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Prediction of Total Drug Clearance in Humans Using Animal Data: Proposal of a Multimodal Learning Method Based on Deep Learning

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ABSTRACT

Research into pharmacokinetics plays an important role in the development process of new drugs. Accurately predicting human pharmacokinetic parameters from preclinical data can increase the success rate of clinical trials. Since clearance (CL) which indicates the capacity of the entire body to process a drug is one of the most important parameters, many methods have been developed. However, there are still rooms to be improved for practical use in drug discovery research; "improving CL prediction accuracy" and "understanding the chemical structure of compounds in terms of pharmacokinetics". To improve those, this research proposes a multimodal learning method based on deep learning that takes not only the chemical structure of a drug but also rat CL as inputs. Good results were obtained compared with the conventional animal scale-up method; the geometric mean fold error was 2.68 and the proportion of compounds with prediction errors of 2-fold or less was 48.5%. Furthermore, it was found to be possible to infer the partial structure useful for CL prediction by a structure contributing factor inference method. The validity of these results of structural interpretation of metabolic stability was confirmed by chemists.

Introduction

Research into pharmacokinetics during drug development plays an important role in the development of new drugs throughout the entire process, from searching for seed compounds to conducting clinical trials.[1] It has been reported that prior to 1985, the reason for around 40% of dropouts during drug development was due to pharmacokinetics.[2] With the subsequent introduction of new experimental systems, including those using human-derived specimens such as human liver microsomes and hepatocytes, and the development of various methods related to in vitro—in vivo extrapolation (IVIVE), the proportion of dropouts due to pharmacokinetics in the 2000s improved to around 10%.[3,4] However, although the proportion of dropouts due to factors arising from drug effects and toxicity has been increasing, it is thought that this may also include cases where exposure to the drug target could not be controlled appropriately, and that not all of the problems, in terms of pharmacokinetics in human clinical settings, have necessarily been solved. As a result, one strategy for further improving the success rate of clinical trials is inference of human clinical dosages that show the best drug effect profile. For this, it is necessary to predict the human pharmacokinetic parameters from

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preclinical data accurately before transitioning to human clinical trials.[5] In general, the parameters that have a large effect on the blood concentration profile of a drug are the volume of distribution (Vd), which quantifies the distribution of the drug inside the human body, and total body clearance (CL_{tot}), which shows the drug processing capacity in the entire body. There are many points where Vd is determined by the physical properties of the drug, such as protein binding and membrane permeability, and predictions from preclinical data have been relatively good.[6,7] However, predicting CL_{tot} is extremely difficult because of the factors described below.

For practical use in drug discovery research, two problems of CL_{tot} prediction method are "improving the prediction accuracy" and "extracting the features of the chemical structure of the drug that determine the magnitude of CL_{tot}". The background that makes predicting the former difficult is that there are multiple drug clearance pathways, including metabolism mainly by the liver, bile excretion of unchanged drug, and excretion in urine. Even for metabolism alone, in recent years, the number of drug candidate compounds that are metabolized by various kinds of not only cytochrome P450 (CYP) molecular species, but also non-CYP Phase I enzymes (Aldehyde Oxidase, Carboxylesterase) and Phase II conjugation enzymes (UDP-Glucuronosyltransferase), has been growing.[8,9] Furthermore, for some drugs, it is known that membrane permeation in the liver and kidneys occurs via a variety of transporters, and cases have also been reported where such membrane permeation acts as the rate-limiting step in organ clearance.[10] Although the IVIVE method, where the intrinsic clearance obtained by in vitro studies using human hepatocytes and microsomes is scaled up to determine hepatic clearance, is frequently used as a method for predicting clearance, many cases cannot necessarily be scaled accurately because of problems such as differences in experimental systems and variations in lots between human specimens. Thus, no suitable in vitro experimental systems currently exist for other organs, and application is difficult.[11] The weight power law, used to scale rat data to fit pharmacokinetic parameters, results in two-fold predictions errors. However, verification has not been performed on external data sets.[12] Furthermore, establishment of the above method originated from the mutual similarity in kidney structure between animals, and it is expected to be difficult to establish for pharmaceuticals that are not excreted via the kidneys. It must be said that many differences are found in the repertoire and substrate recognition of metabolic enzymes and transporter molecular species between animals of different species, and handling the wide variety of structures of drugs using a uniform methodology is fundamentally difficult. In addition, techniques have been proposed for employing machine learning methods that use chemical structure fingerprints, physicochemical parameters, animal clearance, and other factors as explanatory variables.[13–15] Although these methods produced relatively high accuracies, all of them could not solve the problem described in the next paragraph.

