Application of Physiologically-Based Pharmacokinetic Model to Predict Tramadol Concentration in Human Milk

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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 where data are not available, for example to predict drug concentrations in milk in nursing mothers assuming different physiological and clinical conditions.

Objectives

To use a PBPK model for prediction of tramadol milk concentration in 100 mothers with different CYP2D6 Phenotypes.

To calculate the relative infant daily dose (RID) form the predicted milk concentration in different phenotypes.

Methods

A predictive PBPK model for tramadol was developed based on physiological parameters for a healthy population in Simcyp Simulator V16. A virtual population of 100 extensive metabolizers (CYP2D6 EMs) women aged 25–32 years was used to predict tramadol plasma concentration after twice daily administration of 333 umol (100 mg).

The lactation model was coded using the Simcyp Lua scripting functionality, whereby the Milk-to-Plasma (M/P) ratio was predicted according to the equation of Fleishaker et al 1987 [2] and subsequently used to predict tramadol concentrations in milk. Fleishaker's equation was modified in a way that physiological parameters with their distribution were used instead of fixed constants, so the predicted M/P ratio varies between individuals dependent on individual's creamatocrit, fraction unbound in plasma and milk.

Predictions of milk concentration in CYP2D6 Poor metabolisers (PMs) and ultra-rapid metabolisers (UMs) were performed and compared to EMs mothers. The relative infant daily dose (RID) is calculated form the predicted milk concentration in different phenotypes.

Results

The model replicated the clinical observations adequately in EMs mothers during lactation at steady state [3] as shown in Figure 1. The predicted M/P ratio was 1.87±0.06 vs the observed value of 1.9 [3]. Tramadol concentrations in milk for mothers with different CYP2D6 phenotypes are given in Figure 2.

The calculated AUC_{12h} for tramadol in milk at steady state were 43882, 28190, and 21196 nmol/L*hr for PMs, EMs and UMs respectively.

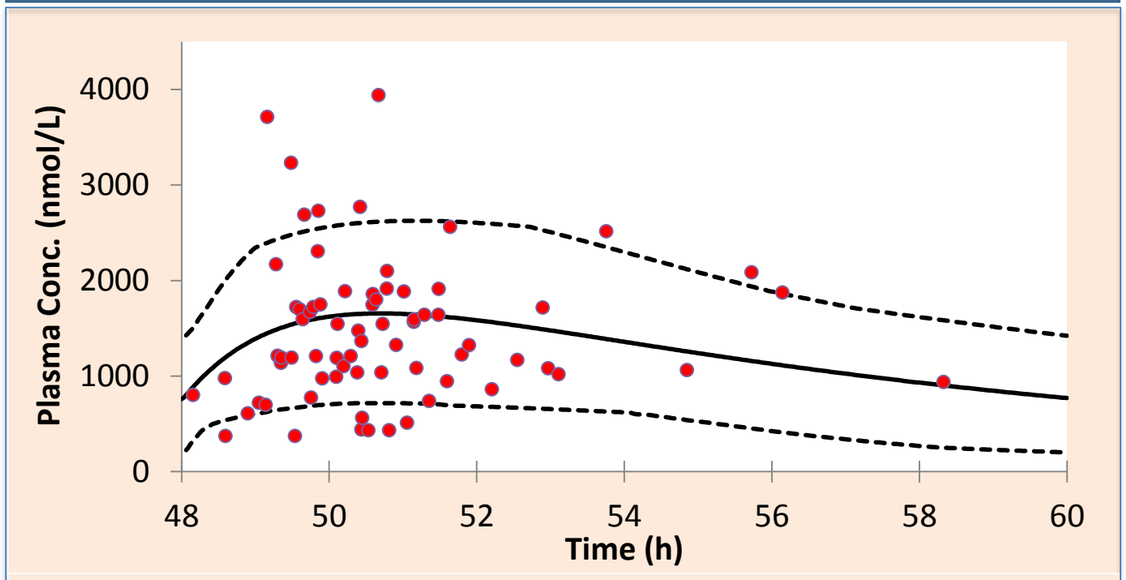
The predicted RID (%) was 5.18±1.47, 3.98±1.19, and 3.31±1.08 for PMs, EMs and UMs mothers, respectively.

conclusions

PBPK models can be used to predict M/P ratio and its inter-subject variability using the drugs physicochemical properties and system (mother and lactation) parameters. While, the predicted RID for tramadol was below 10% of maternal dose, it may pose a potential risk if mothers are poor metabolizers or for a given phenotype taking higher doses.

The PBPK model can be used to explore the impact of other scenarios affecting RID, such as DDIs, dose modification and/or incorporating metabolites data.

Results (cont.)



