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Quantitative structure-interaction relationship analysis of 1,4-dihydropyridine drugs in concomitant administration with grapefruit juice

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Quantitative structure-interaction relationship (QSIR) analyses of 1,4-dihydropyridine drugs were performed on grapefruit juice interaction potentials to characterize the interaction and evaluate drugs not yet tested in clinical research. AUC ratios of drugs with and without grapefruit juice ingestion were estimated as grapefruit juice interaction potentials from clinical studies on dihydropyridine drugs such as amlodipine, azelnidipine, benidipine, cilnidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, and pranidipine. The minimal energy conformation in each dihydropyridine drug was searched for using Merck Molecular Force Field (MMFFaq), and then geometry optimization was performed by density-functional-theory (DFT) calculation (B3LYP/6-31G**). The geometric, electronic, and physicochemical features including molecular size, dipole moment, total energy, HOMO/LUMO energies, and logP values were then obtained. Dragon descriptors were also calculated by optimized 3D-structures. The relation between the potentials and over 1000 of the molecular properties was investigated using statistical techniques including partial least squares analysis with genetic algorithm (GA-PLS) to a variable subset selection. Some PLS regression equations including logP values and dragon descriptors as explanatory variables were constructed in which the maximal contribution coefficient was 94%. These models could be applied to estimate the interaction potentials of other dihydropyridine drugs that have gone unreported in interactions with drugs such as aranidipine, barnidipine, clevidipine, lemildipine, lercanidipine, niguldipine, niludipine, and nilvadipine. In the assessment of major dihydropyridines, amlodipine was found to be the safest drug to avoid interactions among the drugs investigated in the present study.

1. Introduction

Grapefruit juice (GFJ) evokes pharmaceutical interactions with increase in concentration of a variety of drugs in the systemic circulation (Uesawa 2008). Furanocoumarin derivatives such as bergamottin and 6',7'-dihydroxybergamottin, potent CYP3A inhibitors, are identified as causative ingredients of GFJ (Tassaneeyakul 2000; Paine 2004). These compounds inhibit drug-metabolizing activities of intestinal CYP3A, a major drug-metabolizing enzyme in the gastrointestinal tract (Obach 2001). Because this enzyme functions as a barrier in the absorption of low-molecular substances in the intestinal mucosa, breakage of the system by GFJ drinking causes leakage of substrate drugs into the blood from the digestive tract (Lown 1997; Schmiedlin-Ren 1997). As a result, GFJ is able to cause increases in plasma drug concentrations that may result in adverse effects of drugs (Dresser 2000). Dihydropyridine calcium channel antagonists (DHPs), used to treat hypertension and angina pectoris, are in the highest category of drugs that undergo GFJ interactions (Uesawa 2008). Patients receiving DHP treatment might experience hypotension related side effects such as nausea and stagger if they administer the medication concomitantly with GFJ (Dresser et al. 2000; Bailey and Dresser 2004). Thirteen types of DHPs have been reported to be related with the above interactions in clinical studies (Uesawa 2008; Uesawa and Mohri 2008b). In the findings, interaction-strength varied widely according to the DHP. For example, amlodipine showed little increment in plasma concentrations (Josefsson 1996). On the other hand, AUC of azelnidipine was increased more than three times following GFJ administration compared with the control subjects that administrated the drug with water (Hirashima 2006). The chemical structures of DHPs consist of a common dihydropyridine skeleton and a great variety of residues. The discrepancy in the interaction potentials among DHPs is likely due to the differences in structures. In a previous paper, we reported that the strength of pharmacokinetic interaction was related to the lipophilicities of DHPs (Uesawa and Mohri 2008b). That is, logP values (logarithmic octanol/water distribution coefficients) were calculated from the DHP structures by several canonical algorithms and confronted with the interaction potencies of DHPs. As a result, significant relationships were found with correlation coefficients of about 0.6. However, in the simple regression analyses, relationships with a single descriptor of the compounds were accompanied by large deviations. Because

