JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 1537–1542

Received 17 June, 2004
Accepted 13 August, 2004
DOI: 10.1211/0022357044814
ISSN 0022-3573

The effect of quercetin on the pharmacokinetics of verapamil and its major metabolite, norverapamil, in rabbits

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Abstract

We have investigated the effect of quercetin on the pharmacokinetics of verapamil and its major metabolite, norverapamil, in rabbits. Pharmacokinetic parameters of verapamil and norverapamil were determined after the oral administration of verapamil (10 mg kg^{-1}) to rabbits in the presence and absence of quercetin (5.0 and 15 mg kg^{-1}). While co-administration of quercetin concurrently was not effective to enhance the oral exposure of verapamil, pretreatment of quercetin 30 min before verapamil administration significantly altered the pharmacokinetics of verapamil. Compared with the control group (given verapamil alone), the C_{max} and AUC of verapamil increased approximately twofold in the rabbits pretreated with 15 mg kg^{-1} quercetin. There was no significant change in T_{max} and terminal plasma half-life (t½) of verapamil in the presence of quercetin. Consequently, absolute and relative bioavailability values of verapamil in the rabbits pretreated with quercetin were significantly higher ($P < 0.05$) than those from the control group. Metabolite–parent AUC ratio in the rabbits pretreated with quercetin decreased by twofold compared with the control group, implying that pretreatment of quercetin could be effective to inhibit the CYP3A4-mediated metabolism of verapamil. In conclusion, pretreatment of quercetin significantly enhanced the oral exposure of verapamil. This suggested that concomitant use of quercetin or a quercetin-containing dietary supplement with verapamil requires close monitoring for potential drug interaction.

Introduction

Verapamil, a calcium channel-blocker, is widely used as an anti-arrhythmic agent to control supraventricular tachyarrhythmias. Due to its potent vasodilating and negative inotropic properties, verapamil is useful for the treatment of hypertension, ischaemic heart disease, and hypertrophic cardiomyopathy (Fleckenstein 1977; Gould et al 1982; Lewis et al 1978). Verapamil is rapidly absorbed after oral administration and widely distributed throughout the body. Orally administered verapamil undergoes extensive first-pass hepatic metabolism through the portal circulation, resulting in low bioavailability (10–20%) (Schomerus et al 1976). The oxidative metabolic pathway of verapamil and the contribution of the different cytochrome P450 enzymes involved has been studied extensively (Busse et al 1995; Eichelbaum et al 1979; Kroemer et al 1993). The primary metabolic pathways of verapamil include N-demethylation and N-dealkylation. CYP3A4 is mainly responsible for the N-demethylation of verapamil, while the N-dealkylated metabolites are formed by CYP1A2. Norverapamil, a major metabolite, is a N-demethylated metabolite of verapamil and appears to have approximately 20% of the coronary vasodilator activity of the parent compound in dogs (Eichelbaum et al 1984). Verapamil is also known to be a substrate and inhibitor of P-glycoprotein (Doppenschmitt et al 1999). Furthermore, it has been reported that the phase I metabolites of verapamil exhibit different P-glycoprotein substrate and inhibition characteristics (Häußermann et al 1991; Pauli-Magnus et al 2000; Woodland et al 2003). While N-dealkylated metabolites (D-617 and D-620) are P-glycoprotein substrates, norverapamil and O-demethylated metabolite (D-703) are inhibitors of P-glycoprotein function, implying that verapamil metabolites may influence P-glycoprotein mediated drug disposition and elimination. In addition to P-glycoprotein, verapamil is also reported to interact with

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other transporters such as organic cation transporters and organic anion transporters (Yabuuchi et al 1999; Han et al 2001; Morita et al 2001; Wessler et al 2001). Therefore, there can be the potential drug interactions of verapamil via the transport pathways as well as CYP3A4 metabolism in clinical studies. For instance, ketoconazole and cimetidine increased the bioavailability of verapamil in man via the inhibition of metabolic enzymes or transport pathway, respectively (Smith et al 1984; Sandström et al 1999).

