The Role of the Placenta in Fetal Exposure to Drugs

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University of Washington Program on Pharmacokinetics of Drugs of Abuse in Pregnancy (UWPKDAP)

Background

• During pregnancy women take:
  – at least one prescription drug - ~96%
  – over-the-counter medications - 92.6%
  – herbal medications - 45.2%

• The fetus is de facto exposed to the drug

• Neither feasible nor desirable to perform maternal-fetal PK studies of all drugs taken by pregnant women

• Therefore study model/probe drugs to elucidate the magnitude of and mechanisms by which the fetus is exposed to drugs

• Mechanistic studies allow:
  – Extrapolation beyond the drugs (i.e. model/probe drugs) studied using a systems pharmacology approach
What Determines Fetal Drug Exposure?

1. Maternal conc.
2. Transport (influx or efflux) and/or diffusion across the placenta
3. Placental/fetal metabolism

Syncytiotrophoblast of the placenta

Ganapathy, J Pharmacol Exp Ther 2000

Syncytiotrophoblast is Richly Endowed with Transporters
Mechanistic Studies on Placental Transport of Drugs

1. Are HIV nucleoside drugs (AZT, DDI, D4T, DDC) transported across the placenta? Nucleoside transporters are expressed in the placenta.


3. Surprisingly, these nucleoside drugs are NOT transported across the placenta!

Placenta is Richly Endowed with Transporters

HIV protease inhibitors are excellent substrates of the efflux transporter, P-gp

Ganapathy, J Pharmacol Exp Ther 2000
P-gp in the Placenta Protects the Fetus from Avermectin Toxicity

Table 2. Association between fetal P-glycoprotein genotype and induced cleft palate in CF-1 mice

<table>
<thead>
<tr>
<th>Fetal Pgp genotype</th>
<th>Fetuses genotyped</th>
<th>Percent fetuses with cleft palate</th>
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<tbody>
<tr>
<td>++</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>+/-</td>
<td>70</td>
<td>~30</td>
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<td>30</td>
<td>100</td>
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All fetuses in four, seven, and five selected L-652,280-treated litters corresponding to (+/+ × +/+), (+/- × +/+), and (+/- × -/-) matings, respectively, were analyzed for Pgp genotype following external examination for cleft palate.

Pregenotyped mice were mated and females received vehicle or 1.5 mg/kg/d L-652,280 on Gestation Days 6 through 15. On Gestation Day 18, animals were euthanized, and the fetuses were examined for cleft palate. Lankas et al., Reprod Toxicol 1998, 12(4):457-63
**P-gp Expression in the Human Placenta Decreases Dramatically with Gestational Age**

Efflux of $^{11}$C-Verapamil by Placental P-gp in the Nonhuman Primate

Eyal et al., J Nucl. Med, 2009
Chung et al., Br J Pharmacol, 2010
UWPKDAP
University of Washington Program on Pharmacokinetics of Drug Abuse

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Physiologically-Based Pharmacokinetic Model

Fetal PBPK Model

Maternal PBPK Model

Venous Blood

Arterial Blood

Lung
Adipose
Bone
Brain
Heart
Kidney
Muscle
Liver
Pancreas
Spleen
Gut

Cl\text{FOME}
Cl\text{FP}
Cl\text{AM}
Cl\text{AP}
Cl\text{PM}
Cl\text{MA}
Cl\text{AM}
Cl\text{renal}
Cl\text{met
Maternal-Fetal Disposition of Midazolam is Well-Predicted by the PBPK Model

Kanto et al. orally administered 15 mg midazolam to pre-C-section women (n of 8)
Maternal-Fetal Disposition of Theophylline is Well-Predicted by the PBPK Model

Ron et al dosed 200mg oral theophylline every 6 h to asthmatic women with otherwise uncomplicated pregnancies before C-section
O’Sullivan et al. dosed oral AZT 200mg five times per day, followed by 1-h infusion during C-section
Conclusions and Significance

- PBPK modeling well-predicted fetal exposure to drugs that diffuse across the placenta

- Incorporation of placental transporters in our PBPK model should allow prediction of fetal exposure to drugs that are transported

UWPKDAP research should result in tools to predict drug dosing regimens for pregnant women that maximize drug efficacy while minimizing maternal-fetal toxicity
Acknowledgments

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**P-gp is Functional in the Perfused Human Placenta**


**Fig 1.** Transplacental transfer of saquinavir in control perfusions with saquinavir only (open circles) or after preperfusion with P-glycoprotein inhibitor PSC833 (solid circles) or GG918 (squares).