Estimation of Fetal-to-Maternal Unbound Steady-State Plasma Concentration Ratio of P-Glycoprotein and/or Breast Cancer Resistance Protein Substrate Drugs Using a Maternal-Fetal Physiologically Based Pharmacokinetic Model

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ABSTRACT

Pregnant women are frequently prescribed drugs to treat chronic diseases such as human immunodeficiency virus infection, but little is known about the benefits and risks of these drugs to the fetus that are driven by fetal drug exposure. The latter can be estimated by fetal-to-maternal unbound plasma concentration at steady state (Kp,uu,fetal). For drugs that are substrates of placental efflux transporters [i.e., P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP)], Kp,uu,fetal is expected to be <1. Here, we estimated the in vivo Kp,uu,fetal of selective P-gp and BCRP substrate drugs by maternal-fetal physiologically based pharmacokinetic (m-f-PBPK) modeling of umbilical vein (UV) plasma and maternal plasma (MP) concentrations obtained simultaneously at term from multiple maternal-fetal dyads. To do so, three drugs were selected: nelfinavir (P-gp substrate), efavirenz (BCRP substrate), and imatinib (P-gp/BCRP substrate). An m-f-PBPK model for each drug was developed and validated for the nonpregnant population and pregnant women using the Simcyp simulator (v20). Then, after incorporating placental passive diffusion clearance, the in vivo Kp,uu,fetal of the drug was estimated by adjusting the placental efflux clearance until the predicted UV/MP values best matched the observed data (Kp,uu,fetal) of nelfinavir = 0.41, efavirenz = 0.39, and imatinib = 0.35. Furthermore, Kp,uu,fetal of nelfinavir and efavirenz at gestational weeks (GWs) 25 and 15 were predicted to be 0.34 and 0.23 (GW25) and 0.33 and 0.27 (GW15). These Kp,uu,fetal values can be used to adjust dosing regimens of these drugs to optimize maternal-fetal drug therapy throughout pregnancy, to assess fetal benefits and risks of these dosing regimens, and to determine if these estimated in vivo Kp,uu,fetal values can be predicted from in vitro studies.

SIGNIFICANCE STATEMENT

The in vivo fetal-to-maternal unbound steady-state plasma concentration ratio (Kp,uu,fetal) of nelfinavir [P-glycoprotein (P-gp) substrate], efavirenz [breast cancer resistance protein (BCRP) substrate], and imatinib (P-gp and BCRP substrate) was successfully estimated using maternal-fetal physiologically based pharmacokinetic (m-f-PBPK) modeling. These Kp,uu,fetal values can be used to adjust dosing regimens of these drugs to optimize maternal-fetal drug therapy throughout pregnancy, to assess fetal benefits and risks of these dosing regimens, and to determine if these estimated in vivo Kp,uu,fetal values can be predicted from in vitro studies.

Introduction

Pregnant women frequently take drugs (medication) throughout their pregnancy to treat the mother for conditions such as hypertension or cancer or to treat the maternal-fetal pair for conditions such as human immunodeficiency virus (HIV) infection (McGowan and Shah, 2000; Mitchell et al., 2011; Haas et al., 2018). However, these drugs are often prescribed without knowledge of their fetal benefits and risks that are driven by fetal (and possibly by placental) drug exposure. Fetal drug exposure can be quantified only at delivery when simultaneous sampling of umbilical vein blood and maternal blood is possible. However, because these drug concentrations are time dependent, they need to be collected in multiple maternal-fetal dyads to allow the estimation of...
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Development and Validation of Drug PBPK Models for Pregnant Women. After validating the PK of the drug in the nonpregnant population, drug-specific parameters were fixed, and except for the changes in CYP450 activity, the pregnancy-induced changes in physiologic parameters specified in the Simcyp pregnancy module were implemented. The pregnancy-induced changes in hepatic CYP450 activity were based on our previously published data: CYP3A was induced 2-fold during the second and third trimesters (Ke et al., 2012; Zhang et al., 2015), CYP2D6 was induced 1.9- and 2-fold during the second and third trimesters, CYP1A2 was suppressed by 48% and 65% during the second and third trimesters (Ke et al., 2013), CYP2B6 activity was induced by 1.1- and 1.3-fold during the second and third trimesters, and CYP2C9 activity was induced by 1.5- and 1.6-fold during the second and third trimesters.

