Best Practices for Conducting Clinical Lactation Studies

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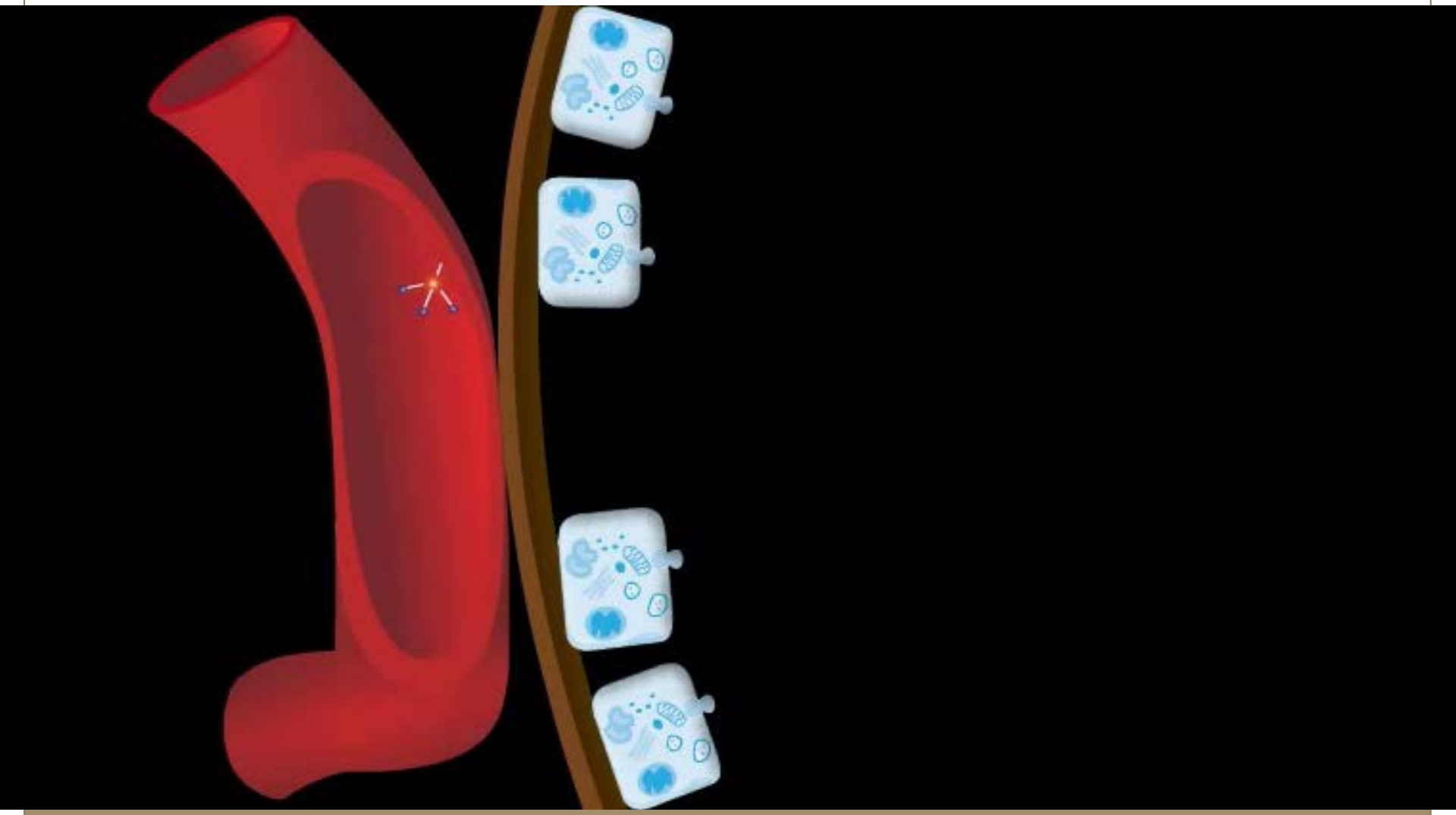
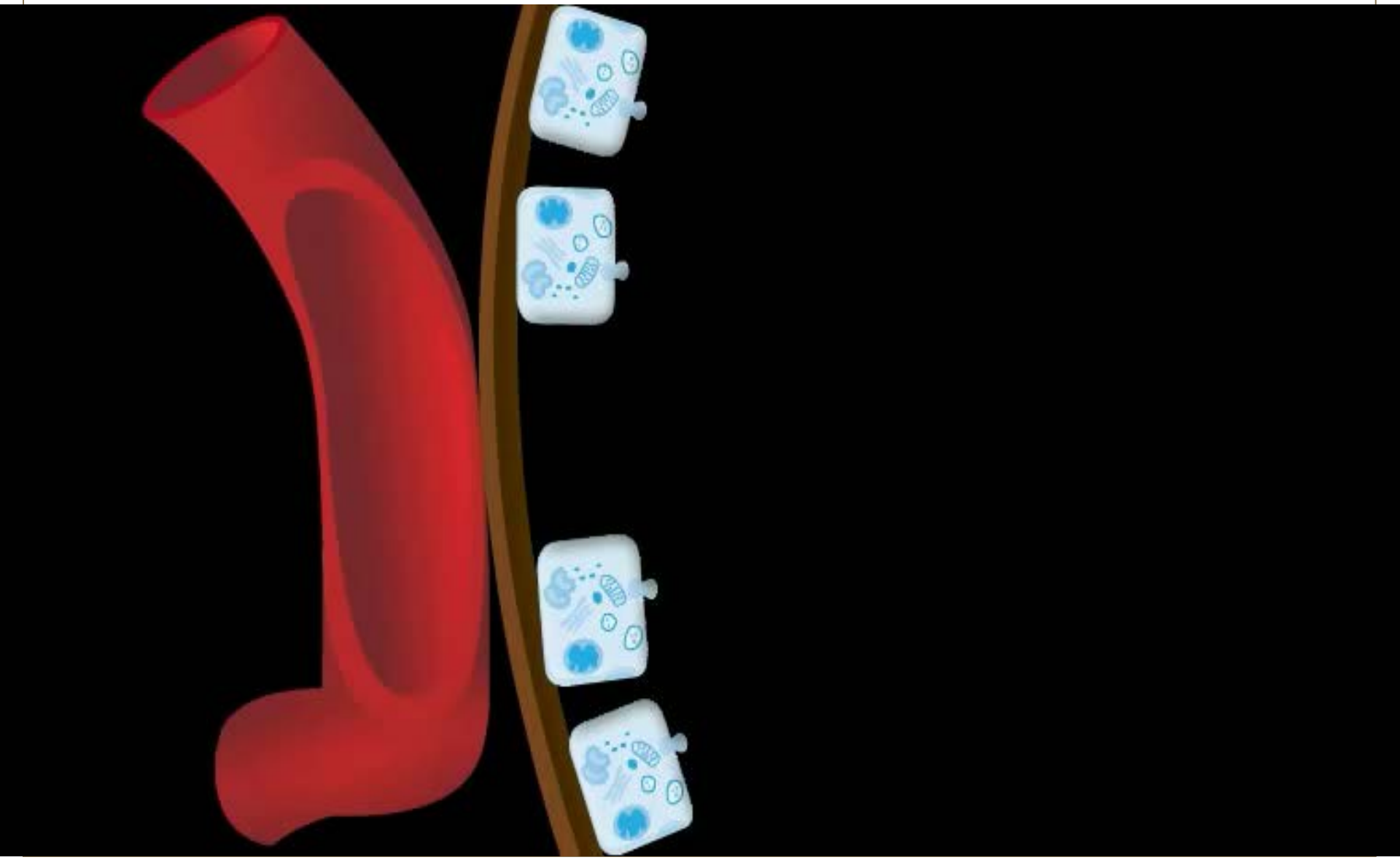
Disclosure

