Evaluating the Transplacental Transfer of Apixaban using a Dually Perfused Isolated Human Placental Lobule

Priya Bapat, PhD student
Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children
Dept. of Pharmacology & Toxicology, University of Toronto

ASCPT Annual Meeting – March 10, 2016
Anticoagulants in Pregnancy

Pregnant women requiring anticoagulation therapy include those with:

- Venous thromboembolism (VTE)
  - Pulmonary embolism
  - Deep vein thrombosis
- Atrial fibrillation
- Mechanical heart valves

(Bates et al, Chest 2012)
Apixaban

- Novel oral anticoagulant (NOAC)
- Approved in 2012

- Protein binding (87% bound)
  - 66% to albumin
  - 9% to α1 acid glycoprotein
  - 12% unknown

[He et al, Eur J Drug Metab Pharmacokinet 2011]

When compared to other NOACs, apixaban had a relatively low risk of bleeding events and a similar efficacy for acute VTE!

- Mantha et al, J Thromb Thrombolysis 2015
Apixaban and Pregnancy

Clinical Practice Guidelines (2012): “There are no published reports describing the use of new oral direct thrombin inhibitors or anti-Xa inhibitors (apixaban) in pregnancy… The human reproductive risks of these medications are unknown.”

Chest 2012; 141: e691S-736S.
Objective

Therefore, the objective of our study was to examine the disposition of apixaban across the term human placenta \textit{ex vivo}, in order to estimate fetal drug exposure.
Human Placenta

Modified from Staud et al, Expert Opin Drug Metab Toxicol 2015
Methods: Placenta Perfusion

Apixaban (150 ng/mL) in both maternal and fetal reservoirs.

(Hutson et al, Clin Pharmacol Ther 2011)
Results: Apixaban

F:M after 3 h: 0.77 (0.76–0.81)  
\( n = 5 \)

Limited transfer (<0.1)  
Transfer (0.1–1.0)  
Fetal accumulation (>1.0)
Prediction of *in vivo* F:M ratio


\[
\frac{F}{M} = \frac{\% \text{ unbound}_M}{\% \text{ unbound}_F} \times \frac{1 + 10^{pK_a - pH_F}}{1 + 10^{pK_a - pH_M}} \times \frac{CL_{MF}}{CL_{FM}}
\]

BEFORE correction

\[R^2 = 0.28, \ P = 0.004\]

(Hutson et al, *Clin Pharmacol Ther* 2011)

AFTER correction

\[R^2 = 0.85, \ P < 0.001\]
Prediction of *in vivo* F:M ratio

\[
F: M = \frac{\% \text{ unbound}_M}{\% \text{ unbound}_F} \times \frac{1 + 10^{pK_a - p\text{H}_F}}{1 + 10^{pK_a - p\text{H}_M}} \times \frac{\text{CL}_{MF}}{\text{CL}_{FM}}
\]

- *In vitro* protein binding (87% bound)
  - 66% to albumin
  - 9% to α1 acid glycoprotein
  - 12% unknown

Drug literature
- Maternal pH = 7.4
- Fetal pH = 7.35

Predicted apixaban
- F:M *in vivo*: 0.74–0.81

Conclusions

- Fetal levels of apixaban *in vivo* are predicted to be 70-80% of the corresponding maternal levels
  - Raises the possibility for neonatal complications due to their hypocoagulability status

- Future studies will need to explore safety before clinicians can consider the use of apixaban in pregnant women.
Acknowledgments

Dr. Shinya Ito
Dr. Howard Berger
Dr. Gideon Koren
Dr. Katarina Aleksa
Leonardo S.R. Pinto
Angelika Lubetsky
Ariane Mandel
Staff at the Labour & Delivery Ward,
St. Michael’s Hospital

Ontario Graduate Scholarship