Got milk? Considerations regarding medication use & lactation

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Conflicts of interest

- None to declare
Objectives

- Review principles influencing transfer of drugs into human milk
- Review drug and patient factors to consider when making decisions regarding medications and breastfeeding
- Discuss common issues/point of care considerations with respect to medications and lactation
Case report

- Mother prescribed codeine 30mg/acetaminophen 500mg ii tablets Q12H following birth of health term baby
- dose reduced to i tablet Q12H after Day 2
- Day 7: infant -- intermittent periods of difficult breastfeeding and lethargy
- Day 11: well-baby visit, showed baby regained weight
- Day 13: baby found dead
- postmortem: morphine level 70ng/mL (usual < 2 ng/mL)
- Mother found to be ultra-rapid metabolizer of codeine

Lancet 2006;368:704.
Drug usage in breastfeeding mothers

- Schrim et al 2002 (Netherlands)
  - New mother questionnaire: 549 respondents
  - Breastfeeding women (infant 1-6 months)
    - 53% used at least one drug during breastfeeding (excluding vitamins, iron, homeopathic medicines)
    - Common medications: analgesics, antibiotics
    - 30% hesitated to use a drug because they breastfed
    - 9% stopped breastfeeding or taking drug to avoid combination
  - Non-breastfeeding - 11.5% decision due to drug use
  - Breastfed/No drug - 17% would have used drug if not breastfeeding
Breastfeeding in Canada

- CPS: exclusive breastfeeding for the first 6 months
- Benefits well documented
- Canadian Community Health survey 2009 – 2010:
  - 87% initiated breastfeeding
  - 26% breastfeeding at 6 months
Drug Transfer into Breast Milk

- Medications generally enter breast milk via passive diffusion
  - Transcellular
    - transverse capillary wall; small non-ionized lipid soluble molecules
    - ionized molecules and small proteins enter basal part of cell from interstitial water
  - Intercellular
    - avoids alveolar cell entirely - large molecules Ig, cow milk protein.
  - Ionophore
  - Active transport
Drug Transfer into Breast Milk

Alveolar Breast Cells

Reprinted from Neonatal and Pediatric Pharmacology 4th Ed.
Factors affecting transfer of drugs into breast milk

- maternal serum drug concentration*
- molecular weight
- degree of protein binding*
- relative drug lipophilicity
- pKa
- half-life
- active transport
Drug Transfer into Breast Milk

- Ion trapping
  - basic drugs with higher pKa
    - relatively greater amount ionized in milk, thus is “trapped”
    - can result in milk / plasma ratio > 1
    - opposite effect for acidic drugs

![Diagram showing ion trapping in drug transfer into breast milk.](Plasma pH = 7.4) ![Diagram showing ion trapping in drug transfer into breast milk.](Milk pH = 7.1)
Case

- While counseling a 26 year old woman Day 3 post C/S regarding her prescription for naproxen 375 mg PO BID, she asks whether she can continue breastfeeding while taking this medication. She is in obvious discomfort, and

- Product monograph (CPS, 2012):
  - “the use of naproxen sodium should… be avoided in women who are breastfeeding”

- Lexi-Comp (on-line, accessed 2013):
  - “enters breast milk/not recommended”
Case

Medications and Mothers’ Milk (15th ed, 2012):
- “[probably safe]… short term use… or occasional use would not necessarily be incompatible with breastfeeding”

Drugs in Pregnancy and Lactation (9th ed, 2011):
- “naproxen passes into breast milk in very small quantities… the AAP classifies naproxen as compatible with breastfeeding”
Goals

- Facilitate treatment of mother
- Preserve ability to breastfeed
- Keep infant safe from medication effects
Patient considerations

- Dose/frequency
- Indication
- Duration of therapy
- Timing of breastfeeding
Infant considerations

- Age
- Morbidities
- Previous in utero exposure
Infant-Drug considerations

- Amount excreted into breast milk
- Oral bioavailability (inc active metabolites)
- Type of drug & AE profile
- Half-life
- Metabolism
  - Pharmacogenetics
Developmental Pharmacokinetics

- Neonates:
  - Larger percentage of body water
  - Stomach acid neutral at birth & erratic GI motility
  - Liver – gradual expression of cytochrome P450 enzymes over first years of life
  - Renal function
    - low at birth
    - adult values by 8 – 12 months
Ideal medications during breastfeeding

- High molecular weight
- Low oral bioavailability
- Highly protein bound
- Short half-life
- Low maternal plasma concentration
Figure 1: Exposure to drugs in breast-fed infants by way of mother’s milk [1–3]

Estimates of Drug Exposure

- **Milk/Plasma ratio (M/P)**

- **Avg milk concentration** = \( \text{avg maternal serum concentration} \times \text{M/P} \)

- **Infant dosage** = \( \text{avg drug concentration in milk} \times \text{volume of milk} \)