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third trimesters (Ke et al., 2014). CYP2C19 activity was suppressed by 62% and 68% during the second and third trimesters (Dickmann and Isoherranen, 2013; Ke et al., 2014). CYP2C19 activity was suppressed by 62% during the second and third trimesters (Ke et al., 2014). CYP2C19 activity was suppressed by 62% during the second and third trimesters (Ke et al., 2014). CYP2C19 activity was suppressed by 62% during the second and third trimesters (Ke et al., 2014). CYP2C19 activity was suppressed by 62% during the second and third trimesters (Ke et al., 2014).

where:  

\[ \text{CLPD, x} = \frac{\text{Papp, x} \times \text{CL}_{\text{PD, placenta}}}{\text{L/h}} \]

in vivo calibrator to estimate \( \text{CL}_{\text{PD, placenta}} \) of nelfinavir, efavirenz, or imatinib.

AUC_{\text{inf}}, AUC from time 0 to last measurable concentration; N, number of subjects of observed data; Ratio, Predicted/Observed values of AUC_{\text{inf}}, AUC_{\text{last}}, o r C_{\text{max}}.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>I.V. Infusion (Day 1) ( ^a )</th>
<th>I.V. Infusion (Day 11) ( ^b )</th>
<th>Single Oral 1250 mg (Day 1)</th>
<th>Oral 1250 mg 2x Daily (Day 15)</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>Sarapa et al., 2005;</td>
</tr>
<tr>
<td>AUC_{\text{last}} (mg.h/l)</td>
<td>23.60 26.74 1.13 29.20 31.88 1.09</td>
<td>26.20 26.94 1.03 4.18 4.25 1.02</td>
<td>33.70 35.06 1.04 5.13 5.55 1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{\text{max}} (mg/l)</td>
<td>24.30 19.33 0.80 24.40 20.19 0.83</td>
<td>4.84 4.91 1.01 0.81 0.87 1.07</td>
<td>31.80 28.91 0.91 4.09 4.67 1.14</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>


AUC_{\text{last}}, AUC from time 0 to time of last measurable concentration; N, number of subjects of observed data; Ratio, Predicted/Observed values of AUC_{\text{last}} or C_{\text{max}}.

1 Single 30-min i.v. infusion of 1 mg nelfinavir.

2 11 days oral 1250-mg dose of nelfinavir with food followed by single 30-min i.v. infusion of 1 mg nelfinavir.

TABLE 2

Observed and PBPK model-predicted plasma pharmacokinetics of nelfinavir in nonpregnant adults

One hundred virtual subjects (10 trials × 10 subjects) were simulated for each study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>I.V. Infusion (Day 1) ( ^a )</th>
<th>I.V. Infusion (Day 11) ( ^b )</th>
<th>Single Oral 1250 mg (Fed)</th>
<th>Single Oral 1250 mg (Fasted)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>52</td>
<td>52</td>
<td>52</td>
<td>12</td>
<td>Karuowski et al., 2002;</td>
</tr>
<tr>
<td>AUC_{\text{last}} (mg.h/l)</td>
<td>32.90 26.41 0.80 4.84 4.91 1.01</td>
<td>4.84 4.91 1.01 0.81 0.87 1.07</td>
<td>31.80 28.91 0.91 4.09 4.67 1.14</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>C_{\text{max}} (mg/l)</td>
<td>4.30 4.36 1.01</td>
<td>4.30 4.36 1.01</td>
<td>4.30 4.36 1.01</td>
<td>4.30 4.36 1.01</td>
<td>Reference</td>
</tr>
</tbody>
</table>

