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PBPK modelling of drug transporters to facilitate individualized dose prediction

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Abstract:
Physiologically-based pharmacokinetic (PBPK) modelling is a commonly used strategy in the drug development and regulatory submissions. This commentary provides a critical overview of the current status of PBPK methodologies to predict transporter-mediated pharmacokinetics, in addition to impact of disease and genetics with respect to local and systemic concentration.
Physiologically-based pharmacokinetic (PBPK) modelling is now commonly used strategy in the drug development and regulatory submissions\(^1\)-\(^6\). A number of recent reports summarized current status on the use and predictive performance of PBPK modelling, and identified challenges in predicting complex metabolic drug-drug interactions (DDI)\(^7\),\(^8\). However, confidence in predictive performance of transporter-mediated pharmacokinetics/DDIs, enzyme-transporter-interplay and changes in both systemic and tissues exposure associated with these scenarios is yet to be adequately established.

Although fold change in the systemic exposure of a victim drug is a common metric to assess the magnitude of DDIs\(^9\), this method may have limitations for interpreting certain transporter-mediated DDIs, as seen in metformin case. Metformin is recommended as the first-line pharmacotherapy for type 2 diabetes; its renal clearance and hepatic disposition are governed by transporter-mediated processes via organic cation transporter/multidrug and toxin extrusion protein (OCT/MATE). Metformin hepatic exposure during OCT/MATE modulation may not necessarily change in proportion to systemic drug concentrations, resulting in scenarios with minimal or no alterations in metformin systemic PK, yet potentially increased liver exposure and subsequently glucose lowering (PD) effect\(^10\),\(^11\). In this case, it would be more relevant to quantify changes in drug exposure in tissues than in systemic circulation, which is challenging.

PBPK approach provides one key advantage in addressing this disconnect; it comes from the ability of these models to simulate tissue concentration-time profiles and gain mechanistic insight into the interplay of multiple processes (e.g., uptake and metabolic/biliary elimination) in different organs\(^12\)-\(^14\). One excellent example of using PBPK to predict a drug’s tissue PK is an integrated population PBPK model of simvastatin that incorporated complex lactone-acid inter-conversion in different tissues\(^15\). Subsequently, this simvastatin model was evaluated by perturbing the system to investigate the effect of reduced organic anion transporting polypeptide (OATP) 1B1 activity (\textit{SLCO1B1} c.521T>C) and inhibition of metabolism via cytochrome P450 (CYP) 3A4 (both reversible and irreversible mechanisms and contribution of parent and inhibitory metabolite were considered). Both scenarios are clinically relevant and have been associated with the development of simvastatin-induced myopathy in patients. In all the cases above, changes in both lactone and acid forms were simulated not only at the systemic level, but
also in the tissues of interest selected either due to efficacy/DDI concerns (liver) or safety (muscle). Validation of such simulated tissue profiles is particularly challenging. However, predicted changes in simvastatin lactone/acid tissue exposure supported clinically observed cholesterol lowering effects and muscle toxicity in the scenarios tested, providing indirect evidence of the model validity. Predicted changes in simvastatin acid liver exposure are supported by understanding of the rate limiting processes affecting its liver disposition provided by the model, as metabolic clearance, rather than active uptake, determines its liver AUC (for underlying principles reader is referred to\textsuperscript{13,15,16}). Predicted simvastatin acid liver AUC is only marginally affected (decreased by 2%) in 521CC homozygotes relative to the wild type, despite substantial increase in the systemic concentrations (Figure 1). This model prediction implies that cholesterol lowering efficacy of simvastatin depends on liver drug exposure and has no association with OATP1B1 polymorphism\textsuperscript{17}. Opposite is seen in the case of metabolic inhibition, where PBPK model predicted substantial increase in simvastatin acid liver exposure, in agreement with enhanced cholesterol reduction when simvastatin is co-administrated with some CYP3A4 inhibitors (e.g., diltiazem)\textsuperscript{15}. Simvastatin dose reduction in the case of decreased OATP1B1-mediated uptake (due to either polymorphism or OATP-inhibition) can reduce the risk of muscle toxicity, but patients may receive a sub-therapeutic dose (simvastatin acid liver exposure is unaffected by the decrease in active uptake clearance). Large scale clinical data are needed to further investigate and validate these model derived conclusions.

**Advantages of integrated population PBPK modelling**

Despite advances in complexity of *in vitro* cellular systems and modelling of transporter kinetic data, this “bottom-up” approach often results in the under-prediction of clearance\textsuperscript{14,18}. Reduction in OATP activity/expression due to hepatocyte isolation, cryopreservation, OATP genotype of the donor or culturing time may all contribute to this trend. In addition, *in vitro-in vivo* extrapolation of transporter kinetic data needs to account for differences in the transporter expression between the cellular system used and the tissue of interest (in a form of relative expression factors)\textsuperscript{19,20}. Uncertainty has also been reported in inhibition parameters for some of the transporters; multiple methodological considerations are currently
considered, including pre-incubation step, addition of albumin and mechanistic modeling of inhibition data for efflux transporters.

