Population pharmacokinetic analysis of amoxicillin in postpartum Göttingen Minipig plasma and milk: a contribution from the ConcePTION project

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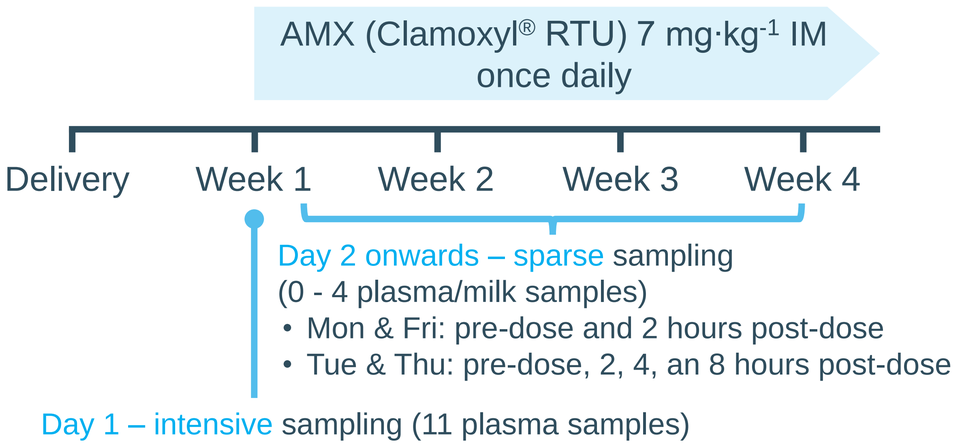
Introduction

- The knowledge gap regarding the extent of medicine milk transfer has existed for most medicines approved for human use[1-2]. The amount of the drug in milk an infant is exposed to via breastfeeding is crucial information for assessing the safety of medicines used in lactating women.
- The Göttingen Minipig (GMP) was considered bio-relevant to humans regarding studying the milk transfer of medicine(s)[3].
- Since amoxicillin (AMX) is a broad-spectrum antibiotic prescribed in humans and GMPs, it can be an example for developing a lactation/milk-transfer study framework. This study aimed to characterize AMX pharmacokinetics (PK) in plasma and milk in postpartum GMPs by population PK (popPK) analysis.

Methods

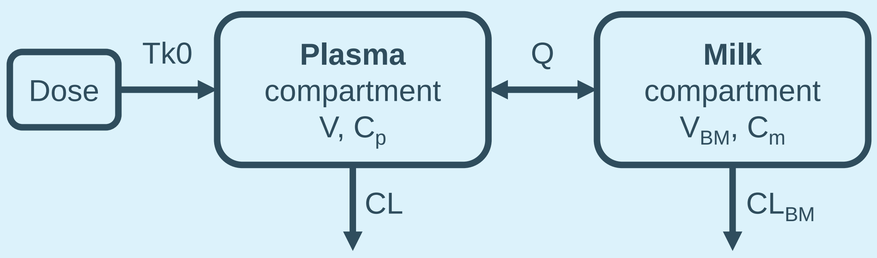
Figure 1. Animal study design



PopPK analysis

- Nonlinear mixed-effects modeling approach using Monolix® 2021R1
- Stepwise Covariate Analysis
  - Forward selection: OFV ↓ >3.84 (p <0.05)
  - Backward elimination : OFV ↑ >6.63 (p <0.01)

Figure 2. AMX PK model structure



- Tk0 fixed to 1 h, V_{BM} fixed to 5.89 L

$$V_{BM} = \frac{\text{Daily milk intake volume per litter piglets}}{\text{Fraction of breast milk volume emptied}}$$

where the assumed daily milk intake volume per litter piglets was scaled based on literature value[4]; the fraction emptied was assumed to be 0.75

- IIV included for V; IOV included for Tk0, V, CL
- No significant covariate was identified

Simulation-based endpoints estimation

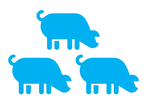
The final model was used to simulate a virtual GMP population, where the median simulated PK profiles were used to calculate the following endpoints in GMP.

