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Altered pharmacokinetics of paclitaxel by the concomitant use of morin in rats

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Abstract

The purpose of this study was to investigate the effect of morin on the pharmacokinetics of orally and intravenously administered paclitaxel in rats. Pharmacokinetic parameters of paclitaxel were determined in rats after an oral (30 mg kg^{-1}) or intravenous (3 mg kg^{-1}) administration of paclitaxel to rats in the presence and absence of morin (3.3 and 10 mg kg^{-1}). Compared to the control given paclitaxel alone, pretreatment with morin 30 min prior to the oral administration of paclitaxel increased C_{max} and AUC of paclitaxel by 70–90% and 30–70%, respectively, while there was no significant change in T_{max} and terminal plasma half-life ($T_{1/2}$) of paclitaxel. Consequently, absolute and relative bioavailability values of paclitaxel in the rats after the pretreatment with morin were significantly higher ($p < 0.05$) than those from the control. In contrast, following an intravenous administration of paclitaxel (3.3 mg kg^{-1}), the pharmacokinetic profiles of paclitaxel were not altered significantly in the presence of morin. Those results suggest that the enhanced oral exposure of paclitaxel should be mainly due to the inhibition effect of morin on the gastrointestinal extraction of paclitaxel during the intestinal absorption. Therefore, the concurrent use of morin or morin-containing dietary supplement may provide a therapeutic benefit in the oral delivery of paclitaxel.

Keywords: Paclitaxel; Morin; Pharmacokinetics; Bioavailability; Rats

1. Introduction

Paclitaxel is an antineoplastic agent widely used in the treatment of advanced breast and ovarian cancer (Wani et al., 1971). Paclitaxel is very poorly absorbed after the oral administration because of its unfavorable physicochemical properties such as low solubility and low permeability (Panchagnula, 1998). Furthermore, the interaction with P-glycoprotein (P-gp) efflux pump adds the barrier against the oral absorption of paclitaxel in the intestinal mucosa (Sparreboom et al., 1997). Therefore, paclitaxel is currently formulated in a mixture of Cremophor EL (polyoxyethyleneglycerol triricinoleate 35) and dehydrated ethanol (1:1, v/v) for the intravenous infusion (Panchagnula, 1998). However, Cremophor EL itself could be toxic and produce vasodilation, labored breathing, lethargy and hypotension when administered intravenously (Rowinsky et al., 1993). Therefore, in attempts to develop safer formulations, many studies have been directed towards a new oral formulation, such as emulsification, micellisation, liposome formation and use of micro-particles (Onyuksel et al., 1994; Wang et al., 1996; Lundberg, 1997; Crosasso et al., 2000). Furthermore, given that the poor bioavailability of paclitaxel would result from the metabolism by enzymes or counter-transport processes by P-gp in the gut wall, there were some attempts to improve the oral delivery of paclitaxel via the inhibition of P-gp and/or metabolic enzymes. For examples, several studies have demonstrated that the coadministration of a P-gp and/or CYP3A4 inhibitors such as enaminones, cyclosporin A, verapamil, MS-209 and KR30031 could enhance the oral exposure of paclitaxel (Berg et al., 1995; van Asperen et al., 1998; Meerum Terwogt et al., 1999; Kimura et al., 2002; Woo et al., 2003; Salama et al., 2004). In particular, verapamil and cyclosporine were the first multidrug resistance (MDR)-reversal agents available in clinical trials (Ozols et al., 1987; Gottesman and Pastan, 1989; Fisher and Sikic, 1995) but the usefulness of those drugs is limited because the plasma concentrations required to reverse MDR could result in cardiac toxicity such as hypotension, congestive heart failure, and heart block (Choi et al., 1997). Therefore, it is still highly demanded

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to discover the compounds that can modulate P-gp or presystemic metabolism without undesired toxicity in order to be used in the combination therapy with oral paclitaxel.

