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Machine Learning Prediction of the Three Main Input Parameters of a Simplified Physiologically Based Pharmacokinetic Model Subsequently Used to Generate Time-Dependent Plasma Concentration Data in Humans after Oral Doses of 212 Disparate Chemicals

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Abstract

Physiologically based pharmacokinetic (PBPK) modeling has the potential to play significant roles in estimating internal chemical exposures. The three major PBPK model input parameters (i.e., absorption rate constants, volumes of the systemic circulation, and hepatic intrinsic clearances) were generated in silico for 212 chemicals using machine learning algorithms. These input parameters were calculated based on sets of between 17 and 65 chemical properties that were generated by in silico prediction tools before being processed by machine learning algorithms. The resulting simplified PBPK models were used to estimate plasma concentrations after virtual oral administrations in humans. The estimated absorption rate constants, volumes of the systemic circulation, and hepatic intrinsic clearance values for the 212 test compounds determined traditionally (i.e., based on fitting to measured concentration profiles) and newly estimated had correlation coefficients of 0.65, 0.68, and 0.77 (p < 0.01, n = 212), respectively. When human plasma concentrations were modeled using traditionally determined input parameters and again using in silico estimated input parameters, the two sets of maximum plasma concentrations (r = 0.85, p < 0.01, n = 212) and areas under the curve (r = 0.80, p < 0.01, n = 212) were correlated. Virtual chemical exposure levels in liver and kidney were also estimated using these simplified PBPK models along with human plasma levels. These results indicate that the PBPK model input parameters for humans of a diverse set of compounds can be reliability estimated using chemical descriptors calculated using in silico tools.

Keywords: PBPK modeling; pharmacokinetics; general chemicals, food components
Introduction

Therapeutic drug monitoring of steady-state plasma concentrations at designated intervals in individual patients for specific medicines, such as antipsychotics drugs, is an accepted clinical practice to maintain drug concentrations in the target ranges.\(^1\)\(^,\)\(^2\) Such monitoring methods could be supported by pharmacokinetic modeling and simulations to address critical questions related to patient care.\(^3\) Full physiologically based pharmacokinetic (PBPK) models\(^4\) can predict drug monitoring results in patients\(^5\)\(^-\)\(^7\) based on the physiological and anatomical properties of the relevant organ and the chemical properties of the modeled substance.\(^8\)\(^,\)\(^9\) Simplified PBPK models, which are easier to handle than full models, have been developed for use by a wide range of paramedical staff for predicting drug monitoring results and have been applied in some nonfatal overdose cases.\(^10\)\(^-\)\(^14\) Such models can predict plasma concentration curves and can quickly determine whether time-dependent treatments with gastric lavage and/or activated charcoal are likely to be beneficial in real-time emergency situations. Rapid treatment with gastric lavage is generally indicated in emergency rooms if it can to be delivered within 60 minutes of ingestion\(^15\); however, this does not take into account the specific pharmacokinetics of the ingested substance, and in some cases, gastric lavage might be beneficial even if delivered outside the 60-min window.

Simplified PBPK models are useful not only in the above-mentioned fields of therapeutic drug monitoring and drug poisoning, but also during drug discovery and chemical risk assessment.\(^16\) Although the toxicological profiles of a variety of chemicals to which humans are exposed have been investigated in rodents, new alternative methods to evaluate compound safety are being developed worldwide using in vitro or in silico approaches.\(^17\)\(^,\)\(^18\) PBPK modeling, which is known as PBK modeling in the European Union,\(^19\) has the potential to
play a significant role in reducing and replacing the use of animals for estimating toxicokinetics or internal exposures.\textsuperscript{20}

The input parameters for PBPK models are generally based on \textit{in vivo} data; however, to investigate the feasibility of making such modeling more accessible in real-time, we generated PBPK model input parameters \textit{in silico} for a broad range of chemicals using a machine learning algorithm without reference to \textit{in vivo} studies.\textsuperscript{21,22} The values of the three major PBPK model input parameters, i.e., the absorption rate constant ($k_a$), the volume of the systemic circulation ($V_1$), and the hepatic intrinsic clearance ($CL_{h,int}$), for this selection of chemicals were previously generated \textit{in silico} for rats.\textsuperscript{21} Therefore, the aim of the present study was to establish \textit{in silico} models for predicting $k_a$, $V_1$, and $CL_{h,int}$ values (for use in human PBPK models) based on a number of chemical descriptors. These estimated input parameters for human PBPK models were then used to generate the plasma and tissue concentrations of 212 disparate chemicals after virtual oral administrations of 1.0-mg/kg doses.