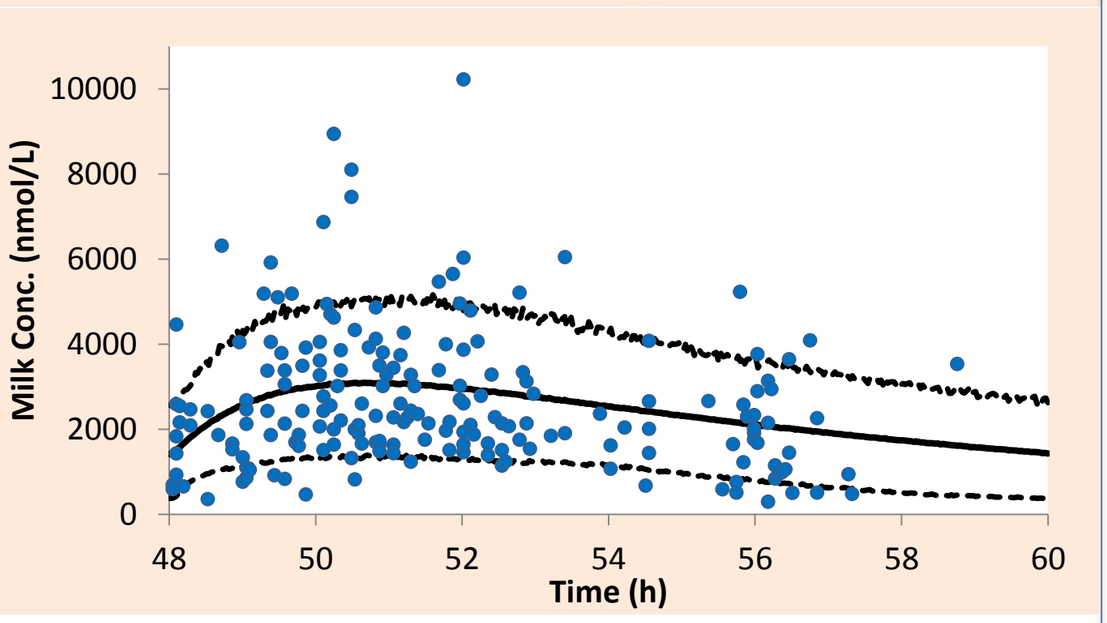


Figure 1. Plasma (top) and milk (bottom) concentration of tramadol in CYP2D6 EMs breastfeeding mothers after oral administration of 100 mg tramadol.

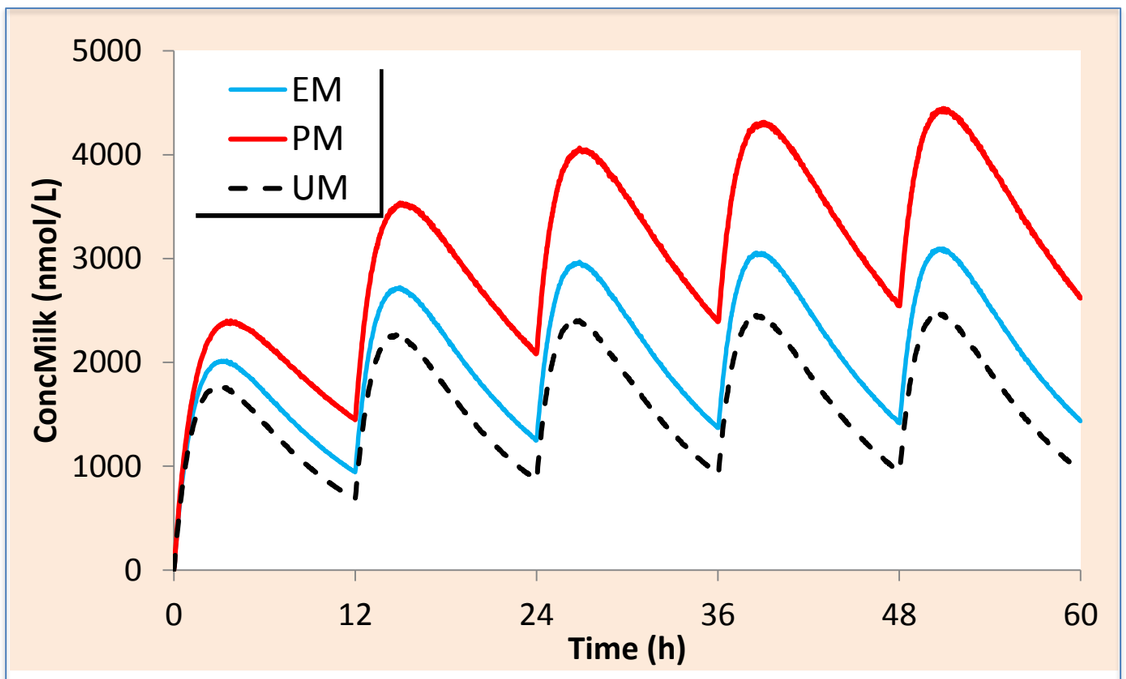


Figure 2. Predicted mean milk concentration of tramadol in breastfeeding mothers with different CYP2D6 phenotypes after oral administration of 100 mg tramadol.

References

[1] Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist. 2014 Dec 4;79(233):72063-103.

[2] Fleishaker JC, Desai N, McNamara PJ. Factors affecting the milk-to-plasma drug concentration ratio in lactating women: physical interactions with protein and fat. J Pharm Sci. 1987 Mar;76(3):189-93.

[3] Salman S, Sy SK, Ilett KF, Page-Sharp M, Paech MJ. Population pharmacokinetic modeling of tramadol and its O-desmethyl metabolite in plasma and breast milk. Eur J Clin Pharmacol. 2011 Sep;67(9):899-908.

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