Flavonoids are the most abundant polyphenolic compounds present in fruits, vegetables and plant-derived beverages such as grape-fruit juice, tea and red wine (Dixon and Steele, 1999). Many flavonoids including quercetin, naringin and silymarin are known to modulate P-gp (Critchfield et al., 1994; Scambia et al., 1994; Eagling et al., 1999) and have showed some effect on the bioavailability of P-gp substrates such as moxidectin and diltiazem (Dupuy et al., 2003; Choi and Han, 2005). Also, Zhang and Morris (2003) have demonstrated that morin could be a fairly potent P-gp inhibitor by examining the effect of 20 naturally occurring flavonoids on P-gp mediated cellular efflux in MCF-7/ADR cells. Morin (3,5,7,2′,4′-pentahydroxyflavone) is found in the figure and other Moraceae that are used as herbal medicines and exhibits various biological activities including antioxidation, anti-mutagenesis and anti-inflammation (Francis et al., 1989; Hanasaki et al., 1994; Fang et al., 2003). In addition to the inhibition of P-gp, morin could modulate the activities of the metabolic enzymes including cytochrome P450 (CYPs) (Hodek et al., 2002). For example, in human liver microsomes, the formation of paclitaxel metabolites such as C3′-hydroxypaclitaxel and C2-hydroxypaclitaxel were inhibited by morin (Vaclavikova et al., 2003). Considering that the bioavailability of paclitaxel is significantly limited by the presystemic metabolism and P-gp mediated efflux during the intestinal absorption, morin, a dual inhibitor of P-gp and CYPs, may provide a therapeutic benefit to improve the pharmacokinetics of paclitaxel in the combination therapy. Therefore, the purpose of this study was to investigate the effect of morin on the pharmacokinetics of paclitaxel in rats.

2. Materials and methods

2.1. Materials

Paclitaxel was obtained from Brystol-Myers Squibb Co. (NY, USA). Saline (0.9% NaCl injectable solution) was obtained from Choongwae Co. (Seoul, Korea). Acetonitrile, methanol, *tert*-butylmethylether were acquired from Merck Co. (Darmstadt, Germany). Morin and *n*-butyl-*p*-hydroxybenzoate (butylparaben) was purchased from the Sigma Chemical Co. (St. Louis, MO, USA). Phosphoric acid was obtained from the Junsei Co. (Tokyo, Japan). All other chemicals were reagent grade and all solvents were HPLC grade.

2.2. Animal studies

Male Sprague-Dawley rats (270–300 g) were purchased from Daehan Laboratory Animal Research and Co. (Choongbuk, Korea), and had free access to normal standard chow diet (JaeIl Chow, Korea) and tap water. Throughout the experiment, the animals were housed, four or five per cage, in laminar flow cages maintained at 22 ± 2 °C, 50–60% relative humidity, under a 12 h light–dark cycle. The animals were kept in these facilities for at least 1 week before the experiment and fasted for 24 h prior to the experiments. This experiment was carried out in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA) and the experimental protocols were approved by the Animal Care Committee of Chosun University. Rats ($n = 6$ for each treatment) were divided into six groups as follows: Group 1 (30 mg kg^{-1} paclitaxel, p.o.), Groups 2 and 3 (pretreatment with morin (3.3 or 10 mg kg^{-1}) 30 min prior to the oral administration of 30 mg kg^{-1} paclitaxel), Group 4 (3 mg kg^{-1} paclitaxel, i.v.), Groups 5 and 6 (pretreatment with morin (3.3 or 10 mg kg^{-1}) 30 min prior to the i.v. injection of 3 mg kg^{-1} paclitaxel). Paclitaxel solution was prepared by dissolving paclitaxel in Cremophor EL and ethylalcohol mixture (1:1, v/v) and diluted with saline as described by Varma and Panchagnula (2005). The oral suspension was prepared with hydroxypropyl methylcellulose and diluted with distilled water as described by Gao et al. (2003). Morin suspension was prepared by mixing morin in 1.5 mL of distilled water. Blood samples were collected from the femoral artery at 0, 0.1, 0.25, 0.5, 1, 2, 3, 4, 8, 12, and 24 h post-dose. Blood samples were centrifuged and the plasma was removed and stored at −40 °C until analyzed by HPLC.

