

Interactions between Grapefruit Juice and Calcium Channel Antagonists

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The extent of interaction between calcium channel antagonists and grapefruit juice varies widely among drugs. Coadministration of calcium channel antagonists with grapefruit juice can elevate the bioavailability of drugs and alter pharmacokinetic parameters of the drug. A calcium channel antagonist with lower bioavailability is likely to be more affected by grapefruit juice. The area under the concentration-time curve and peak serum concentrations of azelnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nisoldipine, nitrendipine and verapamil are influenced by grapefruit juice. Conversely, pharmacokinetic parameters of amlodipine and diltiazem are not affected by grapefruit juice. The action of grapefruit juice is rapid, and a single exposure to one glass of juice can usually produce a significant interaction. Furanocoumarins primarily contribute to grapefruit juice-drug interactions in humans. Cytochrome P4503A4 and P-glycoprotein may act in tandem as a barrier to oral delivery of drugs. The main mechanism for enhanced bioavailability of drugs by grapefruit juice is, presumably, the inhibition of cytochrome P4503A4 in the small intestine and only to a minor extent affected by P-glycoprotein function. There are dose-dependent and time-dependent effects of grapefruit juice on cytochrome P4503A4. Since biosynthesis of new cytochrome P4503A4 is necessary, the duration of the interaction is consistent with the pharmacological mechanism of interaction; inhibition of enzyme activities by grapefruit juice persists for approximately 3 days.

Key words: calcium channel antagonist; cytochrome P450; grapefruit juice; interaction; pharmacokinetic parameter

Patients are frequently treated with multiple medicines concurrently in order to treat one or more medical problems with drug therapy. Although concomitant intake of 2 or more drugs can alter their efficacy, available information regarding drug activity pertains to each drug separately. Hence, an interaction is said to take place when the effects of one drug are modified by the presence of another drug, food or environmental chemical agent. For approximately 2 decades, a major focal point in the area of food-drug interactions has been regarding interactions of grapefruit with several drugs, such as lipid-lowering drugs and calcium channel antagonists (Bailey

and Dresser, 2004). In an initial report regarding grapefruit juice (GFJ) and drug interactions, investigators observed an interaction between felodipine and GFJ in a study of felodipine and ethanol in which GFJ was used to mask the taste of ethanol (Bailey et al., 1989). Subsequent studies confirmed that GFJ significantly increased the oral bioavailability of felodipine (Bailey et al., 1991; Edgar et al., 1992).

Drug concentration at the cellular site of action represents the net result of absorption, distribution and elimination, which is often determined by mechanisms involving the metabolism or transport of a drug (Bailey and Dresser, 2004).

Abbreviations: AUC, area under the concentration-time curve; C_{max}, peak serum concentration; CYP, cytochrome P450; GFJ, grapefruit juice

Many endogenous compounds, in addition to drugs, are metabolized in the body by cytochrome P450 (CYP) enzyme systems through oxidative biotransformation. The isozyme CYP3A4 is the predominant form in the human small intestine (Kolars et al., 1992), while a very limited number of other CYP isoforms are expressed in the small intestine (Zhang et al., 1999). The location of CYP3A4 in the small bowel and liver permits an effect on both presystemic and systemic drug disposition (Dresser et al., 2000b). In most cases, the extent of drug interaction varies markedly among individuals; this is likely to be dependent on interindividual differences in CYP3A4 tissue content, pre-existing medical conditions and possibly age (Dresser et al., 2000b). Clinically important CYP3A4 inhibitors include itraconazole, ketokonazole, clarithromycin, erythromycin, nefazodone, ritonavir and GFJ (Dresser et al., 2000b).

There are more than 10 oral calcium channel antagonists available in Japan. Calcium channel antagonists are used widely in clinical treatment of hypertension and angina pectoris. Calcium channel antagonists are well absorbed from the intestine, and the first-pass metabolism mediated by CYP3A4 in the liver and intestine is a major determinant of bioavailability. The coadministration of these drugs with GFJ can markedly elevate bioavailability of drugs and can alter pharmacokinetic parameters of the drug. Although the extent of interaction between calcium channel antagonists and GFJ varies widely among individuals, in the short term this interaction is reproducible within individuals. A drug with lower bioavailability is likely to be more impacted by GFJ (Fuhr, 1998; Ohnishi et al., 2006). A calcium channel antagonist with lower bioavailability or higher plasma protein binding ratio is likely to exhibit a more potent interaction with GFJ (Ohnishi et al., 2006). Ohnishi et al. (2006) considered that this information should be useful to avoid adverse drug interactions and to predict the extent of interaction in a clinical situation and during drug development. Amlodipine and nifedipine have better inherent oral bioavailability and hence are less affected by

GFJ (Bailey et al., 1991; Josefsson et al., 1996). Although metabolized *in vivo* by CYP3A4, the nondihydropyridine calcium channel antagonists diltiazem and verapamil were not affected by GFJ in small clinical studies (Zaidenstein et al., 1998). Amounts of GFJ in the range normally consumed (up to 3 glasses per day) seem to have intestinal activity only (Garvan and James, 2000).

