Predicting maternal-fetal exposure to drugs using a mechanistic PBPK model

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Predicting Maternal-Fetal Exposure to Drugs by Phenotyping Studies and a Maternal-Fetal (m-f) PBPK Model

• When pregnant women are given standard drug doses, maternal-fetal exposure to these drugs, and their efficacy and safety, will often differ from that in men or non-pregnant women because the PK of drugs are changed by pregnancy (e.g. CYPs are induced or repressed)

• It is neither feasible nor desirable to determine maternal-fetal exposure to all drugs or natural products/supplements taken by pregnant women

• Therefore, to inform correct maternal dosing regimen and minimize fetal risks, we have developed a systems/mechanistic pharmacology approach to predict maternal-fetal exposure to drugs throughout pregnancy:
  – First, elucidate the extent of changes in drug disposition (e.g. drug metabolism and transport) for model drugs (phenotyping studies)
  – Then use a maternal-fetal Physiologically Based Pharmacokinetic (m-f PBPK) model to predict the disposition of other drugs that are also metabolized/transported by the same mechanisms
Can Maternal Disposition of CYP-Cleared Drugs be Accurately Predicted by our m-f PBPK Model?

- Populate the model by pregnancy-specific physiological mechanistic data e.g. changes in CYP and transporter activity
- Then, predict the changes in m-f exposure to drugs not studied in pregnancy

Zhang et al. DMD 2017

Ke et al 2012
Validation of our m-f PBPK model

<table>
<thead>
<tr>
<th>CYP3A</th>
<th>CYP1A2</th>
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<tbody>
<tr>
<td>Midazolam</td>
<td>Caffeine</td>
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<tr>
<td>(Dextromethorphan)</td>
<td>Theophylline</td>
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<tr>
<td>Nifedipine, Indinavir</td>
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<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Multiple CYPs</th>
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<tbody>
<tr>
<td>Metoprolol</td>
<td>Methadone, Glyburide</td>
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<tr>
<td>Dextromethorphan/Dextrorphan, Paroxetine, Clonidine</td>
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Successful Prediction of the Disposition of Several CYP3A-cleared Drugs during T3 Based on Midazolam Phenotyping Data

- Based on midazolam data, our m-PBPK model successfully predicted the 3rd trimester (T3) disposition of two predominantly CYP3A-cleared drugs (i.e. nifedipine and indinavir)
- This induction is hepatic rather than intestinal
- Human hepatocyte studies suggest that CYP3A enzymes are equally induced throughout pregnancy

Ke et al. CPT: Pharmacometrics & Systems Pharmacology, 2012
Successful Prediction of the Steady-State PK of a CYP1A2-metabolized drug, Theophylline, during T3, Based On Caffeine Phenotyping Data

Ke AB et al., Drug Metab Dispos: 2013.

Gardner et al., Eur J Clin Pharmacol 1987 (n=10)
Successful Prediction of the Disposition of Drugs Cleared by Multiple CYP Enzymes during T3 e.g. Glyburide - CYP3A4 (~50%), CYP2C9 (~30%) and CYP2C19 (~20%)

Ke AB et al., Brit J Clin Pharmaco: 2013

- Hepatic OATP1B1 or 2B1 activity was assumed to remain constant throughout pregnancy.
Can our m-f PBPK Successfully Predict Fetal Exposure to Drugs that Passively and Actively Cross the Placenta?

Contains fetal organs that are important for fetal drug disposition

Ke et al 2012
Zhang et al. DMD 2017
Successful Prediction of Fetal Exposure to Drugs that Passively Cross the Placenta: Theophylline and Zidovudine (AZT)

200mg theophylline dosed orally prior to C-section

CYP 1A2 substrate

Zidovudine was dosed to term women 5 times a day followed by a 1-h IV infusion

UGT2B7 substrate
Successful Prediction of Fetal Exposure to Drugs ($K_{p,uu}$, fetal –to-maternal unbound steady-state plasma conc. ratio) Effluxed by Placental P-gp

**P-gp Substrates:**
- Dexamethasone (DEX)
- Betamethasone (BET)
- Darunavir (DRV)
- Lopinavir (LPV)

Anoshchenko et al., DMD 2021
Significance of Our Findings

• This success provides confidence in using our m-f PBPK model to predict maternal-fetal exposure throughout pregnancy:
  ➢ To drugs predominately metabolized by the common CYP enzymes AND
  ➢ Drugs that passively cross the placenta or are transported by placental P-gp or other/multiple placental transporters (e.g., BCRP and P-gp)

• Such predictions can help guide design of drug dosing regimens for pregnant women that are safe and efficacious for the maternal-fetal dyad
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