Breastfeeding and Maternal Medications

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Disclosure

None of the faculty or planning committee has any relevant financial relationships with commercial interests.
“Human milk is a specialized human infant support system that provides protection, information and nutrition to the nursing infant.”

E. Stephen Buescher, M.D.
ABM Annual Meeting, October 2003
Importance to Counseling

- Infant benefits with BF
- Maternal benefits with BF
- Health care cost benefits with BF
- Societal benefits with BF
- Portable, cheap, clean and “green”
Rates

• US BF initiation rates 72%-76%
• Rates at 6 and 12 months still falling short of U.S. Healthy People 2010 and 2020 Initiatives
• Many women discontinue BF due to medication administration, major reason why women wean early
• 90-99% of women postpartum will take some medication (analgesics, hypnotics)
MD Counseling Poor

- Common question to the PCP regarding use of medication during lactation
- AAP and ABM recommendation for BF 2 years and beyond with exclusive BF for first 6 months
- More pressure on PCP’s to support BF from moms and professional organizations
- FDA now calling for drug studies in breastfeeding moms by pharmaceutical companies, new regulations in the works
- Use of package insert or the PDR (worst sources)
- Most never consult the readily accessible literature to find the true evidence-based answer
- Counseling therefore is inaccurate with premature weaning thus increasing risk to dyad
Drug Entry into Milk

• Past 30+ years, many studies published based on pharmacokinetic properties that facilitate transfer (pKa, MW, post-metabolic bioavailability, protein binding and lipophilicity, transport systems), more needed

• Older literature base their conclusions on rodent models
  – Rodent models not analogous to humans
  – Much more albumin in their milk, thus rodent milk studies not helpful
Drug Entry into Milk

• Most medications penetrate into the milk compartment to some extent (esp. during the colostral period) but the doses are usually quite low
• Doses transferred to infants are thus far subclinical
• Almost always options for other medication if genuine concern
General Principles –

Drugs transfer into milk if they:

• Pass into the CNS (relates to lipophilicity)
• Attain high concentrations in maternal plasma (oral absorption, volume of distribution, first pass phenomena through the liver)
• Have low molecular weight, <200 easily passes, >500 does not
• Have low protein binding (<90%)
Milk Secretion

Adapted from *Composition and Physiology of Breastmilk*, Dr. M. Neville, ABM Annual Meeting, October 2005.
Passive Diffusion

The Mammary Alveolus and Its Neighbors

- Blood Supply
- Adipocytes
- Plasma Cells
- Myoepithelial Cells

Adapted from Composition and Physiology of Breastmilk, Dr. M. Neville, ABM Annual Meeting, October 2005.
Passive Diffusion
(Transcellular pathway)

- From capillary loop into lactocyte then milk compartment
- Mother’s plasma level most important determinant of drug penetration, milk levels rises as maternal levels do
- When maternal levels fall, equilibrium forces drive drug out of the milk compartment back into the plasma for elimination
Diffusion

• Ion trapping:
  – Human milk pH 7.0-7.2
  – Charged drugs can not diffuse as easily, unionized species can passively diffuse
  – The more ionic (charged) the drug is, the less it is capable of transferring back from the milk to the plasma, becoming “trapped” into the milk
  – pKa is pH at which the drug is equally ionic and nonionic
  – Higher pKa >7.2, drug more ionic in milk, thus may be sequestered in milk
  – Drugs with higher pKa’s have higher milk/plasma ratios (> 1.0 less desirable)
    • ie barbiturates, weak bases, ionic at milk pH
  – Choose drugs with pKa <7.2 if possible
Active Transport Systems

• Alveolar Cell Wall Cellular Pumps:
  – Iodine pump: same pump found in thyroid created to maintain infant’s iodine and thus thyroxine production
  – Ionic forms of iodides, esp. radioactive iodides (ie: I-131) concentrate in milk due to energy driven pumping to high degree
  – Milk concentrations extremely high, therefore avoid or D/C nursing when taking

Hale, Thomas. Medications and Mother’s Milk, 14th ed., 2010 pp. 7,521, appendix B pp. 1119-1120

• Also described in active transport of nitrofurantoin, cimetidine, ranitidine and lithium (low MW)
New Transporters

• Real time-PCR analysis, discovery of protein transporters on mammary gland epithelium:
  – OCT1, OCT3/EMT, OCTN1, OCTN2
  – Messenger RNA transcripts of CNT1, CNT3, ENT1, ENT3, PEPT1, PEPT2, MRP1, MRP2, MRP5, MDR1
  – Amisulpride (Amipride, used for bipolar disorder and antipsychotic) substrate for MDR1 transporter suggesting active transport and thus concentration in milk
  – Roles being elucidated: balance of influx and efflux out

Receptor-Mediated Endocytosis

- Proposed mechanism for insulin transport into breastmilk in nondiabetic mothers
  Koldovsky, O. Vitam Horm. 1995; 50:77-149.