Table 1: Reported pharmacokinetic interactions of dihydropyridine derivatives following concomitant consumption of grapefruit juice in human subjects

DHP	Dose (mg)	N	GFJ (ml)	AUC ratio
Amlodipine	5	12	250	1.14
Azelnidipine	8	8	250	3.28
Benidipine	4	6	200	1.59
Cilnidipine	10	6	200	2.27
Efonidipine	40	19	250	1.67
Felodipine	5	6	250	2.51
Manidipine	40	6	250	2.36*
Nicardipine	40	6	300	1.43
Nifedipine	10	6	250	1.35
Nimodipine	30	8	250	1.51
Nisoldipine	20	12	250	1.76
Nitrendipine	20	9	150	2.25
Pranidipine	2	16	250	1.73

N: number of subjects in the clinical studies. AUC ratios: (AUC_{DHPs} with GFJ)/(AUC_{DHPs} without GFJ)
* Average ratio between R- and S-manidipine

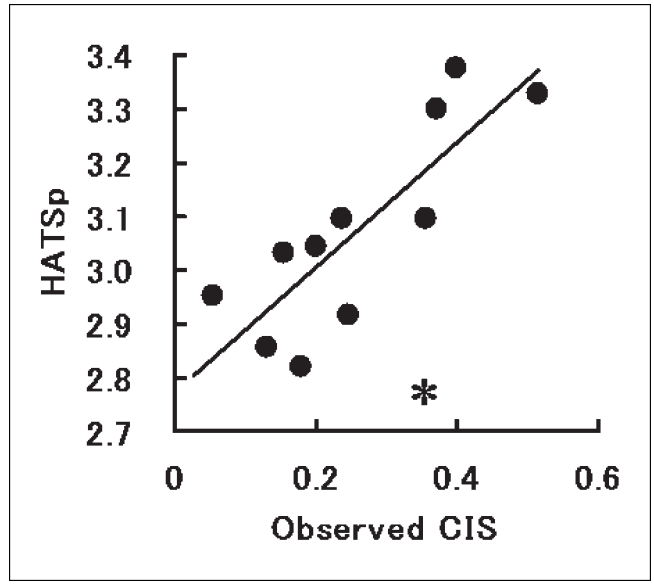

Fig. 1: Scatter plots between observed CIS and HATSp for 12 DHPs. Asterisk indicates a point of nitrendipine

contribution of structural factors other than logP in the interactions was presumable, a further quantitative structure-interaction relationship (QSIR) analysis was performed to construct better predictive models on the GFJ-interaction strength of untested DHPs.

2. Investigations and results

2.1. Clinical interaction strength (CIS)

Thirteen DHPs, amlodipine (Josefsson et al. 1996), azelnidipine (Hirashima et al. 2006), benidipine (Ohnishi 2006), cilnidipine (Ohnishi et al. 2006), efonidipine (Yajima 2003), felodipine (Bailey 1991), manidipine (Sugawara 1996), nicardipine (Uno 2000), nifedipine (Bailey et al. 1991), nimodipine (Bailey et al. 1991), nisoldipine (Bailey 1993), nitrendipine (Soons 1991), and pranidipine (Hashimoto 1998), on which there were confirmable reports of pharmacokinetic interactions with GFJ were selected for the analysis (Table 1). However, efonidipine was eliminated in the analysis because of reasons mentioned in the results section. CISs were defined as common logarithmic values of the AUC increasing ratio, in which the AUC of each DHP with GFJ consumption was divided by the corresponding control AUC.

$$CIS = \log[(AUC_{DHP} \text{ with GFJ})/(AUC_{DHP} \text{ without GFJ})] \quad (1)$$

The first report of a significant interaction with GFJ intake for each drug referred to the AUC value in order to avoid the variations of CIS in publication bias (Uesawa 2010) (Table 1).

