Published in final edited form as:

Clin Pharmacol Ther. 2020 February ; 107(2): 319–320. doi:10.1002/cpt.1607.

Next challenge from the variance in individual PBPK model-predicted to observed morphine concentration in critically ill neonates

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To the Editor:

We previously reported influences of ontogeny and genetic variation of OCT1 on morphine disposition in critically ill neonates¹. For post-term neonates, the majority of clinically-observed morphine clearances fell within a two-fold range of the geometric mean of PBPK model-based predicted clearances for each *OCT1* haplotype. PBPK modeling allows multiple patient-specific information to be integrated in predicting drug exposure. In this letter, predicted plasma morphine concentrations in virtual neonates, which were generated using actual individual patients' data (e.g. postnatal age, gender, dosing history, and OCT1 haplotype)², were compared with measured concentrations in corresponding patients, in order to address remaining knowledge gap between virtual subjects and real-world patients.

PBPK model-predicted concentrations showed a reasonable prediction relative to observed concentrations, where the median ratio of observed to predicted concentrations was: 0.99 (95% CI, 0.84–1.15) for all OCT1 haplotypes – 0.97 (0.78–1.10) for wild type; 1.03 (0.72–1.38) for heterozygous; and 1.58 (0.55–2.91) for homozygous haplotypes (Figure 1)^{1,3}. Model accuracy and precision were lower in the homozygous haplotype than the other types, although morphine concentrations were only available for three homozygous neonates. For each haplotype, approximately 60% and 85% of predicted concentrations were within two- and three-fold of observed concentrations, respectively. Predicted values outside of the two-

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Conflict of interest

As an Associate Editor for Clinical Pharmacology & Therapeutics, Alexander Vinks was not involved in the review or decision process for this paper. All authors declare no competing interests.

and three-fold ranges suggest significant influence of additional unknown factors apart from those represented by patient information used in PBPK simulation. One possible mechanism involves (patho)physiological differences in hepatic protein expression levels of OCT1 and UGT2B7 – due to diseases and/or patients' conditions – between patients and virtual subjects (i.e. settings in the PBPK model). For example, in adults, hepatic OCT1 expression has been shown to be significantly reduced in cholestatic patients⁴, while a significant decrease in hepatic UGT2B7 mRNA expression has been observed in patients with high inflammation scores⁵. Further investigation into the possible influence of (patho)physiological differences between neonatal patients may be warranted, utilizing their electronic-health-records (EHR) and patient charts to evaluate patients' conditions.

Although barriers still exist to applying PBPK results to clinical practice, the current approach contributes to the accumulation of system knowledge and understanding of how a patient's condition may be leveraged to further improve the predictive performance of PBPK modeling. Future model fine-tuning is expected to be valuable in supporting clinical decision-making prior to starting medications in neonates. In particular, well-informed PBPK models could benefit from prospective biomarker studies, using endogenous OCT1 and UGT2B7 substrates to determine protein expression/activity for individual patients.

Acknowledgments

Funding

Research reported in this publication was partly supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R21HD095418. The pharmacokinetic and patient data obtained from the study in part supported by a T1 translational research award by the University of Cincinnati Center for Clinical and Translational Science and Training (CCTST); National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1 TR001425. Joshua Euteneuer was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development under award number 5T32HD069054.

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Figure 1.

Comparison between PBPK model-predicted and observed morphine concentrations in neonates assessed by median percentage error and median absolute percentage error. Data are represented according to OCT1 haplotypes: all haplotypes (open circles), wild type (gray circles), heterozygous (blue circles), and homozygous (pink circles) haplotypes. In this comparison, a total of 114 concentrations were collected from 32 neonates (wild type, n=17; heterozygous type, n=12; homozygous type, n=3). These were a part of the same data set used in Hahn et al (2019)¹. A total of 100 PK simulations were conducted for each neonatal

patient, according to actual patient data such as postnatal age (where patients were selected with gestational age over 37 weeks), gender, dosing history (body weight-based dosages and number of administrations), and OCT1 haplotype, along with time-dependent developmental changes in pediatric physiology during the administration period using Simcyp version 17 (Certara UK Limited, Simcyp Division Sheffield, UK). Each symbol represents the median of 100 PK simulations comparing with the corresponding actual concentration at each time point.

In the PBPK model, the settings of *in vitro* OCT1 activity of morphine transport for each OCT1 genotype and the ontogeny profiles of hepatic OCT1 and UGT2B7 protein expression were described in the previous report¹. The median percentage error (MDPE with 95% CI) and median absolute percentage error (MDAPE with 95% CI) were calculated to describe the model accuracy and precision, respectively, according to the report by Khalil and Ler³. The median values of PE and APE of 114 concentrations from 32 neonates were calculated with the Graphpad Prism software version 8.0.1 (GraphPad Software, San Diego, CA). Solid line, line of unity; dashed line, two-fold error range; dotted line, three-fold error range.