Using Medications in Breastfeeding Mothers

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Disclosure

- Clinical Trial with Ferring Laboratories
- Consultant for UCB Pharmaceuticals

Alveolus
Colostral Phase (Day 1-2)

From Day 3 to Day 4 Postpartum

<table>
<thead>
<tr>
<th>Serum</th>
<th>Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 134-146 meq</td>
<td>Sodium 8-15</td>
</tr>
<tr>
<td>Chloride 95-108</td>
<td>Chloride 10-20</td>
</tr>
<tr>
<td>Albumin 35-50 g/L</td>
<td>Lactose 180</td>
</tr>
<tr>
<td></td>
<td>Albumin 0.3 g/L</td>
</tr>
</tbody>
</table>
Milk Volumes during first week postpartum

Risk to Infant
- Depends on 3 major factors
  - Choice of Drug
  - Age of the infant
    - Premature...some risk
    - Older infant...minimal risk
  - Volume of milk
    - Colostrum...minimal risk
    - Full breastfeeding...some risk
    - Late stage lactation...minimal risk
  - Exposure in utero?
  - Prior Dependence or Tolerance

Pharmacokinetics and Drug Levels in Milk
- Size really matters
- Drugs > 800 daltons enter milk poorly
- Drugs < 300 daltons enter milk easily
- Protein Binding:
  - Higher the binding the poorer the levels in milk
- pKa
  - Higher the pKa the more drug is trapped in milk.
    - "Ion trapping"
- Vd
  - Higher the Vd, the lower the levels in milk
  - They're all in the periphery, not in plasma
### 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 4 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 (most poorly absorbed in milk)
- **Stability in GI tract of infant is important**
  - Proton pump inhibitors are unstable at low pH.

### Anesthetic Drugs

- **Induction:**
  - Propofol, midazolam, etc
  - Rapidly redistribute to peripheral sites. Levels in milk are negligible within an hour or so.
- **Epidural Opiates:**
  - Transfer to fetus to some degree, but limited in milk.
- **Meperidine:**
  - Poor choice, high fetal levels, moderate milk levels, sedation documented...
  - AVOID
- **Anesthetic Gases:**
  - Nitrous oxide, halogenated gases, etc
  - Almost instantly dissipated via expiration. None will enter milk.
Simple Diffusion of Drugs into Human Milk

Drugs with Apparent Transporters (Influx Transporters)

Protein Transporters

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Large drugs and proteins are generally excluded

Birth Control Preparations

- Avoid estrogen-containing products
- Progestin-only mini pills preferred.
  - Progestin receptors not present in 'lactating tissues'
- If suppression occurs, you can stop immediately.
- Lots of calls on Merena IUD ???
- Depo-Provera
  - Some controversy about lowering production (early postnatally), but not proven.
  - Do not use early postpartum, use BCP first, then Depo

Antibiotics

- Penicillins, Cephalosporins are generally safe
  - Dicloxacillin, Flucloxacillin, Cloxacillin good for mastitis.
- Erythromycin, Zithromax are safe except early postpartum.
  - Increase risk of hypertrophic pyloric stenosis with erythromycin
- Clindamycin: safe… RID = 0.8% - 1.8%
  - Good for most MRSA
- Fluoroquinolones
  - Ciprofloxacin - use cautiously. New AAP approved.
  - Ofloxacin, Norfloxacin, Levofloxacin may be preferred.
- Metronidazole
  - Levels moderate but are considered safe. Commonly used in neonates.
  - All may induce changes in intestinal flora...diarrhea, candida overgrowth.
Anticonvulsants

- Lamotrigine (Lamictal):
  - RID = 9.2-18%; probably safe; safest after 1 month
- Valproic acid (Depakene, Depakote):
  - RID = 1.4-1.7%; probably safe; avoid in moms at risk for pregnancy.
- Levetiracetam (Keppra):
  - RID = 3.3 – 7.8%; probably safe; levels fall quickly in infants postpartum.
- Topiramate (Topamax):
  - RID = 3-24%; probably safe, but monitor infant levels.

