Advancements in Pediatric Physiologically-based Pharmacokinetic (PBPK) Modeling of Drugs in Lactation for Guiding Neonatal Exposure Risk Assessment

PRESENTER:
Shirley Wang

UNIVERSITY OF WATERLOO

BACKGROUND

Current methods for predicting infant risk to drugs in lactation:

- Use breastmilk drug concentrations to model infant drug pharmacokinetics.
- Do not account for prenatal drug exposure in the early neonatal period.
- Tend to underpredict exposure in this vulnerable phase of life.[1]

Proposed method for enhancing accuracy of breastfeeding models:

- Account for umbilical cord (UC) drug levels in model predictions.
- Holistically represents all sources of drug exposure to the breastfed infant.
- **Case examples:** Levetiracetam (LEV) and sodium benzoate (SB).

METHODS:

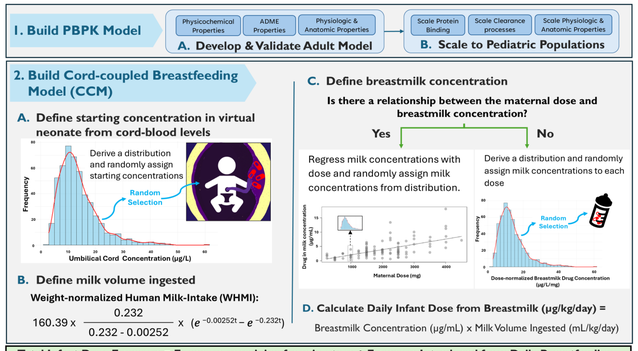


Figure 1. Cord-coupled Model (CCM) inputs for simulating total infant exposure.

RESULTS

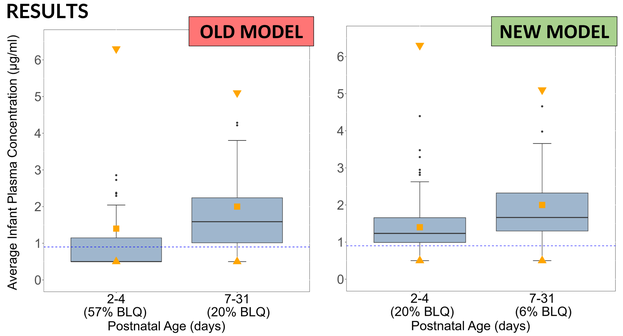
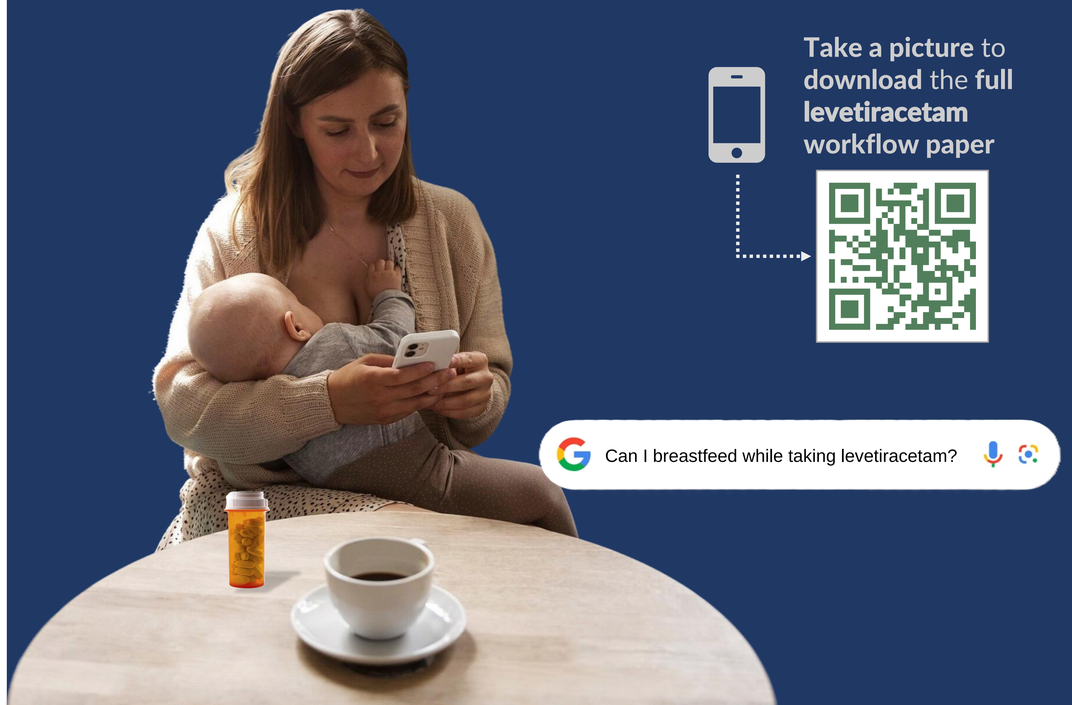


Figure 2. Overlaid simulated (box plot) and observed infant plasma **LEV** levels before and after accounting for prenatal drug exposure. Kacirova et al. values[3] used for 2-4 (n=54, 30% BLQ) and 7-31 day (n=10, 30% BLQ) validation. Median prediction improved by 2.54x (2-4 day) and 1.08x (7-31 day). $T_{1/2}$ = 5.3 ± 1.3 h.[4]

Accounting for prenatal drug exposure improves model-based predictions, showing **low breast-feeding exposure** to both sodium benzoate and levetiracetam and **minimal risk** to the infant.



