—Regular Articles—

Relationship between Lipophilicities of 1,4-Dihydropyridine Derivatives and Pharmacokinetic Interaction Strengths with Grapefruit Juice

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It is well known fact that the strengths of drug interactions with grapefruit juice (GFJ) differ greatly depending on the 1,4-dihydropyridine calcium channel antagonist (DHP) used. However, there are no available data on the relationship between interactions with GFJ and its physicochemical attributes. Therefore we endeavored to study the correlation between calculated logP values, indicating lipophilicity, from chemical structures of DHPs as well as water diffusion, molecular volume, molecular polarization, molecular density, refractive index, topologic polar surface area, and calculated molar refractivity. Thirteen forms of DHP, amlodipine, azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and pranidipine were analyzed due to clinical trials performed with GFJ and these agents. The pharmacokinetic interaction strengths were defined in common logarithmic values of increasing ratios of area under the plasma concentration-time curve (AUC) with GFJ intake compared with controls. Physicochemical properties including three categories of predicted logP values were calculated from the structures of DHPs and their estimated relationship with the interactions. As a result, the logP values indicated significant positive correlations with the interaction strengths. This finding suggests that lipophilicity is an important factor in the strengths of pharmacokinetic interactions of DHPs with GFJ intake.

Key words——grapefruit juice; pharmacokinetic interaction; dihydropyridine antihypertensive; logP; lipophilicity

INTRODUCTION

1,4-Dihydropyridine calcium channel antagonists (DHPs) are one of the major categories of drugs with reported pharmacokinetic interactions, such as the increasing drug levels in plasma with concomitant intake of GFJ.[1–11] This group of compounds has a 1,4-dihydropyridine group in a common chemical structure.

CYP3A[12] is expressed in human intestine[13] and liver[14] which has oxidized the structure of the pyridine ring[15] and, as a result, the calcium channel-blocking capacities of these drugs disappear. GFJ inhibits the activity of CYP3A expressed in the intestine,[16] since it is the first contact enzyme for the oxidation of orally administered DHPs. Intestinal CYP3A decreases through mechanism-based inhibition[17] of GFJ components, furanocoumarin derivatives such as bergamottin, 6′,7′-dihydroxybergamottin, and furanocoumarin dimers such as paradisin A, paradisin B, and paradisin C.[18–22] As a result, part of the intestinal barrier capacity for xenobiotics decreases for at least 3 days.[23] Accordingly, the bioavailability of parent compounds with the 1,4-dihydropyridine ring found in many types of DHP and the level in systemic circulation increase after concomitant intake of GFJ.

Generally, patients who a administered DHPs are instructed in clinical practice to avoid GFJ consumption because these interactions induce side effects.[3] On the other hand, the strength of the interaction is dependent upon the type of drug used.[1–11] For example, the ratio of the area under the plasma concentration-time curve (AUC) of orally administered DHPs between patients drinking GFJ and those who do not was found to vary greatly and ranged from $\times$ 1.1 in the case of amlodipine[1] to $\times$3.3 in the case of azelnidipine.[9] The structural and physicochemical properties of currently used DHPs vary significantly, and the extent of interactions is considered attributable to the physicochemical characteristics. However, little is known about the correlation between the structures and the clinical interaction strengths (CISs). Therefore analysis was performed using the predictive properties calculated from the chemical structures and the reported pharmacokinetic interactions with GFJ consumption.

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METHODS

Thirteen DHPs, amlodipine, azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and pranidipine, on which there were confirmable reports of pharmacokinetic interactions with GFJ were selected for analysis. 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. The first report with a significant interaction with GFJ intake for each drug was referred to the AUC value to avoid the variation of CIS in publication bias. Three types of predicted logP values, ALOGPs,[24] ClogP,[25] and XLOGP,[26] and seven other physicochemical properties, water diffusion, molecular volume, molecular polarization, molecular density, refractive index, topologic polar surface area, and calculated molar refractivity, were calculated from the chemical structures using ChemDraw 10.0 (for CLogP, topologic polar surface area, and calculated molar refractivity, Cambridge Soft Corporation, MA, US), ALOGPS 2.1[27] (for ALOGPs and XLOGP, Virtual Computational Chemistry Laboratory, http://www.vcclab.org), and Sparc On Line Calculator v3.1[28] (for water diffusion, molecular volume, molecular polarization, molecular density, and refractive index, University of Georgia, GA, US) which were used for analyzing the physicochemical characteristics of DHPs. Linear regression analyses were performed using the least-squares method in which objective variable and explanatory variable were CISs and predicted physicochemical properties, respectively. The significance level was set at $p<0.05$.