Furthermore, it is vital to appreciate the importance of suitable clinical PK data for either verification of the developed PBPK model ('learn and confirm') or refinement of transporter parameters associated with high uncertainty (a "middle-out" approach). Alternatively, in the instances when no \textit{in vitro} kinetic data are available for a transporter of interest, one can directly apply clinical PK data to estimate these parameters (a "top-down" method). However, this approach introduces some methodological challenges. Plasma data may be insufficient to inform all parameters of the model, raising identifiability concerns, often manifested in increased uncertainty (standard errors) in the parameter estimates and/or problems in the optimization routines to converge to a minimum. In addition, parameter estimation generally does not account for any uncertainty in other model parameters; these are often fixed during fitting and assumed to be correct. Sensitivity analysis performed on repaglinide PBPK model illustrates nicely this point. Multiple solutions of 'optimized' repaglinide active hepatic uptake clearance can describe its plasma concentration-time profiles almost equally well, conditional on different values used for the fixed parameters (passive diffusion and metabolic clearance). Despite inability to differentiate models on the systemic level, repaglinide liver exposure was substantially different across scenarios investigated, raising concerns if the PBPK model was to be used subsequently for the prediction of DDIs. In addition to liver, requirement for suitable clinical data for validation/estimation of renal uptake and efflux transport parameters has been discussed. For example, use of urine rather than plasma data is necessary for the optimization of MATE kinetic parameters and relative expression factor considering its localization on the apical membrane of renal proximal tubule cell.

To overcome the use of fixed parameters, the integrated population PBPK approach has been introduced. This approach combines physiologically-based approach with nonlinear mixed effects modelling and overcomes the reliance on fixed parameter by using a Bayesian framework. In this method, priors are updated using rich clinical data ('reverse translation') resulting in a statistical distribution of the output parameters, rather than just a single estimate. Emerging data on tissue concentrations (e.g., PET imaging) combined with integrated population PBPK modelling is seen as a powerful tool for
optimization of model input parameters that are associated with high uncertainty, resulting in improved understanding of tissue disposition and local DDIs.

**Extension of PBPK models to predict PK in special populations**

Recent analysis indicated that >40% of drugs approved in 2013-2014 lack any dose recommendations for patients with severe renal impairment\(^{7,28}\), highlighting a need for validated PBPK models to predict the impact of pathophysiological changes associated with chronic kidney disease. Despite recent increased efforts (cidofovir, rivaroxaban, metformin, lesinurad\(^{25,29,30}\)), many challenges still exist. Knowledge gaps are particularly evident in physiological/system data (e.g., transporter expression and proximal tubule cellularity in diseased kidneys), mechanistic in vitro renal transporter parameters and understanding of mechanism(s) causing changes in transporter-mediated secretion in renal impairment\(^{24,31-34}\). Reduced proximal tubule cellularity, reduced transporter expression or inhibition of renal transporters by uremic solutes have all been explored as potential mechanisms using PBPK\(^{30,35}\). Recent examples highlighted that different mechanisms considered in PBPK models for renal impairment each caused comparable net effect on the predicted systemic exposure and renal clearance of cidofovir and digoxin\(^{30,35}\). However, predicted dynamics inside proximal tubule cells were different depending on the assumption made, emphasizing that misspecification of mechanism in the model may have severe consequences for prediction of nephrotoxicity or transporter-mediated DDIs in renally-impaired patients\(^{35}\).

