓ as $\tau$ becomes longer relative to drug $t_{1/2}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unbound F:M AUC ratio</th>
<th>Predicted unbound F:M AUC ratio</th>
<th>The extent of deviation of unbound F:M AUC ratio from unity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilic drugs with insignificant feto-placental metabolism or placental efflux</td>
<td>~1</td>
<td>minimal</td>
</tr>
<tr>
<td>Lipophilic drugs with significant feto-placental metabolism or placental efflux</td>
<td>&lt; 1 or &lt;&lt; 1</td>
<td>↑ as feto-placental metabolism or placental efflux increases relative to $CL_{PD}$</td>
</tr>
<tr>
<td>Polar drugs with insignificant feto-placental metabolism or placental efflux</td>
<td>~1</td>
<td>minimal</td>
</tr>
<tr>
<td>Polar drugs with significant feto-placental metabolism or placental efflux</td>
<td>&lt;&lt; 1 or &lt;&lt;&lt; 1</td>
<td>↑ as feto-placental metabolism or placental efflux becomes larger relative to $CL_{PD}$</td>
</tr>
<tr>
<td>Polar drugs transported into the fetus by placental uptake transporters</td>
<td>&gt;1</td>
<td>↑ as placental uptake becomes larger relative to $CL_{PD}$</td>
</tr>
</tbody>
</table>
Supplementary Figures

Figure S1
Figure S2

a) Fetal Plasma conc. (ng/mL) vs Time (h)
   - Increased fCLR

b) Fetal Plasma conc. (ng/mL) vs Time (h)
   - Increased fCLR

(c) Amniotic fluid conc. (ng/mL) vs Time (h)
   - Increased fCLR

(d) Amniotic fluid conc. (ng/mL) vs Time (h)
   - Increased fCLR

(e) Fetal plasma and amniotic fluid AUCs (mg·h/mL)
   - Increased fCLR

(f) Fetal plasma and amniotic fluid AUCs (mg·h/mL)
   - Increased fCLR

(g) AF/AM ratio vs Time (h)
   - Increased fCLR

(h) AF/AM ratio vs Time (h)
   - Increased fCLR

(i) AF/UV ratio vs Time (h)
   - Increased fCLR

(j) AF/UV ratio vs Time (h)
   - Increased fCLR
Figure S3

\[ \mathbf{X}_c \quad \text{to} \quad \mathbf{X}_p \]

- \( k_{12} \)
- \( k_{21} \)
- \( k_{10} \)
Supplementary Methods

Verification of model implementation using a steady-state infusion three compartment model

At steady-state attained by IV infusion of the drug to the mother (steady-state\textsubscript{inf}), maternal-fetal plasma concentration of drugs can be described by a model consisting of maternal (M), placental (P), and fetal (F) compartments (steady-state\textsubscript{inf} model; Figure S1) even for a drug that demonstrates multi-compartmental behavior. Moreover, at steady-state\textsubscript{inf}, the fetal:maternal (F:M) plasma unbound drug concentration ratio (i.e. the $C_{f,ss,inf} / C_{m,ss,inf}$ ratio below) predicted by this steady-state\textsubscript{inf} model should be equal to the F:M plasma unbound AUC ratio predicted by the m-f-PBPK model after a single dose of the drug or within a dosing interval at steady-state (assuming linear pharmacokinetics).

Therefore, these $C_{f,ss,inf} / C_{m,ss,inf}$ ratios predicted by this steady-state\textsubscript{inf} model were compared against F:M unbound plasma AUC predictions made by our m-f-PBPK model as a means to ensure the correct implementation of our m-f-PBPK model. Of note, the predicted F:M plasma drug concentration ratios and F:M AUC ratios of drug Y equal its corresponding unbound values (Figures 5-9).

For simplicity, all clearances should be read as their corresponding unbound values.