Vaccinations

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>Safe</td>
</tr>
<tr>
<td>Yellow Fever</td>
<td>Safer than getting disease</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Safe</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Safe</td>
</tr>
<tr>
<td>DPT</td>
<td>Safe</td>
</tr>
<tr>
<td>Flumist</td>
<td>Probably safe</td>
</tr>
<tr>
<td>Influenza</td>
<td>Safe</td>
</tr>
<tr>
<td>Varicella</td>
<td>Safe</td>
</tr>
<tr>
<td>Inactivated Polio</td>
<td>Safe</td>
</tr>
<tr>
<td>Gardasil (HPV)</td>
<td>Safe</td>
</tr>
</tbody>
</table>

Viral Diseases

<table>
<thead>
<tr>
<th>Virus</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza</td>
<td>Infant exposed for 2-3 days prior to maternal symptoms</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Safe to breastfeed</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Safe ONLY after HBIG and Vaccination</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Safe</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Depends on timing but is relatively low risk</td>
</tr>
<tr>
<td>HIV</td>
<td>Do not breastfeed in this country</td>
</tr>
<tr>
<td>Varicella Zoster</td>
<td>Hazardous, cover lesions.</td>
</tr>
<tr>
<td>Hpes Simplex</td>
<td>Cover lesions on breast, AAP approved.</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>In milk, but infants seem largely unaffected.</td>
</tr>
<tr>
<td>Lyme Disease</td>
<td>DNA of spirochete present in milk, possibly infectious</td>
</tr>
<tr>
<td>HPV</td>
<td>Present in milk, but not apparently &quot;very&quot; infectious</td>
</tr>
</tbody>
</table>

Remember that in most instances, infant has been exposed for days to weeks prior to diagnosis.
**Antihypertensives**

- Preferred Beta Blockers
  - Preferred: Metoprolol, Labetalol, Propranolol
  - AVOID: Acebutolol, Atenolol (poor choice)
- Preferred Calcium Channel blockers
  - Nifedipine, Nimodipine, Verapamil, Nitrendipine
- ACE inhibitors
  - Avoid in very premature infants
  - Captopril, Enalapril, Benazepril are preferred in breastfeeding mothers.
  - Aldomet, hydralazine are fine.

**Analgesics**

- Hydrocodone, morphine are generally safe in breastfeeding mothers.
- Avoid codeine due to “rapid metabolizers”.
- Avoid High doses of Oxycodone (apnea).
- Fentanyl levels in milk are low.
- Ibuprofen, Ketorolac, and acetaminophen are Ok
- Naproxen is not preferred but can be used briefly.
- Meperidine is poor choice due to neonatal sedation, neurobehavioral delay.
- Buprenorphine is a potent, long-acting narcotic agonist and antagonist. RID = 2 %

**Vitamin D**

- Vitamin D levels in milk are low
- Infants need supplementation
- Vitamin D doses need re-evaluated in our population.
- Newborns need 400 IU/day
- Other Vitamins: be careful, use modest amounts, such as in prenatal vitamins.
Antidepressants

Post-Partum Depression
- Untreated depression produces major sequelae in breastfed or formula fed infants.
- Prematurity, low birth weight, IUGR.
- Past hesitancy in using antidepressants is lessening due to studies that show that postpartum depression interferes with optimal parenting and neurobehavioral development of children at one year.
- In mothers who were depressed first 6 months, infants developed depressed style of interacting, and had inferior Bayley scores at 1 year.