TABLE 3

PK profiles of efavirenz and imatinib in nonpregnant population

One hundred virtual subjects (10 trials × 10 subjects) were simulated for each study.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>400 mg Once Daily</th>
<th>600 mg Once Daily</th>
<th>600 mg Once Daily</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>N</td>
<td>AUC_{\text{last}} (mg.h/l)</td>
<td>49.20 51.81 0.80 4.84 4.91 1.01</td>
<td>36.20 38.91 0.91 4.09 4.67 1.14</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Parameters</td>
<td>Capule (400 mg)</td>
<td>Oral Solution (400 mg)</td>
<td>Oral (100 mg)</td>
</tr>
<tr>
<td>N</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>AUC_{\text{last}} (mg.h/ml)</td>
<td>7836.00 8098.00 1.03</td>
<td>32640.00 30971.88 0.95</td>
<td>1848.00 1539.54 1.24</td>
<td>30729.00 30971.88 1.01</td>
</tr>
<tr>
<td>C_{\text{max}} (mg/ml)</td>
<td>1206.00 1689.60 1.40</td>
<td>1822.00 1560.67 1.15</td>
<td>4.00 4.21 1.05</td>
<td>1848.00 1539.54 1.24</td>
</tr>
</tbody>
</table>

AUC_{\text{inf}}, AUC from time 0 extrapolated to infinity; AUC_{\text{last}}, AUC from time 0 to time of last measurable concentration; N, number of subjects of observed data; Ratio, Predicted/Observed values of AUC_{\text{last}}, AUC_{\text{inf}}, or C_{\text{max}}.
Placental volume = $-1.7646 \times GW + 0.91775 \times (GW^2) - 0.011543 \times GW^3$ (2), where GW is the gestational age (in weeks). After incorporating CL_{int,P-gp,placenta} we predicted the umbilical vein plasma concentrations and estimated the drug K_{p,uu,fetal} (eq. 3) by adjusting the intrinsic placental efflux clearance of the drug at the maternal-placenta barrier (CL_{int,P-gp,placenta} for nelfinavir, CL_{int,BCRP,placenta} for efavirenz, and CL_{int,efflux,placenta} for imatinib) until the predicted UV/MP values best matched the observed data (AAFE = 1.0) using the permeability-limited placenta model of Simcyp. The absolute average fold error (AAFE) in the predictions of UV/MP values was calculated as per eq. 4:

$$K_{p,uu,fetal} = \frac{AUC_{fetal,u}}{AUC_{m,u}}$$ (3)

$$AAFE = 10\left| \frac{\sum_{i=1}^{N} \log_{10}(predicted)}{\sum_{i=1}^{N} \log_{10}(observed)} \right|$$ (4),

where AUC_{fetal,u} is the area under the curve of the unbound umbilical vein plasma concentration-time profile, AUC_{m,u} is the area under the curve of the unbound maternal plasma concentration-time profile, and N is the number of observed and predicted UV/MP values.

**PBPK Model Prediction of K_{p,uu,fetal} of the Drugs at an Earlier Gestational Ages (GW15 and GW25).** To predict the K_{p,uu,fetal} of nelfinavir and efavirenz at an earlier gestational age, total placental P-gp and BCRP abundance, previously quantified by us using quantitative targeted proteomics (Anoshchenko et al., 2020), was incorporated into the Simcyp pregnancy module “Sim-Pregnancy.” A second-order polynomial model was fitted to the gestational age-dependent relative abundance of placental P-gp and BCRP (relative to term value, which was set as 1.0), respectively (see eq. 5 and 6; R-square values of the fitted polynomials were 1.0; Supplemental Fig. 1).

$$P-gp \text{ relative abundance} = 0.003 \times (GW^2) - 0.228 \times GW + 5.010 \ (5)$$

$$BCRP \text{ relative abundance} = 0.001 \times (GW^2) - 0.086 \times GW + 2.899 \ (6)$$

These equations were used to interpolate the placental abundance of the transporters at GW15 and GW25. Then, these interpolated values were used to scale the above estimated (term) placental efflux clearances of nelfinavir and efavirenz (CL_{int,P-gp,placenta} for nelfinavir, CL_{int,BCRP,placenta} for efavirenz) and incorporated in the Simcyp pregnancy module. Within this module, the above-estimated term CL_{int,P-gp,placenta} and CL_{int,efflux,placenta} was scaled based on the mean volume of the placenta for the respective gestational age. Then, the maternal-fetal PK profiles of the drugs were predicted at GW15 and GW25 using the same trial design as...
for term. From these profiles, the $K_{p,uu,fetal}$ of nelﬁnavir and efavirenz was estimated. Such predictions for imatinib were not possible, as the fraction of imatinib transported by P-gp or BCRP is unknown and will need to be determined, as we have described previously (Kumar et al., 2021).

