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Prediction of human pharmacokinetics from animal data and molecular structural parameters using multivariate regression analysis: volume of distribution at steady state

Toshihiro Wajima, Kazuya Fukumura, Yoshitaka Yano and Takayoshi Oguma

Abstract

The aim of this study was to develop a regression equation for predicting volume of distribution at steady state (Vd_{ss}) in humans to enable application to various types of drugs using animal experimental data for rats and dogs and some molecular structural parameters. The Vd_{ss} data for rats, dogs and humans of 64 drugs were obtained from literature. The compounds have various structures, pharmacological activities and pharmacokinetic characteristics. In addition, the molecular weight, calculated partition coefficient (clogP), and the number of hydrogen bond acceptors were used as possible descriptors related to the Vd_{ss} in humans. Multivariate regression analyses, multiple linear regression analysis and the partial least squares (PLS) method were used to predict Vd_{ss} in humans. Interaction terms were also introduced into the regression analysis to evaluate the non-linear relationship. For the data set used in the present study, PLS with quadratic term descriptors gave the best predictive performance. The PLS model using Vd_{ss} data for only two animal species and using easily calculated structural parameters could generally predict Vd_{ss} in humans better than an allometric method. In addition, the PLS model with only animal data gave almost the same predictive performance as the PLS model with quadratic term descriptors. This model may be easier to use and be practical in a realistic situation, and could predict Vd_{ss} in humans better than the allometric method.

Introduction

In the process of developing new drugs, it is very important to predict the pharmacokinetic profile of a drug in humans for decisions on appropriate dosage and best clinical trial design. The volume of distribution at steady state (Vd_{ss}) is one of the most important parameters for characterizing drug pharmacokinetics and is related to the extent of binding in plasma and tissues. An allometric method has been widely used to predict pharmacokinetic parameters for humans and successful results have been reported (Boxenbaum 1982, 1984; Sawada et al 1984a; Mahmood & Balian 1996; Mahmood 1999). However, although allometric scaling is simple and easy to handle, it does not always give an accurate prediction for all drugs (Boxenbaum & D'Souza 1990; MacNamara 1991; Mahmood & Balian 1996), and there are problems with its application to a wide variety of compounds. Experimental data for several animal species are usually required for reliable prediction of pharmacokinetic parameters. The selection of the animal species may also influence the prediction results. Moreover, extrapolation of pharmacokinetic parameters from data from small laboratory animals can lead to inaccurate prediction from a statistical viewpoint.

We previously reported a new regression equation for predicting human clearance from animal data and some molecular structural parameters, and showed that it offered better predictive performance than allometric approaches (Wajima et al 2002). The aim of the present study was to develop a regression equation for predicting

Developmental Research Laboratories, Shionogi & Co., Ltd, Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan

Toshihiro Wajima, Kazuya Fukumura, Yoshitaka Yano, Takayoshi Oguma

Correspondence: Toshihiro Wajima, Developmental Research Laboratories, Shionogi & Co., Ltd, Sagisu 5-12-4, Fukushima-ku, Osaka 553-0002, Japan. E-mail: toshihiro.wajima@shionogi.co.jp

Vd_{ss} in humans ($Vd_{ss,man}$) that could be applied to drugs with various characteristics. We used a multivariate regression approach similar to that of the previous study. We assumed a realistic case in which information from animal experiments and in-vitro experiments was limited. To minimize the experimental data required, Vd_{ss} data for only two species, rats and dogs, which are usually available in a drug development process, were used as descriptors. In addition, some molecular structural parameters, which can be easily calculated, were used.

Methods

Data

Vd_{ss} data for rats ($Vd_{ss,rat}$: range 51.5–84 000 mL kg^{-1}), dogs ($Vd_{ss,dog}$: range 158–49 600 mL kg^{-1}) and humans ($Vd_{ss,man}$: range 99.8–47 640 mL kg^{-1}) after intravenous administration for 64 drugs were obtained from the literature (see Table 1). Vd_{ss} data for other species (mice, rabbits or monkeys) were also obtained to apply an allometric scaling approach. The compounds were selected

Table 1 List of compounds examined in the present study and the observed and predicted $Vd_{ss,man}$ of regression analyses by the LOO and allometric methods.