- Nothing to disclose

Colostral Phase (Day 1-2)



From Day 3 to Day 4 Postpartum



Differences in Colostrum vs Mature Milk

- Colostrum
  - First stage of breast milk
  - Thicker than other milk, Yellow in color/creamy
  - High in protein, High in immunoglobulins
  - Last only a few days after birth
  - Gaps between lactocytes large and allow drugs to transfer easily
  - Limited Volume 30-60 cc per day
- Mature Milk
  - Final milk produced
  - 90% water, 10% carbs, protein, fats
  - 2 types – foremilk and hind-milk – Interesting but clinically irrelevant
  - Gaps between lactocytes are tight and drug transfer is restricted

American Pregnancy Association. “Breastfeeding: Overview." August 2015. Retrieved March 22, 2016, from http://americanpregnancy.org/breastfeeding/breastfeeding-overview/

Current studies

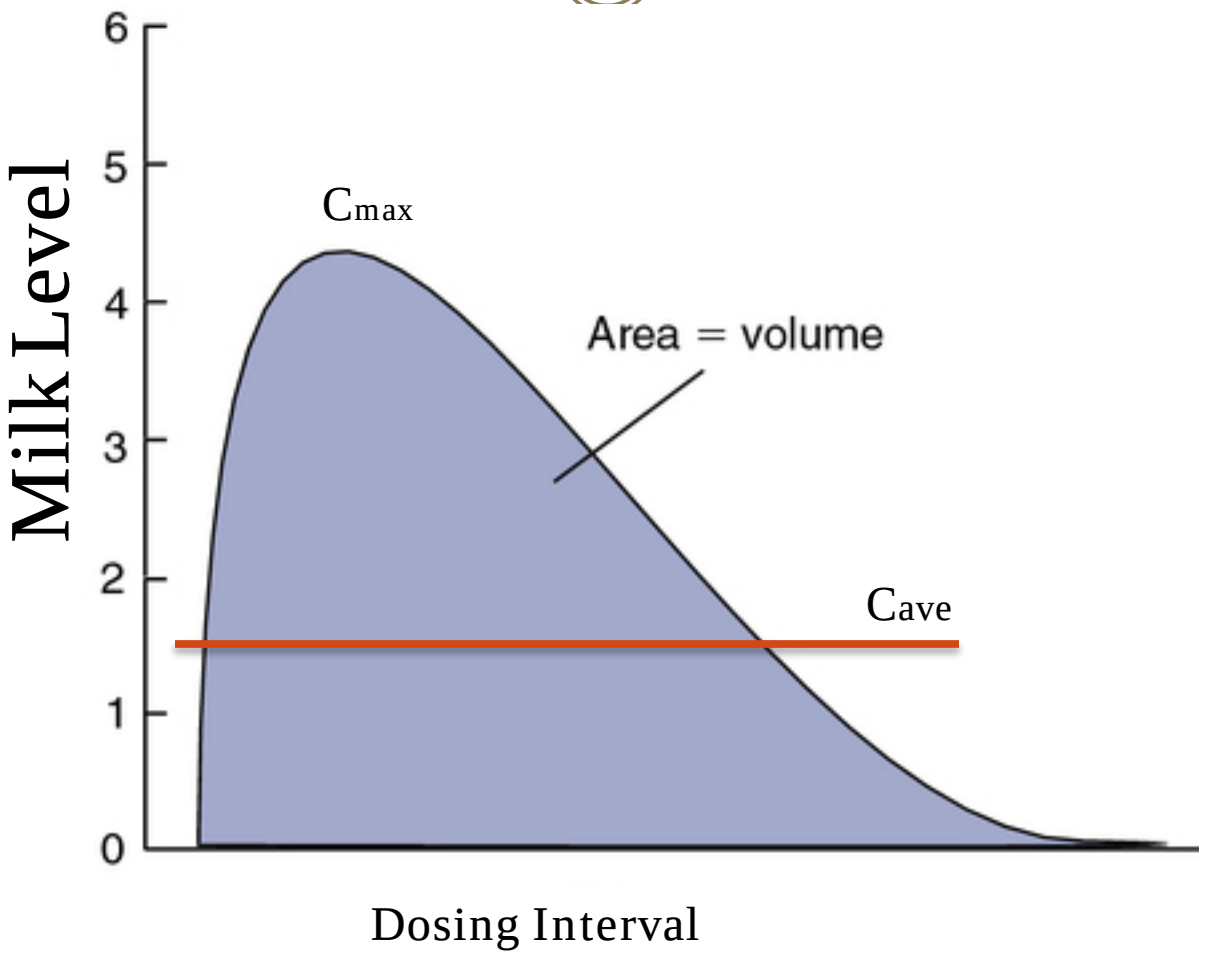
- **20,165** results mention “human milk” or “breast milk”*
  - 802 case reports
  - 417 systematic reviews**
- Only 276 of 1500 total drugs have calculable RIDs