2.2. Simple regression analysis

The calculation of Ghose-Crippen logP (LogPC) value using Spartan software was unsuccessful only with the efonidipine structure, which is among the 13 DHPs for which GFJ interactions have been reported. LogPC was one of the most significant descriptors in the remaining 12 DHPs ($r = 0.705$, $p = 0.0105$). That is because the structure of this DHP is unique in that it has a phosphorus atom directly connected to the DHP ring. This atom is not found in the structures of all other marketed DHPs. Therefore, efonidipine was excluded from the analysis objects as its unique characteristic might not be useful to predict interactions of DHPs that have not been reported to have GFJ interactions in clinical studies.

Statistically significant parameters were extracted from the simple regression analysis between all descriptors calculated by Spartan and Dragon software from the 12 kinds of DHP structures and CSIs from the literatures. As a result, 98 kinds of significant parameters were discovered from a total of 1409 parameters. Investigation of scatter plots between these significant descriptors and CISs revealed that the plot of nitrendipine was an outlier in cases with many descriptors. The diagram between HATSp and CIS is presented in Fig. 1 as an example. Simple regression analyses with 11 DHPs excluding nitrendipine showed much more significant parameters than with 12 DHPs including nitrendipine. That is, 185 kinds of significant variables were found in the relationship with CIS. Furthermore, there were 21 kinds of very significant variables ($p < 0.01$), despite finding only 3 variables in the DHP dataset with nitrendipine. These findings suggest that use of the dataset for 11 DHPs excluding

Table 2: High correlation descriptors ($r > 0.8$) in single regression with CIS and static values

Descriptor	a	b	n	r	RMSE	F	p
HOv	1.629 ± 0.347	-1.660 ± 0.409	11	0.843	0.0774	22.1	0.00112
HATSp	0.598 ± 0.132	-1.578 ± 0.407	11	0.833	0.0796	20.4	0.00145
HATSv	0.661 ± 0.151	-1.488 ± 0.400	11	0.825	0.0814	19.1	0.00179
LogPC	0.088 ± 0.021	0.061 ± 0.054	11	0.814	0.0836	17.6	0.00230
HOp	1.339 ± 0.329	-1.432 ± 0.417	11	0.805	0.0854	16.6	0.00281
ALOGP	0.096 ± 0.024	-0.066 ± 0.084	11	0.803	0.0857	16.4	0.00290
$LogPC^2$	0.019 ± 0.005	0.136 ± 0.040	11	0.802	0.0859	16.3	0.00296

a, slope; b, intercept

Table 3: Final PLS equations selected by genetic algorithm

No.	PLs equations	V	C	R^2	Q^2
1	CIS = 0.258 (HOp)–0.028(BLTA96) + 0.046(Mor15e)+1.255(Mv) + 0.044(Mor15u)–0.032(C005) + 0.185(R3m) +0.326(R4m) +0.003(RDF060m) + 0.064(VEA1)–1.594	10	1	0.939	0.917
2	CIS = 0.020(LogPC) + 0.306(HOp) + 0.055(Mor15e) +1.487(Mv) + 0.053(Mor15u)–0.038(C005)+0.219(R3m) +0.003(RDF060m)–1.300	8	1	0.941	0.915
3	CIS = 0.017(LogPC)+0.255(HOp)+0.046(Mor15e) +1.237(Mv)+0.044(Mor15u)–0.032(C005)+0.182(R3m) +0.321(R4m)+0.003(RDF060m)+ 0.063(VEA1)–1.490	10	1	0.936	0.915
4	CIS = 0.027 (LogPC)+0.073(Mor15e) + 1.979(Mv) +0.070(Mor15u)–0.051(C005) + 0.291 (R3m)–1.209	6	1	0.935	0.915
5	CIS = 0.094 (Mor15e) + 2.539(Mv) + 0.090(Mor15u)–0.065(C005) +0.373(R3m)–1.546	5	1	0.941	0.913
6	CIS = 0.423 (HOp)–0.025(BLTF96) + 0.073(Mor15u)–0.053(C005) + 0.533(R4m) + 0.005(RDF060m)–0.833	6	1	0.936	0.912

V and C: numbers of explanatory variables and PLS components in the equations, respectively

nitrendipine is more suitable than that which includes nitrendipine to explain the structural characteristics related with GFJ interaction. Therefore, the 11 DHP dataset was used in the subsequent multivariable analysis. The most significant descriptors with a high correlation ($r > 0.8$) are listed in Table 2.