Quercetin is a naturally occurring flavonoid and is mainly present as glycoside components of the daily diet such as grapefruit juice, apples, onions, tea and red wine (Cody 1986, 1988). Quercetin displays a variety of biological actions such as anti-oxidation, anti-ulcer, anti-allergic and anticancer (Takahama 1985; Ferry et al 1996; Davis et al 2000). Quercetin has been reported as a CYP3A4 inhibitor as well as a P-glycoprotein modulator and subsequent studies have demonstrated the influence of quercetin on the bioavailability of paclitaxel, digoxin, ciclosporin and moxidectin, which are well-known substrates of CYP3A4 and/or P-glycoprotein (Choi et al 1995; Scambia et al 1995; Doostdar et al 2000; Dupuy et al 2003; Choi et al 2004; Wang et al 2004). Concomitant use of quercetin significantly decreased the bioavailability of ciclosporin, while quercetin enhanced the bioavailability of paclitaxel, digoxin and moxidectin. Therefore, the effect of quercetin on the pharmacokinetics of CYP3A4 substrates or P-glycoprotein substrates should be carefully monitored in combination therapy.

Considering that CYP3A4-mediated metabolism and P-glycoprotein-mediated transport are the major factors limiting the oral bioavailability of verapamil, the concomitant use of potent inhibitors for CYP3A4 and P-glycoprotein could be effective to alter the bioavailability of verapamil. Therefore, we have investigated the effect of quercetin on the pharmacokinetics of verapamil and its major metabolite, norverapamil, after oral administration of verapamil to rabbits either co-administered or pretreated with quercetin. The rabbit was chosen as the animal model because the pharmacokinetics of verapamil have been well characterized in rabbits (Giacomini et al 1985; Mori et al 2001), and recent studies have shown that rabbit MDR1 and human MDR1 share a high sequence homology (89%) (Dey et al 2003).

Materials and Methods

Materials

Verapamil, norverapamil, quercetin and propranolol were purchased from the Sigma Chemical Co. (St Louis, MO). Acetonitrile, triethylamine and diethylether were purchased from Merck Co. (Darmstadt, Germany). Phosphoric acid was purchased from the Junsei Co. (Tokyo, Japan). All other chemicals were reagent grade and all solvents were HPLC grade.

Animal studies

All animal studies were performed in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA). Experimental protocols were approved by the Animal Care Committee of Chosun University. The animals were kept in these facilities for at least one week before the experiments.

White male New Zealand rabbits (2.0–2.4 kg) were fasted for at least 24 h before the experiment but water was freely available. Verapamil and quercetin were dissolved in distilled water for oral administration, whilst for intravenous administration verapamil was dissolved in saline, at the desired doses. Rabbits ($n = 6$ per treatment) were given orally 10 mg kg^{-1} verapamil with either quercetin (5.0 or 15 mg kg^{-1}) concurrently, or quercetin (5.0 or 15 mg kg^{-1}) 30 min before oral administration of verapamil, or no concomitant treatment (verapamil alone). Separately, 2 mg kg^{-1} verapamil was administered intravenously to rabbits via an ear vein. Blood samples were withdrawn from the femoral vein at 0, 0.1, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12 and 24 h post dose. Blood samples were centrifuged at 3000 *g* for 10 min and the plasma (0.5 mL) was removed and stored at −40°C until analysed by HPLC.

HPLC assay

The plasma concentrations of verapamil and norverapamil were determined by HPLC assay, described as follows. Briefly, 0.1 mL propranolol HCl (400 ng mL^{-1}) as the internal standard, 50 μL 2 M sodium hydroxide solution and 6 mL diethylether were added to 0.5-mL plasma samples. The mixture was then stirred for 3 min and centrifuged at 5000 rev min^{-1} for 10 min. A sample of the organic layer (5 mL) was transferred to a clean test tube and evaporated at 35°C under a stream of nitrogen. The residue was dissolved in 250 μL mobile phase, centrifuged at 5000 rev min^{-1} for 5 min and then 50 μL of the supernatant was injected into the HPLC system. The HPLC system consisted of two solvent delivery pumps (Model LC-10AD, Shimadzu Co., Japan), a fluorescence detector (Model RF-10A), a system controller (Model SCL-10A), degasser (Model DGU-12A) and an auto-injector (SIL-10AD). The fluorescence detector was set at an excitation wavelength of 280 nm and an emission wavelength of 310 nm. The stationary phase was a Kromasil KR 100-5C8 column (5 μm, 4.6 × 250 mm, EKA chemicals, Sweden) and the mobile phase was acetonitrile:0.05 M KH_2PO_4 with 0.05% triethylamine (30:70, v/v). The pH of the buffer was adjusted to 4.0 with 20% phosphoric acid. The retention times at a flow rate of 1.5 mL min^{-1} were as follows: internal standard, 4.5 min, norverapamil, 12.2 min, and verapamil, 13.4 min. The calibration curve was obtained from the standard samples over the concentration range of 2–400 ng mL^{-1}.