*PubMed search performed using “Human Milk” OR “Breast Milk,” limited to English language

**PubMed’s algorithm for systematic reviews is designed to retrieve evidence-based medicine, practice guidelines, meta-analyses, reviews of clinical trials, and integrative studies via a complex search strategy. Strategy located at:

https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

Use AUC Data to calculate Cave over any dosing interval



Use Relative Infant Dose (when possible)

$$\mathbf{RID} = \frac{\text{Dose.infant}\ \left(\frac{mg/kg}{day}\right)}{\text{Dose.mother}\ \left(\frac{mg/kg}{day}\right)}$$

Dose.infant = dose in infant/day

Dose.mother = dose in mother/day

Estimated Milk intake = 150 cc/Kg/day

Example of where case studies could offer limited information

- Limited number of subjects
- Limited dosing regimens
  - Amount
  - Timing of interval (qid, tid, bid)
  - IV, Oral, IM, Topical, etc.
- Limited information on breastfeeding phase
    - Early stage or Late stage lactation
- May not be replicable
- Methodology of analysis is variable and difficult
- Pharmacokinetics of drug
  - T1/2, Vd, Bioavailability, Steady State

Streamlining Lactation Studies

Sample Collection

- Evaluate milk production (Exclusive or partial)
- Cover time from dose to trough
- Use as many milk samples as reasonable (7-8/24 hours)
- Pump both breasts completely, mix together, decant and freeze
- Freezing in refrigerator is generally adequate (only exception may be really unstable drugs)

Eliminate Redundant Procedures on Mom

Appendix A Schedule of Study Procedures

	Screening	Treatment					
Study Day:	**Days -28 to -1**	**Day 1**	**Day 4 ±1**	**Day 8 ±2**	**Day 15 ±3**	**Day 29 ±3**	**Day 57±3 Study Exit/ET/Follow-up (a)**
Informed consent (b)	X						
Inclusion/exclusion criteria	X	X					
Demographics and medical history	X						
Medication history	X						
Physical examination (c)	X	X					X
QuantiFERON Screening (d)	X						
PML checklist (e)	X	X					X
Vital signs (f)	X	X	X	X	X	X	X
Weight and height (g)	X	X					X
Concomitant medications (h)	X	X	X	X	X	X	X
12-lead ECG (i)	X						X
Clinical laboratory tests (j)	X	X					X
Urine drug and alcohol screen	X						
Urine pregnancy test (k)	X	X					X
PT/INR (l)	X						X
HBsAg, Anti-HCG	X						
Study Drug Dosing		X					
PK milk collection (m)		X	X	X	X	X	X
PTE/AE assessment (n)	X	X	X	X	X	X	X

Footnotes are on the next page.

9.1.13 ECG Procedure

Standard 12-lead ECGs will be recorded at Screening and at Study Exit/Follow-up (Day 57 [+/-3]) or Early Termination. Single ECGs will be taken at Screening and Day 57 (+/-3)/Early Termination visits. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

When an ECG is scheduled at the same time as milk collection or vital signs then the milk collection and vital signs will take priority and the ECG will be obtained within 0.5 hour before or after the scheduled milk collection/vital sign assessment. If an ECG coincides with a meal, ECG will take precedence followed by the meal.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position following an approximate 10-minute rest period for ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

ECGs will be read automatically and also, the investigator or sub-investigator will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. All 12-lead ECGs will be stored for manual measurement of intervals, if necessary. Twelve-lead ECGs will be recorded using an ECG machine that automatically calculates the heart rate and measures PR interval, RR interval, QRS interval, QT interval, QT interval with Fridericia correction method, and QT interval with Bazett correction method. Paper ECG traces will be recorded for 10 seconds at a standard paper speed of 25 mm/sec and gain of 10 m/mV or digital recordings will be used.

