Integration of placenta transfer in a physiologically based pharmacokinetic model to characterize acetaminophen exposure and metabolic clearance in the fetus

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80% of pregnant women use at least 1 drug during pregnancy\(^1\)

Fetus (probably) exposed to any drug taken by mother

Physiologically-Based Pharmacokinetic modelling (PBPK) valuable tool for predicting fetal drug exposure and metabolism

\(^1\)Pisa FE et al. BMC Pregnancy Childbirth 2015
Introduction (2): Acetaminophen

60% of pregnant women take acetaminophen (paracetamol) at least once during pregnancy\(^1\)

Little is known about acetaminophen PK after therapeutic dosing and potential toxicity in fetus

Safety issues after perinatal acetaminophen exposure\(^2,3\)
- Neurodevelopment
- Pulmonary
- Infertility
- Ductus arteriosus

\(^1\) Nitsche JF et al. Am J Perinatol 2016, \(^2\) McGill MR J of Clin Inves 2012, \(^3\) Allegaert K BJCP 2018
Introduction (2): Acetaminophen$^{1,2}$

$^1$Flint RB et al. Ther Drug Monit. 2017, $^2$Mian P et al. Drugs & Aging 2018

CYP = cytochrome-P-450, GSH = Glutathion, NAPQI = N-acetyl-p-benzoquinone imine, SULT = Sulfotransferase, UGT = UDP-glucuronosyltransferase
Aims

Develop a fetal-maternal physiologically based pharmacokinetic (f-m PBPK) model to:

1. Quantitatively predict and evaluate placenta transfer of acetaminophen in term fetus
   - Ex vivo cotyledon perfusion experiment
   - Caco-2 cell permeability
   - Physicochemical properties [MoBi® default method]

2. Quantitatively predict contribution of different metabolic pathways of acetaminophen in the fetus to total metabolic clearance
Methods (1): Schematic PBPK & ex vivo cotyledon model

\[ \text{Dcot} = \text{diffusion (cotyledon)}, \quad \text{Dpl} = \text{diffusion placenta}, \quad \text{f= fetal, K_{f,m} = partition coefficient, Kpe = placental elimination, IV= intravenous, m=maternal, p= placenta, PBPK= physiologically based pharmacokinetic, PK= pharmacokinetic, phys-chem= physicochemical, Q= flow rate, V= volume} \]
Methods (2): Schematic f-m PBPK model

Enzym expression in the term fetus

**SULT1A1/3** 1-5
6.5 fold adult value

**UGT1A1** 6,7
0 % of adult value

**CYP2E1** 8-10
• 16% of adult value

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CYP= cytochrome-P-450, f-m PBPK= fetal-maternal physiologically based pharmacokinetic, SULT= sulfotransferase, UGT=Uridine 5’-diphospho-glucuronosyltransferase
Results (1): Placenta transfer parameters & predicted maternal and fetal acetaminophen profiles

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<tr>
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<th>$D_p$ (mL/min)</th>
<th>$K_{fm}$</th>
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<tbody>
<tr>
<td>Ex vivo ¹</td>
<td>403</td>
<td>0.737</td>
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<tr>
<td>Caco-2 ²</td>
<td>4354</td>
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<td>Mobi® default</td>
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$D_p =$ placental transfer rate (permeability)

$K_{fm} =$ partition coefficient

Results (2): Median fractions of metabolite formation from acetaminophen

Fetus

Mother

NAPQI = N-acetyl-p-benzochinonimine
Conclusions

• F-m PBPK model adequately predict maternal and fetal PK profiles in term fetus

• Acetaminophen exposure was similar between mother and fetus

• Prediction of formation clearance in fetal liver of sulphate and NAPQI were 0.8% and 0.06% respectively

Limitations

• Contradictory information is known on CYP2E1 expression in fetus at term

Future perspectives

• In vivo validation of metabolite formation clearance predictions

CYP = cytochrome-P-450, F-m PBPK = fetal-maternal physiologically based pharmacokinetic, NAPQI = N-acetyl-p-benzochinonimine