Besides the assumption that the bidirectional maternal-placental and placental-fetal passive diffusion unbound clearances ($CL_{PD}$) are equal and always present, this steady-state\textsubscript{inf} model also assumes for the drug: (1) all clearances do not exceed their respective organ blood flows; (2) uptake and efflux transporters are located on the apical (maternal-facing) side of the placenta; (3) fetal renal excretion is negligible.
Using this steady-state_{inf} model, the F:M plasma and placenta:maternal plasma (P:M) drug concentration ratios at steady-state_{inf} can be described by the following equations (see below for derivation).

\[
\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{CL_{PD} + CL_{MP}}{CL_{PD} + 2CL_{f0} + CL_{p0} + CL_{PM} + \left(\frac{CL_{p0} + CL_{PM}}{CL_{PD}}\right) \cdot CL_{f0}} \tag{Eq. 1}
\]

\[
\frac{C_{p,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{(CL_{PD} + CL_{MP}) \cdot \left(1 + \frac{CL_{f0}}{CL_{PD}}\right)}{CL_{PD} + 2CL_{f0} + CL_{p0} + CL_{PM} + \left(\frac{CL_{p0} + CL_{PM}}{CL_{PD}}\right) \cdot CL_{f0}} \tag{Eq. 2}
\]

where \(C_{f,u,ss,inf}\), \(C_{p,u,ss,inf}\) and \(C_{m,u,ss,inf}\) are steady-state_{inf} drug unbound concentrations in the fetal plasma, placenta, and maternal plasma, respectively; \(CL_{PD}\) is the bidirectional passive diffusion clearance; \(CL_{f0}\) and \(CL_{m0}\) are the irreversible fetal and maternal metabolic clearances, respectively; \(CL_{PM}\) and \(CL_{MP}\) are the efflux and uptake transporter mediated clearances, respectively. Note, all clearances should be read as unbound clearances.

It is immediately evident that the \(\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}}\) ratio is independent of maternal clearance. When fetoplacental metabolism and placental transport are absent, this ratio reduces to unity. The differing impact of these individual clearance pathways on the \(\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}}\) ratio (and therefore, as indicated above, F:M plasma AUC ratio) is further discussed below.

**Derivation of steady-state_{inf} P:M and F:M ratios**

Under steady-state_{inf} when a drug is infused into the maternal compartment,
\[ CL_{PD} \cdot C_{p,u,ss,inf} = (CL_{PD} + CL_{f0}) \cdot C_{f,u,ss,inf} \quad (Eq. 3) \]

where \( C_{f,u,ss,inf} \) and \( C_{p,u,ss,inf} \) are drug unbound concentrations in the fetal plasma and placenta at steady-state after infusion (steady-state \( \text{inf} \)), respectively, \( CL_{PD} \) is the bidirectional passive diffusion clearance, and \( CL_{f0} \) is the irreversible fetal clearance. It is worth keeping in mind that passive diffusion of the drug across the placenta will be present for all drugs and will depend on the drug’s lipophilicity.

Rearrangement of \( Eq. 3 \) gives:

\[ \frac{C_{f,u,ss,inf}}{C_{p,u,ss,inf}} = \frac{CL_{PD}}{CL_{PD} + CL_{f0}} \quad (Eq. 4) \]

Similarly, for the placenta,

\[ CL_{PD} (C_{m,u,ss,inf} - C_{p,u,ss,inf}) + CL_{MP} \cdot C_{m,u,ss,inf} = CL_{PD} (C_{p,u,ss,inf} - C_{f,u,ss,inf}) \]
\[ + (CL_{p0} + CL_{PM}) \cdot C_{p,u,ss,inf} \quad (Eq. 5) \]

where \( C_{m,u,ss,inf} \) is steady-state \( \text{inf} \) drug unbound concentration in the maternal plasma; \( CL_{PM} \) and \( CL_{MP} \) are the non-saturated efflux and uptake placental transporter mediated clearances, respectively.

Rearranging and substituting \( Eq. 4 \) into \( Eq. 5 \) yields:

\[ \frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{CL_{PD} + CL_{MP}}{CL_{PD} + 2CL_{f0} + CL_{p0} + CL_{PM} + \left( \frac{CL_{p0} + CL_{PM}}{CL_{PD}} \right) \cdot CL_{f0}} \quad (Eq. 6) \]

Substituting \( Eq. 4 \) into \( Eq. 6 \) and rearranging yields:
The impact of fetal/placental metabolism and placental transport on the steady-state
fetal:maternal plasma drug concentration ratio is apparent with the following examples:

(1) When, except for CL_{PD}, none of the above fetoplacental clearance pathways are
present, Eq. 6 simplifies to Eq. 8:

\[
\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{CL_{PD}}{CL_{PD}} = 1 \quad (\text{Eq. } 8)
\]

In this case the placenta becomes “transparent”, meaning that the \( \frac{C_{f,ss,inf}}{C_{m,ss,inf}} \) ratio
becomes unity.

