

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

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



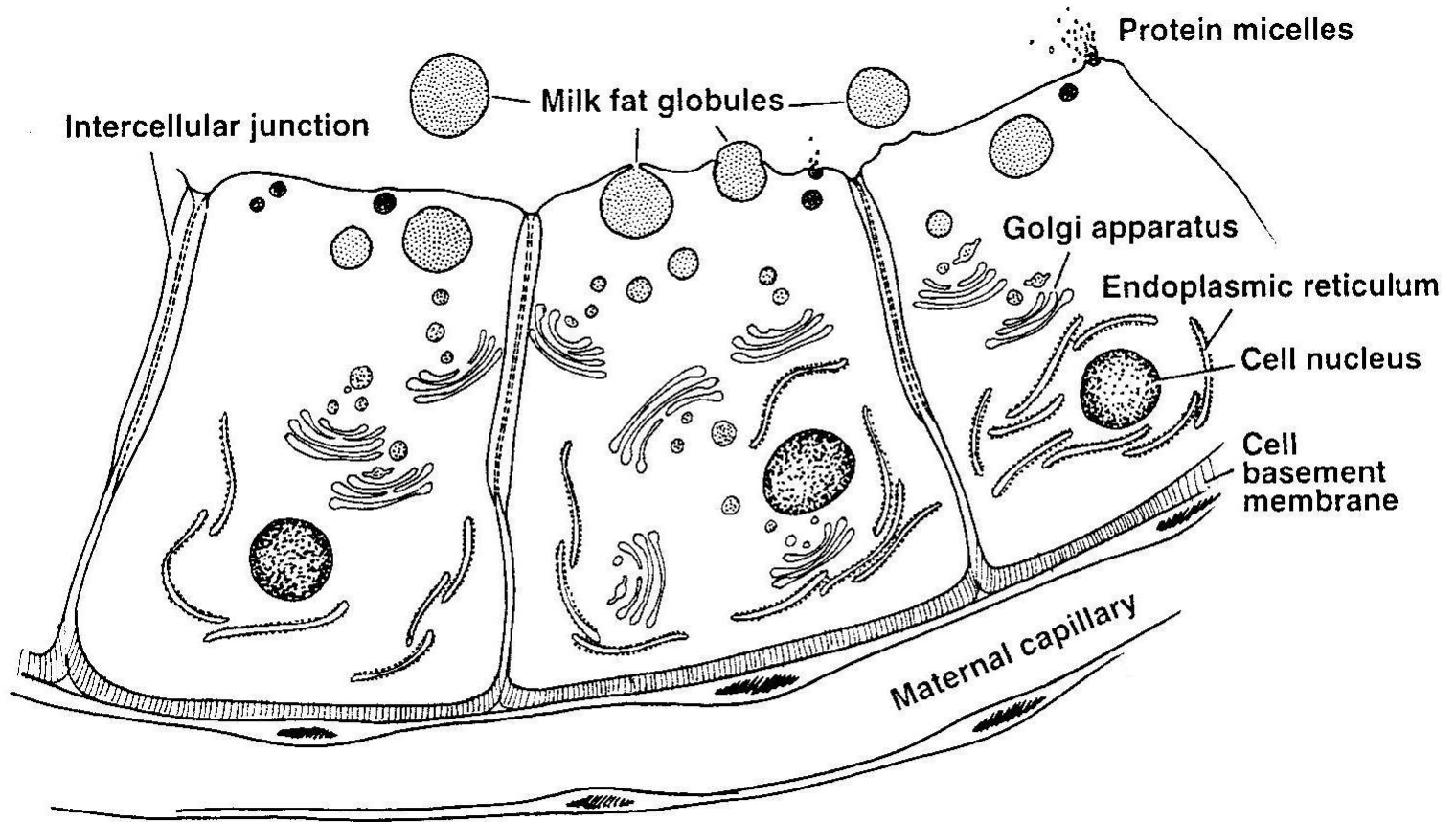
Breastfeeding in Canada

- 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

Factors affecting transfer of drugs into breast milk

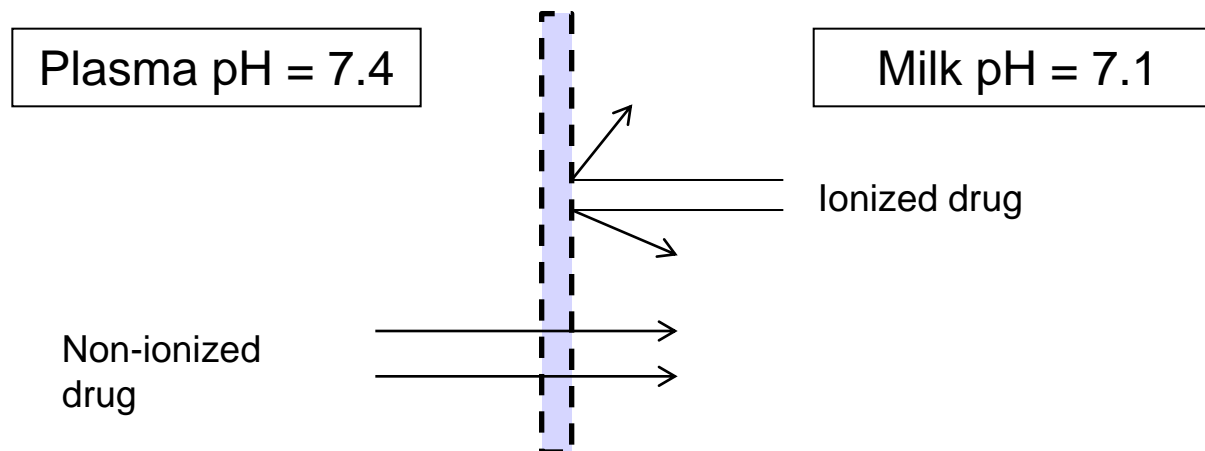
- maternal serum drug concentration*
- molecular weight
- degree of protein binding*
- relative drug lipophilicity
- pKa
- half-life
- active transport

