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Enhanced oral bioavailability of docetaxel in rats by four consecutive days of pre-treatment with curcumin

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ABSTRACT

As with many other anti-cancer agents, docetaxel is a substrate for ATP-binding cassette transporters such as P-glycoprotein and its metabolism is mainly catalysed by CYP3A. In order to improve the oral bioavailability of docetaxel, a component of turmeric, curcumin, which can down-regulate the intestinal P-glycoprotein and CYP3A protein levels, was used for the pre-treatment of rats before the oral administration of docetaxel. Curcumin (100 mg/kg) did not significantly modify the pharmacokinetics of docetaxel when given orally 30 min before the administration of docetaxel. However, the C_{max} of docetaxel in rats pre-treated with curcumin for four consecutive days was significantly increased ($p < 0.01$) by about 10 times compared to that of the docetaxel control, and the area under the plasma concentration–time curve (AUC) was about eight times higher than that of the control. Consequently, the absolute bioavailability of docetaxel in the treatment group (four days of curcumin at 100 mg/kg) was about 40%, which was a significant increase of about eightfold in comparison to the control value. Thus, the oral bioavailability of docetaxel was enhanced by the co-administration of regular curcumin. It could be possible to administer docetaxel orally, besides the established *i.v.* route.

1. Introduction

A second-generation taxoid, docetaxel, has recently been considered as one of the most important anti-tumour drugs in clinical use for cancer. It acts by inhibiting the microtubular network that is essential for mitotic and interphase cellular functions. It accelerates the assembly of tubulin into stable microtubules and hinders their disassembly, causing the inhibition of cell division and eventual cell death (Gueritte-Voegelin et al., 1991; Ringel and Horwitz, 1991). Docetaxel has more affinity than paclitaxel for microtubules (Aapro, 1996). However, its poor solubility in water has created significant problems in developing suitable injection and infusion formulations for use in anti-cancer chemotherapy. The currently marketed form (Taxotere®) of docetaxel for intravenous infusion is formulated utilizing Tween 80 (polysorbate 80) and ethanol. This solvent system frequently causes untoward hypersensitivity reactions and patients receiving this drug require pre-medication (Gelderblom et al., 2001). To avoid these disadvantages, many studies have been directed towards developing new oral formulations. Docetaxel, however, is very poorly absorbed when administered orally. Several investigators reported that the poor bioavailability of docetaxel could result from the cytochrome P450 (CYP) 3A isoforms, mainly CYP3A4 and CYP3A5, and the membrane transporter P-glycoprotein (ABCB1) (Aapro, 1996; Monegier et al., 1994; Shirakawa et al., 1999; Wils et al., 1994). Docetaxel is mainly biotransformed by the CYP3A4 pathway into at least four inactive metabolites. In humans, CYP3A4 is generally the most abundant hepatic and intestinal form. While CYP3A only constitutes 30% of total human hepatic CYP (Shimada et al., 1994), it accounts for approximately 70% of CYP in human enterocytes (Kolars et al., 1992; Watkins et al., 1987). It is worth nothing that although the small intestinal villi receive a much lower blood flow than the liver, the concentration of CYP3A in the villi tips of enterocytes equals or exceeds the concentrations in the liver, facilitating a substantial first-pass metabolism (Watkins et al., 1987). Moreover, in a recent publication, it was reported that expression of CYP3A in the intestine dramatically decreased the absorption of docetaxel into the bloodstream, while hepatic CYP3A expression aided systemic docetaxel clearance in mice (Herwaarden et al., 2007).

P-glycoprotein (P-gp) is a large plasma membrane protein of the ATP-binding cassette (ABC) family of proteins. This is mainly present in epithelial cells in the body, where it localizes to the apical membrane. P-glycoprotein acts as an energy-dependent transporter or efflux pump to decrease the intracellular accumulation of drugs by extruding xenobiotics from the cell. Many inhibitors of P-glycoprotein have been identified, some of which are very effective.

