PBPK modeling to inform drug exposure in breastfeeding infants

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Highlights

• Target population

• Issues prime for PBPK modeling

• Why PBPK may be the best?
Exclusive Breastfeeding is important (even if the mother receives medications).

BREASTFEEDING IS THE STANDARD
Cognitive function
Kramer et al. Arch Gen Psy 2008
Belfort et al. J Ped 2016

Cancer risks
Stuebe et al. Arch Int Med 2009

Infection risks
AAP. Pediatrics 2012
Exclusive Breastfeeding

Many professional organizations recommend **exclusive breastfeeding for about 6 months**, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant, a recommendation concurred to by the WHO and the Institute of Medicine.

Infant drug exposure through breast milk is relatively low in most cases.

DRUG EXPOSURE OF BREASTFEEDING INFANTS
Drug Exposure of Breastfed Infants

Drug → Mother

![Graph showing drug concentration over time with milk intake for infant.]

Infant
Milk intake
150 ml/kg/day
Drug → Mother

Mother → Infant

[C]

Time

plasma

milk

Infant

Milk intake
150 ml/kg/day
Drug Exposure of Breastfed Infants

Drug $\rightarrow$ Mother $\rightarrow$ Infant

Milk intake 150 ml/kg/day
Plasma [C] vs. Milk [C]

Plasma [C] vs. Milk [C]

Tramadol


Tacrolimus

MP (milk-to-plasma) ratio

MP ratio of drugs is mostly 1 or lower

Drug Exposure of Breastfed Infants

Drug exposure in breastfeeding infants involves the transfer of drugs from the mother to the infant through breast milk. The diagram illustrates the concentration ([C]) of a drug in plasma and milk over time. The infant receives 150 ml/kg/day of milk intake.
Drug Exposure of Breastfed Infants

Drug $\rightarrow$ Mother $\rightarrow$ Infant

- Milk intake 150 ml/kg/day

- 2 mo: 140 (SD: 24)
- 4 mo: 124 (SD: 17)
Infant Daily Dose via Milk

Fluoxetine

1000 simulated infants

Median RID

$\text{\triangle} 99^{\text{th}}$ percentile

$\sim 3\%$ of mother’s dose per kg

Escitalopram

$%\text{Relative Infant Dose: mean 2.6\%}$

Infant 8 $\mu$g/kg/day

Mother 300 $\mu$g/kg/day


Delaney et al. Clin Pharmacokinetics 2018
Drug Exposure of Breastfed Infants

Drug Θ → Mother → [C] → milk → Infant

Plasma

Time

Milk intake (150 ml/kg/day) → Infant Dose (mg/kg/day) → Infant

infant plasma

Time
Infant Exposure: escitalopram

Mean AUC in adults at 20 mg

Delaney et al. Clin Pharmacokinetics 2018
Milk/infant PK prediction must address “outliers”.

TOXICITY CASE: A STORY OF OUTLIERS
Toxicity case

• Mother: Tylenol #3 (codeine 30 mg + acetaminophen 500 mg) for 2 weeks postpartum.
  – 2 tabs Q12H: 1 tab Q12H from Day 2 on.
  – Somnolence and constipation

• A term healthy baby: breastfed
  – Poor feeding and lethargy Day 7 on
  – Dead at Day 13

Koren et al. Lancet 2006;368:704
Toxicity case: cont’d

• Stored milk samples: morphine 86 ng/ml
  – Typical milk morphine levels after repeated codeine (60 mg Q6H): 2-20 ng/ml

\[
150 \text{ ml/kg/day} \times 100 \text{ ng/ml} = 15 \text{ microgram/kg/day}
\]

(Neonate IV maintenance dose: 100 microgr/kg/day)

Koren et al. Lancet 2006;368:704
Toxicity case  cont’d

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150 ml/kg/day x 100 ng/ml = 15 microgram/kg/day

(Neonate IV maintenance dose: 100 microgram/kg/day)

Mother: CYP2D6 UM

Infant: low CL?

Koren et al. Lancet 2006;368:704
Multiple study approaches exist.

STUDY APPROACH
What information do we need?

• Estimate of *Infant Plasma [C]*: neonates
  – Its variation and probability (frequency)

• Toxicity risk factors

• For both
  – *marketed drugs*; and
  – *drugs under development*
Conventional study approach

Case reports/series

Mother

Drug

θ

(mg/kg/day)

[Mg]

plasma

milk

Time

x 100

%Relative Infant Dose

Infant

Infant Dose

(mg/kg/day)

Milk intake

(150 ml/kg/day)

Point estimate

± infant plasma level data

Conventional study approach

Case reports/series
1. Population PK modeling approach
2. popPK – *inf* PBPK modeling approach

Population PK

Drug → Mother

%Relative Infant Dose

Infant [C] infant plasma

Time

Milk Intake L/day

1.0

0.5

0.2

0.1

0.5

2

3

6M

Age

Infant PBPK

Likelihood

Plasma drug [C]

Likelihood

Infant PBPK

Infant drug intake through milk

= Infant Dose (mg/kg/day)
3. **MM-Infant PBPK modeling approach**
Challenges

Mother-Milk PBPK

Pregnancy-Postpartum PK
Transition: ? Time profiles

Plasma-milk drug transfer: ? Drug transporters in the mammary gland
Challenges

Infant PBPK

Feeding impact on PK

CYP1A2: others?

PGX profile development

Le Guennec and Billon. Pediatrics 1987