Quantifying placental drug transfer with \textit{ex vivo} cotyledon perfusion assays as PBPK input

Fetal Pharmacology & Therapeutics Workshop, 21\textsuperscript{st} and 22\textsuperscript{nd} of October 2021

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Isolated human cotyledon perfusion

Ex vivo dual perfusion of an isolated cotyledon of human placenta: History and future challenges

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12th European Placenta Perfusion Workshop (EPPW), 2019, Nijmegen
The placenta

http://www.adameducation.com
Histology

Tissue section of villous material from human placenta

FBV: fetal blood vessel
MBS: Maternal blood space
ST: Syncytiotrophoblast layer

Brown staining: P-gp expression

Predicting fetal drug exposure

Determinants of fetal exposure

Maternal pharmacokinetics

- Gastric pH
- Gastric emptying and intestinal motility
- Total body water
- Plasma volume
- Total body fat
- Albumin concentration
- Cardiac output
- CYP2D6 activity
- CYP3A4 activity
- Glomerular filtration rate

Modified from Colbers et al.
Predicting fetal drug exposure

Determinants of fetal exposure

- Maternal pharmacokinetics
- Placental passage
Predicting fetal drug exposure

Determinants of fetal exposure

Maternal pharmacokinetics

Fetal drug clearance

Placental passage
Around 1.4 million HIV-infected women give birth every year.

Antiretroviral therapy reduces HIV transmission chance to <2%.


Assessment of Maternal and Fetal Dolutegravir Exposure by Integrating Ex Vivo Placental Perfusion Data and Physiologically-Based Pharmacokinetic Modeling

Jolien J M Freriksen, Stein Schalkwijk, Angela P Colbers, Khaled Abduljalil, Frans G M Russel, David M Burger, Rick Greupink
Stepwise approach

1. **Maternal exposure** to dolutegravir during pregnancy

   - Simulate maternal plasma concentrations via PBPK modelling (Simcyp / Berkeley Madonna)

2. **Fetal exposure** to dolutegravir

   - Perform *ex vivo* placental perfusion experiments (term placenta)
   - Incorporate transport data into p-PBPK model and simulate fetal plasma concentrations

Stepwise approach

Drug-specific parameters: pKa, logP, fu, B/P, etc.
Clinical PK parameters: F, ka
Physiological parameters: tissue volumes, blood flow, etc.

Healthy volunteer PBPK model

Model validation

Ex vivo placental perfusion model

Determination of CLcot

Transplacental transfer parameters

Modification of physiological parameters:
- body weight, cardiac output, plasma proteins, etc.

Fetal physiological parameters:
- fetal cardiac output, plasma proteins, etc.

Observed PK profile

Pregnant woman + fetoplacental unit PBPK model

Observed PK profile

Model validation

Create a PBPK model for non-pregnant women

Simulated vs Clinical PK (non-pregnant)

Create a pregnancy-PBPK model
Isolated human cotyledon perfusion

Isolated human cotyledon perfusion
Clearance values (mean ± SD):

1.03 ± 0.06 mL/min  
1.03 ± 0.23 mL/min

- Clearance was then corrected for protein binding in maternal and fetal perfusates
- Clearance was scaled from 1 perfused cotelydon to whole placenta
- Used for parameterization of the p-PBPK model

Predicted maternal and fetal exposures

Concentration-time profile following multiple dosing in pregnant women

- Simulated: 0.57 – 1.51
- Observed: 0.64 – 1.81

Conclusion

- The human cotyledon perfusion technique can be used to generate *ex vivo* placental transfer data in the term/3\textsuperscript{rd} trimester placenta.

- The data can be successfully used for parameterization of pregnancy PBPK models.

- The model allows for an integrated assessment of passive and active transport in both directions across the placental barrier.

- Human system in which all placental celltypes are present in their physiological context.

- *In vitro-to-in vivo* scaling is straightforward (based on cotyledon weight or cotelydon number).

- Allows for assessment of interindividual variation in placental transfer / perform studies in placentas obtained from patients with specific morbidities.
Thank you for your attention!

Funding:
Certara/Simcyp
Bill & Melinda Gates Foundation