Pharmacokinetic analysis

Noncompartmental pharmacokinetic analysis was performed by the LAGRAN method using the LAGRAN computer program (Rocci & Jusco 1983). The area under the plasma concentration–time curve from time zero to infinity (AUC) was computed using the LAGRAN method to reduce the errors associated with using the trapezoidal method. The peak plasma concentration (C_{max}) and the

time to reach the peak plasma concentration (T_{max}) were observed values from the experimental data. The elimination rate constant (K_{el}) was estimated by regression analysis from the slope of the line of best fit, and the half-life (t½) of the drug was obtained by $0.693/K_{el}$. The absolute bioavailability (AB%) of verapamil was calculated as follows:

$$AB\% = AUC_{oral}/AUC_{i.v.} \times Dose_{i.v.}/Dose_{p.o.} \times 100$$

The relative bioavailability (RB%) of verapamil was estimated as follows:

$$RB\% = AUC_{verapamil\ w/quercetin}/AUC_{control} \times 100$$

The metabolite–parent ratio was estimated by:

$$(AUC_{norverapamil}/AUC_{verapamil}) \times (MW_{verapamil}/MW_{norverapamil})$$

Statistical analysis

All the means are presented with their standard deviation. The pharmacokinetic parameters were compared with a one-way analysis of variance, followed by a posteriori testing with the use of the Dunnett correction. A P value of < 0.05 was considered statistically significant.

Results

The mean plasma concentration–time profiles of verapamil in the presence and absence of quercetin were characterized in rabbits (Figure 1). The mean pharmacokinetic parameters of verapamil are summarized in Table 1.

As shown in Table 1, co-administration of quercetin did not significantly alter the pharmacokinetic parameters of verapamil compared with the administration of verapamil alone. There was no statistical significance in the difference between the pharmacokinetics of verapamil given alone or with the co-administration of quercetin. This result suggested that concurrent use of quercetin was not effective to enhance the oral exposure of verapamil, although quercetin is a potent inhibitor of CYP3A4 and P-glycoprotein. However, pretreatment with quercetin 30 min before verapamil administration significantly altered the pharmacokinetics of verapamil ($P < 0.05$). Compared with the control group given verapamil alone, the C_{max} and AUC of verapamil increased approximately twofold in the rabbits pretreated with 15 mg kg^{-1} quercetin, while there was no significant change in T_{max} and terminal plasma half-life (t½) of verapamil in the presence of quercetin (Table 1). Consequently, absolute and relative bioavailability values of verapamil in the rabbits pretreated with quercetin were significantly higher ($P < 0.05$) than those from the control group. There was no significant enhancement in the oral exposure of verapamil by increasing the dose of quercetin from 5 to 15 mg kg^{-1}, implying that the inhibition effect of quercetin was not dose-dependent over the dose range of 5–15 mg kg^{-1}.

The pharmacokinetic profiles of norverapamil, a major metabolite of verapamil were evaluated in the presence

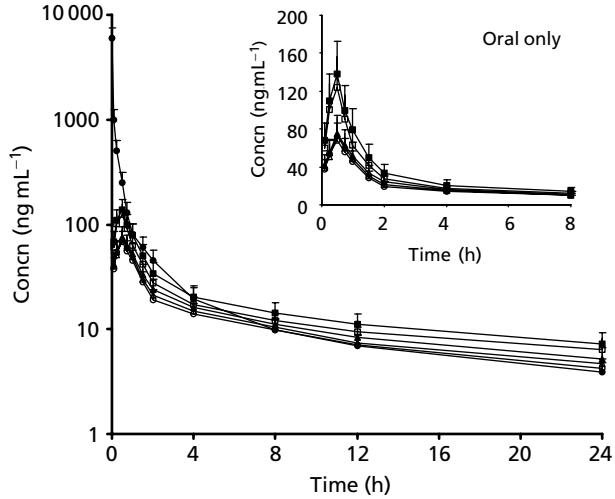

Figure 1 Mean plasma–concentration–time profiles of verapamil after administration of an intravenous (2 mg kg^{-1}) or an oral (10 mg kg^{-1}) dose to rabbits in the presence or absence of quercetin. Values are the mean ± s.d., n = 6. ○, Control (verapamil 10 mg kg^{-1}); ▲, co-administered with quercetin 5 mg kg^{-1}; △, co-administered with quercetin 15 mg kg^{-1}; □, pretreated with quercetin 5 mg kg^{-1}; ■, pretreated with quercetin 15 mg kg^{-1}; ●, intravenous verapamil 2 mg kg^{1}.