Tricyclic Antidepressants
- Most are safe but much less popular due to:
  - more anticholinergic side effects
  - Extraordinarily dangerous in overdose
- Effective for:
  - patients who have used previously
  - younger patients
  - less expensive
  - Chronic pain syndromes
Serotonin Reuptake Inhibitors (SSRIs)

- Fluoxetine
- Sertraline
- Paroxetine
- Fluvoxamine
- Venlafaxine
- Desvenlafaxine
- Citalopram
- Escitalopram
- Reboxetine

Fluoxetine

- Has long half-life “active” metabolite (360 hrs)
- About 14% of consuming breastfeeding mothers use fluoxetine
- Many studies in the literature
  - Concentration in milk levels varies from 28.8 to 181 µg/Liter of milk for fluoxetine
  - 41.6 to 199 µg/Liter for norfluoxetine
- 11 studies of 190 infants, 10 reported adverse effects in some infants.
- Relative Infant Dose = 6.9%
- Caution recommended with:
  - Infants exposed in-utero....discontinuation syndrome
  - Incidence slightly lower with fluoxetine (T1/2 longer)

Fluoxetine Suggestions

- In naïve patients, use Sertraline or Escitalopram. But use the one that works best on the patient.
- In older infants (> 2 months) Fluoxetine should not be a problem.
- If you MUST use Fluoxetine always opt to breastfeed; risk is still probably low.

References:

### Sertraline

- Studies available for more than 49 mother/infant pairs, 2 adverse effect reported.
- In mothers taking antidepressants, 48% used Sertraline.
- Milk concentrations are very low: 18.4 to 95.8 µg/liter.
- In most infants, plasma levels of sertraline were below limit of detection (< 2 ng/mL).
- Stowe study: 7 of 11 plasma levels were undetectable.
- May be poorly absorbed orally in infants.
- RID = 0.4 - 2.2 %
- Preferred SSRI at this time, but again use the one that works!

#### References

### Paroxetine

- Half-life = 21 hours, no active metabolite.
- One case study of breast milk.
  - milk levels 7.6 µg/Liter of milk (dose=20 mg/d).
  - Dose > 0.34% of maternal dose.
  - RID = 1.25 %
  - The drug was not detected in the plasma of all of the 8 infants.
- Stowe… 16 mother/infants. Milk levels varied from 17-101 µg/mL with doses of 10-50 mg/day. Plasma levels in infants were below level of detection.
- Highest risk of Neonatal withdrawal.
- Highest rate of adolescent suicide. Try not to use in adolescents.

#### References

### Citalopram

- M:P ratio is 3
- Relative Infant Dose = 0.7-5.9 %
- At three weeks
  - Maternal serum = 185 nM ... Infant serum = 7 nM
- Mean M/P ratio is 1.6.
- Manufacturer reports two cases of somnolence in breastfed babies.
- I’ve had 2 case reports of somnolence as well.

#### References
Escitalopram

- Active metabolite of citalopram
- Following 10 mg/day dose
  - M/P ratio = 2.2
  - Absolute infant dose = 7.6 ug/kg/day for escitalopram
  and 3.0 ug/kg/day for metabolite.
- RID = 5.3%
- Infant plasma studies were below limit of detection
  (< 3 µg/Liter)
- Appears safe. Preferred over Citalopram


Bupropion

- Bupropion levels in milk = 6.75 µg/kg/day
- Not overly effective.
- Fall back drug for patients with sexual side effects.
- Lowers seizure threshold in patients WITH seizure disorders, not seizure-free patients.
- RID (all metabolites) = 0.2% - 2%
- Observe closely for reduced milk supply.
- Anecdotal data from author !!!
- Do not use in patients with history of seizure.


Using Antidepressants in Breastfeeding Mothers?