In the drug discovery stage, medicinal chemists search for compounds with low clearance. To achieve it, not only accurate clearance prediction but also interpreting chemical structure contributes to clearance are needed. This problem is a form of the "black box" problem that often occurs when using machine learning methods.[16,17] In the case of conventional methods, such as IVIVE and animal scale-up methods, which do not use the chemical structure and prediction methods that convert the chemical structure into a useful descriptor, none were able to obtain hints on how to optimize pharmacokinetics by converting the chemical structures in this way. Among the clearance prediction methods, if the partial structure of the drug that mainly determines the magnitude of the metabolic clearance could be inferred, it would lead to positive proposals for candidate structures for new compounds with improved pharmacokinetic properties.

To solve these two problems, this research proposes a new CL_{tot} prediction method that uses Deep Tensor.[18] Deep Tensor is a deep learning technique that works on graph data, where "graph data" means data representing the connections between objects and chemical structures can be represented as graph data by focusing on the connections between atoms. Deep Tensor handles the graph data represented in tensor (multidimensional array) form. The graph data is decomposed into a core tensor and factor matrices by Structure Restricted Tensor Decomposition (SRTD) and then the core tensor is inputted into a neural network. The core tensor is expected to include the important features of the graph data and to enable an effective prediction. SRTD uses a "target core tensor," which guides the decomposition into desirable one. The optimal target core tensor and the parameters of the neural network are obtained using Extended Backpropagation algorithm. Deep Tensor can also explain the prediction results using structure contributing factor inference method. This method learns an interpretable model (linear regression model) which locally approximates a black box model (neural network). The interpretable model gives the contributions of the core tensor to the prediction result and then these contributions are converted to those of the graph data by inverse conversion of SRTD. As a result, it becomes clear which connection of the graph data is important for the prediction. For the first problem of "improving prediction accuracy", the proposed method learns the Deep Tensor model whose explanatory variables are the chemical structure and the rat CLtot. This multimodal model can be expected to achieve better prediction accuracy like the existing machine learning methods mentioned above. For the second problem of "extracting the features of the chemical structure of the drug that determine the magnitude of CL_{tot}", the chemical structure that contributes to CL_{tot} prediction is extracted using structure contributing factor inference method for Deep Tensor. The contributions of the extracted chemical structure are inferred according to the elimination pathway, thereby providing hints for improving pharmacokinetics. The proposed method is expected to increase the success rate of clinical trials and lead to drug development.

Materials and Methods

Data Set

Data were extracted for 748 compounds for which human CL data were available from Lombardo et al.[12] and ChEMBL ver. 23[19](see Supplementary_Dataset.pdf). Among these, 394 compounds had rat CL data. Preprocessing consisted of calculating the human and rat CL data using the following equation for the respective data sets:

$$z = \frac{log_{10}x - \mu}{\sigma}$$

where z is the value after preprocessing, x is the original data, μ is the mean value of $\log_{10}x$, and σ is the standard deviation of $\log_{10}$. These two data sets were taken as the gold standard for cross-validation (CV) testing. Note that although virtually none of the elimination pathways have been identified in the compounds used in this work, when the data set of Lombardo et al., which has a large collection of data accumulated for drugs, is compared with the data of Varma et al., which investigated human kidney elimination, of the 231 compounds that were compared, 157 had a kidney elimination rate of 50% or less of CL_{tot} and 74 had 50% or more.[20] Furthermore, although data were collected during intravenous

administration, for eptaloprost, it was shown that there were errors in the cited reference, and the human data were from oral administration. Then, although the value of clearance of artesunate was too high from the viewpoint of physiology, this data was used to consider a large clearance compound into our model.

Deep Tensor

To predict CL in humans, a deep learning technique for graph data called Deep Tensor[18] was used (Fig. 1). The chemical structure (graph) and/or rat CL were used as explanatory variables for Deep Tensor. The chemical structure was represented as graph data in the previously reported[18] way. When the chemical structure and rat CL were taken as explanatory variables, the rat CL was inputted to the neural network without SRTD. In other words, the input to the neural network consisted of the core tensor corresponding to the chemical structure and the rat CL. The core tensor size was set to 50 × 50. The neural network structure was set to two intermediate layers with 1000 neurons in each layer, and the number of neurons in the output layer was 1. In the intermediate layers, the ReLU function[21] was used as the activation function, and batch normalization[22] with a decay rate of moving average = 0.9 and epsilon value = 2e-5, and dropout with rate = 0.5[23] were applied. The number of epochs of learning was set to 50 and the minibatch size was set to 100.

The partial structures of the compounds that contributed to each prediction were visualized for the Deep Tensor prediction results. First, a previously reported[18] method was used to calculate the degree of contribution of each explanatory variable to the prediction result. The level of contribution of each bond in the compound was calculated for the case where the compound was taken as the explanatory variable. The levels of contribution of each bond in the compound and the rat CL were calculated for the case where the chemical structure and rat CL were taken as explanatory variables. In the latter case, the inputs of the interpretable model were the core tensor corresponding to the chemical structure and the rat CL. The value of σ was set to 10 for the calculation of the proximity measure.