Compound	Predicted $Vd_{ss,man}$ (mL kg^{-1})					Observed $Vd_{ss,man}$ (mL kg^{-1})	References
	MLR (quadratic)	AC-PLS (quadratic)	MC-PLS (tertiary)	AC-PLS (tertiary, animal)	Allometry		
Ceftriaxone	142	152	125	193	123	99.8	Kovar et al (1997) Matsui et al (1984) Nakashima & Nishijima (1984)
Cefazolin	174	163	168	194	173	107	Lee et al (1980)
Cefpiramide	205	373	183	288	112	111	Sawada et al (1984a)
Tolcapone	195	133	177	130	167	113	Lave et al (1996a)
Cefodizime	125	245	126	180	136	120	Matsushita et al (1988) Saito et al (1988)
GV150526	263	244	369	164	196	121	Ivarone et al (1999)
Cefotetan	111	164	93	185	206	133	Sawada et al (1984a)
Moxalactam	126	129	121	159	172	138	Sawada et al (1984a)
Cefmetazole	179	137	180	201	143	143	Sawada et al (1984a)
Cefoperazone	140	179	119	204	174	144	Sawada et al (1984a)
Valproic acid	417	226	458	258	359	150	Löscher (1978)
Latamoxef	125	143	123	158	140	167	Sugeno et al (1980) Yamada et al (1980)
Cefmenoxime	261	335	222	333	835	170	Tsuchiya et al (1981) Yamamoto et al (1981) Yamaoka et al (1983)
Cefotiam	221	141	422	262	409	207	Saito et al (1979) Tsuchiya et al (1979) Yamaoka et al (1983)
Cefuzonam	307	410	280	393	160	210	Inokawa et al (1986) Saito et al (1986)
Fosmidomycin	375	223	432	335	92	227	Murakawa et al (1982) Tsuchiya et al (1982)
Biapenem	249	210	208	196	270	230	Saito et al (1994) Yamashita et al (1994)
Ceftizoxime	212	190	188	212	192	230	Murakawa et al (1980) Yamasaku et al (1980)
Ceftazidime	166	235	155	198	422	234	Moriyama et al (1992) Yamasaku et al (1992)
Flomoxef	167	212	159	204	312	234	Kimura et al (1987) Yasunaga et al (1987)
FCE 22101	150	189	115	124	478	246	Efthymiopoulos et al (1991) Jannuzzo et al (1989)
Cefozopran	139	162	140	153	185	250	Kita et al (1993) Takenaka et al (1993)
Incadronate	355	315	312	296	522	253	Usui et al (1995, 1997)
Lamifiban	432	501	319	394	920	290	Lave et al (1996b)
Cefclidin	144	176	139	167	229	292	Moriyama et al (1992) Yamasaku et al (1992)

Table 1 (cont.)

Compound	Predicted $Vd_{ss,man}$ (mL kg^{-1})					Observed $Vd_{ss,man}$ (mL kg^{-1})	References
	MLR (quadratic)	AC-PLS (quadratic)	MC-PLS (tertiary)	AC-PLS (tertiary, animal)	Allometry		
Cefpirome	237	223	242	252	279	297	Isert et al (1992) Nakayama et al (1992) Sakamoto et al (1993)
Pidotimod	313	256	293	255	304	313	Coppi & Silingardi (1994) Mailland et al (1994)
Napsagatran	440	417	381	458	520	316	Lave et al (1999)
CI-921	798	881	940	793	292	320	Paxton et al (1990)
Sch 34343	163	176	143	152	219	341	Chung et al (1985)
Theophylline	692	564	602	562	861	486	Gaspari & Bonati (1990)
Enprofylline	531	439	419	376	406	510	Tsunekawa et al (1992)
Phenobarbital	614	532	617	510	718	542	Iven & Feldbusch (1983) Pedersoli et al (1987) Sawada et al (1985)
Actisomide	825	610	1002	615	1267	580	Cook et al (1993)
Clevidipine	215	283	252	173	111	580	Ericsson et al (1999a, b)
Antipyrine	622	472	554	461	547	612	Boxenbaum & Ronfeld (1983) Doyle & Chasseaud (1981)
Remoxipride	1311	1264	1640	1393	1550	700	Widman et al (1993)
Fluconazole	600	454	543	484	677	710	Jezequel (1994)
Sematilide	1087	955	1097	1041	1171	740	Hinderling et al (1993)
Oleandomycin	1258	1283	1451	1545	1361	771	Duthu (1985)
Alfentanil	692	581	658	637	938	843	Björkman & Redke (2000)
Erythromycin	2284	2398	2457	2610	4366	886	Duthu (1985)
Doxazosin	3184	2969	2580	3163	12011	970	Hamilton et al (1985) Kaye et al (1986)
Sildenafil	2958	2731	1977	2403	7301	1200	Walker et al (1999)
Thiopentone	992	886	961	816	1194	1390	Björkman & Redke (2000)
Recainam	1029	1035	1243	1002	1444	1400	Scatina et al (1990)
Amsacrine	2047	2013	2308	2164	1417	1560	Paxton et al (1990)
Sumatriptan	1523	1313	1453	1445	2539	1630	Cosson et al (1997)
Coumarin	2227	1197	1564	1506	4481	1880	Ritschel et al (1988, 1991)
Moxifloxacin	1880	1772	1558	1962	2930	2000	Siefert et al (1999)
Ciprofloxacin	3374	3096	2482	3386	2907	2250	Abadša et al (1994) Siefert et al (1986) Wise et al (1984)
UK-224,671	5197	5391	5181	5919	6024	2400	Beaumont et al (2000)
Ketamine	3366	3317	3485	3041	4733	2700	Björkman & Redke (2000)
Metoclopramide	956	828	932	804	1425	3000	Bateman (1983) Bakke & Segura (1976)
Methohexitone	1372	1453	1513	1436	1238	3290	Björkman & Redke (2000)
Amphotericin B	1174	1352	904	2072	1685	3990	Atkinson & Bennett (1978) Hutchaleelaha et al (1997)
Venlafaxine	2430	3077	3018	2674	2421	4400	Howell et al (1994) Patat et al (1998)
Pentazocine	1168	1403	1914	1388	721	5560	Ritschel et al (1980) Sawada et al (1984b)
Ketanserin	1380	1323	1098	1073	3923	6200	Michiels et al (1988) Reimann et al (1983)
Diazepam	3774	3482	3856	3592	6110	8900	Klotz et al (1976)
Chlorpromazine	15 151	18 796	21 629	19 007	15 857	11 200	Boxenbaum & Ronfeld (1983) Sawada et al (1984b)
Amlodipine	21 213	24 285	18 169	24 329	25 760	21 000	Stopher et al (1988)
Azithromycin	8268	18 655	18 619	16 228	4076	30 100	Luke et al (1996) Shepard & Falkner (1990)
Vinorelbine	38 839	41 129	39 038	28 146	66 114	47 640	Kobayashi et al (1993) Marquet et al (1992)