This short review reveals the effect of GFJ on pharmacokinetic parameters, such as the peak plasma (or serum) concentration (C_{max}) and the area under the concentration-time curve (AUC), as well as pharmacodynamic parameters, such as blood pressure and heart rate, of oral calcium channel antagonists in humans.

Mechanism of interaction

A food-drug interaction may be defined mainly as the alteration of absorption and/or metabolism of a drug by a food component. The underlying mechanisms can be classified into 2 broad categories. The first is pharmacokinetics, including alterations in absorption, distribution, metabolism and excretion; the second is pharmacodynamics, describing alterations in the drug concentration-effect relationship (Dresser et al., 2000b). The action of GFJ is rapid and a single exposure to one glass of juice can usually produce a significant interaction (Lundahl et al., 1998). There are dose-dependent (Lilja et al., 2000) and time-dependent (Lundahl et al., 1995) effects of GFJ on CYP3A4. Uesawa and Mohri (2008) reported that lipophilicity is an important factor in the strength of pharmacokinetics of dihydropyridines with GFJ intake based on the result that logP values indicate significant positive correlations with interaction strength.

CYP enzymes are predominantly expressed in the liver, although they are also present in the extra-hepatic tissues such as the intestinal mucosa. CYP3A comprises on average 30% of all CYP in the liver and as much as 70% in small intestine epithelial cells (Kane and Lipsky, 2000). CY-

P3A4 is the most abundantly expressed isoform and is highly expressed in the intestinal mucosa. Although the liver was assumed to be the major site of grapefruit-drug interactions initially, it is indicated that the interaction may take place during the gastrointestinal absorption phase, based on the result that the interaction only occurs when drugs are administered orally, not intravenously (Lundahl et al., 1997). GFJ can inhibit the activity of intestinal CYP3A4, leading to an interaction with drugs during their first passage from the intestinal lumen into systemic circulation (Lown et al., 1997). Dahan and Altman (2004) reported that only intestinal CYP3A4 is inhibited by GFJ, while liver resident CYP3A4 enzymes are not affected. This result is supported by the finding that interaction with GFJ markedly elevated the AUC, while no significant change has been observed in elimination half-life or systemic clearance (Bailey et al., 1991). The effect of GFJ on felodipine has been shown to exist at approximately 30% of its maximum even when the drug was administered 24 h following juice intake (Lundahl et al., 1995). Since biosynthesis of a new CYP3A4 is necessary, the duration of the interaction is consistent with the pharmacological mechanism of interaction.

P-glycoprotein, one of the multiple drug resistance transporters, reduces the fraction of drug absorbed by carrying the drug from the enterocyte back to the intestinal lumen (Gottesman et al., 1996). GFJ modifies P-glycoprotein transporter activity. Although there was little data suggesting activation of P-glycoprotein efflux by GFJ (Phang et al., 1993; Soldner et al., 1999), most investigators observed inhibition of transporter activity (Takanaga et al., 1998; Eagling et al., 1999; Wang et al., 2001; Tian et al., 2002). Inhibition of P-glycoprotein is a possible mechanism that increases oral drug bioavailability by reducing intestinal and/or hepatic efflux transport (Bailey and Dresser, 2004). Kane and Lipsky (2000) reported CYP3A4 and P-glycoprotein may act in tandem as a barrier to the oral delivery of many drugs.

Goosen et al. (2004) reported that bergamottin enhanced the oral bioavailability of felodipine

and may cause a clinically relevant drug interaction in susceptible individuals. Furthermore, GFJ-drug interactions likely also involve other furanocoumarins, possibly acting in combination by additive or synergistic mechanisms. Kakar et al. (2004) reported that 6',7'-dihydrobergamottin is an important contributor to the GFJ effect. Paine et al. (2006) reported that furanocoumarins (bergamottin, 6',7'-dihydrobergamottin and furanocoumarin dimers) are the active ingredients in GFJ responsible for enhancing systemic exposure of felodipine.

Presumably, the main mechanism for enhanced bioavailability of drugs by GFJ is the inhibition of CYP3A4 in the small intestine (Edwards et al., 1996; Lown et al., 1997), resulting in a significant reduction of presystemic metabolism, and only to a minor extent influenced by P-glycoprotein function (Dahan and Altman, 2004).