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Some examples are cyclosporine, verapamil, valspodar (PSC833) and elacridar (GF120918). Cyclosporine and verapamil are already used in clinics (Fisher and Sikic, 1995; Gottesman and Pastan, 1989; Ozols et al., 1987); they act as competitive inhibitors. However, the usefulness of these drugs is difficult to apply in the clinic, because the plasma concentrations required to reverse MDR could result in cardiac toxicity causing hypotension, congestive heart failure and heart block (Woo et al., 2003).

Curcumin (diferuloylmethane) is a yellow-coloured phenolic substance derived from the spice herb *Curcuma longa*, usually called tumeric, which has beneficial activities including anti-inflammatory, antioxidant and anti-cancer activities. Curcumin can reportedly suppress the tumourigenic activity of a wide variety of carcinogens in cancers of the colon, duodenum, oesophagus, forestomach, stomach, liver, breast, oral cavity and prostate in rodents, and it has also been reported to suppress leukaemia in rodents. Moreover, curcumin has been reported to inhibit both the function and expression of the P-glycoprotein and also the CYP3A4 enzymes (Chearwae et al., 2004; Romiti et al., 1998; Valentine et al., 2006; Zhang et al., 2007).

Curcumin, alone or in combination with docetaxel, was also reported to be highly potent in mice with multidrug-resistant tumours by decreasing both tumour cell proliferation and microvessel density and by increasing tumour cell apoptosis (Lin et al., 2007). Recently, the results of a phase I dose escalation trial including 14 patients with advanced or metastatic breast cancer showed that curcumin could be used in combination with docetaxel. This study determined the maximum tolerated dose of combined curcumin and docetaxel (6000 mg/day of curcumin for seven consecutive days every three weeks in combination with a standard dose of docetaxel) as well as their toxicity, safety and effects on tumour markers. Thanks to the encouraging data obtained by this clinical trial, a comparative phase II clinical trial study is now under investigation. However, there has been no investigation to evaluate whether or not curcumin can enhance the bioavailability of docetaxel. The aim of this study was to investigate oral docetaxel preparations, which would be more convenient than the *i.v.* dosage form, in an attempt to enhance the bioavailability of docetaxel in rats pre-treated with curcumin.

2. Materials and methods

2.1. Materials

Docetaxel was donated from Hanmi Pharm. Co. (Hwaseung, Korea). Curcumin was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Propyl 4-hydroxybenzoate, cyclosporine A and ketoconazole were supplied by Hanmi Pharm. Co. (Hwaseung, South Korea). Acetonitrile and methanol were acquired from Merck Co. (Darmstadt, Germany). The other chemicals were of reagent grade and used without further purification.

2.2. Animal experiments and drug administration

Male Sprague–Dawley rats (6–8 weeks old, 260–280 g) purchased from Orient Bio Co. (Busan, South Korea) had free access to a normal, standard laboratory diet and tap water. The animals were kept at 23–24 °C and 50–60% RH with a normal 12-h light/dark cycle starting one week before the experiment. All animal care measures and experimental procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989, revised in 1999 and amended in 2008 by the Society of Toxicology (SOT, 2008). The protocols for the animal studies were also approved by the Institute of Laboratory Animal Resources of Yeungnam University.

The rats were randomly divided into five groups, with five rats in each group. Rats assigned to the treatment group were gavaged with curcumin (100 mg/kg/day, with 10% Tween 80 as the vehicle) for four consecutive days. Tween 80 was added to the vehicle to ensure curcumin dissolution and accurate dosing. Rats in the remaining groups were treated with an equivalent volume (about 1 ml) of the 10% Tween 80 vehicle in the similar manner taking into consideration reports that suggest Tween 80 has inhibitory effects on the function of P-gp and CYP3A (Mountfield et al., 2000; Zhang et al., 2003). All of the rats were allowed free access to food and water. On day 5, rats in the control group continued to receive only the vehicle, but those in the co-administered and treatment groups were given 100 mg/kg of curcumin and the rats in two comparative reference groups were given cyclosporine A (P-glycoprotein inhibitor, 60 mg/kg) and ketoconazole (CYP3A inhibitor, 30 mg/kg), respectively. Half an hour later, all of the rats were administered with 30 mg/kg docetaxel dissolved at 10 mg/ml in distilled water containing 25% (w/v) Tween 80 and 9.75% (v/v) ethanol. Blood samples for docetaxel oral administration were drawn after 0, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 h from the subclavian vein using a 1 ml syringe. The plasma samples were obtained by centrifuging at 8000 *g* for 5 min. The supernatant plasma fraction was transferred to a clean tube and stored at −70 °C until HPLC analysis.