2.3. PLS regression analysis

The 185 significant variables mentioned above were used for the PLS regression analysis following a random selection by genetic algorithm. A list of the top 6 equations with high-level determination coefficients (R^2) and determination coefficients of the leave-one-out validation (Q^2) values and normal residual plots is shown in Table 3. These equations were composed of LogPC and 10 kinds of Dragon descriptors as the explanatory variables. The Dragon descriptors and the definitions included in the models are summarized in Table 4. Table 5 shows the values of the descriptors in 11 DHPs used to construct the equations and 8 DHPs that have not been reported to interact with GFJ in clinical studies. Furthermore, interaction strength, AUC ratios in DHP with and without GFJ administration for the 8 kinds of unreported DHPs were predicted using 6 equations and the values for each descriptor is shown in Table 5 (Fig. 2).

3. Discussion

3.1. Simple regression analysis

In this study, extraction of factors calculated from the chemical structures of DHPs reported in clinical studies on GFJ interactions was attempted using simple regression analyses with CIS. In the analyses, CIS of nitrendipine tended to consistently be an outlier for many kinds of descriptors including HATSp (Fig. 1). In other words, CIS of nitrendipine (0.353) calculated from the AUC values in the literature (Soons et al. 1991) was higher than that estimated from structural information and from other 11 DHPs. The observation of the outlier possibly suggests that unknown physicochemical properties of nitrendipine might differentiate the inhibitory effects of this DHP from those of other DHPs. However, the structure of nitrendipine is difficult to distinguish from those of other DHPs such as nifedipine, nimodipine, and nisoldipine, which possess relatively small values of CIS; 0.131, 0.180 and 0.245, respectively (Fig. 1 and Table 1). In the simple regression analyses where CIS values of 11 DHPs except nitrendipine were used, the number of significant descriptors with p-value less than 0.05 and 0.01 increased about 2-fold and 7-fold, respectively. These results indicated that the association of a much higher number of significant descriptors in the 11 DHPs supports the clinical study on GFJ-interaction of nitrendipine was performed under conditions that differed from those of the other 11 DHPs. Unfortunately, it is impossible to perform a more elaborate inspection because this is the only report on GFJ-interaction for nitrendipine in humans. Therefore, the following analyses in the present study were accomplished using information from 11 DHPs except nitrendipine. The 8 significant descriptors with a correlation coefficient of over 0.8 in the simple regression between 11 DHPs and CIS are listed in Table 2. H0 v, H0p, and H1p are

Table 4: Dragon descriptors included in the final equations

Dragon descriptors	Dimension	Type	Brief summary
Mv	0	Constitutional descriptors	Mean atomic van der Waals volume (scaled on Carbon atom)
C005	1	Atom-centred fragments	Number of CH3X (X: heteroatom other than carbon)
VEA1	2	Eigenvalue-based indices	Eigenvector coefficient sum from adjacency matrix
HOp	3	GETAWAY descriptors	H autocorrelation of lag 0/weighted by atomic polarizabilities
Mor15e	3	3D-MoRSE descriptors	3D-MoRSE - signal 15/weighted by atoic Sanderson electronegativities
Mor15u	3	3D-MoRSE descriptors	3D-MoRSE - signla 15/unweighted
R3m	3	GETAWAY descriptors	R autocorrelation of lag 3/weighted by atomic masses
R4m	3	GETAWAY descriptors	R autocorrelation of lag 4/weighted by atomic masses
RDF060m	3	RDF descriptors	Radial Distribution Function – 6.0/weighted by atomic masses
BLTA96	Other	Molecular properties	Verhaar model of Algae base–line toxicity for Algae (96h) from MLOGP (mmol/I)

