Development and Integration of a Dynamic Lactation Functionality within a Full PBPK Model

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Background

According to the FDA Pregnancy and Lactation Labelling rules, drug companies are required to provide information about using their drug while breastfeeding, including the likely amount appearing in breast milk and its potential effects on the infant [1]. Physiologically-Based Pharmacokinetic model (PBPK) can help to explore different scenarios and quantify drug levels in milk at different stage of lactations under different physiological and clinical conditions.

Objectives

To develop and integrate a dynamic lactation functionality within a full PBPK model for prediction of drugs concentration in lactating mothers using caffeine and alprazolam as model drugs.

Methods

A lactation model has been developed consisting of three compartments to account for mammary blood, the tissue itself and the milk. The model includes physiological parameters such as the mammary gland tissue volume [2], and its blood flow [3], the milk pH and fu [4] and the milk intake [5]. The model was coupled with the full PBPK model within the Simcyp Simulator (V16) assuming a first order absorption kinetics and the Rodgers & Rowland method [6] to predict partition of drugs between tissues and plasma. In addition, the elimination kinetics were predicted using an the *in vitro in vivo* extrapolation approach in the Simulator (Figure 1). The whole lactation model was coded using the Lua interface within the Simcyp Simulator to make use of the generated individuals physiological parameters and their physiological variability, such as individuals weight, cardiac output, tissues volume and blood flow, plasma fu, etc.

Predicted profiles from 100 virtual individuals were compared with published studies after mimicking the virtual trial design to the clinical settings according to the following studies:

Oo et al, Alprazolam study[4]: eight healthy women during 6-28 wks post partum receiving a single oral doses of 0.5 mg alprazolam.

Oo et al, Caffeine study[7]: Five healthy women during 6-28 wks post partum receiving a single oral dose of 200mg caffeine.

Stavchansky et al, Caffeine study[8]: Six healthy women during 3-17 wks post partum receiving a single oral dose of 100mg caffeine.
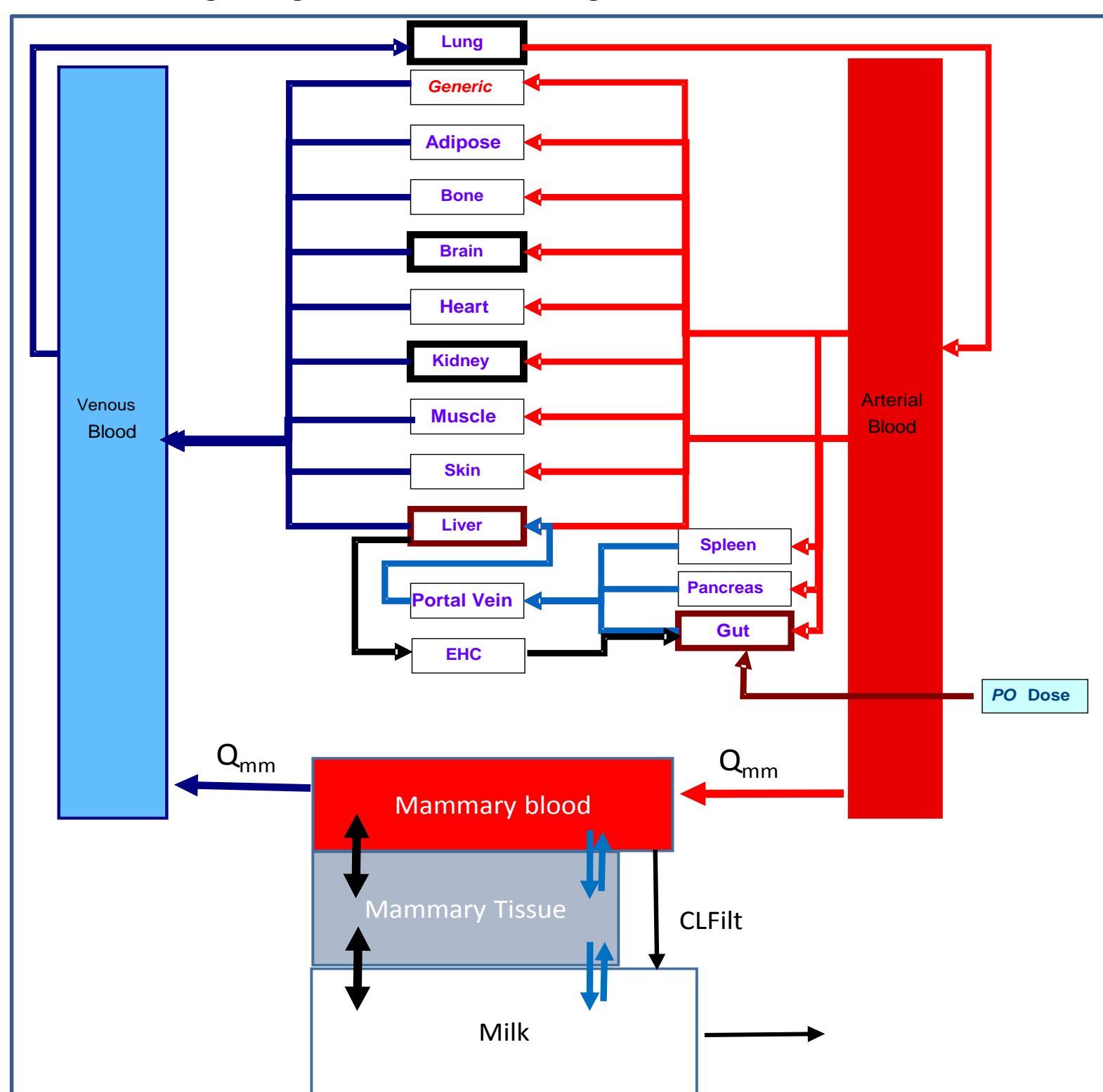

