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

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Objectives: To develop and integrate a dynamic model describing drugs concentration in lactating mothers within a full physiologically based pharmacokinetic model that.

Methods: A lactation model has been developed consisting of three compartments, mammary blood, the tissue itself and the milk. The model incorporates physiological parameters including the tissue volume [2], its blood flow [3], Milk pH & fu milk [4] and the milk intake [5]. The model was integrated within the Simcyp Simulator using a first order absorption kinetics and Rodgers & Rowland method [6] to predict the partition of drugs between tissues and plasma. In addition, the elimination kinetics were predicted using in vitro in vivo extrapolation in the Simcyp Simulator V16. The lactation model was built using the Lua interface within the Simulator utilising the individual physiological parameters and their variability. Mimicking the clinical trial designs following administration of 0.5mg alprazolam [4], and 200mg [5] caffeine as single oral doses, predicted profiles from 100 virtual individuals were compared with the reported studies.

Results: The model predicted the clinical observations adequately, i.e., within 2-fold. For alprazolam the predicted milk AUC_{24h} was 0.058±0.019 (observed 0.066) ug/mL*h, while predicted plasma AUC_{24h} was 0.11±0.04 (observed 0.14) ug/mL*h. For Caffeine, the predicted milk AUC_{24h} was 30.5±17 (observed 29) ug/mL*h, while the predicted plasma AUC_{24h} was 49±27 (observed 42) ug/mL*h.

Conclusions: The three-compartmental model for mammary gland coupled with PBPK model was able to predict the clinical observations for both drugs. While disposition of these compounds are mainly governed by passive permeability, future work aim at extending the model to predict compounds whose kinetics involved transporters.