One copy of the 12-lead ECG with the physician's signature and date of assessment will be filed with the source documents and captured in the appropriate eCRF. If the original ECG is printed on thermal paper, the ECG report must be photocopied and certified. The photocopy will be filed with the original ECG in the source.

9.1.14 Pharmacokinetic Sample/ Milk Collection

9.1.14.1 Collection of Breast Milk for Pharmacokinetic Sampling

Milk from each breast will be completely emptied using an electric milk pump at the specified time points according to Table 9.b for the determination of concentrations in the milk. Milk collected from each breast at each time point will be pooled, and the total volume of milk collected and the starting and finishing time of each collection will be recorded on the source document and eCRF. Two 5-mL aliquots of milk will be stored at -70°C until analysis of concentration by enzyme-linked immunosorbent assay (ELISA). Subjects with mastitis should not have milk samples collected until the infection is completely resolved. If mastitis is not resolved within the allowed window for sample collection, the sample should be collected at an unscheduled visit as close to scheduled time point as possible. If the unscheduled collection overlaps with the next scheduled time point, the missed sample collection should be skipped. For milk sample collection on Days 4 through 57, sites are encouraged to schedule the visit at approximately the same time as the Day 1 postdose sampling time to reduce the effect of

Inclusion Criteria for Breastfeeding Studies

- Sample in period of major milk production
  - Include only Moms “exclusively” breastfeeding
  - Postpartum= 2 weeks to 6 months
- Avoid moms using Formula
  - Alters daily milk production, hence weakens design
- Measure milk production using Hale/Hartmann’s hourly pumping method if needed.
  - > 450 mL/day milk production
  - 18-45 years of age
  - Normal full term pregnancy
  - BMI = 18-34
  - Non smokers

How to find the patients on the drugs of interest?

- Websites (InfantRisk Center 1.1 million/year)
- Call centers such as the InfantRisk Center
  - Immediate recruitement
  - 20% Healthcare professionals
  - 80% Mothers
- Breastfeeding Clinics
- Create Network of Referral Centers
  - SMFM
- National Associations
  - ILCA/USLCA
  - Academy of Breastfeeding Medicine
  - AAP

Study Design

- Unless you have a huge population, design the study to promote Remote sample collection for drugs already consumed by mom
- Full study design with 5-20 patients can still be remotely collected. (All over USA)
  - Mesalamine (n=11)
  - Aspirin (n=7)
  - Montelukast (n=7)
- In-house for PI-Administered drugs possible but difficult
- Case reports