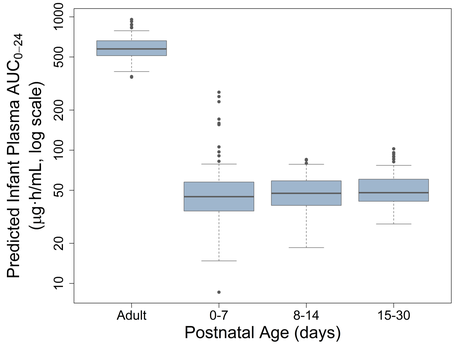


Figure 3. CCM simulated infant **LEV** exposure (as area under the curve, AUC) from breastfeeding while maintaining therapeutic maternal plasma levels of drug. The median milk concentration after a 2000 mg oral dose was used to define milk levels of drug.

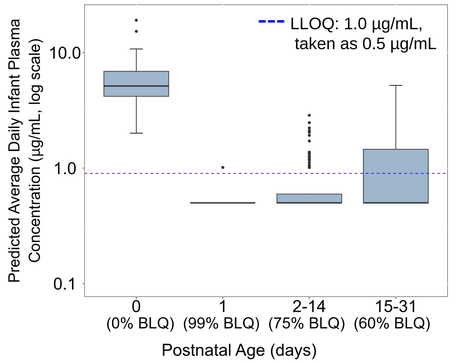


Figure 4. CCM simulated infant breastfeeding exposure to **SB** during maternal SB therapy. A milk to plasma (M:P) ratio of 1:1 was used to define breastmilk levels to be conservative. However, machine-learning algorithms[a] predicted the M:P to be 0.49. Therapeutic plasma levels range from 98 to 285 µg/mL. $T_{1/2}$ =~0.3 h.[5]

RISK METRIC:

$$\text{Upper AUC Ratio (UAR)}^{1} = \frac{95^{th}\text{ percentile breastfeeding infants AUC}_{0\text{-}t}}{\text{Median Therapeutic Exposure AUC}_{0\text{-}t}}$$

Age Group (days)	95th Percentile AUC_{0-24} (µg*h/mL)	UAR (%)
0-7	156	27
8-14	73	13
15-30	86	15

Pediatric trials report no major adverse effects at AUCs of 233±64 µg·h/mL.[4]

Table 1. UAR calculated for infants breastfed by mothers administered **LEV** (2000 mg/day PO).[6] Median therapeutic AUC: 575 µg*h/mL.

Age Group (days)	95th Percentile AUC_{0-24} (µg*h/mL)	UAR (%)
0	217	0.751
1	13	0.046
2-31	49-80	0.17-0.28

Table 2. UAR calculated for infants breastfed by mothers administered **SB** (160 mg/kg/day PO, q6h).[7,8] Median therapeutic AUC: 28,859 µg*h/mL.

Shirley Wang, Santosh Suryavanshi, Dagmar M. Hajducek, Abdullah Hamadeh, Cindy H.T. Yeung, Patricia D. Maglalang, Shinya Ito, Julie Autmizguine, Daniel Gonzalez, Andrea Edginton

[a] Based on unpublished data, courtesy of Dr. Maharaj at the University of British Columbia, Vancouver, BC, Canada.

*Reference list available upon request.

References

1) Yeung CHT, Ito S, Autmizguine J, Edginton AN. Incorporating Breastfeeding-Related Variability with Physiologically Based Pharmacokinetic Modeling to Predict Infant Exposure to Maternal Medication Through Breast Milk: a Workflow Applied to Lamotrigine. AAPS Journal. 2021;23:1–11.

2) Yeung CHT, Fong S, Malik PRV, Edginton AN. Quantifying breast milk intake by term and preterm infants for input into paediatric physiologically based pharmacokinetic models. Matern Child Nutr. 2020;16:1–33.

3) Kacirova I, Grundmann M, Brozmanova H. Umbilical cord, maternal milk and breastfed infant levetiracetam concentrations monitoring at delivery and during early postpartum period. Pharmaceutics. 2021;13:1–12.

4) Glauser TA, Mitchell WG, Weinstock A, Bebin M, Chen D, Coupez R, et al. Pharmacokinetics of levetiracetam in infants and young children with epilepsy. Epilepsia. 2007;48(6):1117–22.

5) Lin, Y. S., Mao, W. C., Yao, N. T. & Tsai, G. E. Pharmacokinetics and Safety of Sodium Benzoate, a d-Amino Acid Oxidase (DAAO) Inhibitor, in Healthy Subjects: A Phase I, Open-label Study. Clin Ther. 2022;44:1326–1335.

6) Suryavanshi S V., Wang S, Hajducek DM, Hamadeh A, Yeung CHT, Maglalang PD, et al. Coupling Pre- and Postnatal Infant Exposures with Physiologically Based Pharmacokinetic Modeling to Predict Cumulative Maternal Levetiracetam Exposure During Breastfeeding. Clin Pharmacokinet. 2024;63:1735–48.

7) Kubota K, Ishizaki T. Dose-dependent pharmacokinetics of benzoic acid following oral administration of sodium benzoate to humans. Eur J Clin Pharmacol. 1991;41:363–8.

8) Häberle J, Burlina A, Chakrapani A, Dixon M, Karall D, Lindner M, et al. Suggested guidelines for the diagnosis and management of urea cycle disorders: First revision. J Inherit Metab Dis. 2019;42:1192–230.