\textbf{Materials and methods}

The pharmacokinetic data sets to which machine learning was applied in this study covered 212 chemicals; these were mainly taken from our literature survey of reported blood concentrations versus time data for oral administration in humans (180 chemicals) and included 46 medicines from a new Japanese drug database (Supplemental Table S1). The details for setting up simplified PBPK models consisting of gut, liver, kidney, and central compartments have been described previously\textsuperscript{10,11,13} and are briefly outlined in the Supplemental materials and methods. The necessary input parameters, i.e., $k_a$, $V_1$, and
$CL_{h,int}$ for PBPK models are conventionally computed to achieve the best fit to reported human plasma concentrations in a similar manner to that done previously for rats (which included 11 of the current test chemicals) and humanized-liver mice (which included 21 of the current test chemicals).\textsuperscript{21} Human input parameters for these 32 chemicals were scaled up from the previous animal PBPK model parameters as previously described.\textsuperscript{23-28} The criterion for acceptable predictive abilities that was previously applied for rat PBPK models was a threefold error for reported/observed values for plasma $C_{\text{max}}$ and AUC after virtual administrations of oral doses of 1.0 mg/kg. Human values for $k_a$, $V_1$, and $CL_{h,int}$ for another six chemicals were estimated in this study by employing a scale-up strategy to humans from preliminary humanized-liver mice data shown in \textbf{Supplemental Fig. S1}, as previously described.\textsuperscript{25,26}

For each substance, the chemical descriptor sets of 1710 parameters describing chemical structural and physicochemical properties were obtained using open-source \textit{in silico} programs (such as Rdkit and Mordred) as described previously.\textsuperscript{21} Before the prediction process, some chemical descriptors were auto-scaled to account for missing data by supplementation with median values. To establish prediction systems based on the \textit{in silico}-derived values, machine learning algorithms were applied that utilized ridge regression\textsuperscript{29} for $k_a$ and $V_1$ and LightGBM\textsuperscript{30} for $CL_{h,int}$. Estimation models for $k_a$, $V_1$, and $CL_{h,int}$ were extensively validated with a modeling approach designed to integrate nested cross-validation.\textsuperscript{21} Average absolute fold errors for $k_a$, $V_1$, and $CL_{h,int}$ values were calculated as described previously.\textsuperscript{31}
Results and Discussion

In the medical field, applications of machine learning to drug discovery or repositioning have been focused. Automated covariate selection in pharmacometrics model building has been reported. On the other hand, humans are generally exposed to unexpected general chemicals or food components from the environments. To illustrate their broad diversity in chemical properties, the current 212 compounds (Supplemental Table S1) underwent projection onto our previously proposed two-dimensional chemical space consisting of 25 partitions (Figure 1). The newly tested 104 chemicals among the total of 212 compounds also demonstrated broad diversity. The relationships between the traditionally determined human PBPK model input values (hereafter referred to as in vivo-derived) and the values estimated using our proposed new computational approach (in silico-derived) for the 212 chemicals included in the current study (Supplemental Tables S1 and S2) are shown in Figure 2. The correlation coefficients of 0.65, 0.68, and 0.77 (p < 0.01, n = 212), respectively, for the $k_a$, $V_1$, and $CL_{h,\text{int}}$ values, were statistically significant for the current 212 chemicals. Average absolute fold errors for the $k_a$, $V_1$, and $CL_{h,\text{int}}$ values were 1.89, 2.02, and 3.28, respectively. These results indicated that the $k_a$, $V_1$, and $CL_{h,\text{int}}$ values in humans for a diverse set of chemicals could be reliably estimated using between 17 and 65 chemical descriptors (Supplemental Table S2) that were calculated using in silico tools.

In the medical field, direct estimation of drug concentrations of the typical single key medicine like cyclosporin A in body fluids has been reportedly proposed. On the other hand, the three input PBPK parameters were used to generate time-series kinetic data in this study because direct estimation for a variety of chemicals is not realistic in non-medical research field. The human plasma concentrations of the current 212 chemicals were generated using PBPK models using two sets of input parameters: either traditional in vivo-derived values
or *in silico*-derived values. When the traditionally determined PBPK model input values for the 212 chemicals were replaced with the *in silico*-estimated values of $k_a$, $V_1$, and $CL_{h,int}$ (as shown in Figure 2 and Supplemental Table S2), the output $C_{\text{max}}$ values in human plasma generated using the two sets of input parameters were well correlated (correlation coefficient, $r = 0.85$, $p < 0.01$, Figure 3A and Supplemental Table S3). Moreover, there was a good correlation between the AUC values in human plasma of the 212 chemicals obtained using PBPK models (Figure 3B and Supplemental Table S3) with empirically determined and *in silico*-estimated input parameters ($r = 0.80$, $p < 0.01$). In this way, the applicability to human pharmacokinetics of these estimated input parameters for PBPK modeling was demonstrated.