RESULTS

Strengths of Interactions between DHPs and GFJ Conditions in the clinical trials for the 13 DHPs (Fig. 1) orally administered with GFJ are shown in Table 1. Drugs used in the trials simultaneously administered with GFJ. The administration volume of GFJ ranged from 150 to 300 ml. Alternatively, AUC ratios between the GFJ and non-GFJ groups ranged

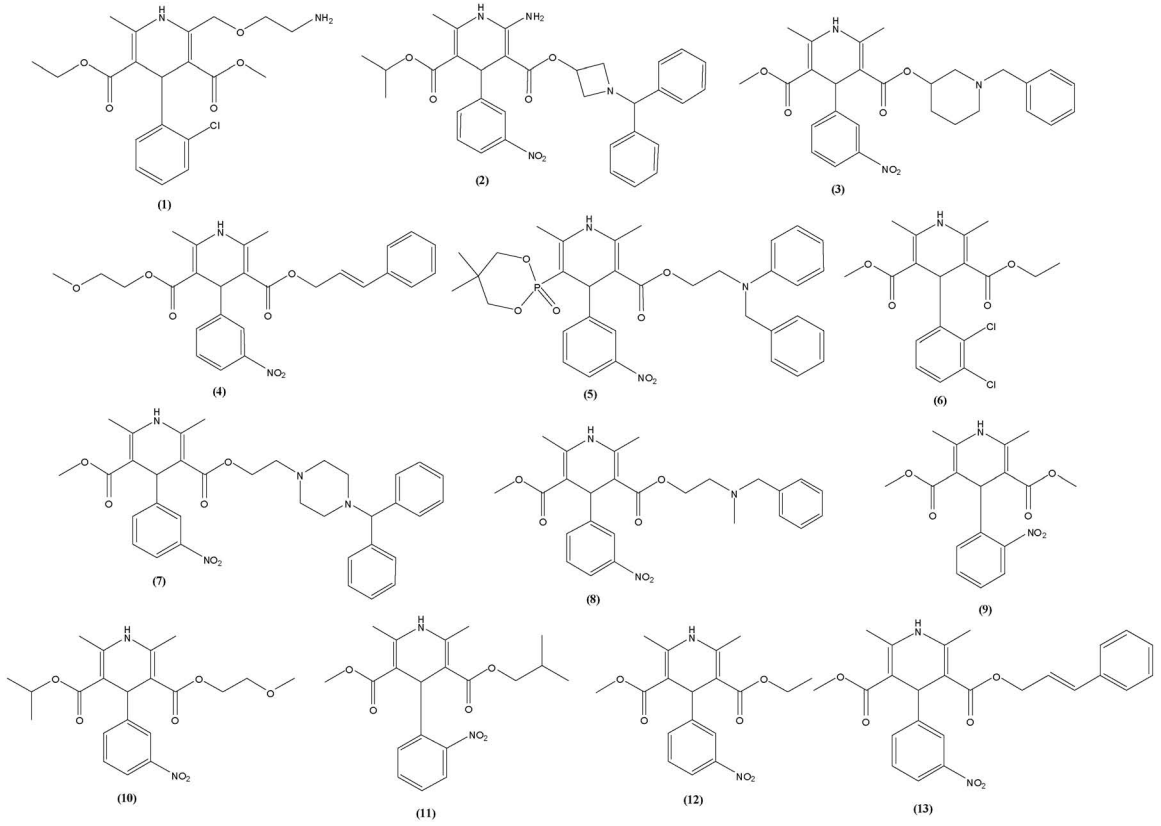

Fig. 1. Chemical Structures of Dihydropyridine Derivatives

Amlodipine, azelnidipine, benidipine, cilnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, and pranidipine are numbered from 1 to 13, respectively.

Table 1. Reported Pharmacokinetic Interactions of Dihydropyridine Derivatives with Concomitant Consumption of GFJ in Humans

Comp. no.	Comp. name	Dose (mg)	N	GFJ (ml)	AUC ratio*	Ref.
1	Amlodipine	5	12	250	1.14	1
2	Azelnidipine	8	8	250	3.28	9
3	Benidipine	4	6	200	1.59	2
4	Cilnidipine	10	6	200	2.27	2
5	Efonidipine	40	19	250	1.67	10
6	Felodipine	5	6	250	2.51	3
7	Manidipine	40	6	250	2.36**	11
8	Nicardipine	40	6	300	1.43	4
9	Nifedipine	10	6	250	1.35	3
10	Nimodipine	30	8	250	1.51	5
11	Nisoldipine	20	12	250	1.76	6
12	Nitrendipine	20	9	150	2.25	7
13	Pranidipine	2	16	250	1.73	8

* AUC_{DPNs} with GFJ/AUC_{DPNs} without GFJ.
** Average ratio bitween R-and S-manidipine.

from 1.14 to 3.28 (Table 1). No significant correlation was observed between each administration volume and the AUC ratio or CIS, or logarithmic values of the AUC ratio.