Table 1 Mean pharmacokinetic parameters of verapamil after an intravenous (2 mg kg^{-1}) or oral (10 mg kg^{-1}) administration of verapamil to rabbits in the presence and absence of quercetin

Parameters	Verapamil (control)	Verapamil + quercetin (co-administration)		Verapamil + quercetin (pretreatment)		Verapamil (i.v.)
		5 mg kg^{-1}	15 mg kg^{-1}	5 mg kg^{-1}	15 mg kg^{-1}	
C_{max} (ng mL^{-1})	67.9 ± 12.7	70.2 ± 16.7	73.3 ± 15.0	117 ± 20.3*	137 ± 27.4*	–
T_{max} (h)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	–
AUC (ng mL^{-1}·h)	333 ± 73	345 ± 91	383 ± 88	487 ± 110*	574 ± 121*	804 ± 149
t½ (h)	13 ± 3.0	13 ± 3.4	13 ± 3.5	15 ± 0.6	15 ± 2.1	9.3 ± 2.4
Absolute bioavailability (%)	8.3 ± 1.8	8.6 ± 2.8	9.5 ± 2.6	12.2 ± 2.7*	14.3 ± 3.0*	–
Relative bioavailability (%)	100	104	115	147	172	–

Values are mean ± s.d., n = 6. *$P < 0.05$, compared with the control group (given verapamil alone). Relative bioavailability compared with the control group.

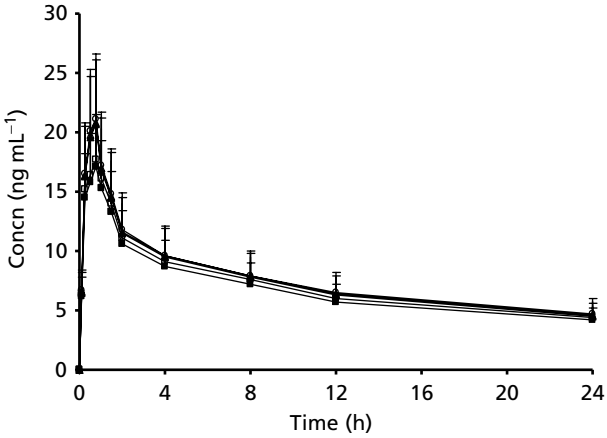

Figure 2 Mean plasma–concentration–time profiles of norverapamil after an oral administration (10 mg kg^{-1}) to rabbits in the presence or absence of quercetin. Values are the mean ± s.d., n = 6. ○, Control (verapamil alone); ▲, co-administered with quercetin 5 mg kg^{-1}; △, co-administered with quercetin 15 mg kg^{-1}; □, pretreated with quercetin 5 mg kg^{-1}; ■, pretreated with quercetin 15 mg kg^{-1}.

and absence of quercetin (Figure 2). As summarized in Table 2, oral exposure of norverapamil in the rabbits co-administered or pretreated with quercetin was not significantly changed in the presence of quercetin ($P > 0.05$). However, the metabolite–parent ratio in the rabbits pretreated with quercetin decreased by twofold ($P < 0.05$) compared with the control group, implying that pretreatment of quercetin could be effective to inhibit the CYP3A4-mediated metabolism of verapamil.

Collectively, pretreatment of quercetin significantly enhanced the oral exposure of verapamil by increasing intestinal absorption as well as reducing the first-pass metabolism.