from an extensive range to include compounds with various structures, pharmacological activities and pharmacokinetic characteristics. The molecular weight (range 144.21–924.08), calculated partition coefficient (clogP; range −4.63 to 5.81), and the number of hydrogen bond acceptors (Ha; range 3–35) were calculated for each drug. We selected these parameters because they are possible descriptors related to Vd, they can characterize the global properties of a molecule, and they can be easily calculated. The parameter clogP was calculated as a free form using the computer software CLOGP for Windows version 4.0 (Biobyte Corp.). The parameter Ha should be equal to the number of the lone electron pairs. Log-transformed values were used for $Vd_{ss,man}$, $Vd_{ss,rat}$, $Vd_{ss,dog}$ and molecular weight.

Regression analysis

In this paper, two types of regression analysis methods are used to predict $Vd_{ss,man}$: multiple linear regression (MLR) analysis and partial least squares (PLS) methods (Geladi & Kowalski 1978; Hasegawa et al 1997). These regression analyses were performed using FORTRAN programs that we developed for a UNIX operating system with a FORTRAN compiler (Sun Pro). In these analyses, $Vd_{ss,man}$ is a dependent variable, and $Vd_{ss,rat}$, $Vd_{ss,dog}$, molecular weight, clogP, and Ha are basic independent variables. Interaction term descriptors were also used to perform the non-linear modelling. Some interaction term descriptors did not show the normality of the regression model assumption. However, simple regression methods such as MLR and PLS are generally said to be robust to this problem and so it may not have influenced the result much.

Evaluation of predictive performance

Leave-one-out (LOO) cross-validation procedures (Wold 1978) were performed to evaluate predictive performance. Prediction accuracy was evaluated based on the squared cross-validated correlation coefficient (q^2) and root mean squared error (RMSE) (Scheiner & Beal 1981), which are defined as follows.

$$q^2 = 1 - \frac{\sum_{i=1}^{N}\{\log(P_{OBS,i}) - \log(P_{PRED,i})\}^2}{\sum_{i=1}^{N}\{\log(P_{OBS,i}) - \log(P_{OBS})_{AVE}\}^2} \quad (1)$$

$$RMSE = \sqrt{\frac{1}{N}\sum_{N=1}^{N}\{\log(P_{OBS,i}) - \log(P_{PRED,i})\}^2} \quad (2)$$

where $P_{OBS,i}$ and $P_{PRED,i}$ denote observed and predicted Vd_{ss} for the i^{th} data set (i^{th} compound), respectively; $\log(P_{OBS})_{AVE}$ denotes the average of log transformed values of observed $Vd_{ss,man}$; and N is the number of data sets that is equal to the number of drugs.

