Drugs and Breastfeeding: An update!

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Transfer of drugs into milk
- Depends mostly on amount in mother’s blood - controlled by dose and her metabolism
- Infant intake in first few months is 150ml/kg/day
- Infant exposure from milk is 10-80 times lower than that when drug is taken during pregnancy

Pathways for drug transport into milk

Passage of drug to infant

Clearance in the infant

Calculation of absolute infant dose
- Absolute dose
  - Drug concentration in milk x volume of milk ingested
- Absolute dose has units of mg/kg/day
- Interpret by comparing with paediatric doses where the drug has a legitimate use in infants or children

<table>
<thead>
<tr>
<th>Post-conceptual age</th>
<th>Estimated clearance (as % of maternal clearance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-28</td>
<td>5</td>
</tr>
<tr>
<td>28-34</td>
<td>10</td>
</tr>
<tr>
<td>34-40</td>
<td>33</td>
</tr>
<tr>
<td>40-44</td>
<td>50</td>
</tr>
<tr>
<td>44-68</td>
<td>66</td>
</tr>
<tr>
<td>&gt; 68</td>
<td>100</td>
</tr>
</tbody>
</table>
Calculation of relative infant dose

- Simply a comparison with the maternal dose
- Relative infant dose = \[ \frac{\text{absolute infant dose (mg/kg/day)}}{\text{mother's dose (mg/kg/day)}} \]
- Expressed as a percentage
- We use our knowledge of infant clearance to set a SAFE dose level for the infant: < 10% is usual very conservative criterion

Transdermal nicotine patch therapy during lactation

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Demographics

<table>
<thead>
<tr>
<th>Mothers (n=15)</th>
<th>Infants (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>32 (21-34)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>72 (40-102)</td>
</tr>
<tr>
<td>Cigarettes†</td>
<td>17 (6-39)</td>
</tr>
<tr>
<td>Years smoked†</td>
<td>15.3 (13-17.6)</td>
</tr>
<tr>
<td>Gest. Age (w)*</td>
<td>38.4 (37-41)</td>
</tr>
<tr>
<td>Birth weight (kg)*</td>
<td>3.4 (2.6-4.1)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:7</td>
</tr>
<tr>
<td>Age at recruitment (m)*</td>
<td>4.8 (2.5-21)</td>
</tr>
<tr>
<td>Fagerström tolerance questionnaire score.†</td>
<td>6.2 (3.7-8.7)</td>
</tr>
</tbody>
</table>

Results

- Average concentrations over 24hr of nicotine (mg/L) and cotinine (mg/L) in milk from 15 subjects whilst smoking and when at steady state on the nicotine patch at 21mg, 14mg and 7mg doses. Data are means ± 95%CI
- ANOVA *P<0.05

| Smoking  | 7.7 (5.3-10.1) |
| 21mg patch | 8.0 (5.9-10.1)* |
| 14mg patch | 7.6 (4.9-10.1)* |
| 7mg patch | 7.5 (4.9-10.1)* |

Plasma cotinine concentration (mean & 95% CI)

- Infants 22 µg/L (19-25)
- Mothers 175 µg/L (136-214)

Infant well being

- Denver developmental ratio
- All had achieved expected age related weight gain

Calculated absolute and relative infant doses (mean & 95% CI)

<table>
<thead>
<tr>
<th>Maternal dose</th>
<th>Absolute Infant dose (mg/kg/day)</th>
<th>Relative Infant dose %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>25.2 (17.0-33.4)</td>
<td>†</td>
</tr>
<tr>
<td>21mg patch</td>
<td>23.0 (13.8-32.2)</td>
<td>7.6 (4.9-10.3)</td>
</tr>
<tr>
<td>14 mg patch</td>
<td>15.8 (11.4-20.2)*</td>
<td>8.0 (5.9-10.1)</td>
</tr>
<tr>
<td>7 mg patch</td>
<td>7.5 (4.9-10.1)*</td>
<td>7.7 (3.3-10.1)</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to smoking
† Not calculated as dose from cigarettes not quantified
Use of nicotine patches in a breast feeding mother as an aid to “quit” smoking is safer than continued maternal smoking because:

- As the mother progresses to lower patch strengths, the transfer of nicotine equivalents to breast milk is significantly decreased. Compared with smoking, the absolute infant dose decreased by about 70% at the 7mg patch level.
- The infant is not exposed to environmental contamination, or to toxic, cigarette derived, xenobiotics via breast milk.
- Use of the nicotine patch has no significant influence on the milk intake of the breast fed infant.