- **Daily dose** = \( \text{average drug concentration in milk} \times \text{volume of milk ingested in 24 hours} \)

- **Relative Infant Dose (RID)** = \( \frac{\text{infant dosage (mg/kg/day)}}{\text{maternal dose (mg/kg/day)}} \times 100 \)
M/P ratio & RID alone do not give a complete picture…

- Phenobarbital
  - M/P ~ 0.4-0.6
  - ↓ protein binding in neonates
  - ↑ half life in premature infants
  - RID ~ 24-33%

- Fluconazole
  - M/P ~ 0.85
  - RID 17-21% (~0.35 mg/kg/day)
  - extensive literature chronicling safety in premature neonates
General approach

- Many drugs excreted in breast milk to small degree
- Risk to infant is often minimal
- If concerned about possible exposure:
  - Emphasize non-pharmacological therapy
  - Choose older medications with published data re: breastfeeding, or those with high protein binding, shorter half life, poor oral bioavailability
  - Consider relative infant dose
  - Use lowest effective dose for shortest possible duration; consider TDM
  - Plan nursing times for periods of low maternal plasma levels
Case

CB, 34 yo G1P1, treated throughout pregnancy for chronic depression with citalopram 40 mg daily, recently gave birth to a healthy term girl.

Mom has done poorly in the past when attempting to discontinue citalopram.

She would like to breastfeed, but is unsure about risks to her baby.
Case

Considerations:
- Long term effects of exposure to SSRIs?
- Likelihood of postpartum depression?
- In utero exposure

Plan:
- Monitor infant (early neonatal follow up important)
- Ensure adequate treatment of depression postpartum (routine follow up)
Antibiotics

- Most are compatible with breastfeeding
- Some diarrhea, rash reported
- Theoretical concern about tetracyclines, fluoroquinolones

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>RID (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>1</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>0.5</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>9 – 13%</td>
</tr>
</tbody>
</table>
Analgesics

- Acetaminophen
  - Compatible with breastfeeding
  - RID 8.8%

- NSAIDS
  - Considered safe
  - Use ibuprofen (0.65%), naproxen (3.3%), celecoxib (0.34%)
  - ASA (10%) – avoid, whenever possible
Analgesics

- Opioids
  - Codeine (0.1 – 1.4%)
    - Caution with ultra-metabolizers -> toxic morphine levels
    - Reports of apnea, bradycardia, sedation
  - Consider morphine, hydromorphone
  - Avoid oxycodone, meperidine, propoxyphene
  - Methadone (1-6%)
    - Recommend continue breastfeeding, esp. if used during pregnancy
    - May help reduce withdrawal symptoms
Antidepressants

- Long term effects largely unknown
- Often long half-lives
- SSRIs
  - Sertraline (0.54), paroxetine (1.4), fluvoxamine (1.6) best options
  - Avoid fluoxetine (9%), citalopram if possible
- Tricyclics
  - generally low RID
- Less is known regarding newer agents
Recreational Drugs

- Alcohol
  - M/P ~ 1
  - larger doses can decrease milk letdown
  - chronic use – delayed psychomotor development?
  - casual use acceptable

- Tobacco
  - nicotine & cotinine RID 10%
  - increased risk of SIDS
  - suggest NRT

- Caffeine
  - long $t_{1/2}$ in neonates
  - considered safe
  - excessive amounts – jitteriness, irritability
Other Drugs

- Benzodiazepines
  - Lorazepam preferred
  - Accumulation of diazepam & metabolites

- Vaccines
  - milk Ab - no effect on response to usual vaccines
  - avoid yellow fever vaccine

- Herbal products
  - lacking data, not recommended
Cautions and Contraindicated Drugs

- **Caution**
  - beta-blockers – reports of hypotension, bradycardia
  - lithium – significant infant serum concentrations (variable)
  - amiodarone
  - lamotrigine – decreased metabolism, sig. plasma levels

- **Contraindicated**
  - Antineoplastics
  - Radioactive isotopes
  - Ergotamine
Other drug considerations

- Dopamine agonists
- Anticholinergics +/- sympathomimetics
- Estrogens
- Diuretics?
Point of care considerations

- Emphasize health benefits of breastfeeding
- Infant Vitamin D supplementation
- Routine immunizations
- Smoking cessation
Lactation References

- **Online**
  - Lactmed (US National Library of Medicine)
  - [http://www.motherisk.org/](http://www.motherisk.org/)

- **Books**
  - Drugs in Pregnancy and Lactation – Gerald G Briggs
  - Medications and Mother’s Milk – Thomas W. Hale
Summary

- With some exceptions, most medications are compatible with breastfeeding
- Consider drug, patient, and infant factors when evaluating risks of medication use during breastfeeding
- Education of parents is important to alleviate concerns
- Knowledge base constantly changing, use most current references
Questions?
Acknowledgements

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References

- Hale W. Medications and Mothers’ Milk. 2012.