Similarly, predictive performance of PBPK is generally considered low with regard to hepatic impairment (HI). A good example that highlights this challenge is the model-based prediction of liver exposure of obeticholic acid (OCA) in subjects with HI. OCA is a modified form of an endogenous bile acid chenodeoxycholic acid (CDCA) in humans and was recently approved in the US and the EU for the treatment of primary biliary cirrhosis\(^{36,37}\). Plasma exposures of OCA and its glyco- and tauro-conjugates (glyco-OCA and tauro-OCA) are significantly increased in subjects with varying degrees of HI compared to subjects with normal liver function. The magnitude of increase in plasma exposure makes it challenging to adjust drug dose proportional to/ based on plasma exposure changes in subjects with HI. For example, the mean increases in AUC were 7, 11, and 37, and 17-fold for OCA, glyco-OCA, tauro-OCA, and total
OCA (parent and two conjugates), respectively in subjects with severe HI compared to healthy subjects. The PBPK model for OCA and its conjugates considered hepatic metabolism, permeation, and active transport of test species between the circulatory, hepatobiliary, and enteral compartments. Parameter changes associated with HI were either fixed in the OCA PBPK model (known ones, e.g., liver volume and hepatic blood flow) or estimated (unknown ones such as hepatic uptake and conjugation) using observed plasma PK of OCA and conjugates in HI subjects\(^{38,39}\). The models were verified using external (not used for model development) plasma PK data in healthy and HI subjects\(^{40}\). Only 2-fold increase in liver exposure of total OCA was predicted in subjects with severe HI compared to healthy, despite a much higher (13-fold) increase in plasma exposure (Figure 2); the latter is consistent with the observed clinical data (17-fold)\(^{39,40}\). To support its prediction of liver exposure, the applicant simulated endogenous CDCA and its conjugates using the same system parameters as for OCA. The simulated AUC ratios of total CDCA (severe HI/healthy) in plasma and liver generally agreed with the reported values comparing subjects with end-stage cholestasis or cirrhosis and healthy subjects. Based on the model-predicted moderate changes in liver OCA exposures, the applicant proposed that “no dose adjustment is required in patients with hepatic impairment”\(^{40}\). Several limitations on applicant’s PBPK analyses were recognized during the FDA review, including simplified representations of tissues, pressure changes and fluid absorption by gall-bladder, fixed ratio of conjugation with glycine and taurine regardless of the severity of HI, lack of information on food-bile acid interaction and specific parameterization regarding transporters in both healthy and HI subjects. Considering multiple assumptions made in the model and inadequate evaluation of some, the use of the model predicted elevation in liver OCA concentration alone was not deemed adequate to support drug dosing in subjects with severe HI. In particular because of significantly higher OCA plasma exposure observed in HI subjects receiving single dose and unknown relationship of OCA plasma or liver exposures to adverse events. The FDA requested additional simulations of OCA PK in plasma and liver under different dosing schedules in healthy subjects and subjects with HI. These simulations informed the FDA proposed conservative approach of adjusting the starting dose in subjects with moderate or severe HI (5 mg once weekly) to target plasma exposures to those of subjects with normal hepatic function (e.g., 5 mg once daily), followed by subsequent up-titrations of dose and dosing frequency based on efficacy and tolerability of the patients. Of note, the predicted liver exposure of OCA
under the initial dosing regimen of 5 mg once weekly in severe HI is approximately one-third that in healthy subjects receiving 5 mg once daily\textsuperscript{37,40}. Although modeling of OCA described above represents fine efforts to use PBPK to support dosing recommendation in subjects with HI, there is a clear opportunity for evolution towards leveraging tissue concentrations with increased confidence to inform dosing\textsuperscript{40}.

**Future directions**

Pediatric population is another cohort of patients in need for increased model-driven dose recommendation in the label\textsuperscript{41}. Emerging transporter expression data\textsuperscript{19,20,42}, together with the information on transporter ontogeny\textsuperscript{43,44} are expected to refine current model system parameters and transporter PBPK modelling in adult and pediatric population. Further work is required to understand the interplay between metabolites (especially conjugates) and transporters in targeted tissues and development of metabolite-parent PBPK models for the prediction of complex DDIs\textsuperscript{12,45}.

Models illustrated here provide examples where efficacy and toxicity of a drug are not linked to the surrogate plasma concentrations, but tissue concentrations, as predicted by the PBPK model. They emphasize that the structure and complexity of PBPK/organ model depends on its purpose and availability of physiological and \textit{in vitro} data to support mechanistic description of processes. Model development and step-wise verification represented here illustrate examples of methodological best practices in the PBPK modelling and simulation. It is evident that this approach is very informative in drug development and regulatory evaluation, with necessary recognition of challenges with respect to appropriate model structure, physiological plausibility and identifiability of parameters. Existence of verified victim drug PBPK models (as shown in simvastatin case), in combination with corresponding perpetrator PBPK model(s), is crucial to inform and guide the design of prospective clinical DDI and/or pharmacogenetic studies. It is envisaged that establishment of methodological best practices and repository of increased number of verified PBPK models for the marker probes and perpetrators will leverage decision-making in drug development and regulatory submissions.
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Figure legends:

**Figure 1.** Simulated concentration-time profiles for simvastatin lactone (SV) and acid (SVA) in plasma, liver tissue and muscle tissue for individuals with the homozygous wild-type TT (black line) and homozygous variant CC (red line) *SLCO1B1* c.521T>C. Full symbols represent observed mean ± SE plasma SVA concentrations for individuals with the TT (black circles) and CC (red circles) genotype. Taken from

**Figure 2.** Observed (open) and model predicted (filled) AUC and Cmax of systemic and liver concentrations of total obeticholic acid by liver function. Taken from page 137 of the OCALIVA Clinical Pharmacology Review.
References:


Observed data values are based on n = 8 subjects by group of hepatic impairment; Predicted data values are based on 200 iterations Monte-Carlo simulations in 6 subjects by group of hepatic impairment; Doxplot whiskers represent 1st and 99th percentile.

AUC = area under the curve; C_{max} = maximum concentration; HEPIMP = hepatic impairment; n = number of subjects; OCA = obeticholic acid