**Results**

**PBPK Model Predictions and Validation for the Nonpregnant Population.** Our predictions of nelﬁnavir PK were successfully validated after intravenous dose, single oral dose (fed and fasted), multiple oral dose administration, and coadministration with ritonavir. The observed concentration-time (C-T) profiles fell within the 5th and 95th percentiles of predicted data (Fig. 2A; Supplemental Fig. 2), and the predicted PK parameters (AUC and $C_{max}$) also fell within 0.80- to 1.25-fold of the observed data (Table 2). The PBPK models for efavirenz and imatinib were successfully reproduced, and except for imatinib $C_{max}$ after coadministration with ketoconazole, their simulated PK profiles were consistent with the reported in vivo data (Fig. 2, B and C; Supplemental Fig. 3; Table 3).

**Estimated Human $K_{p,uu,fetal}$ at Term.** Using our acceptance criteria, the predicted MP concentration-time profiles agreed well with the observed data of nelﬁnavir, efavirenz, and imatinib (Fig. 5, A, D, and G). The estimated CL$_{int,PD,placenta}$ of nelﬁnavir, efavirenz, and imatinib at term were 240, 1480, and 170 $l/min/ml$ placenta volume, respectively (Table 5). Without incorporating placental efflux clearance (CL$_{efflux,placenta}$) that is in the presence of only CL$_{Pgp,placenta}$ of the drug, the UV plasma concentration (Fig. 5, B, E, and H) and UV/MP ratio (Fig. 5, C, F, and I) were considerably overpredicted with AAFE $> 1$ and, as expected, the estimated $K_{p,uu,fetal}$ was 1.0 (Table 5).

By adjusting CL$_{int,efflux,placenta}$ of the drugs (nelﬁnavir: 350; efavirenz: 2200; imatinib: 320 $l/min/ml$ placenta volume), the majority of the observed UV plasma concentrations and the UV/MP ratios fell within the 5th and 95th percentiles of the model predicted data (Fig. 5). As
these data are steady-state data, the predicted AUC_{fetal}/AUC_{m} were close to the mean observed UV/MP ratio and AAFE equaled 1.00. K_{p,uu,fetal} values at term estimated from the UV/MP data were 0.41, 0.39, and 0.35 for nelfinavir, efavirenz, and imatinib, respectively. These data indicate that the fraction of drug transported by placental P-gp or BCRP at term (f_{flux} = 1 - K_{p,uu,fetal}) followed the order imatinib (0.65) > efavirenz (0.61) > nelfinavir (0.59).

**Prediction of Nelfinavir and Efavirenz K_{p,uu,fetal} at Earlier Gestational Ages (GW15 and GW25).** The MP plasma concentrations of nelfinavir and efavirenz were marginally affected by gestational age, and the UV plasma concentration, UV/MP ratio, and K_{p,uu,fetal} all decreased with gestational age (Fig. 6; Table 5).

**Discussion**

Nelfinavir and efavirenz are prescribed to prevent the transmission of HIV from the mother to her fetus (Perry et al., 2005; Vrouenraets et al., 2007). However, as we have shown here, they are prevented from distribution into the fetal compartment by extensive placental efflux, thus potentially reducing their efficacy in preventing maternal-fetal HIV transmission. In contrast, imatinib, a selective tyrosine kinase inhibitor, is used to treat cancers (Ali et al., 2009). When administered to pregnant women, in addition, if these safety and efficacy data dictate, these K_{p,uu,fetal} values can be used to design alternative dosing regimens to enhance drug safety and efficacy, as we have proposed for antenatal corticosteroids (Anoshchenko et al., 2021a).