In rats, the proposed PBPK models were able to simulate concentrations in rat livers and kidneys in a similar manner as rat plasma; the observed hepatic concentrations were confirmed with limited numbers of chemicals.$^{26,28}$ The current human PBPK models were also able to output the virtual concentrations in human tissue in a similar manner. The concentrations of 212 chemicals in human liver and kidney generated by PBPK models were also evaluated using *in vivo*- and *in silico*-derived sets of input parameters. When the traditionally determined PBPK model input values for 212 chemicals were replaced with the *in silico*-estimated values of $k_a$, $V_1$, and $CL_{h,int}$ (as shown in Figure 2 and Supplemental Table S2), the output $C_{\text{max}}$ and AUC values in human liver using the two sets of input parameters were well correlated ($r = 0.89$ and 0.83 for $C_{\text{max}}$ and AUC, respectively, $p < 0.01$, Supplemental Figure S2A and S2B and Supplemental Table S3). There were also good correlations for $C_{\text{max}}$ and AUC values in human kidney of the 212 chemicals between those obtained using PBPK models (Supplemental Figure S2C and S2D and Supplemental Table S3) with empirically determined and *in silico*-derived input parameters, i.e., $r = 0.87$ and 0.84 ($p < 0.01$) for $C_{\text{max}}$ and AUC, respectively.
Recently we developed a computational method to predict the apparent membrane permeability values (both influx and efflux) as determined in an in vitro pH-dependent monolayer cell system for ~200 diverse compounds. These membrane permeability values are essentially related to absorption processes in vivo, and the prediction method primarily used trivariate linear regression with an additional machine learning approach. This trivariate regression analysis used three common physicochemical properties (reflecting the experimental apical and basal pH conditions used in the assays and the molecular weight of the substance) in combination to predict the bidirectional transport parameters. The prediction accuracy was then enhanced by applying a light gradient boosting machine learning system to estimate influx and efflux apparent permeability values by incorporating 17 and 19 less common in silico chemical descriptors, respectively. Although the selected chemical descriptors should fundamentally reflect and be related to chemical solubility/dissolution and/or intestinal permeability in relation to the absorption rate constants in the current study, the physicochemical properties relevant to the overall absorption of compounds may contribute in a diverse manner to these machine learning approaches. Despite the previous chemical descriptors for rat $CL_{h, \text{int}}$ model applying a light gradient boosting machine learning system could be commonly applicable to the current human $CL_{h, \text{int}}$ model, human $k_a$ and $V_1$ models utilized ridge regression with chemical descriptors were differently set up from the previous rat $k_a$ and $V_1$ models (data not shown).

In conclusion, the concentrations of 212 chemicals in plasma, liver, and kidney after virtual oral doses in humans could be reliably estimated using simplified PBPK models with input parameters calculated from sets of between 17 and 65 chemical properties that were generated using in silico prediction tools. Apparently, an increasing number of datasets for non-medical chemicals with pharmacokinetic data is one of determinant factors for updating the established in silico models for three input human PBPK parameter values. It should be noted
that the virtual plasma $C_{\text{max}}$ values of chemicals could represent an inverse marker for rat hematotoxicity (as reflected in the lowest-observed-effect levels),\textsuperscript{36} and the \textit{in silico} predicted values for permeability across intestinal cells could represent a putative indicator for hepatotoxicity (as reflected in the no-observed-effect levels).\textsuperscript{35} On the other hand, areas under the curve of unmetabolized (remaining) dimethylaniline derivatives estimated using rat pharmacokinetic models showed an apparently positive correlation with the reported lowest-observed-effect levels for haematotoxicity of these chemicals such as 3,5-dimethylaniline and 2,6-dimethylaniline.\textsuperscript{39} Consequently, the above-described computational methods represent new alternative approaches that could contribute to chemical safety screening. This approach to human PBPK modeling, with the availability of \textit{in vitro} and \textit{in silico} alternatives for generating pharmacokinetic properties, contributes to the effectiveness of computational toxicology for assessing the potential risk of industrial chemicals and/or food components. The simplified PBPK models described here, which are easy to implement, could be applied for predicting a variety of drug exposures by a wide range of paramedical staff, industry researchers, and regulatory authorities.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains Supplementary Materials.
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**Figure 1.** Coordinate values of 212 compounds in a two-dimensional plane with 25 partitions illustrating variety in the chemical space. The values for 104 newly evaluated compounds (gray circles) and 108 previously evaluated compounds (open circles) are shown. The proposed evaluation of the chemical space\textsuperscript{16,21,34-37} was conducted for the 108 previously examined chemicals in studies on intestinal permeability\textsuperscript{35,37} and rat pharmacokinetics.\textsuperscript{21}
Figure 2. Correlations between determined (in vivo-derived) and estimated (in silico-derived) PBPK model input parameter values $k_a$ (A), $V_1$ (B), and $CL_{h,\text{int}}$ (C) for 212 chemicals. Solid and dotted/dashed lines indicate equivalence and two- and tenfold ranges, respectively.
Figure 3. Correlations of $C_{\text{max}}$ (A) and AUC (B) values for 212 chemicals in human plasma generated by PBPK models using traditionally determined (in vivo-derived) and currently estimated (in silico-derived) values of the three PBPK model input parameters. Solid and dotted/dashed lines indicate equivalence and two- and tenfold ranges, respectively.