Discussion

Intestinal phase I metabolism and active extrusion of absorbed drug have been recognized as major determinants of the bioavailability of many drugs (Kumar et al 1994; Rahman et al 1994; Wacher et al 1996). Both CYP3A4, the major phase I drug metabolizing enzyme in man, and the multidrug efflux pump, P-glycoprotein, are present at high levels in the small intestine, the primary site of absorption for orally administered drugs. Moreover, those proteins demonstrate a broad overlap in substrate and inhibitor specificities, suggesting that they act as a concerted barrier to drug absorption (Cummins et al 2002; Benet et al 2003). Therefore, dual inhibitors against both CYP3A4 and P-glycoprotein should have a great impact on the bioavailability of many drugs where CYP3A4 metabolism and P-glycoprotein-mediated transport are the major barriers to the systemic availability.

This study evaluated the influence of quercetin, a naturally occurring flavonoid, on the pharmacokinetics of verapamil in rabbits to examine a potential drug interaction between quercetin and verapamil via the dual inhibition of CYP3A4 and P-glycoprotein. As shown in Table 1, co-administration of quercetin concurrently did not significantly alter the pharmacokinetic profiles of verapamil compared with the administration of verapamil alone. There was no statistical significance in the difference between the pharmacokinetics of verapamil given alone or with the co-administration of quercetin. This result appeared to be consistent with previous studies reported by Zaidenstein et al (1988). In those studies, a single administration of grapefruit juice (containing quercetin) with verapamil had no significant effect on the pharmacokinetics of verapamil. Although co-administration of quercetin concurrently was not effective to enhance the oral exposure of verapamil, pretreatment of quercetin 30 min before verapamil administration significantly altered the pharmacokinetics of verapamil ($P < 0.05$) (Table 1). The C_{max} and AUC of verapamil increased approximately twofold in the rabbits pretreated with 15 mg kg^{-1} quercetin. Consequently, absolute and relative bioavailability values of verapamil in the rabbits pretreated with quercetin were significantly higher than those from the control group. The results suggested that quercetin should be given with a certain lead-time before verapamil administration to ensure the inhibition effect of quercertin on CYP3A4 and P-glycoprotein. This may be explained by a relatively slower absorption of

Table 2 Mean pharmacokinetic parameters of norverapamil, a major metabolite of verapamil following an oral administration of verapamil (10 mg kg^{-1}) to rabbits in the presence and absence of quercetin

Parameters	Verapamil (control)	Verapamil + quercetin (co-administration)		Verapamil + quercetin (pretreatment)	
		5 mg kg^{-1}	15 mg kg^{-1}	5 mg kg^{-1}	15 mg kg^{-1}
C_{max} (ng mL^{-1})	20.6 ± 5.8	20.1 ± 5.7	20.0 ± 5.5	17.5 ± 5.6	16.8 ± 5.4
T_{max} (h)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
AUC (ng mL^{-1}·h)	309 ± 78	299 ± 73	292 ± 75	285 ± 69	278 ± 67
t½ (h)	20 ± 5.2	19 ± 5.6	19 ± 5.4	20 ± 6.1	20 ± 5.9
Metabolite–parent ratio	0.94 ± 0.20	0.84 ± 0.27	0.74 ± 0.32	0.59 ± 0.12*	0.49 ± 0.11*

Values are mean ± s.d., n = 6. *$P < 0.05$, compared with the control. Metabolite–parent ratio: $(AUC_{norverapamil}/AUC_{verapamil}) \times (MW_{verapamil}/MW_{norverapamil})$.

quercetin than verapamil (Manach et al 1997; Ader et al 2000; Meng et al 2004).

The pharmacokinetic profile of norverapamil, a major metabolite of verapamil was evaluated in the presence and absence of quercetin (Table 2). Similar to the observation in the pharmacokinetics of verapamil, concurrent use of quercetin did not alter the pharmacokinetics of norverapamil. However, the metabolite–parent ratio in the rabbits pretreated with quercetin decreased by twofold ($P < 0.05$) compared with the control, implying that pretreatment of quercetin could be effective to inhibit the CYP3A4-mediated metabolism of verapamil. Collectively, the pharmacokinetics of verapamil could be altered by the pretreatment of quercetin, a dual inhibitor of CYP3A4 and P-glycoprotein, although co-administration of quercetin concurrently was not effective. The clinical importance of these findings requires further investigation in clinical trials.

Conclusion

Pretreatment of quercetin significantly enhanced the oral exposure of verapamil by increasing intestinal absorption as well as reducing the first-pass metabolism of verapamil. Therefore, concomitant use of quercetin or quercetin-containing dietary supplements with verapamil requires close monitoring for potential drug interaction.

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