Although K_{p,uu,fetal} can be estimated at term from UV/MP values, sampling UV blood is not possible at earlier gestational ages. Therefore, to estimate drug K_{p,uu,fetal} at earlier gestational ages, the only recourse is PBPK modeling and simulation. For all the above reasons, we estimated K_{p,uu,fetal} of nelfinavir, efavirenz, and imatinib at term and earlier in gestation (nelfinavir and efavirenz only). In addition, though drugs are frequently taken by pregnant women, no UV/MP data are available for the majority of these drugs. Because obtaining such data is extremely challenging, the only recourse is to estimate K_{p,uu,fetal} for these drugs. We have previously shown that this is possible through in vitro transport studies combined with m-f-PBPK modeling and simulation and the quantitative targeted proteomics-informed relative expression factor (REF) approach (Anoshchenko et al., 2021b). However, such predictive methods need to be validated. Thus, another reason for estimating term nelfinavir, efavirenz, and imatinib K_{p,uu,fetal} values is to use them in the future to validate predictions made by our m-f-PBPK model (Anoshchenko et al., 2021b).

K_{p,uu,fetal} is determined by several factors, namely placental transport (efflux or influx), placental metabolism, and fetal clearance of the drug. Since the placenta is not endowed with the CYP450 enzymes found in adult livers, the metabolism of most drugs within this organ is negligible (Unadkat et al., 2004). The fetal liver size is small. In addition, except for CYP3A7, it also does not express many of the CYP450 enzymes found in the adult liver until about one year after birth (Thakur et al., 2004). The fetal liver size is small. In addition, except for CYP3A7, it also does not express many of the CYP450 enzymes found in the adult liver until about one year after birth (Thakur et al., 2004).
due to pooling UV and MP values from multiple maternal-fetal dyads. Using UV/MP values as an endpoint mitigates the variability observed when using the UV values as endpoints.

In the present study, the PK parameters of three drugs, effluxed by the placental transporters, were successfully predicted and validated after PBPK modeling and simulation of PK data in nonpregnant adults.

### TABLE 5

<table>
<thead>
<tr>
<th>Drug</th>
<th>CL_{efflux,placenta} (µl/min/ml Placenta Volume)</th>
<th>CL_{int,placenta} (µl/min/ml Placenta Volume)</th>
<th>Predicted AUC_{int}/AUC_{MP}</th>
<th>Average Observed UV/MP Ratio (Range)</th>
<th>K_{p,uu,fetal} At Term</th>
<th>GW25</th>
<th>GW15</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelfinavir</td>
<td>240</td>
<td>0.00</td>
<td>2.39</td>
<td>0.61</td>
<td>0.25</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1480</td>
<td>350.00</td>
<td>1.00</td>
<td>0.25</td>
<td>(0.05–5.18)</td>
<td>0.41</td>
<td>0.34</td>
<td>0.23</td>
</tr>
<tr>
<td>Imatinib</td>
<td>170</td>
<td>2200.00</td>
<td>1.00</td>
<td>0.25</td>
<td>(0.37–0.74)</td>
<td>0.49</td>
<td>0.39</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>320.00</td>
<td>2.91</td>
<td>0.43</td>
<td>(0.05–0.22)</td>
<td>0.39</td>
<td>1.00</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, data not available.
Estimation of $K_{p,uu,fetal}$ Using an M-F-PBPK Model

Fig. 6. Simulated steady-state (A and D) maternal plasma (MP) concentrations; (B and E) umbilical vein (UV) plasma concentrations; and (C and F) the UV/MP profiles of (A–C) nelfinavir or (D–F) efavirenz at varying gestational ages. Profiles were simulated after administration of (A–C) nelfinavir (1250 mg, twice daily in fed state for 15 days) and (D–F) efavirenz (600 mg, once daily for 15 days). $K_{p,uu,fetal}$ values for nelfinavir were 0.41, 0.34, and 0.23 at GWs 38, 25, and 15, respectively. $K_{p,uu,fetal}$ values for efavirenz were 0.39, 0.33, and 0.27 at GWs 39, 25, and 15, respectively.