Performance Evaluation Protocol

The accuracies of the animal scale-up method (baseline), SVR method, and proposed method using Deep Tensor were evaluated by using a data set of compounds with assigned human and rat CL data. The animal scale-up method is a linear model that uses rat CL data. For the two types of machine learning methods, a total of four methods were evaluated with a method where the only input was the structure information of the compound and a method where the input was both compound information and rat CL information.

To evaluate the accuracy of the predictions, 5-fold CV tests were performed. First, the gold standard data set was randomly divided into five subsets. Next, one of the subsets was used as the evaluation set, and the remaining four were used as training sets. A prediction model was then constructed using the training sets. Finally, the prediction scores of all of the pairs in the evaluation set were calculated.

The geometric mean fold error (GMFE) and percent of k-fold error (k = 2,3,5) were used as evaluation indicators of the prediction accuracy of the method. For the GMFE, the case of GMFE = X can be interpreted as the difference between the actual and predicted values having a mean of X times. The GMFE is expressed by the following equation:

$$\mathrm{GMFE} = 10^{mean|log_{10}(Predicted/Observed)|}$$

GMFE values closer to 1 indicate better accuracy. Furthermore, the percent of k-fold error is the proportion of data within an error of k times (correct value/k ≤ predicted value ≤ k × correct value). The value of percent of k-fold error indicates better accuracy the closer it is to 100%.

We compared the proposed method with two previous methods: animal scale-up methodand support vector regression (SVR) with the Gaussian radial basis function (RBF) kernel. The reason why we selected SVR was high accuracy was observed in the model of the recent study.[15] Animal scale-up methodand SVR were implemented using the scikit-learn library.[24] The rat CL data with the best accuracy in a previous report[12] were used as the explanatory variable for animal scale-up method. Furthermore, the extended connectivity fingerprint with bond diameter four (ECFP4) and/or rat CL was used as the explanatory variables for SVR. The ECFP4 compound descriptor was calculated using RDKit with parameters of radius 2, 1,024 dimensions, and other parameters at default. The SVR hyperparameters were searched over all combinations of 16 values of hyperparameter C (2^{-5}, 2^{-4}, …, 2^{9}, 2^{10}), 11 values of hyperparameter ε (2^{-10}, 2^{-9}, …, 2^{-1}, 2^{0}), and 21 values of hyperparameter γ (2^{-20}, 2^{-19}, …, 2^{-1}, 2^{0}). The final parameters used the combination with the highest squared correlation coefficient value in the 5-fold CV.

Results

Performance Evaluation of Human Clearance Prediction

The upper half of Table 1 shows the evaluation results for the data set where human and rat CL data were assigned (Fig. 2). First, the animal scale-up method, which was the conventional method used as the baseline, had a GMFE of 2.65 and a 2-fold error of 47.2% in the 5-fold CV. Next, a comparison was performed between chemical structure information only and a multimodal model of

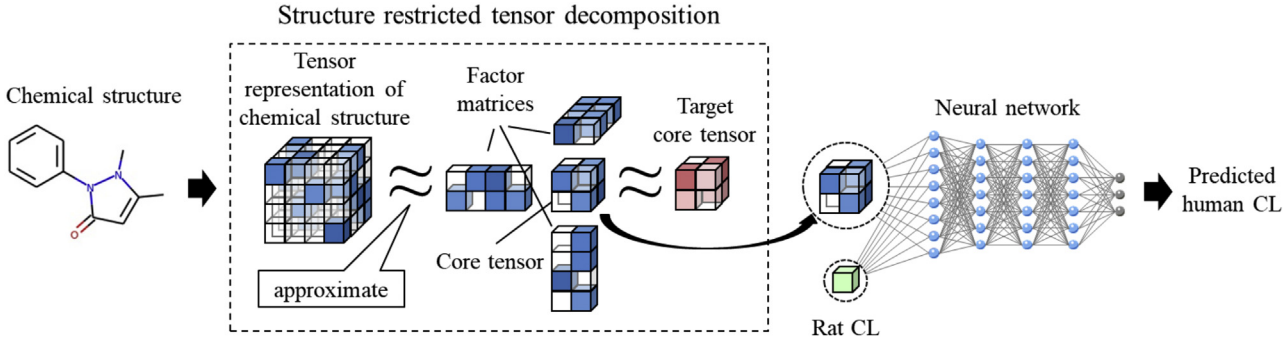

Fig. 1. Overview of human CL prediction using multimodal Deep Tensor model.