The values of fold-error, which is an index for prediction accuracy obtained by the ratio of the predicted and observed values, were calculated for each drug as follows:

$$\text{Fold-error} = \begin{cases} \frac{P_{PRED,i}}{P_{OBS,i}} & \text{if} \quad P_{PRED,i} > P_{OBS,i} \\ \frac{P_{OBS,i}}{P_{PRED,i}} & \text{else} \end{cases} \quad (3)$$

The ratio of the number of drugs where fold-error was less than two or three were calculated.

Multiple linear regression analysis

In the analysis by MLR, quadratic term descriptors were used in addition to the basic independent variables (Wold et al 1989). These descriptors are introduced from five basic descriptors to perform non-linear modelling by considering interaction terms. A total of 20 descriptors (five basic ones and 15 quadratic terms) was chosen as candidates of the descriptor variables. MLR analysis was used for all possible combinations of 20 descriptors. There are $2^{20} - 1$ possibilities.

$$y = a_0 + \sum_i a_{1,i} \cdot x_i \cdot I_i + \sum_{j,k} a_{2,j,k} \cdot x_j \times x_k \cdot I_{j,k} \quad (4)$$

In equation 4, y is $Vd_{ss,man}$; a_0, $a_{1,i}$, and $a_{2,j,k}$ are regression coefficients; x_i is the linear term of the i^{th} basic descriptor; and $x_j \times_k$ is the quadratic term descriptor that corresponds to the interaction between the j^{th} and k^{th} basic descriptors. I_i and $I_{j,k}$ are categorical flags, which take either 1 or 0. When $I_i = 1$, the i^{th} variable is included in the regression model, and when $I_i = 0$, the i^{th} variable is not included. In order to select the best regression model, the combinations of descriptor variables were chosen so that all regression coefficients were statistically significant at the 5% level. Predictive performances were then tested for these selected models based on LOO. The best MLR model was defined as the combination of descriptor variables that gave the maximum q^2 value.

Partial least squares method

In the analysis by PLS, five basic descriptors and 15 quadratic terms were also used. PLS analysis considering all possible combinations of 20 descriptors (AC-PLS) and the standard PLS analysis using all 20 descriptors were performed.

Analyses with the tertiary term descriptors were also performed because PLS analysis is particularly suited to dealing with large numbers of descriptors compared with MLR analysis. A total of 55 descriptors was used (five basic ones, 15 quadratic term ones and 35 tertiary term ones). If all 55 descriptors are used in AC-PLS analysis, the number of possible combinations of descriptors is $2^{55} - 1$, which is too large to allow evaluation of the predictability for all cases. Therefore, combinations of each descriptor were randomly chosen using the Monte-Carlo (MC) random sampling procedure, which we refer to as

Monte-Carlo PLS (MC-PLS) (Wajima et al 2002). In the MC-PLS method, the following equation was evaluated.

$$y = a_0 + \sum_i a_{1,i} \cdot x_i \cdot I_i + \sum_{j,k} a_{2,j,k} \cdot x_j \times x_k \cdot I_{j,k} + \sum_{l,m,n} a_{3,l,m,n} \cdot x_l \times x_m \times x_n \cdot I_{l,m,n} \quad (5)$$

In equation 5, I_i, $I_{j,k}$, and $I_{l,m,n}$ are categorical flags and $x_l \times x_m \times x_n$ is the tertiary term that corresponds to the interaction among the l^{th}, m^{th} and n^{th} basic descriptors. Other terms are the same as those in equation 4. By MC random sampling, I_i, $I_{j,k}$, $I_{l,m,n}$ values (1 or 0) were randomly defined, and the regression analysis by the PLS method was performed for 100 000 combinations. The probability of selecting each descriptor variable was set at 0.5. For a comparative study with the MC-PLS analysis, the standard PLS analysis using all 55 descriptors was performed, that is I_i, $I_{j,k}$ and $I_{l,m,n}$ were defined as 1 in equation 5. MC-PLS analysis with quadratic term descriptors (20 descriptors) was also performed for 10 000 random combinations (about 1/100 of all possibilities) in order to evaluate the effect of the MC approach on the predictive performance of PLS analysis. As a reference, AC-PLS analysis with tertiary term descriptors of only animal data (i.e. $Vd_{ss,rat}$, $Vd_{ss,dog}$, $Vd_{ss}{}^2{}_{rat}$, $Vd_{ss,rat} \times Vd_{ss,dog}$, $Vd_{ss}{}^2{}_{dog}$, $Vd_{ss}{}^3{}_{rat}$, $Vd_{ss}{}^2{}_{rat} \times Vd_{ss,dog}$, $Vd_{ss,rat} \times Vd_{ss}{}^2{}_{dog}$, $Vd_{ss}{}^3{}_{dog}$) was performed to evaluate the effects of the molecular structural parameters.