Descriptor dimension 0D refers to atom and bond type counts, 1D to fragment counts, 2D to topological and related descriptors, and 3D to all the descriptors which depend of the geometrical coordinates of the molecule atom

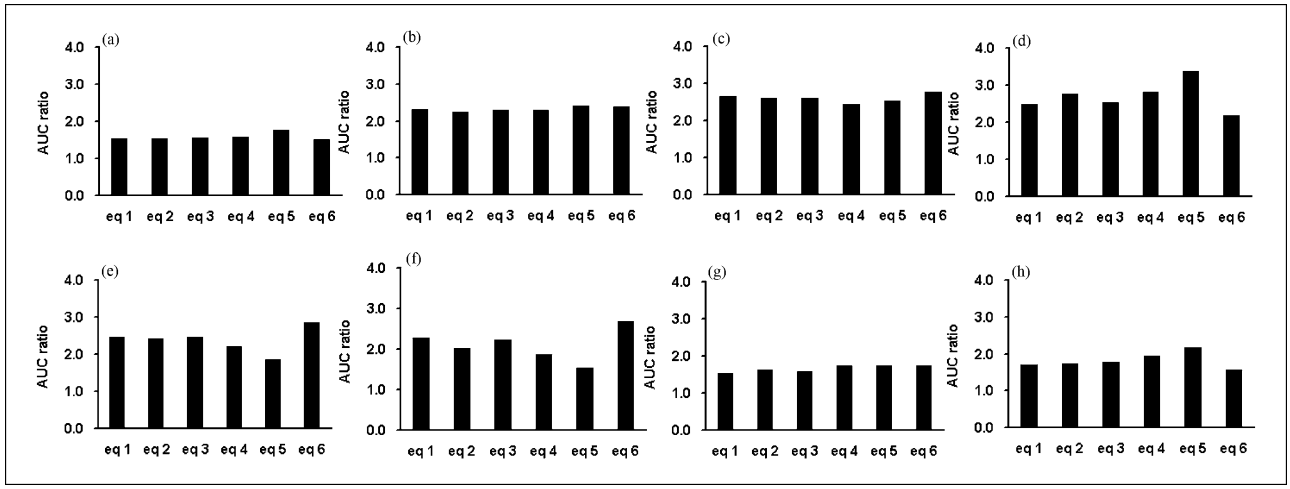

Fig. 2: Predicted ratio between AUC_{DHP} with and without GFJ administration in the interaction-unreported DHPs by equations 1, 2, 3, 4, 5, and 6 listed in Table 3. a, b, c, d, e, f, g, and h indicate aranidipine, barnidipine, clevidipine, lemildipine, lercanidipine, niguldipine, niludipine, and nilvadipine, respectively

H autocorrelations of lag 0 or lag 1 in GETAWAY descriptors estimated by Dragon software from 3D structures (Todeshini and Consonni 2009). HATSp and HATSv are also leverage-weighted total indices in the GETAWAY descriptors (Todeshini and Consonni 2009). LogPC, $LogPC^2$, and ALOGP are logarithmic octanol-water partition coefficients, logP values, estimated from Spartan (LogPC) (Ghose and Crippen 1986)and Dragon (ALOGP) (Todeshini and Consonni 2009). In these descriptors, H0 v was the most significant descriptor, and accounted for the 71 % valiance in the CIS. On the other hand, logP values are the mean lipophilicity of compounds and are related to many kinds of compound-characteristics such as toxic and pharmacokinetic parameters of drugs and xenobiotics (Houston 1975; Watanabe and Kozaki 1978; Cantelli-Forti 1986; Kim 1991; Yamada 1993; Tanii 1995). We have already reported the contribution of the lipophilicity of DHPs to GFJ-interactions (Uesawa and Mohri 2008b).