Correlation between Strengths of Interactions and Lipophilicity of Drugs Three types of predicted logP values and seven physicochemical properties calculated from the two-dimension chemical structure of each drug are indicated in Tables 2 and 3, respectively. Analyses using the linear least-squares method for relationship between the physicochemical properties and CISs represent each logP value, CLogP, ALOGPs, and XLOGP, but not water diffusion, molecular volume, molecular polarization, molecular density, refractive index, topologic polar surface area, and calculated molar refractivity, correlated with CIS : CIS=0.0822ALOGPs−0.0651, r=0.626; CIS = 0.0569ClogP − 0.0276, r = 0.592; CIS = 0.0582XLOGP+0.0272, r=0.587 (Fig. 2).

Table 2. Calculated LogP Values of Dihydropyridine Derivatives

Comp. no.	Comp. name	ALOGPs	CLogP	XLOGP
1	Amlodipine	2.22	3.43	2.23
2	Azelnidipine	5.12	6.96	6.09
3	Benidipine	4.28	5.71	4.48
4	Cilnidipine	4.39	5.54	4.49
5	Efonidipine	5.35	6.96	6.29
6	Felodipine	4.36	5.30	4.15
7	Manidipine	5.11	7.02	5.15
8	Nicardipine	4.34	5.23	3.94
9	Nifedipine	2.49	3.12	2.37
10	Nimodipine	3.41	4.00	3.07
11	Nisoldipine	3.63	4.58	3.45
12	Nitrendipine	3.21	3.73	2.8
13	Pranidipine	4.71	5.58	4.68

DISCUSSION

The present study was conducted to estimate the effects of the physicochemical properties of DHPs on the strength of interaction with GFJ. DHPs are the major focus of studies of the pharmacokinetic interactions with concomitant intake of GFJ.[1–11,29] These compounds have a 1,4-dihydropyridine ring as a common structure. This partial structure is characterized by substrates of cytochrome P450, which form a pyridine ring as a result of the enzymatic reaction.[15,30,31] The aromatic-ring formation reaction is caused by the DHPs losing their calcium antagonistic effect.

It has been considered that interactions relating to GFJ were caused by inhibition of a first-pass metabolism of the dihydropyridine site with CYP3A in the intestinal mucosal cells.[32] DHPs used in clinical practice have a variety of chemical structures, suggesting various physicochemical and pharmacokinetic properties. The extent of interaction varies greatly among DHPs (Table 1). However, there has been little research into the relationship between the variability of the interactions and the physicochemical properties.

Table 3. Calculated Physicochemical Properties of Dihydropyridine Derivatives

Comp. no.	Comp. name	WD (10^{-6} cm^2/sec)	MV (cm^3/mole)	MP (Å^3/molecule)	MD (g/cm^3)	RI	tPSA (Å^2)	CMR
1	Amlodipine	6.10	325	42.1	1.26	1.57	100	10.9
2	Azelnidipine	4.97	458	63.8	1.27	1.62	146	16.5
3	Benidipine	5.32	408	54.6	1.24	1.59	120	14.1
4	Cilnidipine	5.96	396	52.7	1.29	1.61	126	13.6
5	Efonidipine	4.81	483	67.0	1.31	1.62	129	17.4
6	Felodipine	6.50	292	38.2	1.31	1.57	65	9.9
7	Manidipine	4.71	500	67.7	1.22	1.60	123	17.4
8	Nicardipine	5.49	387	51.8	1.24	1.59	120	13.3
9	Nifedipine	6.89	265	35.1	1.31	1.58	116	9.1
10	Nimodipine	5.91	343	43.0	1.22	1.55	126	11.1
11	Nisoldipine	6.20	317	40.6	1.23	1.56	116	10.5
12	Nitrendipine	6.61	284	36.8	1.27	1.57	116	9.5
13	Pranidipine	5.79	355	48.4	1.26	1.60	116	12.6

WD, water diffusion ; MV, molacular volume ; MP, molacular polarization ; MD, molecular density ; RI, refractive index ; tPSA, topologic polar surface area ; CMR, calculated molar refractivity.