All variables were normalized to have a mean of 0 and standard deviation of 1. The combination of descriptor variables and the optimum number of PLS components which gave the maximum q^2 was determined by LOO.

Allometric method

An allometric method, which has been widely used to predict pharmacokinetic parameters, was applied to the data sets used in the present study. Vd_{ss} values in several species (mice, rats, rabbits, monkeys or dogs) were used for the prediction. The log transformation of the simple allometric equation is represented as follows:

$$\log y = \log a + b \log WT \quad (6)$$

In equation 6, y is Vd_{ss} (mL), WT is bodyweight (kg), and log a and b are regression coefficients. The Vd_{ss} of each compound in several species was plotted against the bodyweight on a log-log scale and regression coefficients were determined by a linear least-squares method. $Vd_{ss,man}$ was predicted by extrapolation using bodyweight (70 kg). For some drugs, data from only two animal species were available (i.e. Vd_{ss} data for rat and dog).

Results

MLR analysis led to the selection of three descriptor variables, Ha, $Vd_{ss,rat} \times Ha$, and $Vd_{ss,dog} \times Vd_{ss,dog}$, as statistically significant in the best combination. The relationship between observed and predicted $Vd_{ss,man}$ using this model by LOO is shown in Figure 1. The values of q^2 and RMSE of the MLR model are 0.830 and 0.266, respectively. The ratios of drugs where fold-error was < 2 and < 3 were 73.4% and 90.6%, respectively. This result indicates that $Vd_{ss,man}$ could be predicted with adequate accuracy in interspecies scaling studies. The regression equation obtained for the best MLR model is given as equation 7.

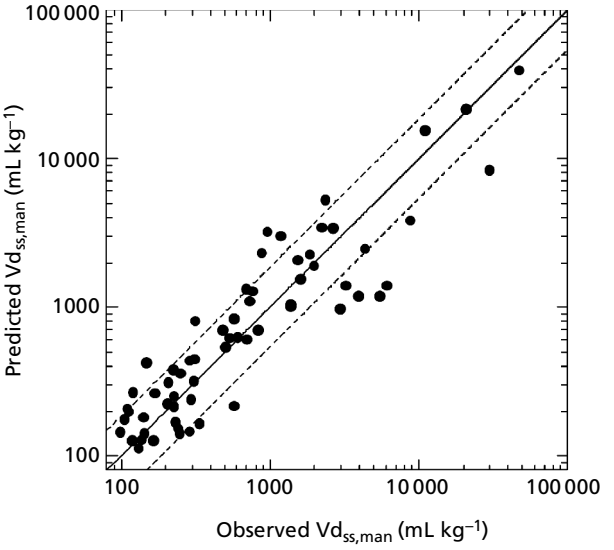

Figure 1 Relationship between observed and predicted $Vd_{ss,man}$ using MLR with quadratic term descriptors by LOO. The solid line represents a 1:1 relationship, dotted lines show the RMSE range.

$$\log(Vd_{ss,man}) = -0.03869 \cdot Ha + 0.009311 \cdot \log(Vd_{ss,rat}) \times Ha + 0.1256 \cdot \log(Vd_{ss,dog}) \times \log(Vd_{ss,dog}) + 1.857 \quad (7)$$

In equation 7, each interaction term has no physiological or physicochemical meaning and is used only to perform the non-linear modelling between $Vd_{ss,man}$ and the five basic descriptors.

PLS analyses were performed using five basic descriptors and 15 quadratic term descriptors. The standard PLS analysis with those 20 descriptors suggests that a three-component PLS model is the best according to LOO. The values of q^2 and RMSE are 0.802 and 0.288, respectively. AC-PLS analysis with quadratic term descriptors was performed, and the result suggests that a three-component PLS model with four descriptor variables is the best PLS model with quadratic term descriptors. The relationship between observed and predicted $Vd_{ss,man}$ using this model by LOO is shown in Figure 2. The values of q^2 and RMSE were 0.844 and 0.255, respectively. The value of q^2 of this model was slightly larger than that of the best MLR model. The regression equation obtained for the best PLS model with quadratic term descriptors is given as equation 8.