Anoshchenko et al., 2020, we were able to predict the $K_{p,uu,fetal}$ of the abundance of placental transporters at various gestational ages as the physiologic data at these earlier gestational ages are not currently available. However, these values can be predicted in the future from in vitro transport data and REF, as we have done before for other drugs. Based on our model, the placenta (f_{efflux} = 1 – $K_{p,uu,fetal}$) was 0.59, 0.61, and 0.65, respectively, demonstrating that placental P-gp and BCRP significantly prevent their distribution into the fetal compartment. To our knowledge, this is the first time that the $K_{p,uu,fetal}$ of a placental BCRP substrate as well as that of a dual P-gp/BCRP substrate have been estimated. Furthermore, this is the first study to construct and validate a PBPK model for the disposition of nelfinavir in nonpregnant adults and pregnant women.

Based on the above term pregnancy data, because we have quantified the abundance of placental transporters at various gestational ages (Anoshchenko et al., 2020), we were able to predict the $K_{p,uu,fetal}$ of nelfinavir and efavirenz earlier in gestation (GW15 and GW25). The Simcyp pregnancy module does not allow predictions any earlier (<GW15), but the decrease in the latter was greater than the former. Therefore, the $K_{p,uu,fetal}$ of both nelfinavir and efavirenz was greater at GW15 (0.23, 0.27) and GW25 (0.34, 0.33) was lower than at term (0.41, 0.39). These data can inform the fetal efficacy and toxicity of these drugs at earlier gestational ages.

There are a few limitations to our study. First, the PBPK model of imatinib was not validated for pregnant women due to a lack of such data. Second, imatinib may be transported by human organic anion transporting polypeptide 1A2 (OATP1A2) and multidrug resistance protein 4 (MRP4) (Hu et al., 2008; Yamakawa et al., 2011). However, data on pregnancy-induced changes in OATP1A2 and MRP4 activity are not available and therefore were not included in our model. Third, for our nelfinavir PBPK model, f_m by each CYP450 isoform was based on CYP450 inhibition of nelfinavir metabolism in HLMs, and enzyme cross-inhibition by these inhibitors was not taken into consideration (Patilea-Vrana et al., 2019). However, none of the above limitations detracts from correctly estimating $K_{p,uu,fetal}$ provided that the maternal plasma concentrations are predicted well. Fourth, we assumed that nelfinavir solely binds to AAG rather than albumin (I), as the association constant of nelfinavir for AAG (7.25 × 10^7/M) is 70 times higher than that for HSA (1.11 × 10^7/M) (Motoya et al., 2006). Fifth, the fraction unbound of the drugs in fetal plasma was the Simcyp-predicted value (Supplemental Table 2) because the corresponding experimentally measured values are not available in the literature. Any inaccuracy in our estimate of the fraction of drug bound in the maternal and fetal compartment will result in inaccuracy in our $K_{p,uu,fetal}$ estimate. Sixth, the potential effects of HIV or cancer comorbidity on the placental drug permeability or transporters are unknown and were therefore not incorporated in the model. Again, this does not detract from our estimate of $K_{p,uu,fetal}$, as it was based on the observed data from women who had these clinical conditions. Seventh, the Simcyp model does not allow passage of drug from the placenta directly into the amniotic fluid, which can be swallowed by the fetus. Irrespective of the route of drug passage, our $K_{p,uu,fetal}$ values will be unaffected, as they are based on the observed UV/MP values.

In summary, we estimated the in vivo $K_{p,uu,fetal}$ of nelfinavir, efavirenz, and imatinib through PBPK modeling and simulation. Prospective, the $K_{p,uu,fetal}$ of these drugs could be used to design dosing regimens of these drugs for pregnant women throughout pregnancy.
maximize their efficacy and minimize their fetal toxicity. Furthermore, in the future, these \( K_{\text{pass,final}} \) could be used to validate their predictions made through in vitro studies using the proteomics-informed REF approach. Once validated, these \( m\)-f-PBPK models, in combination with in vitro studies, could be used in the future to predict fetal exposure throughout pregnancy to any drug that is actively effluxed by placental \( P\)-gpg or \( BCRP \\

Authorship Contributions

Participated in research design: Peng, Ladumor, Unadkat.
Conducted experiments: Peng, Ladumor.
Performed data analysis: Peng, Ladumor, Unadkat.
Wrote or contributed to the writing of the manuscript: Peng, Ladumor, Unadkat.

References

Estimation of $K_{p,uu,fetal}$ Using an M-F-PBPK Model 623


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