3.2. PLS regression analysis

The pharmacokinetic interactions of DHPs with GFJ following concomitant administration are known to be caused by increased absorption as a result of inhibition of intestinal CYP3A (Obach et al. 2001), one of the barrier systems for low molecular compounds such as medicines and xenobiotics as well as furanocoumarin derivatives in GFJ. On the other hand, it was pointed out that inhibitory effects of naringin and 6',7'-dihydroxybergamottin, ingredients in GFJ, for the barrier capacity of P-glycoprotein expressed in intestinal mucosal cells, are also capable of contributing to the interactions (Eagling 1999). Moreover, naringin in GFJ as well as hesperidin in orange juice suppress the absorption of the antihistamine fexofenadine (Dresser 2002, 2005; Bailey 2007) and some kinds of β-blocking agents such as celiprolol (Lilja 2003, 2004; Uesawa and Mohri 2008a; Kato 2009) due to the inhibition of OATP, an organic anion uptake transporter in intestinal cells. Although the contribution of these transporters to the pharmacokinetic interaction between DHPs and GFJ has not been reported, DHPs might be substrates of multiple drug-metabolizing enzymes and/or transporters controlled by GFJ components. Thus, the interaction might be difficult to explain based on a single descriptor only. In fact, even the descriptor included in the simplest regression model, H0 v, could account for only 71% of the variance in the interaction. Therefore, we attempted to construct multiple regression models. The partial least squares analysis with genetic algorithm (GA-PLS) was applied to select explainable descriptors to the valiance of CIS.

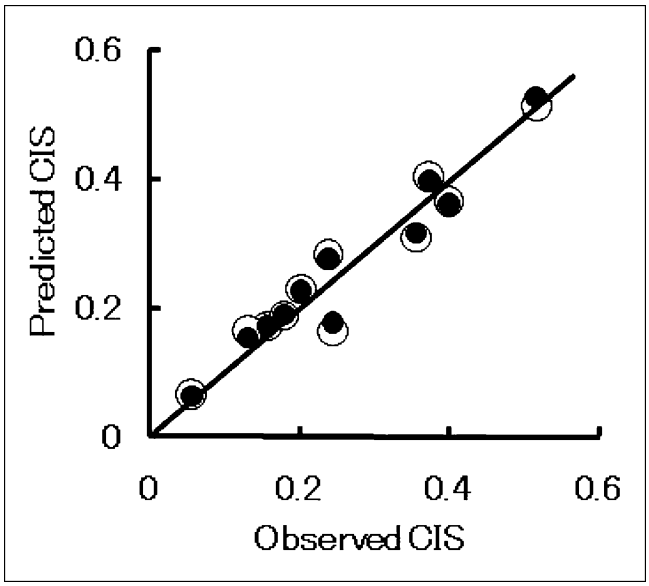

Fig. 3: Scatter plots between observed and predicted CIS for 11 DHPs by the equations 1 listed in table 3. Closed and open circles indicate the training set and the test set in the leave-one-out cross validation approach

The principal components calculated in the PLS algorithm are sorted by decreasing information. Each PLS component was extracted from the explanatory variables and maximally correlated with the objective variable (Navalon 1999; Luis 2004; Rezaei 2005). PLS has proven to be able to define the relationship between objective variables and explanatory variables (Zhang 2008). That is, this regression method has important features in which a smaller number of PLS components is used to construct the models, and the components are not correlated with each other. As a result, PLS models do not have the problem of multicollinearity and produce less over-fitting unlike ordinary multiple-regression analyses methods. Since PLS models are described by several variables, a major goal in PLS analysis is to extract relevant information and exclude redundant and noisy information. However, an exhaustive search of all possible solutions is usually not feasible. GA-PLS methods have addressed this problem by genetic algorithm (GA) (Leardi 1992; Hasegawa 1999), which is an evolutionary method widely used for complex optimization problems such QSAR.