- Seen in vascular endothelial cells

- However, insulin degraded by the low pH in the stomach, thus pharmacologic effect negligible

- Mechanism only plays a role in a few drugs, significance?
Paracellular Pathway

Adapted from Composition and Physiology of Breastmilk, Dr. M. Neville, ABM Annual Meeting, October 2005.
Paracellular Pathway

• 1\textsuperscript{st} 72 hours (colostral stage), large gaps between alveolar cells
• Permits enhanced access for most drugs, Ig’s, maternal living cells (lymphocytes, poly’s, macrophages), other large maternal proteins
• End of 1\textsuperscript{st} week, alveolar cells swell under influence of PRL, closes gaps with resultant reduce entry of above substances
• If lactogenesis 2 delayed, theoretical effects?
• Commonly accepted that most drugs enter milk more during colostral phase, however absolute dose usually quite low as the total milk volumes ingested are 30-100ml/day
Paracellular Pathway

Protein Binding

• Drugs bound to albumin or are freely soluble in the plasma
• Unbound fraction enters the milk, protein bound stays in maternal circulation
• Drugs with high protein binding (ie: Coumadin, NSAIDS) have low milk levels, remain in maternal circulation (effectively increases their MW)
• Good protein binding >90%
Lipid Solubility

- Drugs cross 2 cell (lipid) membranes in order to enter milk fraction
- The higher the lipid solubility, the more they penetrate into the breast milk and CNS
- Converse about CNS drugs is true; if drugs active in CNS, they enter the milk fraction easily, though often levels still are subclinical
Oral Bioavailability

• Ability of drug to reach systemic circulation after oral administration
• Good indication of amount absorbed into maternal bloodstream
• Most studies are with 70 kg. adults thus neonatal data lacking
• Low oral BA either poorly absorbed or first pass through liver
• Most texts list as % of oral dose found in the plasma compartment
Neonatal Oral Bioavailability

• Once ingested, drug in milk must go through infants GI tract
• Infant’s stomach with proteolytic enzymes and acidic environment, denatures many drugs (aminoglycosides, Omeprazole, large peptides like Heparin or Insulin)
• First pass phenomena in neonates, thus may never reach circulation
• Don’t forget local effects of drug in GI tract (ie: pseudomembranous enterocolitis)
Relative Infant Dose

- RID = infant’s dose via milk (mg/kg/day) divided by mother’s dose (mg/kg/day)
  - Many authors do not normalize for maternal and infant weights
  - Provides the clinician a general idea of how much medication the infant is exposed to on a weight-normalized basis
  - RID<10% widely accepted as safe
  - Keep in mind even if RID >20% such as with metronidazole or fluconazole, they are safe drugs (L2) and can be safely used
Theoretic Infant Dose

• Maximum likely dose per kg per day that infant would ingest based on the peak milk level (C max)

• Based on standard milk intake of 150 ml/kg/day X concentration in milk = (0.150L/kg/day X C max/Liter)

• Most often actual dose to infant much lower
Infant Considerations

• **Age**: premies and newborns at somewhat greater risk, exposed to colostrum
  – hepatic elimination: neonates 33% of mature elimination capacity, reach adult levels by 7 mo

• **Medical Problems**: GI disease, liver disease, cardiac disease, sepsis; unstable infants more at risk

• **Dose**:
  – more concerning in premies due to weight but milk production low early PP and neonate with limited milk ingestion thus low overall dose
  – older babies/toddlers: less milk ingestion since eating complementary foods
Other Considerations

- Pediatric approved drugs, if OK in kids, OK in lactating mothers (ie: fluconazole, penicillins, furosemide, digoxin, etc.)

- Don’t forget – in utero exposure: level of exposure in pregnancy 5-10x higher than breastmilk, drugs with long T1/2 may be around 1-2 weeks PP

- Drugs that effect milk production, especially important in the early postpartum period
  - Progestins
  - Estrogens
  - Ethanol
  - Bromocriptine
  - Ergotamine
  - Cabergoline
  - Pseudoephedrine
  - Testosterone
  - Antiestrogens
  - Clomiphene

$T^{\frac{1}{2}}$ (Half life)

- Shorter the better
- If $T^{\frac{1}{2}}$ is 1-3 hours, milk levels will be declining when infant feeds again
- Longer $T^{\frac{1}{2}}$ (12-24 hours) seen with long acting drugs less desirable, stay in plasma longer, more exposure to infant
- Half life can differ in plasma vs peripheral compartments thus affect Vd
Milk/Plasma Ratio