2.3. HPLC assay

The plasma concentrations of paclitaxel were determined by the modified HPLC method reported by Lee et al. (1999). Briefly, 50 μL of *n*-butyl-*p*-hydroxybenzoate (2 μg mL^{-1}) as the internal standard and 4 mL of *tert*-butylmethylether were added to 0.25 mL of the plasma samples. It was then vortexed for 20 min and centrifuged at 5000 rpm for 15 min. Three milliliters of the organic layer were transferred to a clean test tube and evaporated at 30 °C. The residue was then dissolved in a 0.5 g mL^{-1} zinc sulfate solution [zinc sulfate:methanol:ethylene glycol (0.5 g:100 mL:1 mL)] and centrifuged at 5000 rpm for 5 min and a 50 μL of the solution was injected into the HPLC system. The HPLC system consisted of a Waters 1515 isocratic HPLC Pump, a Waters 717 plus auto sampler, a Waters 2487 Dual λ absorbance detector (Waters Co., Milford, MA, USA) and a computing integrator. The UV detector was set at 227 nm. The stationary phase was a symmetry C_{18} column (4.6 mm × 150 mm, 5 μm, Waters Co., USA) and the mobile phase was acetonitrile:methanol:0.05 mM phosphate buffer (pH 4.0) (45:10:45, v/v/v). The retention times at a flow rate of 1.2 mL min^{-1} are as follows: internal standard for 5.3 min and paclitaxel for 7.7 min.

2.4. Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed by using Kinetica-4.3 (InnaPhase Corp., Philadelphia, PA, USA). The area under the plasma concentration–time curve (AUC) was calculated using the linear trapezoidal method. The maximum plasma concentration (C_{max}) and the time to reach the maximum 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 ($T_{1/2}$) of the

drug was obtained by $0.693/K_{el}$. Total plasma clearance (CL) was calculated by Dose/AUC. Additional estimated parameters using non-compartmental pharmacokinetic analysis were the volume of distribution (V_{dss}) and the mean residence time (MRT). The absolute bioavailability (A.B.) of paclitaxel was calculated by $AUC_{p.o.}/AUC_{i.v.} \times Dose_{i.v.}/Dose_{p.o.} \times 100$, and the relative bioavailability (R.B.) of paclitaxel was estimated by $AUC_{paclitaxel/morin}/AUC_{control} \times 100$.

2.5. Statistical analysis

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

3. Results and discussion

The plasma concentration–time profiles of paclitaxel after the oral administration of the paclitaxel (30 mg kg^{-1}) in the presence or absence of morin (3.3 and 10 mg kg^{-1}) were characterized in rats and illustrated in Fig. 1. The mean pharmacokinetic parameters of paclitaxel were also summarized in Table 1.

As shown in Table 1, the pretreatment with morin prior to the oral administration of paclitaxel significantly altered the pharmacokinetic parameters of paclitaxel compared to the control given paclitaxel alone. C_{max} and AUC of oral paclitaxel increased by 70–90% and 30–70%, respectively in the presence of morin while there was no significant change in the T_{max} and terminal plasma half-life ($T_{1/2}$). Consequently, the absolute and relative bioavailability values of paclitaxel in the rats pretreated with morin were significantly higher ($p < 0.05$) than those from the control.