Table 1
The GMFE and % of 2-, 3-, and 5-Fold Errors in the CV Experiments for Three Methods.

Regression Algorithm	Animal Scale-Up Method	Support Vector Regression		Deep Tensor	
Explanatory Parameters	Rat CL	ECFP4	Rat CL + ECFP4	Chemical Graph	Rat CL + Chemical Graph
Compounds including human and rat CL					
GMFE	2.65	2.96	2.88	3.23	2.68
% of 2-fold error	47.2	41.9	43.9	38.3	48.5
% of 3-fold error	66.2	60.7	61.9	55.8	67.3
% of 5-fold error	83.5	77.9	78.4	74.6	84.0
Compounds including human CL					
GMFE	–	2.72	–	2.93	–
% of 2-fold error	–	44.4	–	42.1	–
% of 3-fold error	–	65.2	–	63.0	–
% of 5-fold error	–	80.9	–	78.5	–

chemical structure information and rat CL information. In the case of the SVR method, for chemical structure information (ECFP4 descriptor) only, the GMFE was 2.96 and the proportion of compounds with prediction errors of 2-fold or less was 41.9%. On the other hand, for the multimodal model of chemical structure (ECFP4) and rat CL information, the GMFE was 2.88 and the proportion of compounds with prediction errors of 2-fold or less was 43.9%. In the SVR results, the accuracy of the multimodal model with the rat CL was higher than that of chemical structure information only. Similarly, in the case of the Deep Tensor method, for chemical structure information only, the GMFE was 3.23 and the proportion of compounds with prediction errors of 2-fold or less was 38.3%. On the other hand, for the multimodal model of chemical structure information and rat CL information, the GMFE was 2.68 and the proportion of compounds with prediction errors of 2-fold or less was 48.5%. In the results of the Deep Tensor method, the accuracy of the multimodal model was higher than that of chemical structure information only. Furthermore, similar trends were observed in the results for percent of 3-fold and 5-fold errors. It is thought that these results show the multimodal effect.

The lower half of Table 1 shows the evaluation results for the data set where human CL data were assigned (Supplementary