Transfer of metformin into human milk

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Diabetologia 2002; 45:1509-1514

Background

- Diabetes - (mostly type II, NIDDM) affects around 6% of the population and in the last decade there has been a 30% increase in younger individuals
- Metformin - oral antidiabetic agent – first line Rx for NIDDM. Also has beneficial effects in polycystic ovary syndrome (PCOS). No data on transfer of metformin into milk.
- Metformin – small highly water soluble molecule, oral availability 50-60% half-life 4-5 hours

Results

Maternal data:

Mean age 34y (range 26-38 y) and mean body weight 97 kg (range 73-116 kg)

Six women took 500 mg of metformin orally, thrice daily before meals, while one (#6) took 500 mg of a slow release metformin formulation once daily

Median daily metformin dose was 14 mg kg⁻¹ day⁻¹ (range 6.9-20 mg kg⁻¹ day⁻¹)

Five being treated for PCOS, and two for NIDDM

Diabetologia 2002; 45:1509-1514
Results

Infant data:
- 4 M and 4 F with a mean age of 14.3 months (range 5-25 months) and a mean body weight of 10.8 kg (range 6.5-15 kg)
- All infants progressing well according to mother/paediatrician reports (no data available for patient #3).
Detailed Denver Development assessments in infants of patients # 1 & 2 were normal

Conclusions

- Mean M/P of 0.35 is quite low, but in keeping with high water solubility of metformin
- Mean relative infant dose of 0.28% is well below the 10% level of concern
- Absence of any adverse effect in the infants is also reassuring, although our data on this area are sparse and somewhat subjective
- Women who need to take metformin for control of NIDDM or PCOS should be encouraged to breastfeed their infants

Milk:plasma ratio

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Milk (mg l⁻¹)</th>
<th>Plasma (mg l⁻¹)</th>
<th>M/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.30</td>
<td>0.52</td>
<td>0.58</td>
</tr>
<tr>
<td>2</td>
<td>0.26</td>
<td>0.52</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>0.39</td>
<td>1.07</td>
<td>0.36</td>
</tr>
<tr>
<td>4</td>
<td>0.24</td>
<td>0.76</td>
<td>0.32</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>0.96</td>
<td>0.16</td>
</tr>
<tr>
<td>4</td>
<td>0.07</td>
<td>0.52</td>
<td>0.13</td>
</tr>
<tr>
<td>7</td>
<td>0.43</td>
<td>1.15</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean</td>
<td>0.27</td>
<td>0.79</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Infant dose & plasma levels

<table>
<thead>
<tr>
<th>Infant of patient #</th>
<th>Absolute dose (mg kg⁻¹ day⁻¹)</th>
<th>Relative dose (%)</th>
<th>Plasma metformin (mg l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.045</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>0.039</td>
<td>0.29</td>
<td>0.05*</td>
</tr>
<tr>
<td>3</td>
<td>0.059</td>
<td>0.42</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.036</td>
<td>0.24</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.023</td>
<td>0.15</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>0.011</td>
<td>0.50</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>7</td>
<td>0.064</td>
<td>0.15</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mean</td>
<td>0.04</td>
<td>0.28</td>
<td>-</td>
</tr>
</tbody>
</table>

*mean for twins

Escitalopram (Lexapro)

Maternal dose 10mg
Relative infant dose 5.74%
M:P escitalopram 1.72
M:P desmethylcitalopram 2.41
**Escitalopram**
- Subjects to date: 4
- Maternal dose: 213mcg/kg
- M:P escitalopram: 2
- M:P desmethylcitalopram: 2.3
- RID escitalopram eqivs: 6.38%

**Mirtazapine (Avanza)**
- Maternal dose: 45mg
- Relative infant dose: 1.1%
- Infant plasma <1.5μL

**Mirtazapine**
- Subjects to date: 5
- Maternal dose: 30-120mg/day
- RID mirtazapine: 1.41 (0.57 - 2.5)%
- RID desmethylmirtazapine: 0.42 (0.13 - 0.7)%