Fig 1. Structure of the lactation PBPK model

Results

The model replicated the clinical observations adequately, i.e., within 2-fold. For alprazolam the predicted mean±SD AUC24h (ug/ml*h) for milk and plasma was 0.058±0.019 (observed 0.066 [4]) and 0.11±0.04 (observed 0.14, respectively[4]).

For Caffeine, the predicted milk AUC24h was 29±15 (observed 29[7]) ug/ml*h, and the predicted plasma AUC24h was 49±27 (observed 42[7]) ug/ml*h.
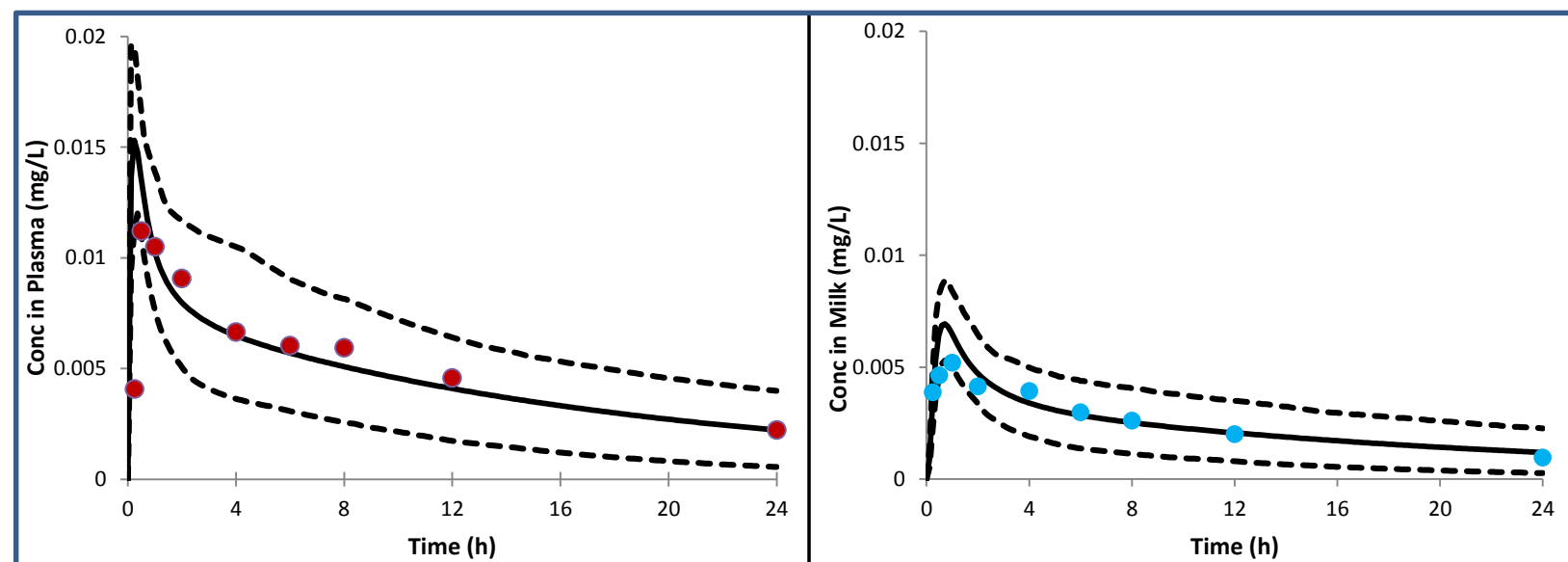