(2) When only CL_{p0} and CL_{PD} are present, Eq. 6 simplifies to Eq. 9:

\[
\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{CL_{PD}}{CL_{PD} + CL_{p0}} \quad (\text{Eq. } 9)
\]

Now the \( \frac{C_{f,ss,inf}}{C_{m,ss,inf}} \) ratio is determined by the magnitude of CL_{PD} relative to CL_{p0}.
For instance, when these two clearances are of the same magnitude, this ratio becomes
0.5.

(3) When only CL_{f0} and CL_{PD} are present, Eq. 6 simplifies to Eq. 10:

\[
\frac{C_{f,u,ss,inf}}{C_{m,u,ss,inf}} = \frac{CL_{PD}}{CL_{PD} + 2CL_{f0}} \quad (\text{Eq. } 10)
\]
Now the $C_{f, ss, inf} / C_{m, ss, inf}$ ratio is determined by the magnitude of $CL_{PD}$ relative to $CL_{f0}$. Note that the $CL_{f0}$ term has a coefficient of 2. Therefore, the introduction of fetal clearance results in a further decrease in the $C_{f, ss, inf} / C_{m, ss, inf}$ ratio compared with the above case. For instance, when $CL_{PD}$ and $CL_{f0}$ are of the same magnitude, this ratio becomes 0.33.

(4) When both $CL_{p0}$ and $CL_{f0}$ as well as $CL_{PD}$ are present, Eq. 6 simplifies to Eq. 11:

$$\frac{C_{f, ss, inf}}{C_{m, ss, inf}} = \frac{CL_{PD}}{CL_{PD} + 2CL_{f0} + CL_{p0} + \frac{CL_{p0} \cdot CL_{f0}}{CL_{PD}}} \quad (\text{Eq. 11})$$

Now the $C_{f, ss, inf} / C_{m, ss, inf}$ ratio becomes a composite function that is determined by the magnitude of $CL_{f0}$ and $CL_{p0}$ relative to $CL_{PD}$. When $CL_{f0}$ and $CL_{p0}$ are of the same magnitude as $CL_{PD}$, this ratio reduces to 0.2. Furthermore, when $CL_{p0} \ll CL_{PD}$, Eq. 11 simplifies to Eq. 10, whereas when $CL_{f0} \ll CL_{PD}$, Eq. 11 simplifies to Eq. 9.

(5) When only $CL_{PM}$ and $CL_{PD}$ are present, Eq. 6 simplifies to Eq. 12:

$$\frac{C_{f, ss, inf}}{C_{m, ss, inf}} = \frac{CL_{PD}}{CL_{PD} + CL_{PM}} \quad (\text{Eq. 12})$$

Again, when placental efflux clearance is invoked the $C_{f, ss, inf} / C_{m, ss, inf}$ ratio is determined by the magnitude of $CL_{PD}$ relative to $CL_{PM}$. For example, when these two clearances are of the same magnitude, the $C_{f, ss, inf} / C_{m, ss, inf}$ ratio is 0.5.

(6) When only $CL_{MP}$ and $CL_{PD}$ are present, Eq. 6 reduces to Eq. 13:
Unlike the above cases, introduction of placental uptake clearance results in an increase in the $\frac{C_{f,ss,inf}}{C_{m,ss,inf}}$ ratio. Nonetheless, this ratio is dependent on the magnitude of $\text{CL}_{PD}$ relative to $\text{CL}_{MP}$. For example, when these two clearances are of the same magnitude, the $\frac{C_{f,ss,inf}}{C_{m,ss,inf}}$ ratio is 2.

Under various scenarios of our sensitivity analyses, the m-f-PBPK model simulated steady-state $\text{F:M}$ and $\text{P:M}$ ratios of drug X or Y were consistent with those predicted by the above maternal-placental-fetal three compartment model, confirming the correct implementation of our m-f-PBPK model. In addition, this exercise, as detailed above, yielded novel and surprising quantitative information on the impact of fetoplacental metabolism and placental transport on fetal exposure to drugs.