- $\text{Milk} - \text{to} - \text{plasma ratio} = \frac{AUC_{\tau,Milk}}{AUC_{\tau,Plasma}}$
- $\text{Daily infant dose (DID, mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}) = \frac{AUC_{\tau,Milk}}{\tau} \times \text{Daily milk intake volume}$

where τ was 24 h, and the assumed daily milk intake volume in a GMP piglet was 1072 mL · kg^{-1}

- $\text{Relative infant dose (RID, \%)} = \frac{\text{Daily infant dose}}{\text{Daily maternal dose}} \times 100\%$

where the daily maternal dose in GMP was 7 mg · kg^{-1}



Virtual population (n = 1000)

Results

Table 1. GMP characteristics

	Mean ± SD	Min. – Max.
Bodyweight (kg)	43.2 ± 5.19	34 – 48
Day 1 or earlier	43.0 ± 7.81	34 – 48
Day 3 / 6	40.3 ± 4.92	34 – 46
Days postpartum on Day 1	7.00 ± 1.00	6 – 8
Offspring litter size	8.33 ± 1.25	7 - 10

Figure 3. Flow chart of data inclusion & exclusion

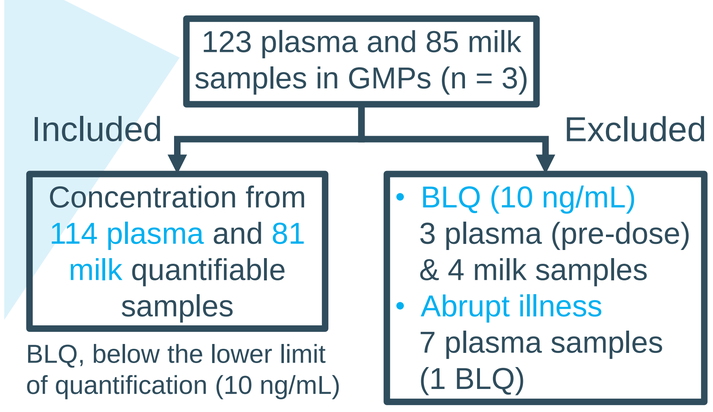
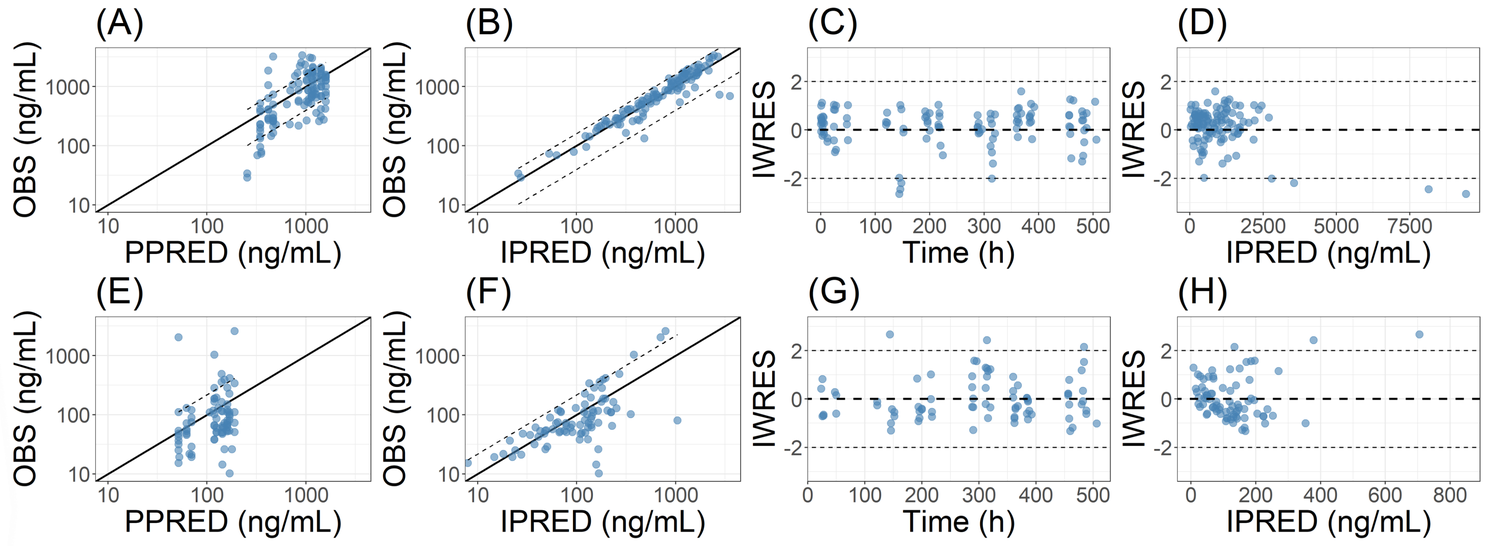