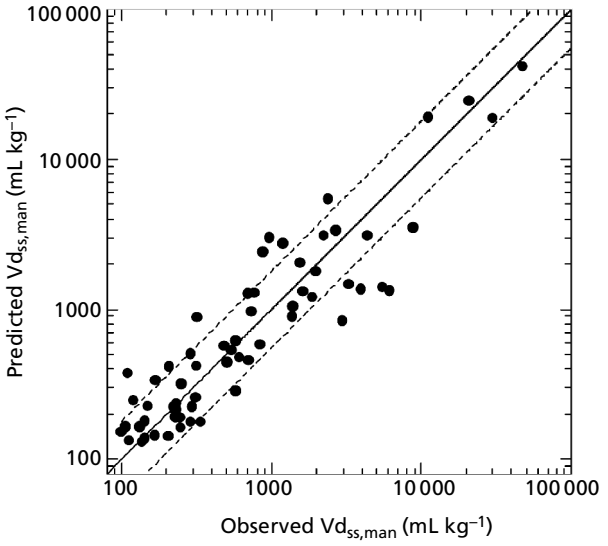

Figure 2 Relationship between observed and predicted $Vd_{ss,man}$ using AC-PLS with quadratic term descriptors by LOO. The solid line represents a 1:1 relationship, dotted lines show the RMSE range.

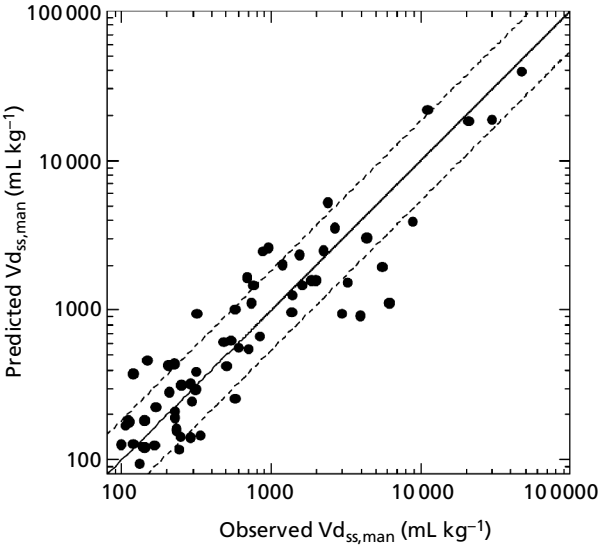

Figure 3 Relationship between observed and predicted $Vd_{ss,man}$ using MC-PLS with tertiary term descriptors by LOO. The solid line represents a 1:1 relationship, dotted lines show the RMSE range.

$$\begin{aligned}\log(Vd_{ss,man}) = {} & 0.1859 \cdot \log(Vd_{ss,rat}) \times \log(Vd_{ss,rat}) \\ & - 0.3887 \cdot \log(Vd_{ss,rat}) \times \log(MW) \\ & + 0.3089 \cdot \log(Vd_{ss,dog}) \times \log(MW) \\ & + 0.003306 \cdot \log(MW) \times c\log P + 1.710 \quad (8)\end{aligned}$$

MC-PLS analysis with quadratic term descriptors was performed for 10 000 random combinations to evaluate the effect of the MC approach on the predictive performance of PLS analysis. A two-component PLS model with five descriptor variables was indicated to be the best according to LOO evaluation. The values of q^2 and RMSE were 0.834 and 0.263, respectively. The value of q^2 was improved from 0.802 (standard PLS) to 0.834 by the MC approach and was almost the same as that by the AC-PLS model with quadratic term descriptors ($q^2 = 0.844$).

Next, PLS analyses with tertiary term descriptors were performed. The standard PLS analysis with all 55 descriptors suggests that a three-component PLS is the best according to LOO evaluation. The values of q^2 and RMSE were 0.795 and 0.293, respectively. AC-PLS analysis with tertiary terms could not be performed because there were too many combinations of those 55 descriptors. MC-PLS analysis with 55 descriptor variables was performed for 100 000 combinations. The MC-PLS analysis with tertiary terms suggests that a two-component PLS with 29 descriptor variables is the best MC-PLS model. The relationship between observed and predicted $Vd_{ss,man}$ using this model by LOO is shown in Figure 3. The values of q^2 and RMSE were 0.829 and 0.267, respectively. The value of q^2 was improved from 0.795 (standard PLS) to 0.829 by the MC approach. Although this value was an improvement over the standard PLS, it was still smaller than that achieved by AC-PLS with quadratic term descriptors ($q^2 = 0.844$).