For the intravenous bolus experiments, docetaxel (10 mg/kg, the above docetaxel solution was further diluted with normal saline to 2 mg/ml) was administrated into the femoral vein and blood samples were collected after 0.033, 0.083, 0.167, 0.25, 0.5, 1, 2, 4 and 8 h. After dosing, it was cannulated through a femoral artery with polyethylene tubing.

2.3. HPLC analysis of plasma docetaxel

Each plasma sample (150 μl) was mixed with 50 μl of internal standard *n*-propyl *p*-hydroxybenzonate solution (10 μg/ml in acetonitrile) before the addition of 2 ml of acetonitrile to precipitate the plasma proteins. After vortex mixing for 4 min, the mixture was centrifuged for 10 min at 3000 g, and 1.5 ml of supernatant was transferred to a clean test tube and evaporated using a vacuum centrifugal evaporator. The residue was reconstituted in 100 μl of the mobile phase. Then, 50 μl of the resulting solution was analysed by HPLC (Hitachi, Japan) equipped with an Intensil C8 column (GL science, 3.5 μm, 4.6 × 150 mm) and a UV-VIS detector (L-2420). The mobile phase consisted of acetonitrile: 0.01 M acetate buffer (pH 5.0) (49:51, v/v). The eluent was monitored at 232 nm with a flow rate of 1 ml/min. The retention times were as follows: internal standard, 5.5 min and docetaxel, 7.7 min.

The non-compartmental pharmacokinetic analysis was performed using the WinNonlin software version 4.1 (Pharsight Co., Mountain View, CA, USA) computer program, which uses the WinNonlin method to calculate the area under the curve (AUC) of the plasma concentration (C_p) as a function of time (t). The maximum plasma concentration (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were determined by a visual inspection of the experimental data. The ratio of C_{max} to T_{max} was also obtained. The elimination rate constant (K_{el}) was calculated by regression analysis from the slope of the line, and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. The absolute bioavailability (AB%) of docetaxel after oral administration compared to the *i.v.* administration was calculated as follows:

$$AB\% = \frac{AUCoral}{AUCiv} \times \frac{IVdose}{Oraldose} \times 100 \quad (1)$$

2.4. Statistical analysis

All mean values are presented with their standard deviations (mean ± S.D.). The pharmacokinetic parameters were compared

using a one-way ANOVA, followed by a posteriori testing with the use of the Dunnett's correction. Differences were considered to be significant at a level of $p < 0.05$.

3. Results and discussion

It has been well reported that improved pharmacokinetics of P-gp and CYP3A substrates could be achieved by co-administration or pre-treatment with P-gp or CYP3A inhibitors (Choi et al., 2004). Since the four-day administration of curcumin at a dose of 60 mg/kg/day was shown to down-modulate P-glycoprotein levels in epithelial cells in the gastrointestinal tract and to down-regulate CYP3A expression in rats (Zhang et al., 2007), a similar approach was employed in the present study. However, given that the extent to which the CYP3A and P-gp activities were inhibited and the extent to which the inhibitory effects caused by curcumin at this dose could modify the pharmacokinetics profile of docetaxel after oral administration remained unclear, a slight higher dose (100 mg/kg/day) was used in an attempt to obtain a more obvious response to the pre-treatment with curcumin.

