Physiologically Based Pharmacokinetic (PBPK) Modelling to Predict Human Milk Exposure to medicines: a contribution from the ConcePTION Project

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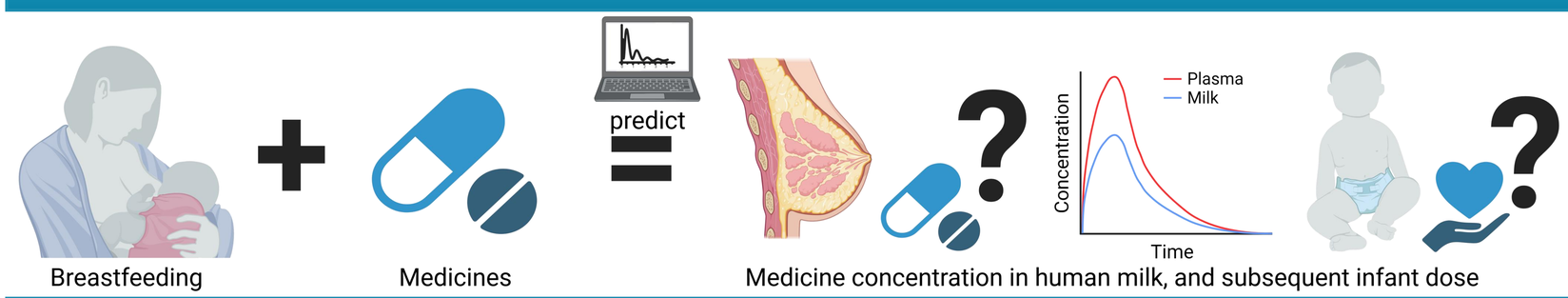
Introduction