The pharmacokinetic profiles of paclitaxel following an intravenous administration of paclitaxel (3 mg kg^{-1}) in the presence and absence of morin were also evaluated in rats and summarized in Table 2 and Fig. 2. Overall, the pharmacokinetic parameters following an intravenous administration of paclitaxel alone appeared to be comparable with those from the previous study reported by Rai et al. (2005). After the pretreatment with morin, the clearance values of paclitaxel tend to decrease and consequently the systemic exposure of paclitaxel slightly increased but there was no statistical significance compared to the control. Therefore, the intravenous pharmacokinetics of paclitaxel was not affected much by the concurrent use of morin in contrast to the oral administration of paclitaxel. Those results suggest that the increase in the

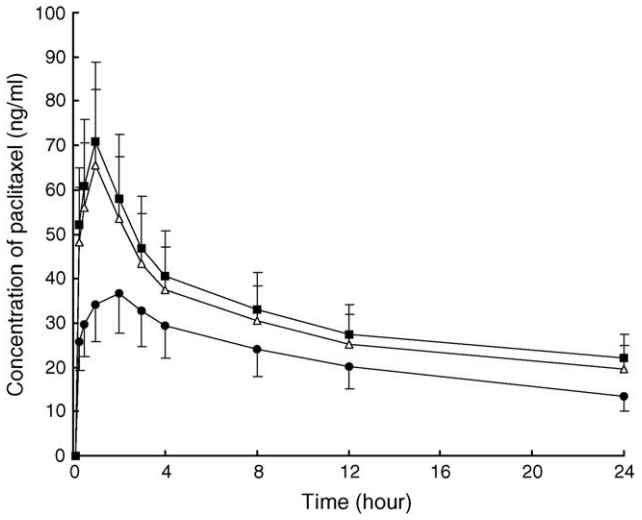

Fig. 1. Mean plasma concentration–time profiles of paclitaxel after an oral administration of paclitaxel (30 mg kg^{-1}) to rats in the presence and absence of morin (mean ± S.D., $n = 6$). (●) Control (paclitaxel, 30 mg kg^{-1}, p.o.); (△) pretreated with 3.3 mg kg^{-1} of morin; (■) pretreated with 10 mg kg^{-1} of morin.

Table 2
Pharmacokinetic parameters of paclitaxel following an intravenous administration of paclitaxel (3 mg kg^{-1}) to rats in the presence and absence of morin (mean ± S.D., $n = 6$)

Parameter	Control	Pretreatment with morin	
		3.3 mg kg^{-1}	10 mg kg^{-1}
$AUC_{0-\infty}$ (ng h mL^{-1})	4150 ± 854	5680 ± 984	6011 ± 1059
CL (L h^{-1} kg^{-1})	0.75 ± 0.17	0.54 ± 0.09	0.51 ± 0.10
V_{dss} (L kg^{-1})	11.8 ± 3.19	8.10 ± 4.09	7.98 ± 4.42
$T_{1/2}$ (h)	11 ± 2.1	8.2 ± 1.5	8.2 ± 1.6
MRT (h)	6.4 ± 1.2	6.8 ± 0.9	6.9 ± 1.0

Table 1
Pharmacokinetic parameters of paclitaxel after an oral administration of paclitaxel (30 mg kg^{-1}) to rats in the presence and absence of morin (mean ± S.D., $n = 6$)

Parameter	Control	Pretreatment with morin	
		3.3 mg kg^{-1}	10 mg kg^{-1}
$AUC_{0-\infty}$ (ng h mL^{-1})	777 ± 31.4	1040 ± 169*	1337 ± 151*
C_{max} (ng mL^{-1})	38.2 ± 6.82	66.6 ± 13.0*	73.0 ± 12.8*
T_{max} (h)	0.8 ± 0.3	0.5 ± 0.2	0.6 ± 0.2
$T_{1/2}$ (h)	14 ± 1.6	14 ± 2.6	17 ± 8.2
CL/F (L h^{-1} kg^{-1})	38.6 ± 1.63	28.6 ± 6.06*	22.7 ± 2.70*
V_{dss}/F (L kg^{-1})	0.81 ± 0.11	0.56 ± 0.15	0.54 ± 0.21
A.B. (%)	1.9 ± 0.1	2.5 ± 0.4*	3.2 ± 0.4*
R.B. (%)	100	132	168

F: Bioavailability.
* $p < 0.05$, compared to the control.