Drug interactions in each calcium channel antagonist (Table 1)

Dihydropyridines

Amlodipine

Amlodipine has a different pharmacokinetic profile from other dihydropyridines (Abernethy, 1989; Meredith and Elliott, 1992). Specifically, amlodipine has a lower hepatic extraction ratio, hence its higher oral bioavailability, and a later time to peak plasma concentration in addition to a longer plasma elimination half-life compared with other dihydropyridines. When amlodipine (5 mg) was coadministered with a glass of GFJ (250 mL), C_{max} was 115% and AUC (0–72 h) was 116% compared with water administration in healthy volunteers. There were no significant differences in blood pressure and heart rate between the 2 treatments (Josefsson et al., 1996). The AUC ratio of GFJ (250 mL once daily for 9 days) to water for amlodipine (10 mg) was 107.8% and the C_{max} ratio was 107.1%. There were no statistically significant treatment effects on blood pressure during

Table 1. Pharmacokinetic interactions between calcium channel antagonists and GFJ

Calcium channel antagonist	Dose (mg)	GFJ (mL)	AUC (value relative to control)	Cmax (value relative to control)	Bio-availability (%)	Reference
Dihydropyridine						
Amlodipine	5	250	1.14	1.15	64	Josefsson et al., 1996
	10	240	1.08	1.07		Vincent et al., 2000
Azelnidipine	8	250	3.28	2.49	NA	Hirashima et al., 2006
Efonidipine	40	250	1.67	1.55	NA	Yajima et al., 2003
Felodipine	5	200, 250	2.51–2.88	2.23–4.00	15	Bailey et al., 1991
	10	200, 240	1.72–2.16	2.38–3.25		Lown et al., 1997
						Lundahl et al., 1997, 1998
						Dresser et al., 2000a
Manidipine	40	250			NA	Uno et al., 2006
(S)-manidipine			2.37	2.40		
(R)-manidipine			3.03	3.39		
Nicardipine	40	300			15–45	Guengerich et al., 1991
			(+)-nicardipine	1.43		—
(–)-nicardipine			1.84	—		
Nifedipine	10	200	1.47–1.58	1.04–1.16	43	Waller et al., 1984
	20	200, 250	1.09–2.02	1.27–2.00		Rashid et al., 1993, 1995
						Sigusch et al., 1994
						Azuma et al., 1998
Nisoldipine	10	250	4.55	3.06	3.7–8.4	Friedel and Sorkin, 1988
	20	250	1.76	3.50		Bailey et al., 1993
						Azuma et al., 1998
Nitrendipine	20	150			5–30	Krol et al., 1987
(S)-nitrendipine			2.22	2.01		Mikus et al., 1987
(R)-nitrendipine			2.36	2.15		Soons et al., 1989, 1991
Non-dihydropyridine						
Diltiazem	120	200, 250	1.10–1.18	1.02–1.14	40–50	Buckley et al., 1990
						Sigusch et al., 1994
						Christensen et al., 2002
Verapamil	120	250			20	McTavish and Sorkin, 1989
(S)-verapamil			1.36–1.47	1.58–1.70		Ho et al., 2000
(R)-verapamil			1.28–1.41	1.40–1.54		Fuhr et al., 2002

AUC, area under the concentration-time curve; Cmax, peak plasma (or serum) concentration; GFJ, grapefruit juice; NA, not available.

amlodipine administration. Vincent et al. (2000) concluded that once daily GFJ administration with usual oral doses of amlodipine is unlikely to alter the profile of response in clinical practice.

Azelnidipine

Azelnidipine is an L-type calcium channel antagonist, which is categorized as third generation type-B (Toyo-oka, 2006). The remarkable characteristics of azelnidipine that differentiate it from other analogues are i) the lower possibility to

cause sinus bradycardia in patients and ii) longer-lasting pharmacological effects even with a once daily dose of 8 to 16 mg (Kuramoto et al., 2003). Concomitant administration of azelnidipine with GFJ increased the Cmax of azelnidipine by 2.5-fold and the AUC by 3.3-fold compared with water. No serious adverse events were observed except one subject described mild symptoms of drug-related headache and flushing accompanied with orthostatic hypotension at 4 h after administration of GFJ (Hirashima et al., 2006).

Efonidipine

Efonidipine has longer-lasting pharmacological effects. C_{max} and AUC of efonidipine (40 mg) in 20 male volunteers coadministered with GFJ were 155% and 167% of those taking efonidipine without GFJ, respectively. There were no significant differences in the incidence of adverse events between administrations with or without GFJ. The transitional patterns of blood pressure and heart rate were very similar between those with GFJ and those without (Yajima et al., 2003).