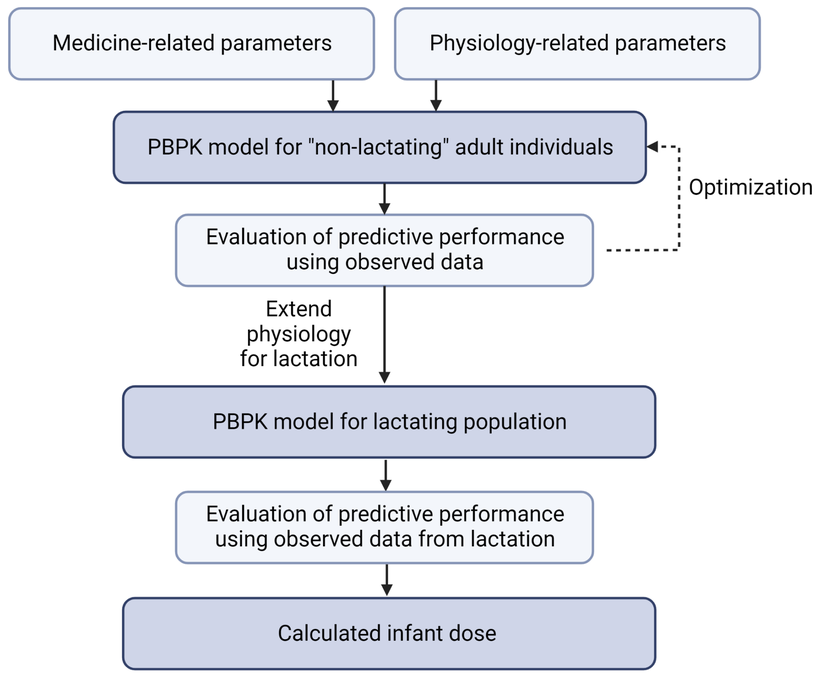
Objective

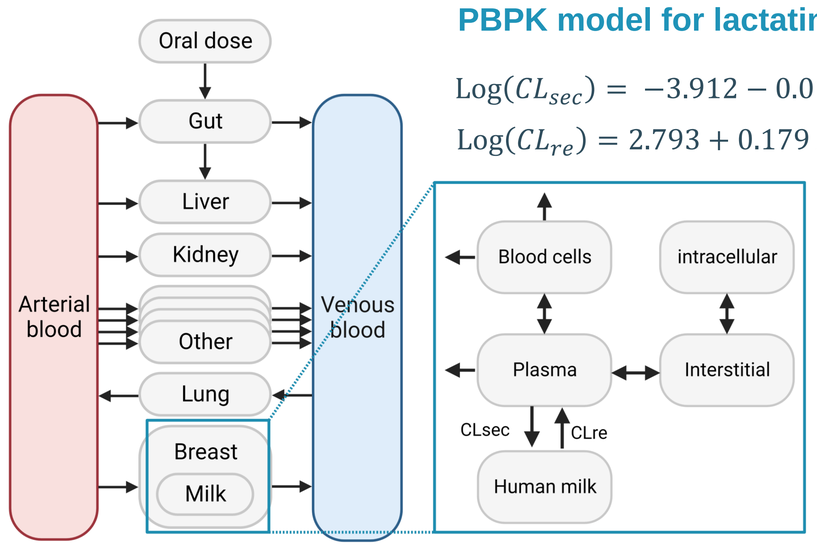
To evaluate the predictive performance of a generic lactation physiologically-based pharmacokinetic (PBPK) model for ten physiochemically diverse medicines.

Methods: workflow for development and evaluation of lactation PBPK models

Workflow for lactation PBPK model development

PK-Sim® and MoBi v9.1 (Open Systems Pharmacology) were used to develop the PBPK models for ten physiochemically diverse medicines [1].





PBPK model for lactating population

$$\mathrm{Log}(CL_{sec}) = -3.912 - 0.015\,PSA + 3.367\,\mathrm{Log}(MW) - 0.164\,\mathrm{Log}\left(\frac{P}{D_{7.4}}\right)$$

$$\mathrm{Log}(CL_{re}) = 2.793 + 0.179\,LogP - 0.132\,HBD$$

The PBPK models were extended with a breasts and human milk compartment [2,3]. Secretion (CLsec) and reuptake (CLre) from human milk were calculated using equations from an empirical model [4]. A previously published postpartum population was used to create a three months postpartum population (n=1000) [5].

$$M/P\ ratio = \frac{AUC_{human\ milk}}{AUC_{plasma}}$$

Calculated infant dose

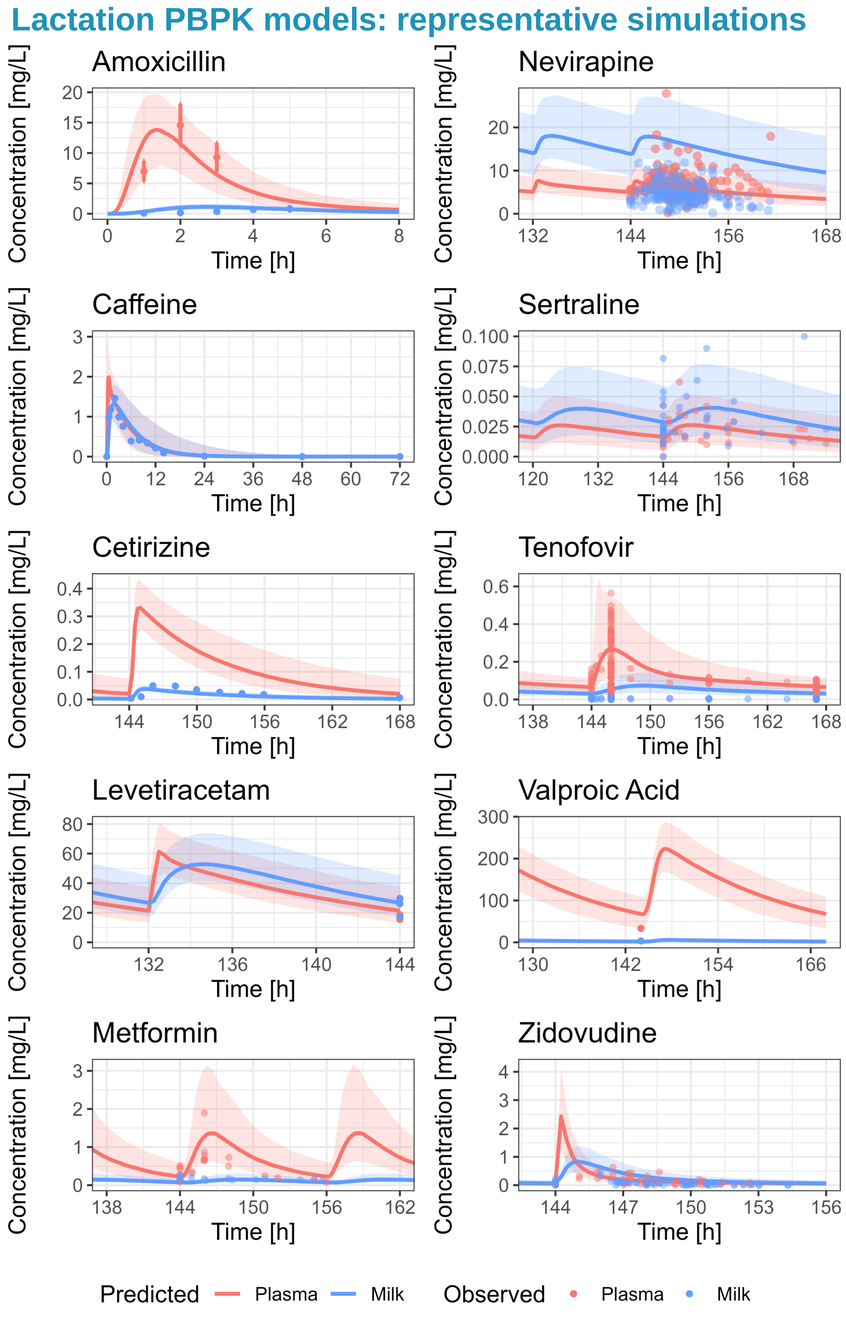
$$Daily\ infant\ dosage\ (DID, \frac{\frac{mg}{kg}}{day}) = Concentration_{milk} * 150\ mL/kg/day$$