**Impact of fetal renal clearance and amniotic fluid fetal swallowing rate on amniotic fluid exposure to drug X**

The reported physiological value of fetal renal clearance ($\text{fCL}_{R}$) ([Supplementary Table 1](#)) and fetal amniotic fluid swallowing rate ($\text{fCL}_{\text{reabsorp}}$) (Pritchard, 1966) was varied by 0.5-, 1-, and 5-fold respectively. As anticipated, changes in neither pathway altered maternal PK (data not shown). Within the tested range, only a 5-fold increase in $\text{fCL}_{R}$ modestly altered the shape of fetal C-T curve. When $\text{fCL}_{R}$ (0.098L/h) was increased from to 0.196L/h or 0.981L/h, the corresponding $C_{\text{max},f}$ decreased by 2.6% and 16.4% respectively ([Figure S2a](#)) but the $\text{AUC}_f$ remained unchanged ([Figure S2e](#)). In contrast, alterations in $\text{fCL}_{\text{reabsorp}}$ did not affect $C_{\text{max},f}$ or $\text{AUC}_f$ ([Figure S2b](#) and [Figure S1f](#)).
Increase in f\(\text{CL}_R\) or f\(\text{CL}_{\text{reabsorp}}\) significantly affected drug distribution into amniotic fluid in opposite direction. As f\(\text{CL}_R\) increased from 0.098 L/h to 0.196 L/h, the predicted amniotic fluid AUC (AUC_{af}) increased from 13.4 mg·h/L to 26.8 mg·h/L (Figure S2c, e). When f\(\text{CL}_{\text{reabsorp}}\) was increased from 0.01 L/h to 0.02 L/h the respective AUC_{af} value was reduced from 53.4 mg·h/L to 26.7 mg·h/L (Figure S2d, f). Similar trends were observed with the amniotic fluid:maternal plasma (AF:MP) and amniotic fluid:UV (AF:UV) drug concentration ratios. Both ratios increased rapidly with time (Figure S2g-j). Moreover, after the establishment of fetal plasma-amniotic fluid distributional equilibrium, both ratios significantly deviated from the corresponding AF:MP and AF:UV AUC ratios.

See Table 2 for the clearance values used in these simulations.

**Supplementary Discussion**

Amniotic fluid drug concentration is often mistaken for an indicator of fetal drug exposure. For example, high amniotic fluid concentrations were associated with continuous fetal exposure to bupropion. (Fokina et al., 2016) But this is not the case. When a renally cleared drug enters the fetal circulation, it is excreted into amniotic fluid via fetal urination (f\(\text{CL}_R\)) and then reabsorbed through fetal swallowing of amniotic fluid (f\(\text{CL}_{\text{reabsorp}}\); assuming instant and complete absorption) at late gestation. (Underwood et al., 2005) Therefore, high amniotic fluid drug concentrations do not necessarily result from high fetal exposure but rather is due to the much greater f\(\text{CL}_R\) relative to f\(\text{CL}_{\text{reabsorp}}\). This disconnect between the amniotic fluid and fetal plasma drug concentrations is illustrated in **Supplementary Figure S2**. Amniotic fluid effectively acted as a “reservoir” for drug X because of its 9-fold higher f\(\text{CL}_R\) (0.192 L/h) compared to f\(\text{CL}_{\text{reabsorp}}\) (500mL/day). Drug X amniotic fluid drug concentrations, and therefore amniotic fluid drug AUC
(AUC\textsubscript{af}), increased proportionally with fCL\textsubscript{R} but was inversely related to fCL\textsubscript{reabsorp} (Figure S2c-f). In contrast, AUC\textsubscript{f} remained independent of the variations in fCL\textsubscript{R} or fCL\textsubscript{reabsorp} (Figure S2e,f). This is because the amniotic fluid acts as a distribution compartment not a compartment where drug elimination takes place. Indeed, the observed AUC\textsubscript{af}/AUC\textsubscript{m} of tenofovir, a placental P-gp substrate, is as high as 2.76, although tenofovir AUC\textsubscript{f}/AUC\textsubscript{m} of 0.45 was observed in the same study.(De Sousa Mendes et al., 2016) Again, like the UV:MP ratio, AF:UV ratio does not reflect fetal drug exposure (Figure S2g-j).

Theoretical discussion on the effect of CL\textsubscript{m0} and CL\textsubscript{PD} on fetal:maternal drug concentration ratio

Drug distribution in the coupled maternal-fetal pair may be envisioned to be analogous to the distribution of a drug between a central compartment (mother) and a peripheral compartment(fetus). For a drug that demonstrates two compartment pharmacokinetics, the differential equations for the rate of change in the amount of drug in the central and peripheral body compartments based on the model presented in Supplementary Figure S3 are

\[
\frac{dX_c}{dt} = -(k_{10} + k_{12})X_c + k_{21}X_p \quad (1)
\]

and

\[
\frac{dX_p}{dt} = k_{12}X_c - k_{21}X_p \quad (2)
\]

respectively.
where $X_c$ and $X_p$ are the amount of drug in the central compartment and the peripheral compartments, respectively, $k_{10}$ is the central compartment elimination rate constant, and $k_{12}$ and $k_{21}$ are the inter-compartmental distribution rate constants.