Felodipine

Bioavailability of felodipine is low (15%) at a dose of 5 mg per person (Edgar et al., 1992). There are many reports about interaction between felodipine and GFJ. Six men with borderline hypertension received felodipine (5 mg) with 250 mL of water or with 250 mL of GFJ. GFJ increased AUC and bioavailability by 284% (range 164–469) and 134% (range 108–169), respectively. Diastolic blood pressure was reduced more (–20 versus –11) and heart rate increased more (22 versus 9) with GFJ than with water (Bailey et al., 1991). When felodipine (5 mg) was administered with either 200 mL of water or GFJ in 9 healthy male volunteers, GFJ increased C_{max} of felodipine from 6 to 16 nmol/L, and AUC from 23 to 65 nmol/L compared to water. Blood pressure measured in the morning 3 h after dosing with GFJ was 9% lower compared to control (Edgar et al., 1992). In a randomized cross-over study in 9 volunteers, GFJ administered 1, 4, 10 or 24 h before and simultaneously with drug administration resulted in a 32–99% increase in C_{max} of felodipine (10 mg), relative to concomitant water and felodipine intake. The effect on AUC was also significant when GFJ was ingested up to 10 h before administration of the drug. Interaction decreased with an increase in time between GFJ and drug intake (Lundahl et al., 1995). Twelve healthy volunteers received 150 mL water or 150 mL of GFJ 15 min prior to oral felodipine (10 mg) administration. GFJ increased AUC, C_{max} and the absolute bioavailability by 72%, 173% and 112%, respectively. GFJ intake

immediately before felodipine administration resulted in more pronounced hemodynamic effects of the drug in diastolic blood pressure and heart rate (Lundahl et al., 1997). Twelve elderly subjects received oral felodipine (5 mg) with 250 mL of GFJ or water; AUC and C_{max} of felodipine were 2.9- and 4.0-fold greater, respectively, with GFJ. Systolic and diastolic blood pressures were lower with GFJ in the single-dose study (Dresser et al., 2000a).

Manidipine

Manidipine has potent and long-lasting activities (Cheer and McClelln, 2001). The pharmacological effects of manidipine enantiomers are known to be different and the pharmacological potency of (S)-type has been found to be greater than that of (R)-type (Kajino et al., 1989). GFJ significantly increased C_{max} and AUC of (S)-manidipine by 2.4- and 2.3-fold, respectively; and C_{max} and AUC of (R)-manidipine increased by 3.4- and 3.0-fold, respectively. There were significant differences in GFJ-mediated percentage increases in C_{max} and AUC of (S)-manidipine compared with those of (R)-manidipine. There were no significant differences in pharmacodynamic variables, arterial blood pressure and heart rate, between the 2 enantiomers (Uno et al., 2006).

Nicardipine

Containing a chiral center like other dihydropyridines, nicardipine possesses potent activities (Freedman and Waters, 1987). Bioavailability of nicardipine is low (15–45%) at a dose of 10 to 40 mg per person, due to extensive presystemic elimination (Guengerich et al., 1991). When nicardipine (40 mg) was administered 30 min after ingestion of 300 mL of water or concentrated GFJ in 6 normal healthy male volunteers, GFJ increased the mean oral bioavailability of (+)- and (–)-nicardipine, 48.6% and 105.6% respectively, compared with water intake. AUC was 143% and 191% compared with water for (+) and (–) enantiomers, respectively. Compared against water, GFJ did not alter the mean pharmacodynamic variables assessed in the study except for heart

rates at 1 h and 2 h, following the oral dosing of racemic nicardipine (Uno et al., 2000). However all of the mean kinetic parameters of both enantiomers following intravenous dosing of racemic nicardipine did not differ between the GFJ and water intake. Uno et al. (2000) concluded that the gut is the major presystemic disposal site of racemic nicardipine in humans.

Nifedipine

Nifedipine is a lipid-soluble drug which is absorbed completely from the gut but has a low bioavailability due to extensive presystemic metabolism (Foster et al., 1983; Waller et al., 1984). Bioavailability of nifedipine was reported as 43% (Waller et al., 1984). Eight healthy volunteers received nifedipine (10 mg) with 200 mL of water or double strength GFJ; the AUC for nifedipine with GFJ (320 ng•h/mL) increased significantly compared with the AUC when nifedipine was given alone (218 ng•h /mL). The C_{max} was unchanged by administration of GFJ (Rashid et al., 1993). In another study, 8 healthy volunteers received nifedipine (10 mg) with 200 mL of water or double strength GFJ both 2 h before and at the time of dosing; the administration of GFJ resulted in a significantly increased AUC (191 versus 301 ng•h/mL) and bioavailability (0.63 versus 0.86). The elimination half-life was unchanged by administration of GFJ (Rashid et al., 1995). Ten healthy volunteers received 20 mg nifedipine (control-released tablet) with 200 mL of GFJ or water; the AUC and C_{max} of GFJ phase were on average 103% (range 48–265) and 94% (range –23 to 259) higher than those in the control phase (Sigusch et al., 1994). Eight healthy volunteers received oral nifedipine (20 mg), and no particular differences were shown in the plasma concentrations of nifedipine with GFJ (250 mL) or water ingestion. Nifedipine was also well tolerated in 4 dosing schedules (Azuma et al., 1998).