The plasma concentration–time profiles of docetaxel after oral administration of 30 mg/kg docetaxel in the control, co-administered and treatment groups are illustrated in Fig. 1. The corresponding pharmacokinetic parameters are shown in Table 1. Compared with rats in the oral vehicle control group, rats treated with curcumin for four days prior to docetaxel administration had significantly increased AUC and C_{max} values of the oral docetaxel. Administration of 30 mg/kg docetaxel in the treatment group resulted in a marked increase in the AUC from 282.6 ± 18.4 (control) to 2244.1 ± 68.0 ng h/ml, an approximate eightfold increase in the AUC, and in the C_{max} from 102.5 ± 11.5 (control) to 1024.2 ± 121.7 ng/ml, an approximate tenfold increase in C_{max}. The bioavailability of docetaxel was increased by about eightfold from 5.5% in the control group (docetaxel alone) to 43.7% in the treatment group. There was no significant difference in the time taken to reach the peak concentration (T_{max}) of docetaxel between the control group (1.0 ± 0.0 h) and the co-administered group (0.7 ± 0.3 h). By contrast, the T_{max} in the treatment group was slightly prolonged to 1.5 h. Any effect on the $t_{1/2}$ was not observed in any of the groups. However, rats administered with curcumin 30 min before docetaxel (co-administered group) did not have significantly different AUC or C_{max} values compared to those in the control group.

The pharmacokinetic profile of docetaxel was significantly different in rats fed with 100 mg/kg/day curcumin for four days compared with the control rats, with an increase of oral bioavailability by about eightfold. Such pharmacokinetic modulations might be attributed to changes in the function and/or expression of proteins which participate in the transport and metabolism of docetaxel. Indeed, curcumin has been shown to inhibit the P-gp efflux activity in vitro (Songyot et al., 2002), and to attenuate the activity of CYP3A enzymes in liver microsomes (Zhang et al., 2007). However, the administration of a single dose of curcumin 30 min before drug treatment did not change the pharmacokinetic profiles of docetaxel. It is well reported that curcumin exhibits poor bioavailability (Aggarwal and Harikumar, 2009). The major reasons attributed to the low bioavailability of curcumin are poor absorption, rapid metabolism and rapid systemic elimination. Nevertheless, when the rats were treated with curcumin for four consecutive days, the accumulative absorption of curcumin into the general circulation was adequate to modify the expression of P-glycoprotein and CYP3A in these rats.

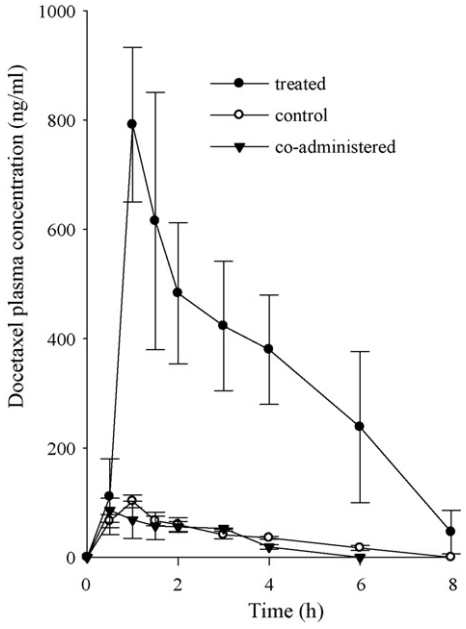

Fig. 1. Plasma concentration–time curves of docetaxel in the rats assigned to the control, co-administered and treatment groups. Rats were treated with curcumin (100 mg/kg/day, p.o., treatment) or vehicle (10% Tween80, control, co-administerd) for four consecutive days. On day 5, the rats were gavaged with the vehicle (control) or 100 mg/kg curcumin (co-administered and treatment group) 30 min before they were gavaged with 30 mg/kg docetaxel. Each value represents the mean ± S.D. ($n = 5$).

Cyclosporine A is the most extensively characterized inhibitor of P-glycoprotein and was the first multidrug resistance (MDR)-reversal agent to reach clinical trials (Fisher and Sikic, 1995). Furthermore, ketoconazole, a competitive CYP3A inhibitor, was reported to improve the bioavailability of certain drugs metabolized by cytochrome P450 3A (CYP3A) (Woo et al., 2003). In order to assess the clinical potential of combined use of curcumin and docetaxel, two kinds of clinically tested drugs (i.e. cyclosporine A (60 mg/kg) and ketoconazole (30 mg/kg)) were used in the reference groups, and the changes in pharmacokinetics parameters of docetaxel after pre-treatment with curcumin were compared with those after co-administration of these two drugs, respectively. As shown in Fig. 2 and Table 2, the bioavailability and

Table 1
Pharmacokinetic parameters of rat plasma in control, co-administered, treatment (30 mg/kg) and intravenous (10 mg/kg) administration groups.

