Using Medications in Breastfeeding Mothers

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http://neonatal.ttuhsce.edu/lact/

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What’s the problem with Drugs and Breastfeeding?

Nursing Mothers—It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman.

Zoloft prescribing information 2007

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Alveolus

First Four Days Postpartum
Two - Four Days Postpartum

Protein Transporters

Extracellular Proteins Transported

IgA
Prolactin
IGF-1
????
Drugs with Apparent Transporters (Influx Transporters)

Iodine
Acyclovir
Cimetidine
Nitrofurantoin
Ranitidine
???

Simple Diffusion of Drugs into Human Milk
Drugs always establish a Variable Equilibrium between Plasma and the Milk Compartment.

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<tr>
<th>Plasma</th>
<th>Milk</th>
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<tr>
<td><img src="image1" alt="Plasma" /></td>
<td><img src="image2" alt="Milk" /></td>
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High Plasma Levels Lead to HIGHER Milk Levels.

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<tr>
<td><img src="image3" alt="Plasma" /></td>
<td><img src="image4" alt="Milk" /></td>
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High Low to high
Drugs Exit the Milk Compartment.

Plasma  |  Milk

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Citalopram Levels in Human Milk

Pharmacokinetics and Drug Levels in Milk

- Size exclusion really matters
  - Drugs > 800 daltons enter milk poorly
  - Drugs < 300 daltons enter milk avidly
- Protein Binding:
  - Higher the binding the poorer the levels in milk
- pKa
  - Higher the pKa the more trapped in milk. “Ion trapping”
- Vd
  - Higher the Vd, the lower the levels in milk
Pharmacokinetics and Drug Levels in Milk

- Lipid Solubility
  - More lipid soluble, the higher drug levels in milk
- Plasma levels
  - The Higher, the more drug enters milk
  - The Lower, the less enters milk (fluticasone)
- Transport processes are poorly understood
  - At least 5 drugs are thought to be transported but most do not attain clinical levels
  - Ranitidine, Cimetidine, Iodine, Nitrofurantoin, Acyclovir

Other Kinetic Factors

- Oral bioavailability
  - Drug exposure via milk depends on the bioavailability of the drug in the infant.
    - Morphine (26%)
    - Large proteins unabsorbed (heparin, etanercept, etc)
    - Sumatriptan (14%)
    - Domperidone (13%)
    - Tetracyclines
- Stability in GI tract of infant is important
  - Proton pump inhibitors are unstable at low pH.
Galactagogues

- Stimulate Milk Production by increasing **Prolactin** release.
- Prototypical Drugs Include:
  - **Metoclopramide**
    - Problems include depression, GI symptoms
    - Long-term (> 1-2 months) use should be avoided.
  - **Domperidone**
    - Ideal, no CNS problems, only headache.
    - hERG receptor antagonist but complications are rare.
    - Use 10-20 mg QID. Avoid higher doses.
- These drugs work only if Prolactin levels are LOW.
- Prolactin is ‘permissive’ of lactation, and increasing already high levels may not increase milk production.

Drugs that are usually Safe

- **Antibiotics**
- Most antihypertensives
  - CCBs
  - Some beta blockers
  - ACE inhibitors
  - Aldomet, Hydralazine
- **Radio contrast agents**
- Some Radioisotopes
  - Delay may be required
  - Discontinuation may be required
- **Analgesics**
  - Hydrocodone
  - Morphine
  - Codeine with care?
  - NSAIDS with care
- **Antidepressants**
  - SSRI's
  - TCAs
  - Bupropion
  - Numerous others
Medications to Avoid

- Drugs of abuse
- Ergot alkaloids
  - Bromocriptine
  - Ergotamine
  - Cabergoline
- Pseudoephedrine ??
- Cancer chemotherapeutic agents
- Methotrexate

- Radioactive I-131, I-125
  - Do not use.
- Estrogens
- Progesterone within 48 hours of birth.
- Chronic use of Tetracyclines

Drug Study Design in Human Lactation

- Sampling
  - Best if you can do at Steady State (helps with infant levels too)
  - Choose exclusive breastfeeding mothers at the same stage of lactation if possible.
    - 1-6 months if possible.
  - Fore / Hind milk samples are OK but not always ideal
    - Determines the effect of milk LIPIDs on milk drug levels.
  - “Ideal Method”:
    - Pump breasts completely (left and right)
    - Remove sample after mixing.

- Patient Access
  - In-laboratory is ideal. But for rarely used drugs, remote collection is possible.
Drug Study Design

- Design your study to Calculate AUC if possible.
  - Do metabolites (particularly if ACTIVE)
- Avoid single point or “Peak” determinations
  - They provide “over-estimates” of daily infant dose.
- Collect milk samples for at least 2-3 X the T1/2 after absorption.
  - May not be able to do this due to replicate dosing.
  - Maternal and infant plasma samples are wonderful to have, but many mothers refuse to allow infant phlebotomy.

Drug Study Design

- Calculating Dose
  - Absolute Infant Dose : Units per mL of milk.
    - Useful, but most clinicians cannot use it successfully.
  - RID (Relative Infant Dose)
    - Percent of Maternal Dose in milk.
      - Presumes milk intake = 150 mL/kg/day
      - If RID < 10% then it is considered safe according to Bennett. But this depends on “drug”.

\[
\text{RID} = \frac{\text{Infant dose (mg/kg/day)}}{\text{Maternal dose (mg/kg/day)}}
\]
Drug Study Design

- If possible, do some sort of evaluation of the INFANT OUTCOME.
- Mathematical algorithms for determining milk drug levels are interesting, but not always accurate.
- Rodent studies of milk levels of drugs are ABSOLUTELY WORTHLESS.
  - Levels are always higher than in humans

References