AC-PLS analysis with only animal data was performed to evaluate the effect of molecular structural parameters. The result suggests that a one-component PLS model with two descriptor variables, $Vd_{ss,dog}$ and $Vd_{ss,rat} \times Vd_{ss,dog}$, is the best according to LOO evaluation. AC-PLS selected linear and quadratic term descriptors, and any tertiary term descriptors were not selected as significant. The values of q^2 and RMSE were 0.830 and 0.266, respectively. Although q^2 was improved from 0.830 to 0.844 by introducing the molecular structural parameters, the difference was not so large. The relationship between the observed $Vd_{ss,man}$ and the predicted $Vd_{ss,man}$ using this model by LOO is shown in Figure 4. The regression equation obtained for the best PLS model with only animal data is given as equation 9.

$$\begin{aligned}\log(Vd_{ss,man}) = {} & 0.07714 \cdot \log(Vd_{ss,rat}) \times \log(Vd_{ss,dog}) \\ & + 0.5147 \cdot \log(Vd_{ss,dog}) + 0.5860 \quad (9)\end{aligned}$$

For comparison, an allometric method that has been generally used to predict pharmacokinetic parameters was applied to the data set in this study. For some compounds, Vd_{ss} data were available for only two species. The values of q^2 and RMSE achieved by the allometric method were 0.718 and 0.343, respectively. The relationship between the observed and predicted $Vd_{ss,man}$ by the allometric method is shown in Figure 5. The value of q^2 was smaller than that achieved by AC-PLS with quadratic term descriptors ($q^2 = 0.844$), which suggests that the predictive performance of the AC-PLS model was better than that of the allometric method. The mean and the standard deviation of the slopes of regression equations in the allometric method (regression coefficient b in equation 6) were 0.96 and 0.18, respectively.

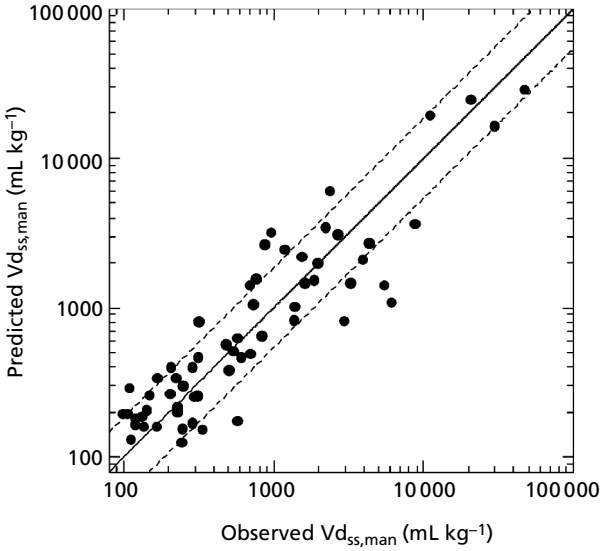

Figure 4 Relationship between observed and predicted $Vd_{ss,man}$ using AC-PLS with only animal data by LOO. The solid line represents a 1:1 relationship, dotted lines show the RMSE range.

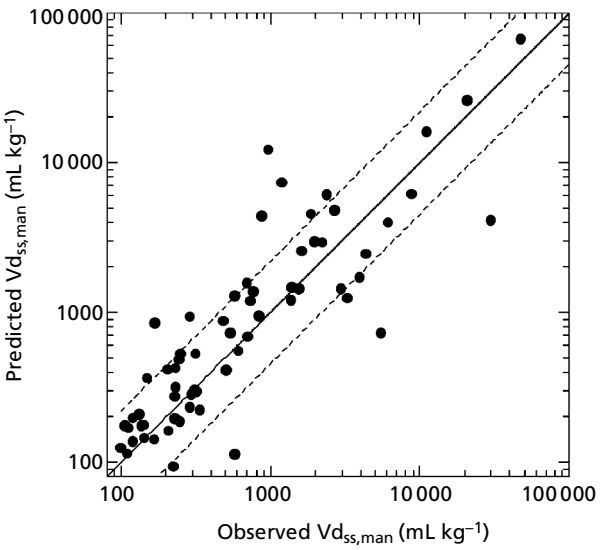

Figure 5 Relationship between observed and predicted $Vd_{ss,man}$ by an allometric method. The solid line represents a 1:1 relationship, dotted lines show the RMSE range.

Discussion

Prediction of pharmacokinetic profiles is of great interest and much effort has been expended on the allometric approach. This approach is easy to handle, but is problematic in that it does not always give adequate prediction for all drugs and the prediction results depend on the animal species selected.

The aim of the present study was to develop a regression equation for predicting $Vd_{ss,man}$ from animal data and some molecular structural parameters using multivariate regression analyses. A summary of the predictive performance of the regression analyses and the allometric method is shown in Table 2. The predicted values for $Vd_{ss,man}$ from each method and the observed values are listed in Table 1.

The values of q^2 in the present study were generally higher than those achieved for predicting human clearance in our previous study (Wajima et al 2002) (q^2 for the best model was 0.682 in the previous study). The ratios of drugs where fold-error was < 2 and < 3 in the present study were also higher than those in case of clearance (the ratios with fold-error of < 2 and < 3 for the best model were 64.7% and 86.8% for clearance). This is probably because $Vd_{ss,man}$ is better correlated with Vd_{ss} in rats and dogs.