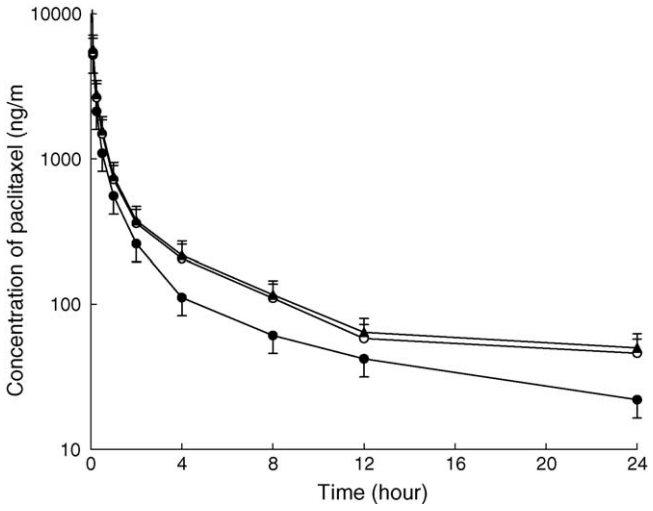

Fig. 2. Mean plasma concentration–time profiles of paclitaxel following an intravenous administration of paclitaxel (3 mg kg^{-1}) to rats in the presence and absence of morin (mean ± S.D., $n = 6$). (●) Control (paclitaxel, 3 mg kg^{-1}, i.v.); (○) pretreated with 3.3 mg kg^{-1} of morin; (▲) pretreated with 10 mg kg^{-1} of morin.

oral exposure of paclitaxel should be mainly attributed to the enhanced absorption of paclitaxel in the gastrointestinal tract via the inhibition of P-gp efflux and intestinal metabolism by morin. Woo et al. (2003) have demonstrated that about 54% of a paclitaxel oral dose is extruded to the gut lumen by P-gp and only 3.5% of paclitaxel dose is eliminated by intestinal and first-pass hepatic metabolism. Previous reports also indicated that the inhibition of both P-gp and CYP3A4 increased bioavailability of paclitaxel in rats by only 20% in comparison to inhibition of only P-gp, and thus intestinal and hepatic metabolism seem to contribute relatively less to paclitaxel absorption (Woo et al., 2003). Moreover, studies using *mdr1a*(−/−) mice have directly demonstrated that P-gp strictly limits the uptake from the intestinal tract of paclitaxel administered orally (Sparreboom et al., 1997). Therefore, the major factor leading to the low bioavailability of orally administered paclitaxel is considered to be the active efflux by P-gp within the intestinal tract. Accordingly, the enhanced oral exposure of paclitaxel in the presence of morin, while there was no significant change in the intravenous pharmacokinetics of paclitaxel, could be mainly due to the increased intestinal absorption via the inhibition of P-gp by morin rather than the reduced elimination of paclitaxel. Based on the AUC, the effect of morin on the oral exposure of paclitaxel tends to be greater as the dose of morin increases, implying that the morin may interact with the P-gp in a competitive manner. This result appeared to be comparable to the previous report by Zhang and Morris (2003). In their studies, the cellular P-gp level showed no significant changes after preincubation with morin, suggesting that morin may interact with P-gp directly either by competitive binding to the substrate-binding site or by binding to other drug-binding sites (Zhang and Morris, 2003). Given that a large number of drugs are substrates for P-gp, the concomitant use of morin may be widely applicable to improve the pharmacokinetics of many P-gp substrates in addition to paclitaxel.

4. Conclusion

Pretreatment with morin significantly enhanced the oral exposure of paclitaxel in rats, while the intravenous pharmacokinetics of paclitaxel was not affected much by the concurrent use of morin. Therefore, the concomitant use of morin or morin-containing dietary supplement may provide a therapeutic benefit in the oral delivery of paclitaxel.

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