Fig2. Predicted mean (and 9th, 95th percentiles) of alprazolam concentration in plasma (left) and in milk (right). Dots are observed values [4].
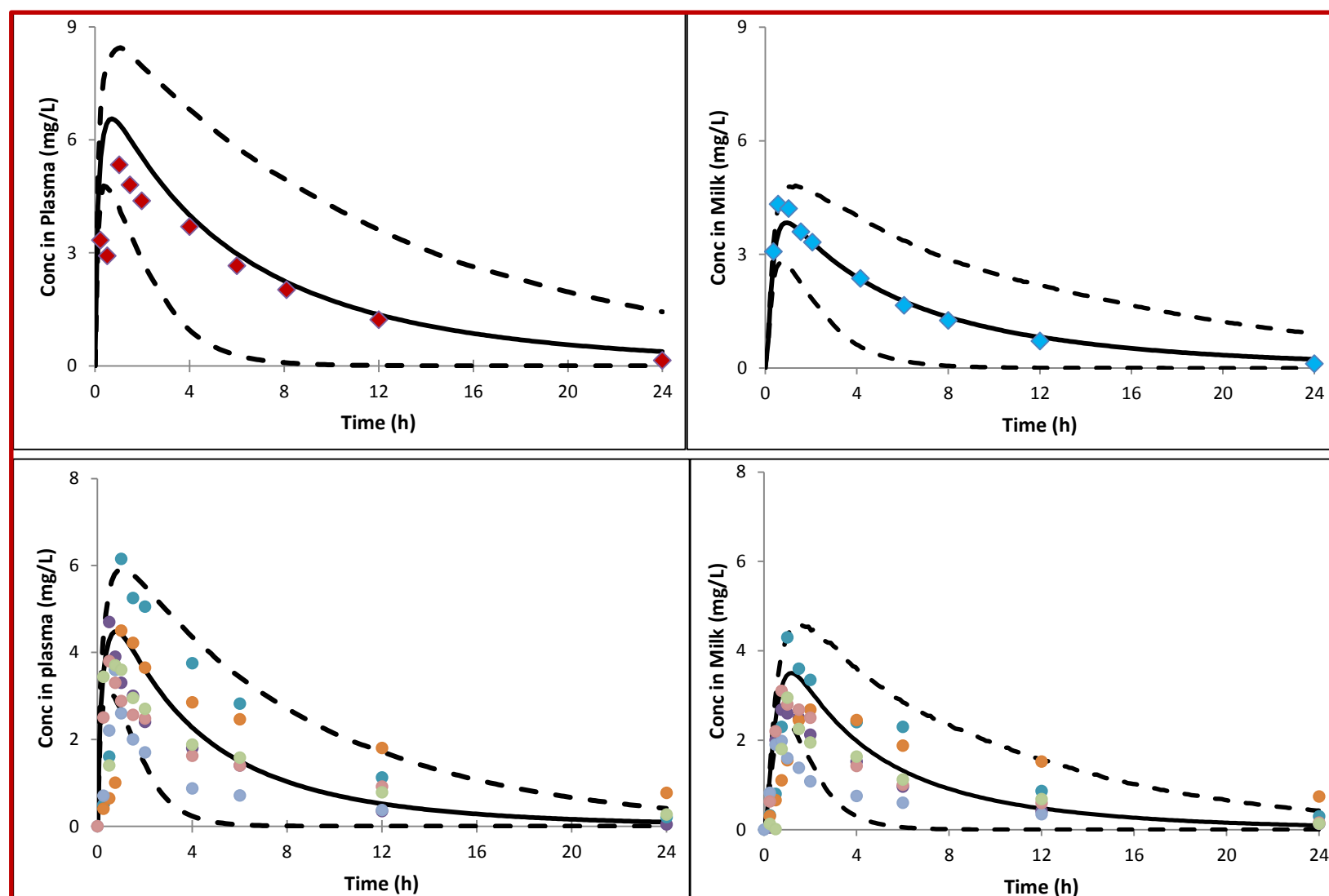

Fig 3. Predicted mean (and 9th, 95th percentiles) of caffeine concentration in plasma (left) and in milk (right). Top panel shows mean values and bottom individuals. Observed values gives as diamonds [7] and circles [8].

Conclusion

The three-compartmental model for mammary gland was integrated with a full PBPK distribution model and was able to replicate the clinical observations for both drug. The model is an extension of previously published model with a minimal PBPK model [9] and can be used to calculate drug doses for breast fed infants. The breast distribution of both of these compounds is governed mainly by passive permeability. Further work will aim to extend the model to predict compounds whose kinetics involved permeability limitations including transporter.

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