Nisoldipine

Twelve healthy men received nisoldipine (20 mg) with either 250 mL water or 250 mL GFJ; GFJ increased plasma nisoldipine concentrations be-

tween 90 min to 6 h compared with water. Nisoldipine C_{max} was 406% (range 107–836), and AUC was 198% (range 81–682) compared with water. Minor effects on supine blood pressure and heart rate were observed, probably because subjects were normotensive (Bailey et al., 1993). Eight healthy volunteers received oral nisoldipine (10 mg), and significant increases in C_{max} and AUC were observed when the drug was administered with GFJ and 1 h after subjects ingested GFJ compared with drug administration with water only. Nisoldipine was also well tolerated in 4 dosing schedules (Azuma et al., 1998). In a clinical study investigating the effect of various schedules of GFJ intake on nisoldipine pharmacokinetics and pharmacodynamics with 8 healthy volunteers, the effect of GFJ decreased time dependently and lasted for at least 3 days after ingestion (Takanaga et al., 2000). They suggested that it is necessary to withhold GFJ for at least 3 days before administration of the nisoldipine to prevent GFJ-drug interaction.

Nitrendipine

Nitrendipine is a chiral 1,4-dihydropyridine calcium channel antagonist. The systemic bioavailability of racemic nitrendipine is low and variable (5–30%) despite its almost complete gastrointestinal absorption (Krol et al., 1987; Mikus et al., 1987; Soons et al., 1989). In 9 subjects, the AUC of oral racemic nitrendipine (20 mg) was increased by 150 mL of GFJ (mean increase 106%; interval 64–158%). Comparable results were obtained for the C_{max} and both parameters of (S)- and (R)-nitrendipine. There were highly significant differences in the AUC and C_{max} between enantiomers. There were no consistent effects on blood pressure with GFJ, and GFJ did not affect hemodynamic parameters (Soons et al., 1991).

Nondihydropyridines

Diltiazem

Diltiazem is a benzothiazepine calcium channel antagonist. The oral bioavailability of diltiazem is approximately 40 to 50% due to extensive

presystemic metabolism (Buckley et al., 1990). Consumption of a single dose of diltiazem (120 mg) with GFJ (200 mL) followed by repeated GFJ administration (at 0, 2, 4, 8 and 12 h) did not alter the AUC or C_{max} of diltiazem. No statistically significant differences were found between the GFJ treatment and the control values of the mean arterial pressure, heart rate, and PR-interval (Sigusch et al., 1994). In another report, GFJ intake resulted in a statistically significant average individual increase in AUC of 20% compared with water. The average individual increase in C_{max} of diltiazem after GFJ administration was 22%. However, there were no statistically significant differences in blood pressure and heart rate between the 2 treatments in healthy volunteers (Christensen et al., 2002).

Verapamil

Verapamil is used therapeutically as a racemate. The systemic bioavailability of verapamil is only about 20% because of its extensive first-pass extraction (McTavish and Sorkin, 1989). In 9 healthy volunteers, GFJ significantly increased AUC of S-verapamil by 36% during 12 h dose interval, and increased that of R-verapamil by 28% in steady state. There were no significant differences in the pharmacodynamic parameters, blood pressure, heart rate and PR-interval (Ho et al., 2000). GFJ significantly increased the AUC of (R, S)-verapamil at steady state by a mean of 45% and C_{max} at steady state by 63% in 24 volunteers. Prolongation of PR intervals by GFJ coadministration was borderline significant; an increase above 350 msec occurred in 2 individuals during the GFJ period (Fuhr et al., 2002). Fuhr et al. (2002) concluded that patients on verapamil treatment should abstain from GFJ.

This short review summarizes recent data about the interaction between GFJ and calcium channel antagonists. The extent of interaction between calcium channel antagonists and GFJ varies widely among drugs. It is necessary to withhold GFJ for at least 3 days prior to administration of the

drugs to prevent GFJ-drug interaction. Although the AUC and C_{max} of azelnidipine, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nisoldipine, nitrendipine and verapamil are elevated by GFJ intake, both pharmacokinetic parameters of amlodipine and diltiazem are not affected by GFJ. It is advisable to avoid combination, especially with the more affected agents, azelnidipine, felodipine, manidipine, nisoldipine and nitrendipine. Among dihydropyridines, amlodipine could be an alternative drug with diltiazem as the alternative in the non dihydropyridine class. It is important that awareness of food-drug interactions increases, and actions must be taken to avoid undesired and harmful clinical events.