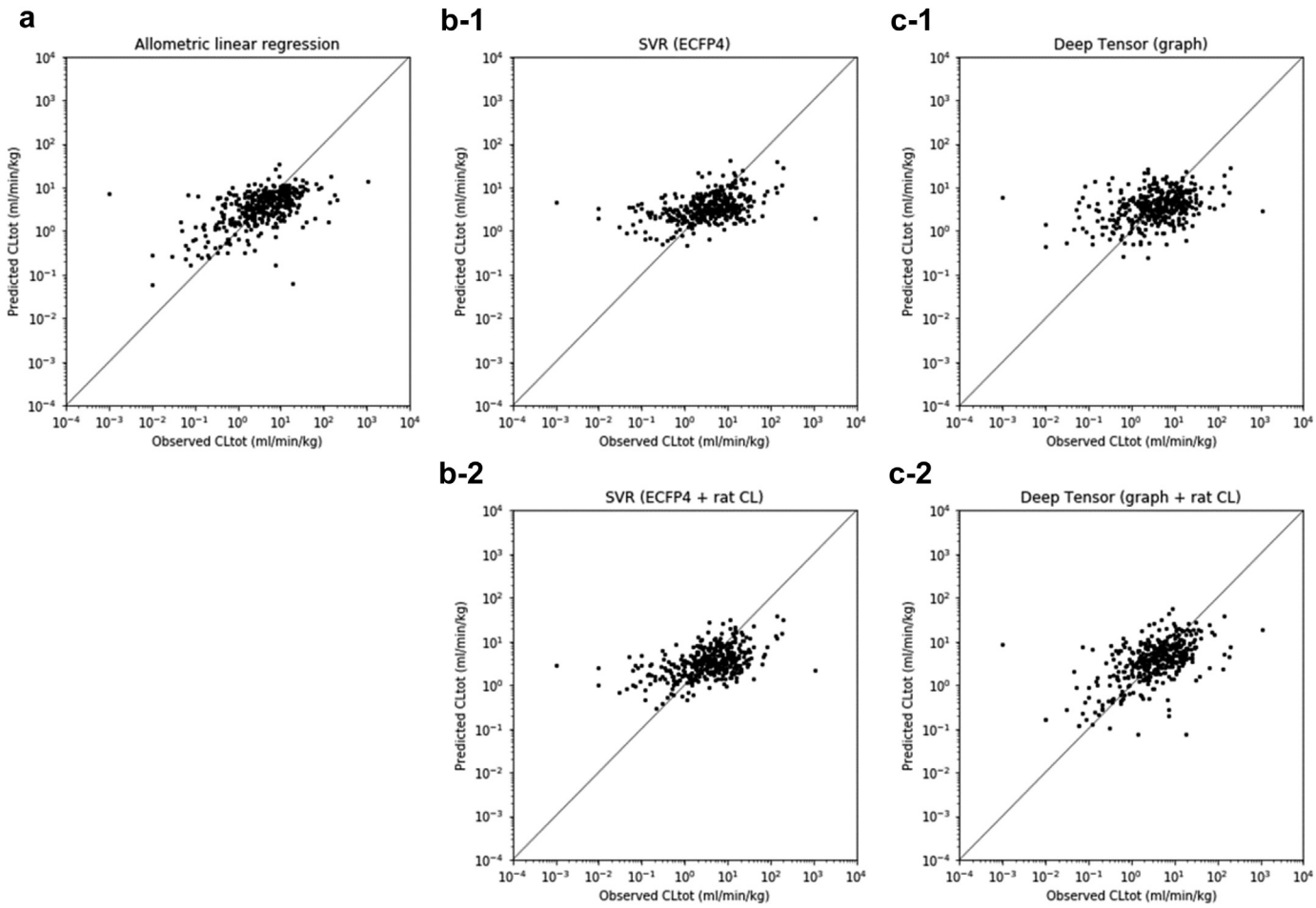

Fig. 2. Plot of cross-validation regression. The x-axis shows the actual measured value, and the y-axis shows the predicted value. (a) Allometric linear regression. (b-1) ECFP4. (b-2) ECFP4 + rat CL by support vector regression (SVR). (c-1) Chemical structure. (c-2) Chemical structure + rat CL by Deep Tensor.

Fig. S1). When SVR was used taking ECFP4 as the explanatory variable, the GMFE was 2.72 and the compounds with prediction errors of 2-fold or less were 44.4%, 3-fold or less were 65.2%, and 5-fold or less were 80.9%. Furthermore, when Deep Tensor was used taking the chemical structure information as the explanatory variable, the GMFE was 2.93 and the compounds with prediction errors of 2-fold or less were 42.1%, 3-fold or less were 63.0%, and 5-fold or less were 78.5%. This result suggests that machine learning methods using only chemical structure information give good prediction accuracy, even under conditions where there is absolutely no in vitro or animal experimental data. Since prediction is possible by inputting only the structure formula, this may also make a large contribution to compound design in the early stages of drug development.

Discussion

Although items, where there was a large difference between the prediction and actual measurement were investigated in all of the models created up to this point, obtaining a discussion was difficult from the perspective of physical properties. However, when the fold errors in the actual and predicted values were plotted for actually measured human CL, a trend was found in all of the models for the fold error to be larger in compounds where the actually measured human CL was significantly small or significantly large (Fig. 3 and Supplementary Fig. S2). This indicates that the training was insufficient in regions of human CL values where there were few data in the training data set. However, in the rat multimodal deep learning model, this trend was comparatively small, and compounds, where the human CL value was significantly small or significantly large were predicted more accurately compared with other models (Fig. 3).

For the compounds where the difference between the predicted results by the Deep Tensor method and actual measured values were 3-fold or less than the actual measurement results, inference of the chemical structures that contribute to CL prediction using a structure contributing factor inference method was performed, and the validity of this was evaluated by chemists. First, inference of the chemical structure that contributes to CL prediction (human: 20 mL/min/kg, rat: 70 mL/min/kg) (Fig. 4a and b) was performed on the eight high CL compounds (Fig. 4a), where the actual measured human and rat values are greater than or equal to the hepatic blood flow rates (human: 20 mL/min/kg, rat: 70 mL/min/kg). Note that the compounds where inference was performed below are those that are all known to be eliminated mainly as a result of metabolism. Since the model used for estimating structure contributing factor is the rat multimodal deep learning model, the contribution of rat CL was evaluated before confirming the contribution of the chemical structures. The results showed that the contribution of rat CL was larger than any other chemical structure in these eight high CL compounds.

Although the human data for eptaloprost was for oral administration, they were predicted with good accuracy. While the metabolism of eptaloprost is via the process of beta oxidation of carbonic acid into the metabolite cicaprost,[25] the predicted regions matched this area, and these findings were thought to indicate a valid level of contribution. Although the most easily metabolized part of R-apomorphine was the catechol part,[26] the predicted region was the neighboring aromatic ring part with high lipid solubility, and it is thought that this is a valid suggestion as the structure contributing factor inferred to degrade the metabolic stability. The metabolisms that propofol undergoes are known to be O-glucuronic acid conjugation of the phenol and hydroxylation of the para position of its OH group.[27] The inferred structure contributing regions indicate phenol metabolism and metabolism of the para position of the phenol, and this completely reflects experimental facts, which suggests that the prediction results are