$$Relative\ infant\ dose\ (RID, \%) = \frac{Daily\ infant\ dosage}{Daily\ maternal\ dosage} * 100\ \%$$

$$Relative\ therapeutic\ infant\ dose\ (RID_{\mathrm{therapeutic}}, \%) = \frac{Daily\ infant\ dosage}{Daily\ \mathrm{therapeutic\ infant}\ dosage} * 100\ \%$$

Results: reasonable prediction for eight of the ten medicines

Lactation PBPK models: representative simulations



Secretion and reuptake clearance values

Medicine	CL_{sec} (mL/h)	Cl_{re} (mL/h)
AMX	47	263
CAF	824	603
CET	3031	1923
LEV	445	358
MTF	22	138
NVP	2414	1015
SER	8926	3597
TFV	52	129
VPA	248	1423
ZDV	431	345

Milk-to-plasma ratio (M/P ratio) and infant dose

Medicine	Predicted M/P ratio (observed range)	DID (mg/kg/day) RID (%)	$RID_{therapeutic}$ (%)
AMX	0.15 (0.04-0.06)	0.12 (0.24)	0.24
CAF	0.95 (0.52-1.16)	0.30 (5.95)	5.96
CET	0.12 (0.2)	0.002 (1.24)	0.41
LEV	1.11 (0.46-1.79)	6.16 (12)	15.40
MTF	0.16 (0.13-1.00)	0.052 (0.10)	-
NVP	2.68 (0.2-1.5)	2.43 (37)	20.23
SER	1.62 (0.12-5.2)	0.005 (0.63)	-
TFV	0.40 (0.025-0.11)	0.01 (0.15)	0.12
VPA	0.03 (0.013-0.25)	0.52 (1.50)	1.31
ZDV	1.10 (0.3-3.21)	0.04 (0.41)	0.17

Conclusion

- ✓ **The workflow resulted in a reasonable prediction of maternal plasma and human milk concentration-time profiles for eight of the ten physiochemically diverse medicines, while an overprediction in human milk was observed for nevirapine and tenofovir.**
- ✓ Unique quantitative information on infant exposure to maternal medicines can be generated in an early drug development stage, *i.e.,* before clinical data becomes available.

References:
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Abbreviations: Cl_{sec}: secretion clearance; Cl_{re}: reuptake clearance; PSA: polar surface area; HBD: hydrogen bond donor; M/P: milk-to-plasma ratio; AUC: area-under-the-curve; AMX: amoxicillin; CAF: caffeine; CET: cetirizine; LEV: levetiracetam; MTF: metformin; NVP: nevirapine; SER: sertraline; TFV: tenofovir; VPA: valproic acid; ZDV: zidovudine

Publication

Linkedin

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