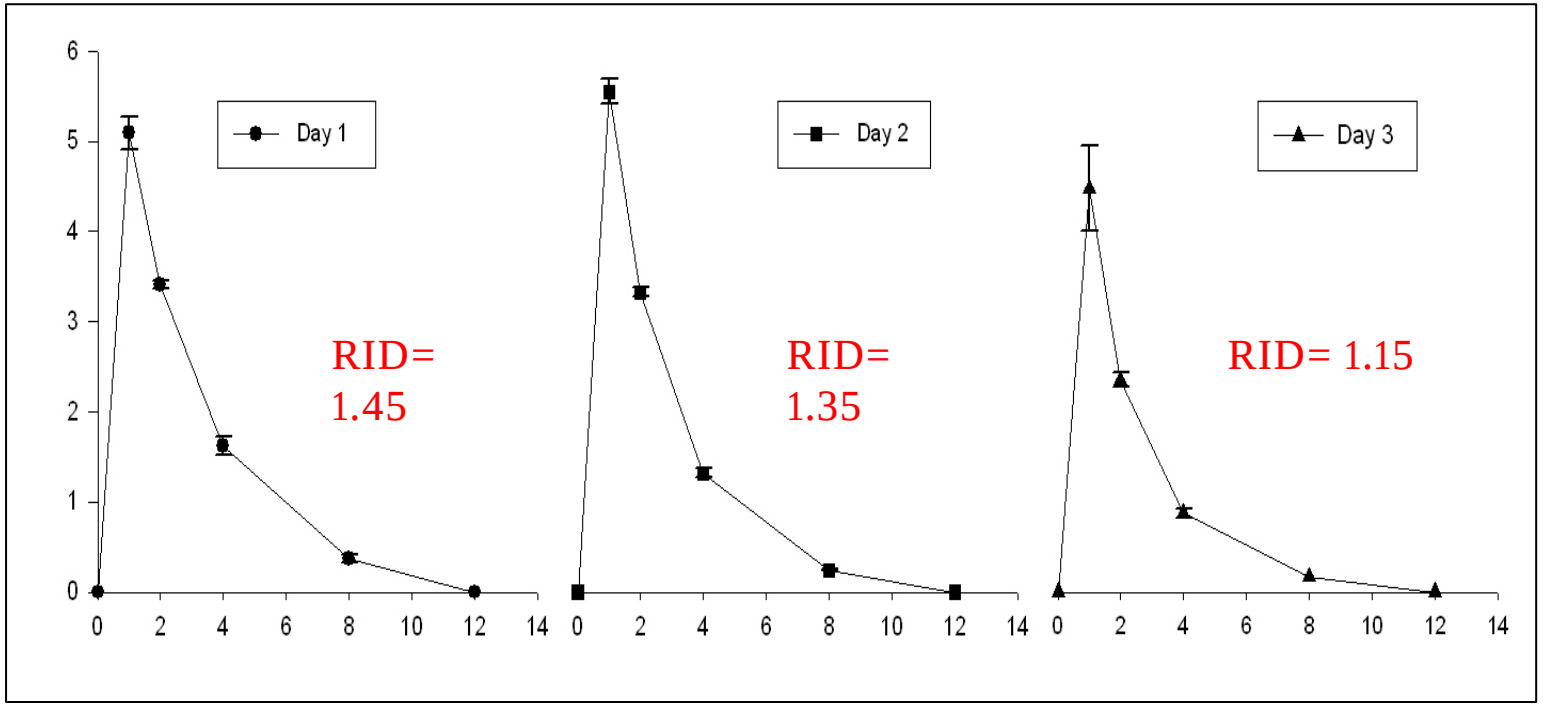
Pharmacokinetics in Design

- Try to sample at Steady State
- Try to thoroughly sample one dosing period
  - 8 hours-24 hours
    - 0, 1, 2, 4, 6, 8, 12, and 24 hours
  - 14 days
    - 0, 2, 4, 8, 12, 24 hours, daily thereafter.
- Make sampling convenient. Limit 0300 samples.
- Let mom collect her own samples and freeze before transport. Greatly reduces cost.
- Provide exact hours for sampling to mom.
- Limit Plasma sampling
  - Its interesting but of limited value.
  - Limit sampling of infant. Traumatic, phlebotomists must be capable

Ethics

- How do you handle the study of ‘dangerous’ drugs
  - Lithium, methamphetamine, Marijuana, Phencyclidine
  - Is it proper to do such a study? Does this “reinforce or support” moms to use them by your studying of them?
- What about drugs of abuse
  - How do we protect patient confidentiality?
  - How do we keep them from being charged with “Child Endangerment” by aggressive law enforcement?
    - Baker and Hale’s marijuana study ?
- What about drugs with significant risks, but also significant benefits
  - Biological IgG drugs (anti TNF, anti MS drugs, etc)
  - Anticancer drugs
  - Antipsychotic drugs