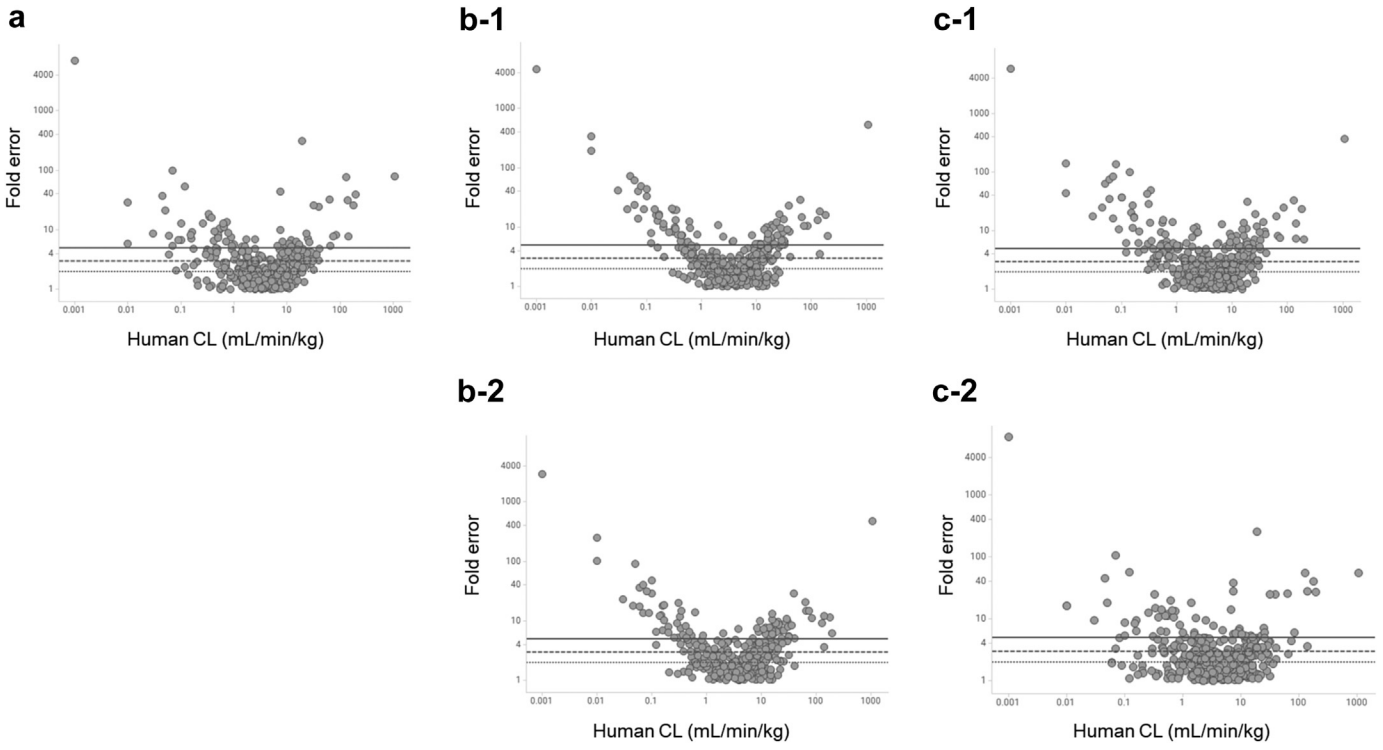

Fig. 3. A plot of fold error and human CL. The x-axis shows the actual measured value, and the y-axis shows the fold error (>1). (a) Allometric linear regression. (b-1) ECFP4. (b-2) ECFP4 + rat CL by support vector regression (SVR) (c-1) Chemical structure. (c-2) Chemical structure + rat CL by Deep Tensor. Lines show five times, three times, and two times starting from the top.

a

Name	Human CL (mL/min/kg)	Predicted value by Deep Tensor (graph + rat CL)	Rat CL (mL/min/kg)
Eptaloprost	66	24	170
R-Apomorphine	40	18	196
Propofol	36	19	107
Cocaine	32	27	253
Isosorbide dinitrate	31	15	122
Vorinostat	28	19	130
Idarubicin	24	14	79
Nalbuphine	22	18	111

