LACTATION STUDY BASICS
LESSONS LEARNED

Mary F. Hebert, Pharm.D., FCCP
Professor of Pharmacy
Adjunct Professor of Obstetrics & Gynecology
University of Washington
CONFLICT OF INTEREST

• Consultant UCB Bioscience
IDEAL STUDY DESIGN

• Intensive sampling maternal pharmacokinetics
• All milk collected every 2-3 hours over dosing interval or 24 hours
• Nursing infant concentrations measured
• Pharmacodynamic outcome measured in nursing infant
• Infant developmental outcomes and other long-term effects (e.g. cancer risk for immunosuppression)
DRUGS WITH VERY LONG HALF-LIVES

• Intensive PK study on day with highest expected infant exposure (i.e. worst case scenario).

• Determination of how long drug is detectable in breast milk (i.e. intermittent samples until drug is cleared)

• When Mom is “Pumping and Dumping”, sometimes can obtain all milk for prolonged period of time.

• Nursing infant sample.

• Infant outcomes.
MAMMARY DRUG TRANSPORTERS

• Organic cation
  • OCT1
  • OCT2
  • OCT3
  • OCTN1
  • OCTN2
  • MDR1
  • MDR3

• Organic anion
  • OAT1-4
  • OATP-A
  • OATP-B
  • OATP-C-E
  • MRP1,2,5
  • MRP3,4

• Other
  • BCRP
  • CNT1,3
  • CNT2
  • ENT1,3
  • ENT2
  • SVCT1
  • SVCT2
DOES IT MATTER HOW AND WHEN YOU COLLECT BREAST MILK SAMPLES?

Colostrum
24-48 hours, Teaspoons
Low in Fat, High in Carbohydrates, Protein, and Secretory IgA

Foremilk
Beginning of Feeding, Ounces,
Low in Fat, High in Volume

Hindmilk
End of Feeding,
Higher in Fat

Gradual Transition
## FOREMILK VS HINDMILK

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reboxetine</td>
<td>No significant difference in foremilk and hindmilk concentrations (95% CI for difference -1.79 to 0.56 µg/mL, p=0.28)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Significant gradient effect was observed, with greater paroxetine concentrations found in hindmilk than in foremilk</td>
</tr>
<tr>
<td>Sertraline</td>
<td>The breast milk concentrations of sertraline and des-methylsertraline concentrations were lowest in the foremilk and ~2-fold higher in the hindmilk</td>
</tr>
<tr>
<td>Imipramine, Amitriptyline, Clomipramine, Dothiepin</td>
<td>Drug concentrations in foremilk, but not in hindmilk, increased in line with its fat content, which was maximal in hindmilk. Foremilk and hindmilk:maternal plasma concentration ratios were 1.0 and 1.5 respectively</td>
</tr>
<tr>
<td>Vitamin K₁</td>
<td>Higher vitamin K₁ concentrations in hindmilk than foremilk</td>
</tr>
<tr>
<td>Calcium, Magnesium, Sodium, Potassium</td>
<td>No significant differences were found in the mineral concentrations in fore and hindmilk</td>
</tr>
<tr>
<td>Selenium</td>
<td>Significantly higher concentration in hindmilk than foremilk, p&lt;0.05</td>
</tr>
</tbody>
</table>

COLOSTRUM VERSUS MATURE MILK

<table>
<thead>
<tr>
<th></th>
<th>Energy (measured)</th>
<th>Protein (true protein)</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preterm</td>
<td>Term</td>
<td>Preterm</td>
</tr>
<tr>
<td>Colostrum</td>
<td>49</td>
<td>54</td>
<td>2.7</td>
</tr>
<tr>
<td>Mature milk</td>
<td>73</td>
<td>63</td>
<td>1.1</td>
</tr>
<tr>
<td>Difference</td>
<td>49%</td>
<td>16%</td>
<td>−61%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.00001*</td>
<td>&lt;0.00001*</td>
<td>&lt;0.00001*</td>
</tr>
</tbody>
</table>