• Concentration of drug in mother’s milk divided by Concentration of drug in mother’s plasma

  • If high >1-5, sequestered in milk
  • Levels <1.0 preferable
  • Remember, may have a high M/P ratio but low maternal plasma levels, thus amount transferred in milk is still low
T max

• Time from administration of drug to C max, maternal plasma peak
• Shorter the better
• Try not to nurse when at T max
• Nurse just before taking next dose of drug
Volume of Distribution (Vd)

- How widely drug is distributed throughout the body.
- Drugs with higher Vd (1-20 L/kg) distribute to remote places in the body, cleared out of bloodstream early but require much longer times to clear the body than ones with lower Vd (0.1 L/kg).
- Example: gentamicin Vd=0.28L/kg clears in a few hours vs amitriptyline Vd=10L/kg, clears in weeks.
- However, drugs with higher Vd tend to have lower milk levels.
Side Effects/Interactions

• Adult side effects: drugs which may effect milk supply (ie: progestins), diarrhea, anti-cholinergic, CNS depression/irritability, etc.
• Pediatric side effects: respiratory depression, CNS, GI, hypotonia, etc.
• Drug interactions with multiple medications, synergistic effects
• Don’t forget about IUD’s, patches, herbs
Risk Categories

• Pregnancy risk Categories A – X
• Based on the level of risk drug poses to developing fetus
• NOT useful in assigning risk to nursing infant
• Lactation Risk better indicators based on evidence-based principles
Lactation Risk Scores

**L1**: safest, drug taken by large number of nursing mothers without any observed increase in adverse effects in infants

**L2**: safer, drug studied in limited number of nursing mothers without an increase in side effects in their infants

**L3**: moderately safe, no controlled studies in lactating women however the risk of untoward effects is possible or controlled studies show only minimal non-threatening adverse effects. Drug should be given if maternal benefit > potential infant risk
Lactation Risk Scores (cont’d)

**L4:** possibly hazardous, evidence of risk to infant or breastmilk production but benefits to lactating mother may be acceptable despite risk to infant (i.e.: quinolones in septic mom)

**L5:** contraindicated, studies show significant and documented risk to infant based on human experience or it is a medication that has a high risk of causing significant damage to infant. Risk of using drug outweighs any benefit from breastfeeding

General Recommendations

- Determine if drug absorbed by GI tract, if not, safe (e.g., vancomycin and insulin)
- Is the drug really necessary to take?
- Duration of therapy and maternal dose
- Consider infant’s age, intensity of BF
- Remember if M/P high but C max is low, dose of drug in milk still low and thus subclinical to infant
- Tell moms not to BF at T max if possible
Recommendations (cont’d)

- Beware of drugs with long pediatric half lives as they can build up in infant (i.e., benzodiazepines, meperidine, fluoxetine, and barbiturates)
- Choose drugs with higher protein binding
- Neuroleptic drugs get into the breastmilk: if CNS side effects in mothers, similar effects can be seen in their infants; i.e.: sedation seen in moms, increases risk of sedation (and potentially SIDS) in infants
Recommendations (cont’d)

• Be careful of herbal drugs as many contaminated (ie: Pb, arsenic), consult a knowledgeable herbalist, use pure forms of herbs, not mixtures of unknown herbs

• With radioactive compounds, check Hale’s tables at the back of his book with NRC recommendations

• Chemotherapeutics, radioactive nuclides are generally contraindicated but not necessarily an indication for permanent weaning
Recommendations (cont’d)

• Remember ingested volumes of milk 30-100 ml/day for first several days thus even if drug in milk, will produce subclinical levels

• Choose drugs with published data rather than newly introduced medications

• Consider nonpharmacologic methods of treatment (therapy)
Recommendations (cont’d)

• Evaluate all of the risks of the drug in relationship to its absolute dose received by the infant and the infant’s ability to handle the drug before making a decision. “Keep in mind the risks of formula feeding are significant and should not be trivialized.”


• Interruption of BF for medication administration due to lack of proper knowledge is not an option. In most scenarios, BF can continue without incident.