- Depressed women and their infants are at high risk.
- Infantile neurobehavioral delay is well known.
- Try your best to support them.
- Most antidepressants are safe for breastfed infants.
- From numerous studies, there are no data to date that antidepressants alter long-term neurobehavioral outcome in infants.
Bipolar/Mood Disorders

Bipolar Disorders/Mania

- Bipolar disorder is a diagnosis describing low (clinically depressed) and high (manic or hypomanic) mood swings
- Symptoms of Mania include:
  - Inflated self-esteem or grandiosity
  - Elevated, expansive, irritable mood
  - Decreased need for sleep
  - More talkativeness
  - Reckless, foolish activities

Bipolar Disorders/Mania

- Drugs for Mania
  - Lithium
  - Olanzapine (Zyprexa)
  - Valproic acid (Depakote) (avoid if possible)
  - Lamotrigine (Lamictal)
  - Carbamazepine (Tegretol)
  - Aripiprazole (Abilify)
  - Seldom if ever SSRIs
Therapy With Lithium

- Lithium transfers readily into human milk.
- Slow...Takes 2-3 weeks for activation.
- Infant levels approach 30-40% of maternal levels
- Relative Infant dose = 12 - 30%
- Clinicians must keep mom in normal range
  - <$ 1.1 mEq
  - Occasional monitoring of infant recommended
  - Monitor infant thyroid function.
- New therapies include: Valproic acid, carbamazepine, Lamotrigine.

Bipolar Therapy in Breastfeeding Mothers

- Lithium is hazardous.
- HCP must follow infant closely and monitor levels routinely.
- Preferred Agents
  - Lamotrigine (Lamictal)
  - Aripiprazole (Abilify)
  - Carbamazepine (Tegretol) (pregnancy caution)
  - Other atypical antipsychotic agents
- For psychotic symptoms
  - Aripiprazole, Quetiapine, Risperidone (weight gain problems)

Treatment of Psychosis

- Breastfeeding research in this area is poor.
- Older Drugs studied thus far:
  - Chlorpromazine (Thorazine) (RID= 0.25%)
  - Chlorprothixene (Taractan) (RID= 0.15%)
- There is concern that phenothiazine family may increase risk of SIDs and sleep apnea.
  - Promethazine (Phenergan)
- If you need an antiemetic use ondansetron (Zofran)
- Avoid them, use atypical antipsychotics instead.
Antipsychotics

- Haloperidol (Haldol)
  - Good choice. Low milk levels...even after weeks of therapy.
  - RID = 0.2-2.1% (20 mg/day) and 9.6% (30 mg/d)
- Risperidone (Risperdal)*
  - Less likely to induce extrapyramidal symptoms
  - Milk level is low...130 μg/L
  - RID = <3.5% of maternal dose.
- Olanzapine (Zyprexa)**
  - RID = 1.05% of the maternal dose.
- Quetiapine (Seroquel)
  - RID = < 0.4%


Brief Facts about Neuroleptic Drugs

- Withdrawal from SSRIs is normal and occurs in 10-30% of infants postnatally (gestation use only).
- No data yet suggests that neurobehavioral outcome in the infant is affected following gestational or breastfeeding exposure.
- Following Gestational use, data is mixed.
  - Slight increase in pulmonary hypertension (but fleeting).
  - Slight increase in Premature birth (but no different from untreated moms)
  - Slight increase in Lower birth weight
  - However, risk of untreated depression and psychosis is MAJOR, so lack of treatment is actually more dangerous than drug.

Radioisotopes
Radiocontrast Agents
X Rays

- X-rays are high energy electromagnetic waves that can pass through many materials including human tissue.
- X-rays ionize matter with which they interact, by ejecting electrons from their atoms.
- Important: X rays PASS through body. While they may damage tissues, they leave no radioactive residue that would harm an infant.
- Thus... no hazard to breastmilk or infant.

