

## COMMENTARY

# Using Physiologically Based Pharmacokinetic Modeling for Mechanistic Insight: Cases of Reverse Translation

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## INTRODUCTION

Observation of a clinical event can spur reflective thinking on its source. In pharmacology, adverse events are examples of observations for which deriving the cause is important. Moving from observation to mechanistic understanding requires the use of tools that explicitly delineate biological systems, mode of action, and disease pathophysiology. By expanding understanding of biological factors that influence these events, such tools may allow scientists to discover triggering processes, and once confirmed, a means of mitigation.

## PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELS

Quantitative Systems Pharmacology (QSP) is a discipline that uses mathematical modeling of organism biology and its interaction with pharmaceuticals for the purposes of hypothesis generation and testing. The tools of QSP are varied but rely heavily on defining biological systems as a series of differential equations to describe the time course of drug disposition (pharmacokinetics), efficacy/safety, and/or disease progression. One commonly used tool is the PBPK model. PBPK models are mathematical representations of an organism that aim to predict the time course of tissue-specific drug disposition and are based on the explicit interaction of the drug and the body. Their use in planning or replacing clinical trials makes them an increasingly popular platform to translate preclinical or early clinical knowledge into an understanding of drug disposition and effect in human populations.

The aim of this commentary is to demonstrate where PBPK models have been used for reverse translation where a clinical phenomenon or a biological knowledge gap is resolved into its building blocks with the goal of evolving understanding.

## FROM CLINICAL OBSERVATION TO PRECLINICAL *IN SILICO* INTEGRATION: THE CASE OF SORAFENIB

Sorafenib is a multikinase inhibitor approved for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, and advanced thyroid cancer. Sorafenib displays a high degree of interindividual variability in pharmacokinetics, with hand–foot skin reaction (HFSR) being a significant exposure-related toxicity.<sup>1</sup> Boudou-Rouquette *et al.*<sup>1</sup>

determined that the occurrence of HFSR was associated with high plasma AUC<sub>0–12</sub> (day 30) and high albuminemia, although a multivariate analysis failed to identify any clinical or biological predictors of HFSR. Deconstructing the drivers of sorafenib disposition, which includes multiple enzymatic and transport processes, is a first step in understanding the link between the high exposure and the probability of HFSR. Edginton *et al.*<sup>2</sup> used a PBPK mouse model to reconstruct the observed pharmacokinetics of sorafenib and its two main metabolites in wildtype and single and multiple transporter knockout mice. The mouse model provided a means of isolating parameters thought to be important to pharmacokinetic variability despite not every parameter value being unique. The PBPK model allowed for integration of multiple *in vivo* and *in vitro* data sets and the use of uncertainty and global sensitivity analysis to test the hypothesis that these processes could produce extremes in exposure. The results showed that transporters greatly affected their substrates' liver and plasma concentrations (the only two matrices analyzed), while metabolizing enzymes were globally important to the systemic exposure of both sorafenib and its metabolites. Further evaluation (hypothesis testing) of the link between HFSR and skin exposure to sorafenib and/or its metabolites, sorafenib dose, and single nucleotide polymorphisms of important enzymes and transporters, as identified in a PBPK model (hypothesis generation), may allow for advanced dosing algorithms aiming to enhance efficacy and reduce dose-limiting toxicities.

## THE USE OF CODEINE DURING BREASTFEEDING

In Toronto, Ontario, Canada in 2005, a newborn died from a morphine overdose due to exposure via breastmilk from a mother prescribed Tylenol 3 (30 mg codeine + 300 mg acetaminophen) for postpartum pain.<sup>3,4</sup> Seven days postpartum, the newborn developed difficulty in breastfeeding and was lethargic. By day 11, the pediatrician noted a change in skin color and reduced milk intake. The child died on day 13. A postmortem blood concentration of morphine, the primary metabolite of codeine, in the newborn was 70 ng/mL; previously studied levels were <0.5–2 ng/mL in infants of breastfeeding mothers receiving codeine.<sup>5</sup> A day 10 milk morphine concentration was 87 ng/mL. This was the first report of an infant death from this cause and the case spurred regulatory response as well as response from the academic community to assess risk factors.

CYP2D6 converts codeine to morphine, which is primarily responsible for the analgesic activity of codeine. CYP2D6 is a polymorphic enzyme with humans presenting as poor metabolizers (PM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). Elimination of morphine is primarily due to glucuronidation catalyzed by UGT2B7 with a small component of renal excretion. Transfer from mother to infant occurs during breastfeeding events. A PBPK modeling exercise was undertaken to assess the risk factors for CNS depression in the infant as well as to identify the conditions that had to have been met for a fatal outcome in the Toronto case.<sup>6</sup>

A mother–infant model was created to capture drug metabolism and transfer of codeine and morphine. Infant PBPK models captured the immaturity of renal excretion and hepatic metabolism via CYP2D6 and UGT2B7 as compared with PBPK models of adults. A sensitivity analysis was undertaken at varying but relevant maternal codeine doses where infant morphine exposure over time was assessed under all permutations of mother and infant presenting as CYP2D6 PM, EM, and UM with corresponding permutations of age-relevant high and low UGT2B7 activity.