References

- 1 Abernethy DR. The pharmacokinetic profile of amlodipine. *Am Heart J* 1989;118:1100–1103.
- 2 Azuma J, Yamamoto I, Watase T, Orii Y, Tanigawa T, Terashima S, et al. Effects of grapefruit juice on the pharmacokinetics of the calcium channel blockers nifedipine and nisoldipine. *Current Ther Res* 1998;59:619–634.
- 3 Bailey DG, Arnold JM, Strong HA, Munoz C, Spence JD. Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. *Clin Pharmacol Ther* 1993;54:589–594.
- 4 Bailey DG, Dresser GK. Interaction between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 2004;4:281–297.
- 5 Bailey DG, Spence JD, Edgar B, Bayliff CD, Arnold JM. Ethanol enhances the hemodynamic effects of felodipine. *Clin Invest Med* 1989;12:357–362.
- 6 Bailey DG, Spence JD, Munoz C, Arnold JM. Interaction of citrus juices with felodipine and nifedipine. *Lancet* 1991;337:268–269.
- 7 Buckley MMT, Grant SM, Goa KL, McTavish D, Sorkin EM. Diltiazem. A reappraisal of its pharmacological properties and therapeutic use. *Drugs* 1990;39:757–806.
- 8 Cheer SM, McClelln K. Manidipine: a review of its use in hypertension. *Drugs* 2001;61:1777–1799.
- 9 Christensen H, Asberg A, Holmboe AB, Berg KJ. Coadministration of grapefruit juice increases systemic exposure of diltiazem in healthy volunteers. *Eur J Clin Pharmacol* 2002;58:515–520.
- 10 Dahan A, Altman H. Food-drug interaction: grapefruit juice augments drug bioavailability—mechanism, extent and relevance. *Eur J Clin Nutr* 2004;58:1–9.