Half-lives of Radioisotopes

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo-99</td>
<td>8.76 Days</td>
</tr>
<tr>
<td>Tl-204</td>
<td>3.08 Days</td>
</tr>
<tr>
<td>Ga-67</td>
<td>3.26 Days</td>
</tr>
<tr>
<td>Ga-67</td>
<td>78.3 Hours</td>
</tr>
<tr>
<td>I-131</td>
<td>8.00 Days</td>
</tr>
<tr>
<td>Xe-133</td>
<td>5.84 Days</td>
</tr>
<tr>
<td>In-111</td>
<td>2.80 Days</td>
</tr>
<tr>
<td>Er-153</td>
<td>27.8 Days</td>
</tr>
<tr>
<td>Ir-192</td>
<td>60.1 Days</td>
</tr>
<tr>
<td>Ir-192</td>
<td>50.5 Days</td>
</tr>
<tr>
<td>Tc-99m</td>
<td>6.82 Hours</td>
</tr>
<tr>
<td>Tc-99m</td>
<td>13.2 Hours</td>
</tr>
<tr>
<td>Sm-153</td>
<td>47.0 Hours</td>
</tr>
</tbody>
</table>

131- Iodides

- Rapidly absorbed from GI tract
- Distributed to extracellular body water
- Largely trapped in thyroid
  - ≈ 27% goes to Thyroid
  - ≈ 27% goes to Lactating Breast
- Most Excreted by kidneys:
  - Excretion:
    - 30% of dose has T1/2 of 0.3 days
    - 60% of dose has T1/2 of 7.61 days
Radioactive $^{131}$ Iodine in Breastmilk

**Recommendations**

- Use Technetium-99 whenever possible.
- Avoid any form of $^{131}$I or $^{125}$I.
  - Long half-life, concentrates in milk – infant.
  - If dose of $^{131}$I < 14 µCi, then wait at least 20 days.
  - Other/higher doses, then monitor milk levels in laboratory before reinstating breastfeeding.
- Use $^{99}$TcO$_4^-$ or $^{123}$I for thyroid scanning.
- Use fresh $^{123}$I Sodium for scanning of thyroid followed by wait: 11-65 hours.
- Safest to wait 5 half-lives with any isotope, and particularly with Iodine-containing isotopes.

**Radiocontrast Agents**
### Soluble Iodinated Radiocontrast Agents

![Molecules]

**Diatrizoate**

**Conray**

### Radiocontrast Agents and Milk Concentrations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Milk (Cmax)</th>
<th>Significance</th>
<th>Bioavail.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadopentetate*</td>
<td>6.5 g</td>
<td>3.09 µmol/L</td>
<td>Dose = 0.023%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Iohexol</td>
<td>0.77 g/kg</td>
<td>35 mg/L</td>
<td>Absorption Nil; &lt; 0.1%</td>
<td></td>
</tr>
<tr>
<td>Iopanoic Acid</td>
<td>2.77 g</td>
<td>20.8 mg</td>
<td>0.08% of maternal dose</td>
<td>Nil</td>
</tr>
<tr>
<td>Metrizamide</td>
<td>5.06 g</td>
<td>32.9 mg/L</td>
<td>0.02% of maternal dose</td>
<td>0.4%</td>
</tr>
<tr>
<td>Metrizoate</td>
<td>580 mg</td>
<td>14 mg/L</td>
<td>0.3% of maternal dose</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* Gadolinium ion not indicated.

### Recommendations for Iodinated and Gadolinium-containing Radiocontrast agents

- Discontinuing breastfeeding is not necessary.
- Mom may opt to pump and discard several hours after the procedure. *Useful with troublesome radiologists.*
- Dose to infant less than 1% administered dose.
- Less than 1% of this is orally bioavailable to the infant.
- Use American College of Radiology Statement on my website: [www.infantrisk.com](http://www.infantrisk.com)
In Summary:

Avoid

- Drugs of abuse
- Ergot alkaloids
- Migraine preps
- Ergotamine
- Cabergoline
- Pseudoephedrine
- Anti-cancer drugs

- Radioactive drugs
- Discontinue briefly
- Radioactive I-131
- Do not use.
- Chronic use of sedatives
- Estrogens, Antiestrogens
- Progesterone within 48 hours of birth.

Some Suggestions

- Always evaluate stage of lactation.
- Premature...higher risk
- First 4 days, low milk volume...low risk
- Late stage...low milk volume...low risk
- Calculate and use the Relative Infant Dose. If less than 10% then it is probably safe.

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