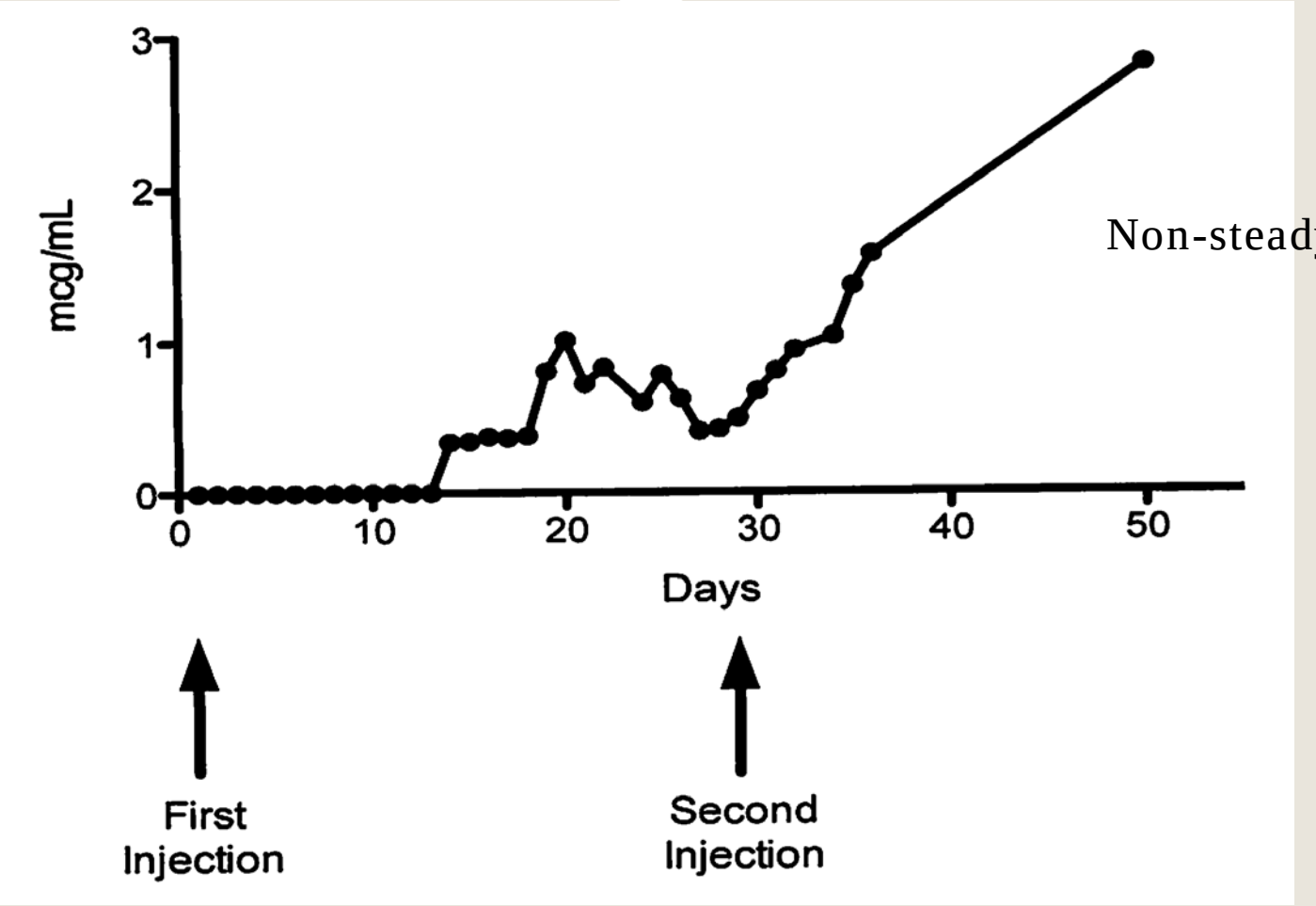
Methylprednisolone into Human Milk Following High IV Doses for Multiple Sclerosis*



Concentrations of methylprednisolone in human milk at day 1, day 2, and day 3 after intravenous doses of methylprednisolone (1000 mg).