Take the Laplace transform of both sides of (1)

$$s \cdot \bar{X}_c - X_0 = -(k_{10} + k_{12}) \cdot \bar{X}_c + k_{21} \cdot \bar{X}_p \quad (3)$$

where $X_0$ is the dose available to the central compartment.

Similarly for (2)

$$s \cdot \bar{X}_p = k_{12} \cdot \bar{X}_c - k_{21} \cdot \bar{X}_p \quad (4)$$

Rearrange (3) and (4) to get:

$$\begin{cases} (s + k_{10} + k_{12}) \bar{X}_c - k_{21} \bar{X}_p = X_0 \\ -k_{12} \bar{X}_c + (s + k_{21}) \bar{X}_p = 0 \end{cases} \quad (5)$$

Solving Eq. 5 gives:

$$X_c = X_0 \cdot \left( \frac{\lambda_1 - k_{21}}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} + \frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_1 t} \right)$$

$$X_p = X_0 \cdot \left( \frac{-k_{12}}{\lambda_1 - \lambda_2} e^{-\lambda_2 t} + \frac{k_{12}}{\lambda_1 - \lambda_2} e^{-\lambda_1 t} \right) \quad (6)$$

where $\lambda_1$ and $\lambda_2$ are microconstants. (Gibaldi and Perrier, 1982)
Hence, \( \frac{X_p}{X_c} = \frac{X_0 \cdot (\frac{-k_{12}}{\lambda_4 - \lambda_2} e^{-\lambda_1 t} + \frac{k_{12}}{\lambda_4 - \lambda_2} e^{-\lambda_2 t})}{X_0 \cdot (\frac{\lambda_1 - k_{21}}{\lambda_1 - \lambda_2} e^{-\lambda_1 t} + \frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2} e^{-\lambda_2 t})} \) \hspace{1cm} (7)

Rearranging Eq. 7 yields:

\[ \frac{X_p}{X_c} = \frac{-k_{12} e^{-\lambda_1 t} + k_{12} e^{-\lambda_2 t}}{(\lambda_1 - k_{21}) e^{-\lambda_1 t} + (k_{21} - \lambda_2) e^{-\lambda_2 t}} \] \hspace{1cm} (8)

In the post-distributive phase (i.e., as \( e^{-\lambda_1 t} \) approaches zero)

Eq. 8 reduces to:

\[ \frac{X_p}{X_c} = \frac{k_{12}}{k_{21} - \lambda_2} \] \hspace{1cm} (9)

Substituting \( X_p \) and \( X_c \) with \( C_p V_p \) and \( C_c V_c \), respectively, and rearranging yields:

\[ \frac{C_p}{C_c} = \frac{k_{12}}{k_{21} - \lambda_2} \cdot \frac{V_c}{V_p} \] \hspace{1cm} (10)

where \( C_p \) and \( C_c \) are drug concentrations in the peripheral and central compartment, respectively, and \( V_p \) and \( V_c \) are the volume of distribution for the central and peripheral compartments, respectively.

\( \lambda_2 \) is a hybrid parameter \( (\lambda_2 = \frac{1}{2} \left[ (k_{12} + k_{21} + k_{10}) - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}k_{10}} \right] ) \) that reflects the drug elimination from the body. It increases as \( k_{10} \) increases. (Gibaldi and
Perrier, 1982) Therefore, increasing $k_{10}$ will result in higher $\frac{C_p}{C_c}$ and thereby elevating the peripheral (fetal):central (maternal) plasma drug concentration ratio.

On the other hand, for a passively diffused drug:

$$k_{12} = \frac{CL_{pD}}{V_c} \quad \text{and} \quad k_{21} = \frac{CL_{pD}}{V_p}$$

where $CL_{pD}$ is the inter-compartmental passive diffusion clearance.

Substituting for $k_{12}$ and $k_{21}$ in Eq. 10 yields:

$$\frac{C_p}{C_c} = \frac{1}{1 - \frac{\lambda_2 V_p}{CL_{pD}}}$$

It is evident from Eq. 11 that increasing $CL_{pD}$ will reduce the peripheral:central (fetal:maternal) drug plasma concentration ratio.
References