• Remember risk vs benefit to mother AND infant with taking or not taking drug

• You owe it to your patients: make an informed decision
Example: Depressed Mom with Polypharmacy

- On lorazepam (Ativan), escitalopram (Lexapro), and ramelteon (Rozerem)
- Does she need all of these???
  Psychologist involved? Family helping?
- Escitalopram/Lexapro:
  - T1/2 = 27-32 hours, Tmax = 5 hours
  - MW = 414, Vd = 12, M/P = 2.2
  - Protein binding = 56%, Oral Bio = 80%, RID = 5.3%, low, recent data shows levels in nursing infants undetectable

Depressed Mom

• Escitalopram
  – SSRI, active S (+) enantiomer of citalopram (Celexa)
  – Anticholinergic, cardiovascular and sedative side effects
  – Citalopram found in infant serum though no adverse reactions reported

Depressed Mom

- Escitalopram

  - Studies:
    Case report- 32 yo taking 5-10 mg /day, milk levels 24.9-76.1 ng/mL (low), estimated infant dose 3.74-11.4 ug/kg (very low), no adverse effects in infant
    8 women, 10 mg/day, M/P 2.2, RID 5.3%, Max infant dose 7.6 ug/kg (very low), drug and metabolites undetectable in infants, no adverse effects
Depressed Mom

• Lorazepam (Ativan)
  – Benzodiazepine, not ideal drug (long half life and risk for dependence)
  – Studies:
    • Newborns have hard time clearing it; can have respiratory depression, hypothermia, feeding problems in one prenatal study
    • Case report- 2.5 mg BID for 5 days, milk levels 12 ug/L, low
    • Case report- 3.5 mg q day, milk level 8.5-9 ug/L, M/P = 0.22, low
Depressed Mom

• Lorazepam
  – T½ = 12 hours, T max = 2 hours
  – MW = 321, Vd = 0.9-1.3, M/P = 0.15-0.26
  – Protein binding = 85%, Oral bio = 90%, RID = 2.5%
  – Interacts with CNS depressants, TCAs, morphine and EtOH
  – Can cause sedation, agitation, respiratory depression, potential for abuse/dependancy/withdrawal
  – OK for short-term / intermittent use after 1rst week


– L3
Depressed Mom

- Ramelteon (Rozerem)
  - Melatonin receptor agonist, hypnotic
  - No studies
  - Side effects: HA, fatigue, excessive somnolence, dizziness, nausea
  - Interacts with other CNS depressants additive effect, increases concentrations of fluconazole and ketoconazole
  - $T_{1/2}=1\text{-}2.6$ hours, $T_{\text{max}}=0.5\text{-}1.5$ hours
  - $\text{MW}=259$, $\text{Vd}=1.06$, no M/P reported
  - Protein binding=82%, Oral bio=1.8%, no RID
  - L3
Depressed Mom

• Recommendations?
  – Get help
  – OK for Escitalopram but consider using safer alternatives more studied such as sertraline (L2) and paroxetine (L2), little get into the milk
  – Try to avoid both lorazepam AND ramelteon together, additive effect, don’t like “sleepers” in nursing moms
  – Consider lorazepam after 1rst week if REALLY necessary but use intermittently
Depressed Mom

- Majority of antidepressants usually not contraindicated though most detected in milk
- First line of therapy is psychotherapy/ family help
- Medical and psychological benefits of BF to mom and baby well established, BF gives mom sense of accomplishment and active participation in infant’s care thus may help resolve the depression
- Risks of BF (sleep deprivation, guilt and anxiety about taking meds while nursing) must be discussed
- Use previous used med if successful in the past if possible

ABM Protocol #18,2008. www bfmed org
Depressed Mom

- SSRIs usually produce undetectable levels in nursing infants
- In most studies, no infant adverse events reported
- Some cleared better than others though fluoxetine has longer T1/2 (4-6 days), case reports of an infant seizure, reduced weight gain, though use in children, considered L2

New Information

• Davanzo R. et al: Nice Review Article on Antidepressants
  – Knowledge of pharmacokinetic characteristics somewhat useful, subsidiary to clinical reports
  – Studies seeing direct effects on infants more helpful
  – Majority of antidepressants not contraindicated
  – SSRI’s and Nortryptiline better safety profile
  – Caution with fluoxetine
  – Try to avoid doxepine and nefazodone (hypotonia and sedation)
  – Lithium can be used but follow levels on dyad closely and use low doses in mom
  – Health Care professionals should set aside any prejudices toward depressed women who wish to nurse

Useful References

- Micromedex.com (Thomas Reuters)
- LactMed
- Teris (Teratogen Information System)
- AAP Committee on Drugs, Policy Statement, “Transfer of Drugs and Other Chemicals into Human Milk.”
- Avoid the PDR
- Epocrates (??)
- ibreastfeeding.com (Hale’s MD chatline)
- ABM listserv
Selected References

- October 2005, lecture from the Academy of Breastfeeding Meeting, Dr. M. Neville, Composition and Physiology of Breastmilk.
- LactMed
- Hale’s website: i.breastfeeding.com
- ABM Protocol #18: Use of Antidepressants in Nursing Mothers. www.bfmed.org