- 11 Dresser GK, Bailey DG, Carruthers SG. Grapefruit juice-felodipine interaction in the elderly. *Clin Pharmacol Ther* 2000a;68:28–34.
- 12 Dresser GK, Spence D, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 2000b;38:41–57.
- 13 Eagling VA, Profit L, Back DJ. Inhibition of the CYP3A4-mediated metabolism and P-glycoprotein-mediated transport of the HIV-1 protease inhibitor saquinavir by grapefruit juice components. *Br J Clin Pharmacol* 1999;48:543–552.
- 14 Edgar B, Bailey D, Bergstrand R, Johnsson G, Regårdh CG. Acute effects of drinking grapefruit juice on the pharmacokinetics and dynamics on felodipine—and its potential clinical relevance. *Eur J Clin Pharmacol* 1992;42:313–317.
- 15 Edwards DJ, Bellevue FH, Woster PM. Identification of 6',7'-dihydroxybergamottin, a cytochrome P450 inhibitor, in grapefruit juice. *Drug Metab Dispos* 1996;24:1287–1290.
- 16 Foster TS, Hamann SR, Richards VR, Bryant PJ, Graves DA, McAllister RG Jr. Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. *J Clin Pharmacol* 1983;2:161–170.
- 17 Freedman DD, Waters DD. 'Second generation' dihydropyridine calcium antagonists. Greater vascular sensitivity and some unique applications. *Drugs* 1987;34:578–598.
- 18 Fuhr U. Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. *Drug Saf* 1998;18:251–72.
- 19 Fuhr U, Müller-Peltzer H, Kern R, Lopez-Rojas P, Jünemann M, Harder S, et al. Effects of grapefruit juice and smoking on verapamil concentrations in steady state. *Eur J Clin Pharmacol* 2002;58:45–53.
- 20 Garvan CK, James JL. Drug-grapefruit juice interaction. *Mayo Clin Proc* 2000;75:933–942.
- 21 Goosen T, Cillió D, Bailey DG, Yu C, He K, Hollenberg PF, et al. Bergamottin contribution to the grapefruit juice-felodipine interaction and disposition in humans. *Clin Pharmacol Ther* 2004;76:607–617.
- 22 Gottesman MM, Pastan I, Ambudkar SV. P-glycoprotein and multidrug resistance. *Curr Opin Genet Dev* 1996;6:610–617.
- 23 Guengerich FP, Brain WR, Iwasaki M, Sari MA, Baarnhielm C. Oxidation of dihydropyridine calcium channel blockers and analogues by human liver cytochrome P450 IIIA4. *J Med Chem* 1991;34:1838–1844.
- 24 Hirashima H, Uchida N, Fukazawa I, Ishigaki S, Uchida E, Yasuhara H. Effect of a single glass of grapefruit juice on the apparent oral bioavailability of the dihydropyridine calcium channel antagonist, azelnidipine, in healthy Japanese volunteers. *Jpn J Clin Pharmacol Ther* 2006;37:127–133.
- 25 Ho PC, Ghose K, Saville D, Wanwimolruk S. Effect of grapefruit juice on pharmacokinetics and pharmacodynamics of verapamil enantiomers in healthy volunteers. *Eur J Clin Pharmacol* 2000;56:693–698.
- 26 Josefsson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlodipine in healthy volunteers. *Eur J Clin Pharmacol* 1996;51:189–193.
- 27 Kajino M, Wada Y, Nagai Y, Nagaoka A, Meguro K. Synthesis and biological activities of optical isomers of 2-(4-diphenylmethyl-1-piperaziny) ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (manidipine) dihydrochloride. *Chem Pharm Bull* 1989;37:2225–2228.
- 28 Kakar SM, Paine MF, Stewart PW, Watkins PB. 6'7'-dihydroxybergamottin contributes to the grapefruit juice effect. *Clin Pharmacol Ther* 2004;75:569–579.
- 29 Kane GC, Lipsky JJ. Drug-grapefruit juice interactions. *Mayo Clin Proc* 2000;75:933–942.
- 30 Kolars JC, Schmiedlin RP, Schuetz JD, Fang C, Watkins PB. Identification of rifampin-inducible P450 III A4 (CYP3A4) in human small bowel enterocytes. *J Clin Invest* 1992;90:1871–1878.
- 31 Krol GJ, Lettieri JT, Yeh SC, Burkholder DE, Birkett JP. Disposition and pharmacokinetics of ¹⁴C-nitrendipine in healthy volunteers. *J Cardiovasc Pharmacol* 1987;9(Suppl):S122–S128.
- 32 Kuramoto K, Ichikawa S, Hirai A, Kanada S, Nakachi T, Ogihara T. Azelnidipine and amlodipine: a comparison of their pharmacokinetics and effects on ambulatory blood pressure. *Hypertens Res* 2003;26:201–208.
- 33 Lilja JJ, Kivisto KT, Backman JT, Neuvonen PJ. Effect of grapefruit juice dose on grapefruit juice-triazolam interaction: repeated consumption prolongs triazolam half-life. *Eur J Clin Pharmacol* 2000;56:411–415.
- 34 Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortiage LA, et al. Grapefruit juice increases felodipine oral availability in humans by decreasing intestinal CYP3A protein expression. *J Clin Invest* 1997;99:2545–2553.
- 35 Lundahl J, Regårdh CG, Edgar B, Johnsson G. Relationship between time of intake of grapefruit juice and its effect on pharmacokinetics and pharmacodynamics of felodipine in healthy subjects. *Eur J Clin Pharmacol* 1995;49:61–67.
- 36 Lundahl J, Regårdh CG, Edgar B, Johnsson G. Effects of grapefruit juice ingestion-pharmacokinetics and haemodynamics of intravenously and orally administered felodipine in healthy men. *Eur J Clin Pharmacol* 1997;52:139–145.
- 37 Lundahl J, Regårdh CG, Edgar B, Johnsson G. The interaction effect of grapefruit juice is maximal after the first glass. *Eur J Clin Pharmacol* 1998;54:75–81.
- 38 McTavish D, Sorkin EM. Verapamil: an update review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension. *Drugs*

