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COMMENTARY

Modeling Drug Disposition and Drug–Drug Interactions Through Hypothesis-Driven Physiologically Based Pharmacokinetics: a Reversal Translation Perspective

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1 Introduction

A crucial feature of physiologically based pharmacokinetic (PBPK) modeling is the ability to separate compound-dependent properties from population-dependent properties, enabling prospective prediction of compound exposure and disposition in a specific population by accounting for the demographic, physiological, and biological information of the population of interest. The impact of PBPK modeling for prospective prediction relies heavily on predictive accuracy, which is challenged by the scarcity of system-specific physiological or biological data, the quality of compound data measured from in vitro experiments, and the mechanistic understanding of processes governing the pharmacokinetics. It is, therefore, vital to regularly revisit and update the PBPK model for a special population, such as neonates and infants [1, 2], individuals of various ethnicities [3, 4], patients with renal impairment [5, 6], patients with chronic heart failure [7], or patients with cancer [8], when more data or new knowledge on the population become available, ensuring the system component of the model as physiologically accurate as the literature allows.

Even if the system-specific information has been adequately calibrated and widely accepted, the PBPK-simulated pharmacokinetic profile of the compound may not always match the observed profile in human. Large discrepancies of a simulated pharmacokinetic profile from the observed one could be indicative that key processes affecting the pharmacokinetics of the compound have not been sufficiently characterized by the PBPK model [9]. As such, the confidence of forward projections using the PBPK model with input data solely from in vitro and preclinical studies would be low. However, from a reversal translation perspective, the availability of clinical pharmacokinetic data offers a unique opportunity for the refinement of the PBPK model by means of hypothesis-driven approaches. Hypotheses could be generated by accounting for the prior knowledge of the compound and the disagreement of the predicted pharmacokinetic profile in virtual individuals against the clinical pharmacokinetic profile. The reversal translation processes generally involve sensitivity analysis, deconvolution, or model fitting, which take full advantages of the clinical observations to gain a greater understanding of the underlying mechanisms driving drug disposition. Ultimately, the reversal translation of clinical pharmacokinetic data could enhance the confidence of PBPK modeling for quantitative prediction of pharmacokinetics in untested clinical scenarios.

The PBPK modeling of cytochrome P450 2C9 (CYP2C9)-mediated tolbutamide drug interactions by Perkins and colleagues [10] could be viewed as a good example to illustrate how a substrate PBPK model is refined to improve the predictive accuracy from a hypothesis-driven and reversal translation perspective.

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2 The Contribution of CYP2C9 to Tolbutamide Clearance

Two crucial determinants for a "victim" compound or substrate PBPK model for drug–drug interactions are quantitative determination of the relative contribution of the intended drug-metabolizing enzyme to the substrate metabolism (the fraction metabolized, fm) [11] and the predictive power of the model to reproduce the pharmacokinetic profile of the substrate. In views of the importance of fm in predicting drug–drug interactions, Perkins and colleagues [10] revisited the default PBPK model of tolbutamide implemented in a PBPK platform. They noticed that tolbutamide was assumed to be completely metabolized by CYP2C9 (i.e., $fm_{CYP2C9} = 1$) in the default model [12], which appeared to be inconsistent with the estimated value ($fm_{CYP2C9} = 0.85$) on the basis of clinical and in vitro data [13–17]. Furthermore, the default tolbutamide model failed to reasonably predict the clinical drug–drug interaction with a CYP2C9 inhibitor sulfaphenazole [18], indicating the fm_{CYP2C9} in tolbutamide PBPK model may not be accurately assigned. A hypothesis that 0.85 of fm_{CYP2C9} may better reflect the clearance mechanism of tolbutamide was then generated through the PBPK analysis.

3 The Refinement of Tolbutamide PBPK Model for CYP2C9-Mediated Drug Interactions

In the proposed tolbutamide PBPK model by Perkins and colleagues [10], the CYP2C9 unbound intrinsic clearance of tolbutamide was optimized by means of a reversal translation approach using clinical pharmacokinetic data following intravenous administration, resulting in approximately 0.85 of the clearance fraction via the CYP2C9 pathway. The refined tolbutamide PBPK model was successfully predicted tolbutamide pharmacokinetic profiles in the absence and presence of sulfaphenazole or tasisulam, showing the ability of the refined model in the adequate prediction of CYP2C9-mediated tolbutamide drug interactions.

Of note, the default sulfaphenazole model (inhibitor model) implemented in the same PBPK platform was directly used without further justification in the sulfaphenazole–tolbutamide interaction simulations, which assumed that the default sulfaphenazole model had been adequately established and evaluated. Although it has been reported that assessment of the adequacy of inhibitor models prior to intended drug interaction prediction did not seem to improve its predictive power [19], it would be better if the predictive accuracy of the sulfaphenazole model for CYP2C9-related drug interactions with other substrates could be demonstrated before applying it to predicting its inhibitory effect on tolbutamide pharmacokinetics.

Another important efforts made by Perkins and colleagues [10], were further verified the proposed tolbutamide model using clinical drug–drug interaction data with tasisulam from a registered clinical study. Although the drug–drug interaction study of tasisulam and tolbutamide was conducted in a cohort of patients with cancer, it was reasonable to assume that there was no significant difference in the pharmacokinetics of tasisulam and tolbutamide between healthy subjects and participants with cancer enrolled in the clinical trial. On the one hand, as mentioned by Perkins et al. [10], the serum albumin levels in the volunteers with cancer were similar to those in healthy individuals. On the other hand, as shown previously [20], CYP2C9-mediated metabolism, using tolbutamide as a probe substrate, in subjects with cancer did not differ significantly from those without cancer. Comparable pharmacokinetic parameters between healthy individuals and patients with cancer were also seen in other oral oncology medications, such as copanlisib [21] and ribociclib [22].

Overall, the study by Perkins and colleagues [10] highlights the importance of qualification of the ability of a substrate PBPK model for drug–drug interactions. It also shows how clinical pharmacokinetic data can facilitate the fit-for-purpose refinement of a substrate PBPK model for predicting drug–drug interactions when the system component has been sufficiently established. The refined tolbutamide PBPK model could be expected to serve as a useful substrate model for exploring CYP2C9-mediated drug interactions.

Compliance with Ethical Standards

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Conflict of interest The authors have no conflicts of interest to declare.

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