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



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

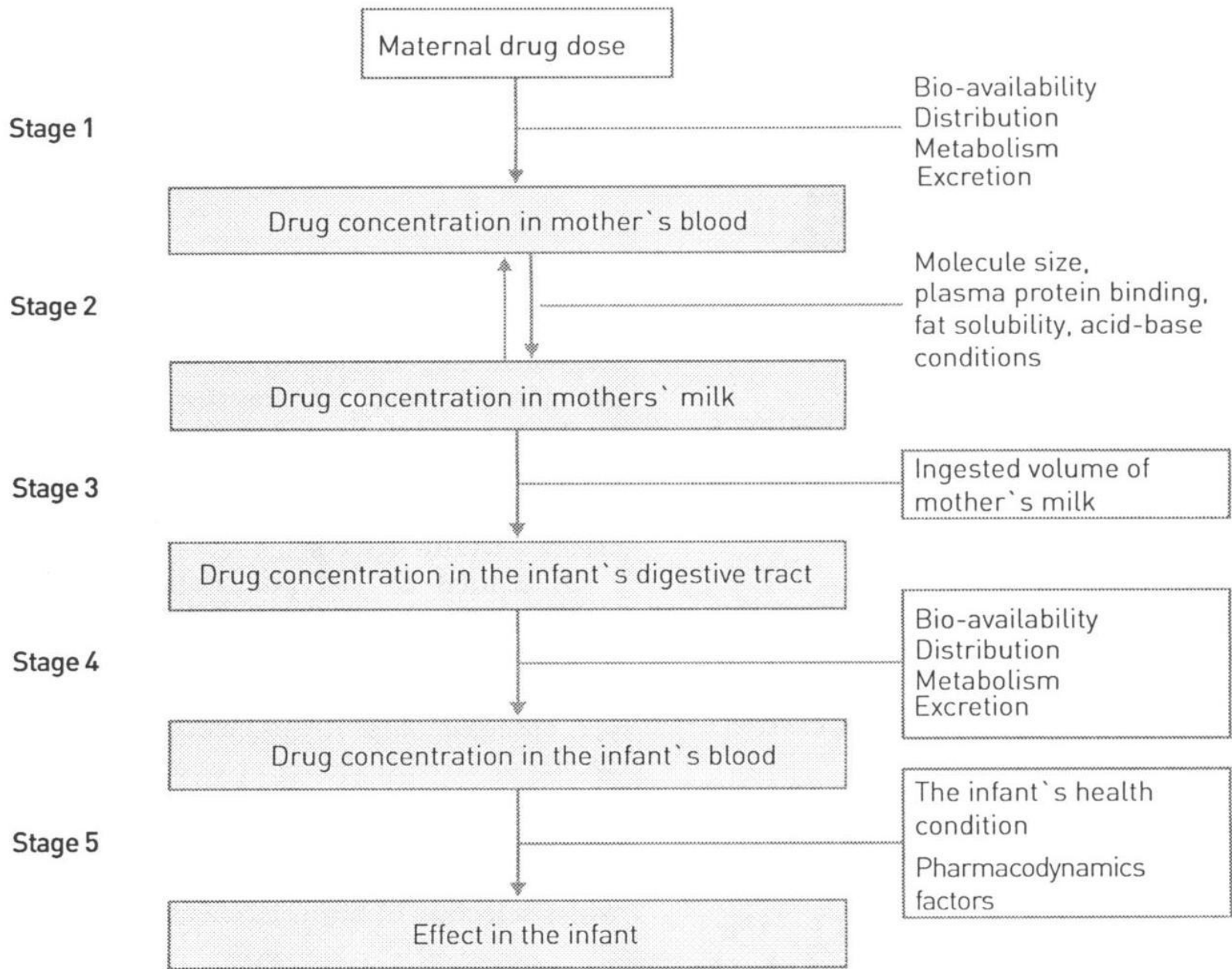


Figure 1: Exposure to drugs in breast-fed infants by way of mother's milk [1-3]

Estimates of Drug Exposure

- **Milk/Plasma ratio (M/P)**
- **Avg milk concentration** = avg maternal serum concentration x M/P
- **Infant dosage** = avg drug concentration in milk x volume of milk
- **Daily dose** = average drug concentration in milk x 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

<u>Antibiotic</u>	<u>RID (%)</u>
Amoxicillin	1
Cephalexin	0.5
Metronidazole	9 – 13%

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://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>
- <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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