The 185 significant kinds of descriptors estimated above were incorporated into the GA-PLS analysis. At that time, the leave-one-out cross validation method (Verweij and Van Houwelingen

Table 5: Values of descriptors included in the final equations listed in Table 3

DHP	Descriptor										
	LogPC	Mv	C005	VEA1	H0p	Mor15e	Mor15u	R3m	R4m	RDF060m	BLTA96
Amlodipine	0.147	0.61	1	4.25	1.22	−0.116	−0.310	0.463	0.423	18.0	−2.87
Azelnidipine	4.329	0.64	0	5.14	1.36	1.272	0.945	0.626	0.586	30.8	−5.12
Benidipine	2.704	0.62	1	4.50	1.24	0.017	−0.213	0.639	0.511	20.9	−4.71
Cilnidipine	2.768	0.63	1	4.34	1.27	0.786	0.582	0.590	0.527	27.1	−4.44
Felodipine	2.096	0.65	1	4.23	1.42	0.247	−0.001	0.813	0.593	19.6	−4.45
Manidipine	3.876	0.63	1	4.39	1.35	1.009	0.846	0.669	0.606	19.7	−5.08
Nicardipine	2.408	0.62	2	4.30	1.24	0.117	0.028	0.611	0.543	14.0	−4.31
Nifedipine	0.676	0.62	2	4.24	1.17	0.440	0.431	0.552	0.590	12.2	−3.30
Nimodipine	1.177	0.60	1	4.33	1.16	0.600	0.329	0.540	0.532	25.7	−3.48
Nisoldipine	1.899	0.61	1	4.31	1.20	0.339	0.266	0.522	0.533	14.6	−4.00
Pranidipine	2.924	0.64	1	4.28	1.27	0.185	0.082	0.612	0.551	20.4	−4.77
Aranidipine	0.451	0.62	1	4.31	1.21	0.484	0.419	0.535	0.548	16.1	−2.95
Barnidipine	2.424	0.63	1	4.52	1.25	0.906	0.763	0.650	0.584	26.4	−4.51
Clevidipine	2.818	0.63	1	4.28	1.43	0.455	0.219	0.944	0.653	22.9	−4.71
Lemildipine	1.461	0.64	1	4.41	1.33	1.470	1.176	0.728	0.521	26.1	−3.34
Lercanidipine	5.159	0.62	2	4.54	1.33	0.753	0.622	0.664	0.601	31.7	−5.99
Niguldipine	4.864	0.63	1	4.73	1.27	−0.257	−0.434	0.695	0.642	31.0	−5.99
Niludipine	2.013	0.59	0	4.32	1.15	0.601	0.423	0.526	0.496	20.9	−3.60
Nilvadipine	1.085	0.63	1	4.32	1.20	0.725	0.582	0.616	0.582	13.6	−2.95

1993) was adopted. This validation was considered suitable for the limited number of compounds under test (11 kinds of DHPs) because all the compounds could be used as a test set in the procedure. In other words, each object was taken away, one at a time in the leave-one-out technique. In this case, for 11 objects, 11 reduced models had to be calculated. For each reduced data set, the model was calculated and responses for the deleted object were predicted from the model. The squared differences between the true response and the predicted response for the object left out were added to the predictive residual sum of squares (PRESS) (Cruciani et al. 1992).

The explained variance in prediction:

$$Q^2 = 1 - \frac{PRESS}{TSS} = 1 - \frac{\sum_{i=1}^{11}(y_i - \hat{y}_{i/i})^2}{\sum_{i=1}^{11}(y_i - \bar{y})^2} \qquad (2)$$

where *TSS* is the total sum of squares. $y_{i/i}$ denotes the response of the *i-th* object estimated by using a model obtained without using the *i-th* object. Using validation techniques minimizes this quantity.