Judging from global indices such as q^2 or RMSE, the predictive performances of the regression analysis methods were better than that of the allometric method, and the AC-PLS model with quadratic term descriptors gave the best predictive performance for the data set used in the present study. The ratios of drugs with fold-error of < 2 and < 3 for the AC-PLS model with quadratic term descriptors were also higher than those for the allometric method. Moreover, whereas the values of fold-error for five drugs were > 5 with the allometric method, there were no drugs with fold-error of > 5 with the AC-PLS model with quadratic term descriptors (data not shown). These results indicate that the AC-PLS model with quadratic term descriptors is conservative, suggesting that it should be useful for predicting $Vd_{ss,man}$ prospectively with limited information for a compound.

Table 2 Comparison of predictive performances.

Method	q^2	RMSE	r^2	Number of latent components	% of drugs with fold-error < 2	% of drugs with fold-error < 3
MLR (with quadratic terms)	0.830	0.266	0.856	–	73.4	90.6
PLS (with all quadratic terms)	0.802	0.288	0.844	3	68.8	90.6
MC-PLS (with quadratic terms)	0.834	0.263	0.852	2	75.0	89.1
AC-PLS (with quadratic terms)	0.844	0.255	0.848	3	76.6	92.2
PLS (with all tertiary terms)	0.795	0.293	0.848	3	70.3	93.8
MC-PLS (with tertiary terms)	0.829	0.267	0.871	2	71.9	92.2
AC-PLS (with animal data)	0.830	0.266	0.840	1	78.1	92.2
Allometric method	0.718	0.343	–	–	71.9	87.5

Thus, $Vd_{ss,man}$ could be predicted with a reasonable degree of accuracy using equation 8.

The AC-PLS model with only animal data ($q^2 = 0.830$) has almost the same predictive performance as the AC-PLS model with quadratic term descriptors ($q^2 = 0.844$). The ratio of drugs with fold-error of < 2 for the AC-PLS model with only animal data was even higher than that for the AC-PLS model with quadratic term descriptors. However, one of the drugs had fold-error of > 5 in the AC-PLS model with only animal data. The AC-PLS model with only animal data is easier to use and more practical because it has fewer descriptor variables and calculation of molecular structural parameters is not required.

An allometric method is usually applicable for cases in which Vd_{ss} data for three or more species are available. In the present study, Vd_{ss} data were available for only two species for some drugs and the allometric method was applicable to 52 drugs. We therefore compared the predictability of the AC-PLS model with quadratic terms and the AC-PLS model with only animal data with that of the allometric method for these 52 drugs. The values of q^2 by the AC-PLS model with quadratic terms, the AC-PLS model with only animal data, and the allometric method were 0.834, 0.830 and 0.737, respectively, suggesting that the AC-PLS models have higher predictive performances even though the AC-PLS models use animal data for only two species.

The MC approach improved the values of q^2 from 0.802 to 0.834 in the PLS analysis with quadratic terms, and from 0.795 to 0.829 in the PLS analysis with tertiary terms. Although the MC approach may be useful for selecting descriptor variables in the PLS analysis, the MC-PLS model with tertiary term descriptors showed a lower predictive performance than the AC-PLS model with quadratic term descriptors. This is probably because the MC approach was insufficient for selecting the descriptors and/or there were few significant descriptors among the tertiary term descriptors. Of course, if AC-PLS analysis with tertiary term descriptors can be performed, the predictive performance of its model should be better than or equal to that of the AC-PLS model with quadratic term descriptors.

To improve the predictive accuracy of the present model, the use of other experimental data or other molecular structural parameters may be useful. For example, protein binding data may be useful for predicting $Vd_{ss,man}$. In the present study, we did not take these parameters into consideration because we assumed a limited and realistic situation in which little information is available, such as in the early stage of drug development. In addition, we used only three molecular structural parameters because they are possible descriptors related to Vd_{ss}, they can characterize the global properties of a molecule, and they are easily calculated.

Conclusions

For the data set used in the present study, AC-PLS with quadratic term descriptors gave the best predictive performance. The AC-PLS model using animal Vd_{ss} data from only two species and using easily calculated structural parameters could generally predict $Vd_{ss,man}$ better than an allometric method. $Vd_{ss,man}$ can be predicted using equation 8 with reasonable accuracy. In addition, the AC-PLS model with only animal data gave almost the same predictive performance as the AC-PLS model with quadratic term descriptors and $Vd_{ss,man}$ can also be predicted using equation 9 with reasonable accuracy. This model may be easier to use and practical in a realistic situation. These PLS models may be conservative, suggesting that they should be useful for predicting $Vd_{ss,man}$ prospectively with limited information for a compound.

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