**Reboxetine (Edronax)**
- Maternal dose: 4mg/day
- RID: 2.3%
- M:P <0.1
- Infant serum <4mg/L
- 2.83h post maternal dose

**Olanzapine (Zyprexa)**
- Maternal dose: 136mcg/kg
- M:P (AUC): 0.32
- RID: 0.93%
- 6 mother/infant pairs
- M:P (AUC): 0.38
- RID: 1.02%
- Not detected in infant plasma
- All infants healthy, no adverse effects

**Risperidone**
- 2 papers in literature
  - single case study (Hill et al)
    - M:P <0.42, 0.24 risperidone, 9-OH risperidone
    - RID: 4.3%
  - 3 cases (Ilett et al) Am Pharmacother 2004;38:273-6
    - M:P <0.5 risperidone, 9-OH risperidone
    - RID 2.3%, 2.8%, 4.7%
  - Not detected in plasma of infants
  - No adverse infant effects noted
Dexamphetamine

- Used to treat Attention Deficit Hyperactivity Disorder (ADHD)
- Some patients now of reproductive age
- Safety of breastfeeding not established rigorously
  - insufficient information on relative infant doses and safety
  - use of psychoactive drugs in babies usually considered undesirable

**Maternal dose (mg/kg)**
- 0.26
**M/P**
- 1.96
**Relative infant dose**
- 3.8%
**Infant plasma (mg/L)**
- 1.7
**Infant age (months)**
- 5
**No adverse effects on infant assessment**

Dexamphetamine

**Maternal dose (mg/kg)**
- 0.64
**M/P**
- 2.7
**Relative infant dose**
- 7.3%
**Infant plasma (mg/L)**
- 18
**Infant age (months)**
- 3
**No adverse effects noted on infant assessment**

Methylamphetamine

**Mother:** 29y, 64 kg  
**Infant:** 4m, 6 kg  
**Absolute infant dose (μg/kg/day):** 17  
**Methylamphetamine in milk:** not detected; LOD 20 μg/L

**Mother:** 27y, 68 kg  
**Infant:** 4m, 3.5kg  
**Methylamphetamine Absolute infant dose (μg/kg/day):** 68  
**Methylamphetamine in milk:** LOD 20 μg/L

**Conclusions for ADHD drugs**
- Use of drugs for ADHD in pregnancy and lactation should be undertaken on a case basis with due consideration of the risks and benefits to mother and infant
- For any drug, exposure of the foetus in pregnancy is very much larger than that of the newborn to drug in milk
Pseudoephedrine

Study design:
- Single blind, randomised cross over of a single dose of pseudoephedrine HCl (960mg) versus placebo in 8 lactating women
- Assessed
  - Change in prolactin levels
  - Breast blood flow
  - Milk production
  - Infant exposure

Pseudoephedrine - results
- Milk production decreased by 24% after 60mg dose
  - Placebo: 784 ± 288mL/day
  - Pseudoephedrine: 623 ± 330mL/day
- Serum prolactin post-feed surge decreased by 13.5%
- Pseudoephedrine did not alter flow in the internal mammary and/or lateral thoracic arteries

Pseudoephedrine - results

Domperidone

Historically
- 5 human studies
  - 30mg daily (10mg tds)
    - Milk volume increased 44-300%
    - Prolactin increased 100-400%
- Current study
  - Measures the effectiveness of 30mg daily and 60mg daily doses of domperidone
  - Assesses risk to infant
  - 5 completed study (4 preterm, 1 fullterm)

Domperidone - results
- 3 responders
  - 300-600% increase in milk production
  - 500-2000% increase in serum prolactin
- 2 non responders
  - 20-116% increase in milk production
  - 150-3000% increase in serum prolactin
- Side effects > with 60mg dose

Domperidone-prolactin
- Increase in serum prolactin
**Domperidone**

- Effective galactogogue 60mg >30mg/day
- Minimal adverse effects
  - dry mouth, headache, abdominal cramps
- Absolute infant dose
  - 30mg/day dose 0.07 µg/kg/day
  - 60mg/day dose 0.12 µg/kg/day
- Infant dose (clinical) 0.2-0.4mg/kg/dose 4-8 hourly
- Relative infant dose 0.01-0.02%

**Tramadol**

- Ongoing single point study
- Relative infant dose approx 3%