b

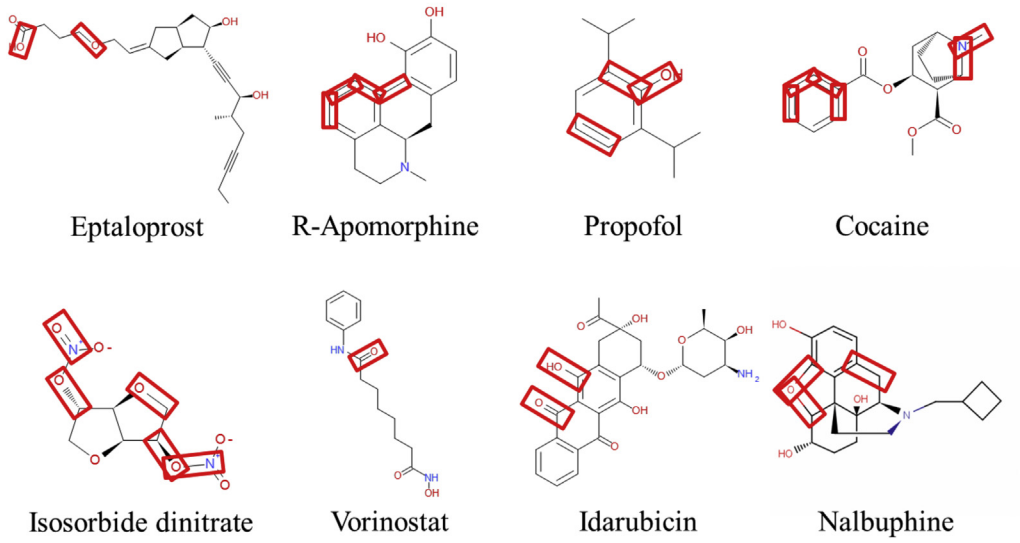

Fig. 4. Inference results for chemical structures that contribute to CL prediction by the Deep Tensor structure contributing factor inference method on high CL compounds. (a) Data for compounds where the difference between the predicted results and actual measured values is three times or less from among the high CL compounds where the human and rat actual measured values were greater than or equal to the hepatic blood flow. (b) Inference results for the chemical structures that contribute to CL prediction for the compounds shown in (a). Structures that contribute 5% or more in the stable direction (coefficient is negative) for these metabolically stable compounds are shown highlighted in red. In other words, the structures highlighted in red show the atoms that contribute to the prediction of high CL.

valid. It is also known that cocaine is mainly metabolized in two ester moieties by esterase and that an N−Me demethylation reaction occurs because of CYP, which converts it into norcocaine.[28] One of the inferred contributing structures is part of the benzene ring, and it is thought that lipophilicity, which is a cause of metabolic instability, was identified in this predicted region. Another predicted region indicated the N−Me demethylation reaction site, and it is thought that the inferred structure factor was a valid suggestion. For isosorbide dinitrate, it has been reported that the nitric ester is the main site of metabolism,[29] and the inferred structure contributing factor matched this part and was thought to be valid. The main metabolic pathways of vorinostat are O-glucuronic acid conjugation of hydroxamic acid and its beta-oxidation.[30] The inferred structure contributing factor was the amide part, and interpretation of the predicted structure for the site of metabolism was difficult. However, the inferred amide part could be inferred to be metabolically unstable from the perspective of medicinal chemistry. For idarubicin, it is known that the main metabolic pathway is the reductive metabolism of the ketone on the side chain.[31] The inferred structure contributing factor is the metabolically unstable phenol part, and although this does not match the experimental site of metabolism, it can be inferred to be metabolically unstable from the perspective of medicinal chemistry. For nalbuphine, it is known that the sites of metabolism are hydroxylation of the cyclobutane and O-glucuronic acid conjugation of the cyclohexanol near the ether.[32] The two inferred structure contributing factors suggest that the methoxy and the para position of the phenol are readily metabolized, and although they do not match the experimental site of metabolism, they can be inferred to be metabolically unstable sites from the perspective of medicinal chemistry.

From the above, the results for the eight compounds with high CL largely match the sense of the medicinal chemist.

Among the compounds where the difference between the predicted results by the Deep Tensor method and actual measured values were 3-fold or less, there were nine low CL compounds where the actual measured human and rat values were less than or equal to 1/50th of the hepatic blood flow. However, the three compounds caspofungin, micafungin, and teicoplanin A2-1, which have huge molecules, were excluded from the discussion (Fig. 5a and b). The contribution of rat CL was estimated for the low CL compounds as well as the high CL compounds. The contribution of rat CL was larger than any other chemical structure in these six low CL compounds.