- 1989;38:19–76.
- 39 Meredith PA, Elliott HL. Clinical pharmacokinetics of amlodipine. *Clin Pharmacokinet* 1992;22:22–31.
 - 40 Mikus G, Fischer C, Heuer B, Langen C, Eichelbaum M. Application of stable isotope methodology to study the pharmacokinetics, bioavailability and metabolism of nitrendipine after i.v. and p.o. administration. *Br J Clin Pharmacol* 1987;24:561–569.
 - 41 Ohnishi A, Ohtani H, Sawada Y. Major determinant factors of the extent of interaction between grapefruit juice and calcium channel antagonists. *Br J Clin Pharmacol* 2006;62:196–199.
 - 42 Paine MF, Widmer WW, Hart HL, Pusek SN, Beavers KL, Criss AB, et al. A furanocoumarin-free grapefruit juice establishes furanocoumarins as the mediators of the grapefruit juice-felodipine interaction. *Am J Clin Nutr* 2006;83:1097–1105.
 - 43 Phang JK, Poore CM, Lopaczynska J, Yea GC. Flavonol-stimulated efflux of 7,12-dimethylbenz(a)anthracene in multi-drug-resistant breast cancer cells. *Cancer Res* 1993;53:5977–5981.
 - 44 Rashid TJ, Martin U, Clarke H, Waller DG, Renwick AG, George CF. Factors affecting the absolute bioavailability of nifedipine. *Br J Clin Pharmacol* 1995;40:51–58.
 - 45 Rashid TJ, McKinstry C, Renwick AG, Dirnhuber M, Waller DG, George CF. Quercetin, an in vitro inhibitor of CYP3A, does not contribute to the interaction between nifedipine and grapefruit juice. *Br J Clin Pharmacol* 1993;36:460–463.
 - 46 Sigusch H, Henschel L, Kraul H, Merkel U, Hoffmann A. Lack of effects of grapefruit juice on diltiazem bioavailability in normal subjects. *Pharmazie* 1994;49:675–679.
 - 47 Soldner A, Christians U, Susanto M, Wachter VJ, Silverman JA, Benet LZ. Grapefruit juice activates P-glycoprotein-mediated drug transport. *Pharm Res* 1999;16:478–485.
 - 48 Soons PA, de Boer AG, van Brummelen P, Breimer DD. Oral absorption profile of nitrendipine in healthy subjects: a kinetic and dynamic study. *Br J Clin Pharmacol* 1989;27:179–189.
 - 49 Soons PA, Vogels BAPM, Roosemalen MCM, Schoemaker HC, Uchida E, Edgar B, et al. Grapefruit juice and cimetidine inhibit stereoselective metabolism of nitrendipine in humans. *Clin Pharmacol Ther* 1991;50:394–403.
 - 50 Takanaga H, Ohnishi A, Matsuo H, Sawada Y. Inhibition of vinblastin efflux mediated by P-glycoprotein by grapefruit juice components in caco-2 cells. *Biol Pharm Bull* 1998;21:1062–1066.
 - 51 Takanaga H, Ohnishi A, Murakami H, Matsuo H, Higuchi S, Urae A, et al. Relationship between time after intake of grapefruit juice and the effect on pharmacokinetics and pharmacodynamics of nisoldipine in healthy subjects. *Clin Pharmacol Ther* 2000;67:201–214.
 - 52 Tian R, Koyabu N, Takanaga H, Matsuo H, Ohtani H, Sawada Y. Effects of grapefruit juice and orange juice on the intestinal efflux of P-glycoprotein substrates. *Pharm Res* 2002;19:802–809.
 - 53 Toyo-oka T. [Therapeutic evolution brought by a new generation (3rd generation type-b) calcium channel antagonist, Azelnidipine.] *Progress in Medicine* 2003;23:1145–1150 (in Japanese).
 - 54 Uesawa Y, Mohri K. Relationship between lipophilicities of 1,4-dihydropyridine derivatives and pharmacokinetic interaction strengths with grapefruit juice. *YAKUGAKU ZASSHI* 2008;128:117–122.
 - 55 Uno T, Ohkubo T, Motomura S, Sugawara K. Effect of grapefruit juice on the disposition of manidipine enantiomers in healthy subjects. *Br J Clin Pharmacol* 2006;61:533–537.
 - 56 Uno T, Ohkubo T, Sugawara K, Higashiyama A, Motomura S, Ishizaki T. Effects of grapefruit juice on the stereoselective disposition of nicardipine in humans: evidence for dominant presystemic elimination at the gut site. *Eur J Clin Pharmacol* 2000;56:643–649.
 - 57 Vincent J, Harris SI, Foulds G, Dogolo LC, Willavize S, Friedmen HL. Lack of effect of grapefruit juice on the pharmacokinetics and pharmacodynamics of amlodipine. *Br J Clin Pharmacol* 2000;50:455–463.
 - 58 Waller DG, Gruchy BS, Renwick AG, George CF. The first pass metabolism of nifedipine in man. *Br J Clin Pharmacol* 1984;18:951–954.
 - 59 Wang EJ, Casciano CN, Clement RP, Johnson WW. Inhibition of P-glycoprotein transport function by grapefruit juice psoralen. *Pharm Res* 2001;18:432–438.
 - 60 Yajima Y, Iijima H, Yokoyama R. Influence of grapefruit juice on the plasma concentration ofefonidipine hydrochloride. *Jpn Pharmacol Ther* 2003;31:579–588 (in Japanese with English abstract).
 - 61 Zaidenstein R, Dishi V, Gips M, Soback S, Cohen N, Weinstein J, et al. The effect of grapefruit juice on the pharmacokinetics of orally administered verapamil. 1998;54:337–340.
 - 62 Zhang Q, Dunbar D, Ostrowska A, Zeisloft S, Yang J, Kaminsky LS. Characterization of human small intestinal cytochromes P-450. *Drug Metab Dispos* 1999;27:804–809.

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