Figure 4. Goodness-of-fit plots for plasma (A to D) and milk (E to H)



OBS, observation; xPRED, prediction (x = I for individual; P for population); IWRES, individual weighted residuals

Figure 6. Prediction-corrected visual predictive checks for plasma (A) and milk (B)

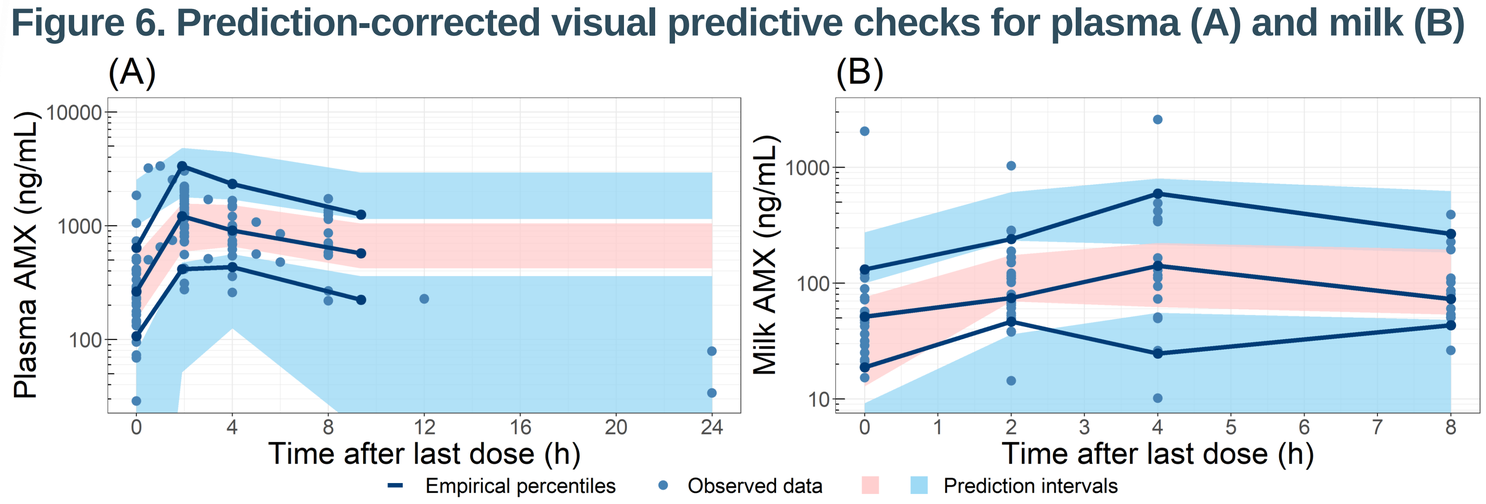


Table 2. Milk-to-plasma (M/P) ratio and infant dose of AMX in GMP

	Observed value	Simulated value	Simulation / Observation
M/P ratio	0.153 ± 0.0778	0.139	0.906
DID (mg·kg^{-1}·day^{-1})	0.161 ± 0.0861	0.106	0.662
RID (%)	2.30 ± 1.23	1.52	0.662

Observed values were expressed as mean ± standard deviation; simulated values were calculated based on the median profile in the dosing interval with the highest plasma AUCτ.

Conclusion

- ✓ The developed popPK model well described the AMX plasma and milk levels in GMPs.
- ✓ **The simulated M/P ratio of AMX in GMPs was close to the observed value in GMPs and the predicted value (0.15) in the human lactation physiologically-based PK model[5].**

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LinkedIn

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