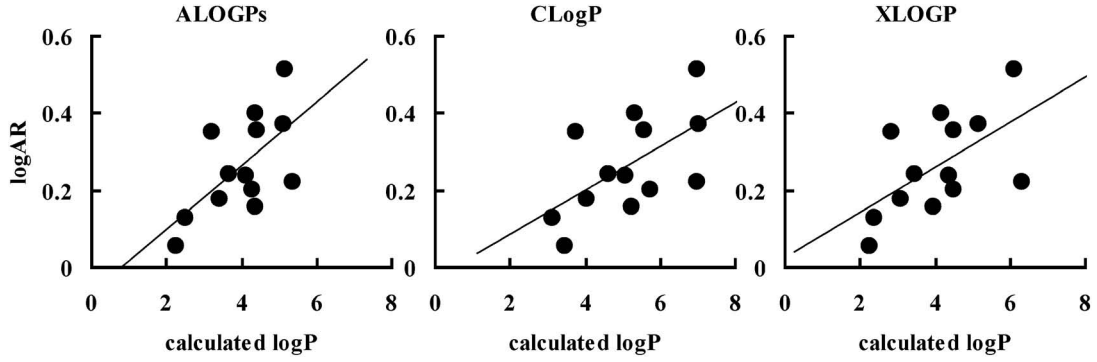

Fig. 2. Relationship between Calculated LogP Values of Dihydropyridine Derivatives and the Corresponding Logarithmic AUC Ratios in Clinical Trials with GFJ Consumption

Lines are drawn with the least-squares approach. AR, AUC ratio.

In the present study, findings from clinical trials were used in calculating CISs, and the conditions of pharmacokinetic investigation in the reports differed, resulting in errors among pharmacokinetic data. Nevertheless, the results showed that the relationship between CISs and the predicted logP values for the 13 DHPs indicated significant correlation, which was expressed as simple linear regression formulae. These results suggest that the lipophilicity of the drugs is an important factor in the interactions. It is considered that the clearance of DHPs in first-pass metabolism is regulated by intestinal and hepatic intrinsic clearance.

Because the target organ of GFJ is the intestine, it has been speculated that DHP with a higher contribution ratio of intestinal clearance in the first pass has stronger interaction with the concomitant consumption of GFJ. Ohnishi *et al.* reported that the plasma protein-binding ratio correlated with an increasing ratio of AUC for calcium-blocking agents with the consumption of GFJ.[2] This suggested the possibility that drugs that have higher plasma unbound fractions reflect a higher percentage of contribution of the intestinal metabolism in first-pass effect due to a lower hepatic extraction ratio.

LogP values are a parameter-informed correlation with the plasma protein binding of drugs[33,34] and, because of this, it is conceivable that the present results support the report showing a correlation between the extent of the interactions and protein-binding ratios.[2] Furthermore, it is known that lipophilicity is one of the parameters contributing to absorption,[35] distribution,[36,37] metabolism,[38] and excretion[36,39] in pharmacokinetics. For example, enzymatic affinities and kinetic properties in CYP oxidation of various

compounds are regulated by the logP values of the substrates.[40] Therefore it is speculated that the lipophilicity of drugs contributes to the pharmacokinetic properties of DHPs oxidizing with intestinal CYP3A. On the other hand, some DHPs showed values that were distant from the linear regression in Fig. 2. This observation possibly suggests that alternative factors other than CYP3A, such as drug transporters in the intestine, may be involved in the interactions. It has been reported that concomitant intake of GFJ causes an increase in the plasma concentration of P-glycoprotein substrates such as cyclosporine[41] and a decrease in the plasma concentration of organic anion transporting peptide (OATP) substrates such as fexofenadine.[42]

ALOGPs were considered to be the most appropriate algorithm to assess the interactions between the three types of predicted logP values examined in this study because they showed the best correlation. ALOGPs were used to predict the extent of GFJ interactions with DHPs, which has not been reported to date. As a result, lercanidipine and niguldipine (ALOGPs: 6.42 and 6.27, respectively) were estimated to be high-risk drugs showing a predictive increase of 300% in the AUC with GFJ intake. Alternatively, it was suggested that aranidipine and nilvadipine (ALOGPs: 2.71 and 2.97, respectively) which are used in Japanese clinical practice, are relatively safe drugs comparable to nifedipine, with a predicted AUC increase with GFJ of about 150%. The adequacy of these prognostics has yet to be demonstrated in terms of clinical trials, although the structural analyses in this study will be useful to predict the harmfulness of drugs in interactions with GFJ.

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