Maternal  $C_{max}$  values in breastmilk varied 60-fold such that the lower bound represented the CYP2D6 PM with high UGT2B7 activity and an upper bound defined by the UM with a low UGT2B7 activity. Low UGT2B7 activities were more important to breastmilk exposure than CYP2D6 activity for EM and UM, as EM and UM have overlapping activity in the population. With respect to the infant, maternal codeine dose was a significant risk factor to achieving potentially toxic morphine concentrations. Owing to the immaturity of CYP2D6 in the infant, regardless of genotype, conversion of codeine to morphine by the infant was of low importance to overall morphine exposure. Infant and maternal morphine exposure was highly sensitive to clearance via UGT2B7. Overall, maternal dose and the presence of the EM or UM CYP2D6 genotype with low UGT2B7 activity in both mother and child are risk factors for CNS depression in breastfeeding infants. Using the morphine concentrations from the Toronto case and the maternal Tylenol 3 dosing regimen, the model could only reproduce the concentrations by accounting for actual CYP2D6 UM status of the mother and the hypothesized low morphine elimination capability in both the mother and the infant.

In 2007, the US Food and Drug Administration (FDA) and Health Canada issued warnings of the increased risk of adverse events in breastfeeding neonates related to use of codeine in mothers who are CYP2D6 UMs. The 2009 model by Willmann *et al.*<sup>6</sup> led to the hypothesis that toxic morphine concentrations can be achieved in infants of mothers who are either CYP2D6 EMs or UMs. As of April 2017, the FDA now explicitly states that maternal codeine is not recommended during breastfeeding, regardless of CYP2D6 genotype.<sup>7</sup>

The death of the Toronto infant precipitated research from Willmann *et al.*,<sup>6</sup> as well as many others, to assess the underlying risk factors leading to morphine overdose in breastfeeding infants (reverse translation). The totality of this research (see the reference section of,<sup>7</sup> which includes Willmann *et al.*<sup>6</sup>) was then translated to policy statements aimed to protect both mother and child.

## BUILDING VIRTUAL CHILDREN

PBPK models are commonly used for translating the dose–exposure relationship from one group to another (i.e., monkey to human; adult to child) or from one dosing regimen to another (i.e., single to multiple dosing). These extrapolation exercises are used to determine, for example, an age-dependent dosing algorithm for the planning of first-in-pediatric trials. The use of these models, which are built on anatomical and physiological knowledge, can only be as good as our understanding of the knowledge. When it comes to children, experts agree that the knowledge gaps on pediatric anatomy and physiology is our greatest barrier to developing predictive pediatric PBPK models. Virtual children must “look like” real children if we are to have any confidence in pediatric PBPK model outcomes.

Allegaert *et al.*<sup>8</sup> specifically addressed the need to use pediatric PBPK models, integrated with *in vivo* PK data in children, to improve our understanding of developmental biology. In this way, we use the model to account for the anatomical and physiological information that is relatively certain and use *in vivo* data to determine isolated uncertain parameters. This parameter isolation is a hallmark of mechanistic models. An excellent example of the use of PBPK models for parameter identification was published by Villiger *et al.*<sup>9</sup> where oral absorption in children was being assessed. Models for pediatric oral absorption are relatively underdeveloped as compared with pediatric models of systemic disposition. Within the oral model, gastric emptying time (GET) is an important input that defines the rate at which an orally administered drug empties into the upper small intestine. For a soluble, permeable drug, GET rate limits absorption. Within a PBPK model framework, pediatric PK simulations were completed from two exemplary compounds with relatively high oral solubility and permeability. The predicted PK profiles were compared with observed PK profiles and, for children over 2 years of age, prediction accuracy was very good. For children less than 2 years of age,  $C_{max}$  was overpredicted and  $T_{max}$  was underpredicted. Using the data to optimize GET, the most sensitive and uncertain model parameter in that age range, the authors determined that GET is greater in this age range as compared with older children and adults. This information provides us with a quantitative understanding of GET as a function of age and will allow for refinement of virtual children. Similarly, my group used meta-analysis and PBPK modeling to contravene previously held assertions that small intestinal transit time (SITT) was different in children as compared with adults.<sup>10</sup> To highlight our findings we used modeling and simulation to demonstrate that the extent of sustained-release (SR) theophylline absorption was insensitive to changes in SITT, inferring that previous observations of altered SR theophylline disposition between children and adults are not the result of age-related changes in SITT. Indirect measurements of GET or SITT are published in the literature and can provide some confirmatory evidence of PBPK model outcomes; however, the data, especially as they relate to children, are usually sparse. PBPK models are able to fill knowledge gaps when sound methodology is used.

Deriving mechanistic understanding from clinical observation can be facilitated with tools that delineate the relationship between the two; here I present examples of this reverse translation using PBPK modeling. In some cases, this understanding remains unresolved or unable to be mitigated leading to contraindication, monitoring, or a recommendation of alternative drugs.

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