META-ANALYSIS SUMMARY ESTIMATES OF BREAST MILK COMPOSITION PER 100 ML

<table>
<thead>
<tr>
<th>Preterm</th>
<th>Energy (kcal)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st week</td>
<td>60 (45–75)</td>
<td>2.2 (0.3-4.1)</td>
<td>2.6 (0.5-4.7)</td>
</tr>
<tr>
<td>2nd week</td>
<td>71 (49–94) *</td>
<td>1.5 (0.8-2.3)</td>
<td>3.5 (1.2-5.7)</td>
</tr>
<tr>
<td>Week 3/4</td>
<td>77 (61–92) *</td>
<td>1.4 (0.6-2.2)</td>
<td>3.5 (1.6-5.5)</td>
</tr>
<tr>
<td>Week 10/12</td>
<td>66 (39–94)</td>
<td>1.0 (0.6-1.4)</td>
<td>3.7 (0.8-6.5)</td>
</tr>
<tr>
<td>Term</td>
<td>Energy (kcal)</td>
<td>Protein (g)</td>
<td>Fat (g)</td>
</tr>
<tr>
<td>1st week</td>
<td>60 (44–77)</td>
<td>1.8 (0.4-3.2)</td>
<td>2.2 (0.7-3.7)</td>
</tr>
<tr>
<td>2nd week</td>
<td>67 (47–86)</td>
<td>1.3 (0.8-1.8)</td>
<td>3.0 (1.2-4.8)</td>
</tr>
<tr>
<td>Week 3/4</td>
<td>66 (48–85)</td>
<td>1.2 (0.8-1.6)</td>
<td>3.3 (1.6-5.1)</td>
</tr>
<tr>
<td>Week 10/12</td>
<td>68 (50–86)</td>
<td>0.9 (0.6-1.2)</td>
<td>3.4 (1.6-5.2)</td>
</tr>
</tbody>
</table>

Estimates as +/- 2 standard deviations assumed no skew. Energy values were bomb calorimeter measured values except for 10–12 weeks, which were calculated values. Protein values are true measured protein, not based on total nitrogen content.

* Significantly different than term.  
MILK FRACTIONS

Cream

Skim milk
(plasma phase)

High speed Centrifugation

Casein
(Curd)

Whey
(Supernatant)

Water, lactose and Non-casein proteins
Distribution of protein concentration of skim, whey, and casein fractions in fore and hindmilk collected during breast expression. Values are shown by box plots illustrating median (indicated by the bold line), quartiles (box), range (error bars), and outliers (o). No significant differences were found.
LIPID CONTENT IN FOREMILK AND HINDMILK

BREAST MILK DURING WEANING

• Longer duration between nursing -> lower fat content in milk

• Lower total milk volume during weaning
MUST HAVE RESOURCES FOR MOTHER AND BABY
BREAST PUMPS
HOSPITAL GRADE DOUBLE ELECTRIC VS MANUAL

Medela Classic

Medela Symphony

Nuk Expressive

Spectra Dew 350

Evenflo

Avent
COMPARING PUMP-ALONE TO PUMP-PLUS-HAND-EXPRESSION: MILK VOLUME IN ML/DAY AT 2 WEEKS POSTPARTUM

Meier 2012, Morton 2009
TRICKS OF THE LACTATION NURSES
WHEN NURSING NOT ALLOWED

BPA-Free Bottles
CLEAN AND STERILIZED
CONSIDER DRUG BINDING TO COLLECTION EQUIPMENT
MATERNAL AND BREAST MILK ATENOLOL CONCENTRATIONS

- peak concentrations are later and higher than maternal peak.
- Mammary clearance higher 2-4 weeks postpartum than 3-8 months postpartum.
- All breastfeeding infant concentrations at 3-4 months postpartum are below limit of quantification for assay (<10 ng/mL).

MATURATION OF GFR SHOWING THE PREDICTIONS OF THE SIGMOID HYPERBOLIC FUNCTION.

![Graph showing maturation of GFR with predictions using a sigmoid hyperbolic function.](image_url)
P450 ENZYME ONTOGENY

SUMMARY-STUDY DESIGN MATTERS

- Need to accommodate mother and infant on research unit
- No nursing during study
  - Returning milk to infant
- How breast milk is collected
  - Colostrum vs. Foremilk vs. Hindmilk
  - Breast pump vs. Manual vs. Both
  - Glass vs. Plastic
  - Frequency of collections
- When breast milk is collected
  - 2-4 weeks vs. 3-8 months postpartum
  - Peak maternal concentrations not necessarily the same as peak breast milk concentrations
SUMMARY – INFANT CONSIDERATIONS

• Just because a drug is excreted into breast milk does not mean that breastfeeding is contraindicated

• Infant outcomes
  • Value of breast milk vs. risks of drug exposure

• Infant concentrations dependent on:
  • Premature vs. Term Infant
  • Total drug excretion in breast milk
  • Oral bioavailability
  • Infant renal function
  • Enzyme ontogeny
THANK YOU FOR YOUR ATTENTION