The top 6 models with R^2 and Q^2 over 0.96 and 0.91, respectively, are shown in Table 3. These equations include over 5 kinds of descriptors. However, each model was constructed from only one PLS component. A brief summary of the Dragon descriptors in the equations is shown in Table 4. These models were considered to possess high predicting performance with a low possibility of over fitting because of the high Q^2 values obtained in the leave-one-out cross validation and only one component was included. Accordingly, we attempted to predict the interaction strengths of DHPs not reported of interacting with GFJ in clinical studies such as aranidipine, barnidipine, clevidipine, lemildipine, lercanidipine, niguldipine, niludipine, and nilvadipine. As a result, GFJ consumption was estimated to cause a relatively high increase in interaction strengths with more than a 2-fold variation in AUC in the case of barnidipine, clevidipine, lemildipine, and lercanidipine concomitant administrations (Fig. 2, b, c, d, and e). On the other hand, aranidipine, niludipine, and nilvadipine might interact gently with GFJ (Fig. 2, a, g, and h).

We succeeded in constructing models to predict GFJ- interaction strength using the GA-PLS technique. Furthermore, the possibilities of clinical risks of the interaction-unreported DHPs were estimated based on the PLS equations.

The results suggested that all DHPs investigated in this study are capable of producing clinically significant interactions when GFJ is taken concomitantly. Amlodipine with a 1.1-fold increase in AUC when administered with GFJ, is the safest DHP to avoid the risks associated with GFJ consumption among the drugs examined in this study. These findings might also be useful for avoiding interactions in the drug discovery phase of DHPs.

4. Experimental

4.1. Optimization of the DHP structures

The minimal energy conformation in each DHP was searched for using Merck Molecular Force Field (MMFFaq) by Spartan'06 for Windows (Wavefunction, Inc., Irvine, CA, U.S.A). Geometry optimization was then performed using density-functional-theory (DFT) calculation (B3LYP/6-31G**) by Spartan.

4.2. Calculation of descriptors

Thirteen kinds of descriptors were calculated by Spartan software such as the geometric, electronic, and physicochemical features including molecular surface area, molecular volume, polar surface area, dipole moment, heat of formation, HOMO energy, LUMO energy, electronegativity (Mulliken 1934), chemical hardness (Parr and Pearson 1983), maximum electrostatic potential, minimum electrostatic potential, Ghose-Crippen logP (LogPC) (Ghose and Crippen 1986), and $LogPC^2$. Furthermore, 3224 kinds of Dragon descriptors (Todeshini and Consonni 2009) were also calculated from information on the 2D and optimized 3D-structures of DHPs by Dragon software version 5.5 (Talete srl, Pisani, Milano, Italy) with the 3D geometry optimized structures of DHPs. No variance (constant) dragon descriptors or incomputable descriptors were excluded. As a result, 1409 kinds of dragon descriptors were used in this study.

4.3. Data analysis

The objective and explanatory variables were defined as CIS and the calculated descriptors from DHP structures, respectively. Simple linear regression analyses were performed using the least-squares method by JMP version 8.0.1 (SAS Institute Inc., Cary, NC, U.S.A.). The significance level was set at

$p < 0.05$. Furthermore, the relation between the potentials and the properties was investigated using statistical techniques including partial least squares analysis with genetic algorithm (GA-PLS) (Ghose and Crippen 1986) to variable subset selections with leave-one-out cross-validation (Cruciani 1992) as the selection pressure by Chemish ver 4.6 (ChemInfoNavi Ltd., Iwakuni, Yamaguchi, Japan). All descriptors that showed a significant relationship with CIS in the simple regression analysis were put into the PLS analysis. The variables were standardized. In the genetic algorithm, number of generations, number of chromosomes, cut-off, survival ratio, number of crossover, mutation ratio were 10000, 100, 30, 30, 5, and 1, respectively. The maximum number of PLS-components was set at 2 to avoid over fitting of the regression models constructed by the GA-PLS. Determination coefficients (R^2), determination coefficients of the leave-one-out validation (Q^2), and residual plots were considered to decide the final models for the equations. Furthermore, CIS in 8 kinds of DHPs, aranidipine, barnidipine, clevidipine, lemildipine, lercanidipine, niguldipine, niludipine, and nilvadipine, that have not been reported to interact with GFJ were predicted by the final models. That is, the structures of the DHPs were optimized, and the descriptors included in the models were calculated as mentioned above.

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