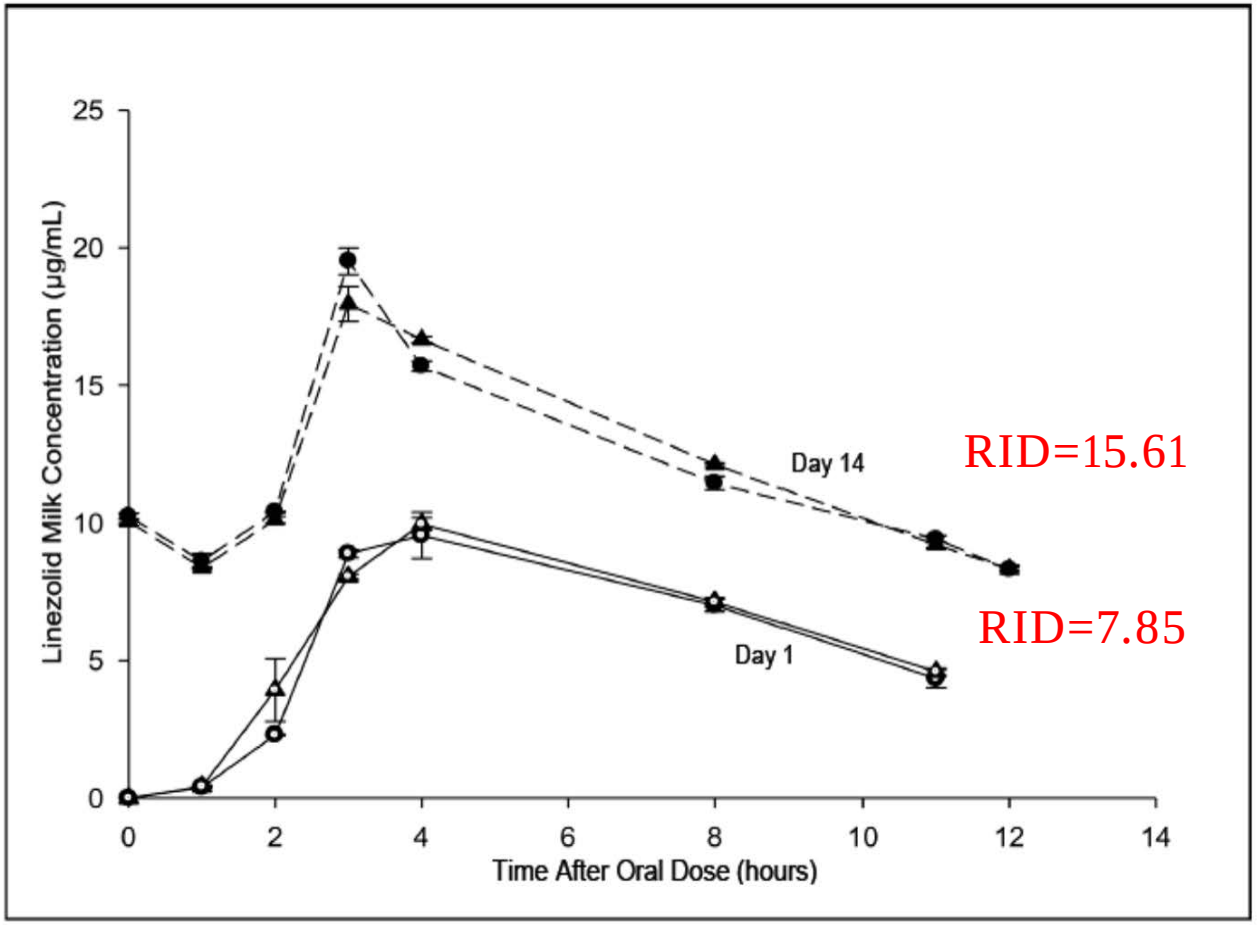
*Cooper C., Felkins K, Baker T, Hale T. Transfer of Methylprednisolone into Human Milk. J Hum Lact. 2015 May;31(2):237-9. doi: 0.1177/0890334415570970.Epub 2015 Feb 17.

The case of Nataluzimab



Non-steady state

Transfer of Linezolid into Human Breastmilk



Concentrations of linezolid in human milk at day 1 in left (open circle) and right (open triangle) breasts and at day 14 in left (closed circle) and right (closed triangle) breasts after oral doses of linezolid (600 mg)

Hilary E. Rowe, Kathleen Felkins, Shaun D. Cooper and Thomas W. Hale. Transfer of Linezolid into Breast Milk. J Hum Lact published online 6 August 2014. DOI: 10.1177/0890334414546045

InfantRisk Center

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