The predicted region in warfarin was part of the coumarin structure. The coumarin structure is an endocyclic ester and also

a

Name	Human CL (ml/min/kg)	Predicted value by Deep Tensor (graph + rat CL)	Rat CL (ml/min/kg)
Warfarin	0.06	0.12	0.17
Phenobarbital	0.06	0.12	0.80
Meloxicam	0.12	0.13	0.25
Tolbutamide	0.21	0.28	0.42
Sulfinpyrazone	0.34	0.46	0.46
Ro25-6833	0.38	0.49	0.95

b

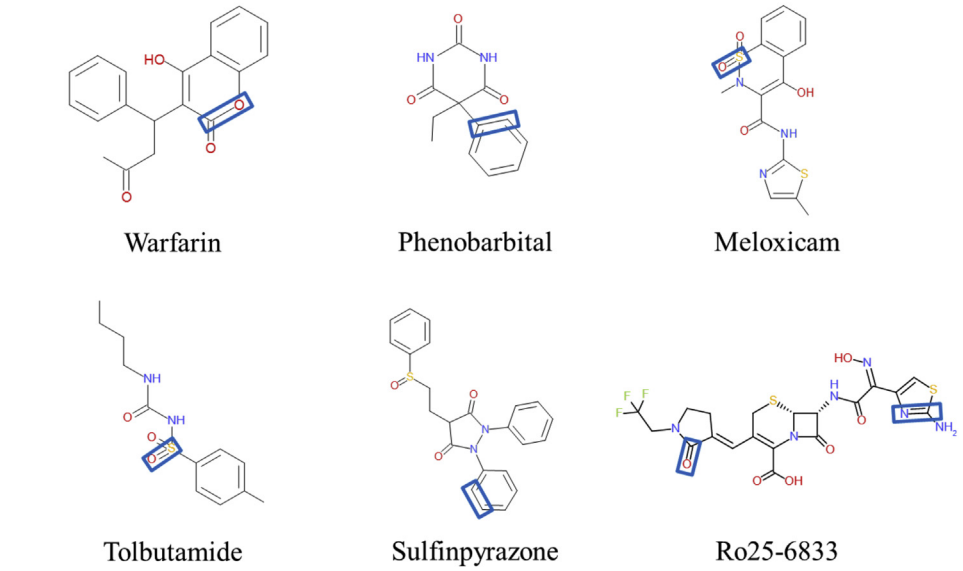

Fig. 5. Inference results for chemical structures that contribute to CL prediction by the Deep Tensor structure contributing factor inference method on low CL compounds. (a) Data for compounds where the difference between the predicted results and actual measured values is three times or less from among the low CL compounds where the human and rat actual measured values were less than or equal to 1/50th of the hepatic blood flow. (b) Inference results for the chemical structures that contribute to CL prediction for the compounds shown in (a). Structures that contribute 5% or more in the unstable direction (coefficient is positive) for these metabolically unstable compounds are shown highlighted in blue. In other words, the structures highlighted in blue show the atoms that contribute to the prediction of low CL.

has keto-enol tautomerism, which can be interpreted as contributing to metabolic stability. Although the ethyl group on the side chain in phenobarbital is thought to be the most easily metabolized, the benzene ring containing the predicted region can be interpreted as blocking the metabolism of the ethyl group sterically, and the level of contribution is thought to be valid. Since the sulfonamide indicated at the predicted region in meloxicam is less likely to be metabolized, the level of contribution is thought to be valid. The sulfonamide, the predicted region in tolbutamide, can be interpreted as making a large contribution to metabolic stability. In sulfinpyrazone, if the metabolism of the keto-enol part is assumed to dominate, then the benzene ring containing the predicted region can be interpreted as blocking metabolism. In Ro25-6833, it is suggested that the carbonyl group, one predicted region, was introduced to block the metabolism. This idea is based on the assumption that the original structure was the hydroxy group, which is the most easily metabolized, and was replaced by the carboxy group. The aminothiadiazole, another predicted region, is a polar group, suggesting metabolic stability.

From the above, the results for the six compounds with low CL largely match the sense of the chemist. Then, huge molecules were removed from only the above discussion from the structural viewpoint; however, if we had removed from the analysis itself, there would be some possibility of the increasing of the prediction accuracy.

We developed a new CL prediction method using Deep Tensor, which is a type of deep learning model, to predict human CL data. Training was performed using a multimodal model that takes the chemical structure and rat CL information, which is a form of preclinical data, as inputs. As a result, the constructed prediction model achieved higher accuracy than models that take only the chemical structure as input. Furthermore, a relatively good model could be constructed, even for models that take only the chemical structure as input, and it was found that compounds, where there is no preclinical data could be predicted to some degree.

In this research, we collected the dataset of clearance regardless the clearance routes. As we mentioned in the Material and method section, most of compounds clearance routes were not able to be determined. However, if we could identify each compound's clearance route, it is considered that the prediction accuracy would be improved.

Furthermore, since the developed prediction model is used by inputting the chemical structure as a graph, it can predict the chemical structures that contribute to the prediction. When a chemist evaluated eight high and six low CL compounds, good results were largely obtained for the inference of metabolically stable structures. Since the chemical structure that contributes to metabolism can be inferred, this gives hints for improving pharmacokinetics. The proposed method is expected to increase the success rate of clinical trials and lead to drug development.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.xphs.2021.01.020.

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