Parameters	Groups			
	Control	Co-administered	Treatment	*i.v.* (10 mg/kg)
AUC (ng h/ml)	282.6 ± 18.4	309.1 ± 84.1	2244.1 ± 68.0*	1711.4 ± 202.3
C_{max} (ng/ml)	102.5 ± 11.5	86.0 ± 22.0	1024.2 ± 121.7*	–
T_{max} (h)	1.0 ± 0.0	0.7 ± 0.3	1.5 ± 0.3	–
C_{max}/T_{max} (ng/ml/h)	102.5 ± 11.5	111.7 ± 23.7	703.0 ± 125.6*	
$t_{1/2}$ (h)	2.3 ± 0.8	3.2 ± 0.3	2.4 ± 0.3	–
AB (%)	5.5	6.0	43.7*	–

Each value represents the mean ± S.D. ($n = 5$).
* $p < 0.01$ significant difference compared with control.

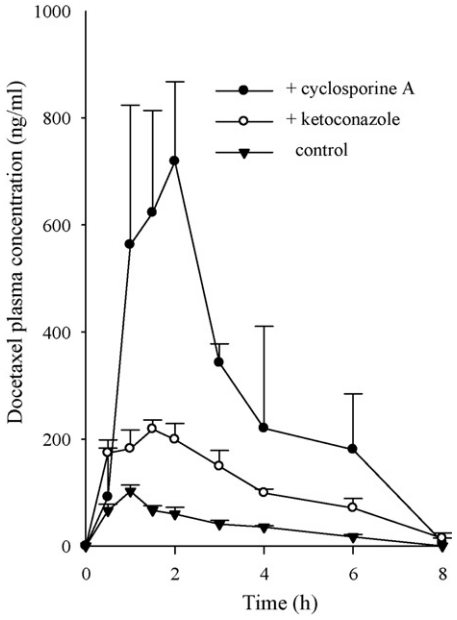

Fig. 2. Plasma concentration–time curves of docetaxel in the rats after oral administration of docetaxel (30 mg/kg) alone (control), cyclosporine A (60 mg/kg) or ketoconazole (30 mg/kg). Each value represents the mean ± S.D. ($n = 5$).

C_{max} values of docetaxel were significantly increased by these two compounds, although by a lower extent for ketoconazole compared to the control group. This finding was consistent with the results reported previously, which showed that cyclosporin A increased the bioavailability of docetaxel (Malingré et al., 2001). However, the effect of concomitant oral cyclosporine A on the AUC of docetaxel was not significantly different from that of the curcumin (100 mg/kg) treatment group (1987.5 ± 348.8 vs. 2244.1 ± 68.0 ng h/ml). The curcumin-treated rats showed greater bioavailability enhancement than those treated by ketoconazole.

Interestingly, the T_{max} values in both the cyclosporine A and ketoconazole groups were also prolonged to 1.5 h without significance in a manner similiar to that of the curcumin treatment group. These findings were in agreement with a previous study in which the T_{max} of saquinavir after upper small intestine administration was delayed by both CYP3A and P-gp inhibitors (Sinko et al., 2004). Another study also reported that the T_{max} of talinolol was prolonged after oral administration in rats (Kagan et al., 2010). It was thought that P-gp and CYP3A inhibition could alter the drug disposition (enhanced oral bioavailability by diminishing drug elimination or increasing its net intestine absorption) (Sinko et al., 2004). In the current study, the disposition profiles of docetaxel after pre-treatment with curcumin or co-administration of cyclosporin A or ketoconazole were characterized as having remarkably increased AUC as well as C_{max} values, and unchanged (for the curcumin treatment group) or even shortened (for both cyclosporin A and ketoconazole) $t_{1/2}$ elimination. On the other hand, when two groups had no significant different C_{max} values, the increase in T_{max} was generally due to the decreased intestinal absorption rate. However, as shown in Tables 1 and 2, the ratios of C_{max}/T_{max} for the treatment, cyclosporine A, and ketoconazole groups were significantly higher than that of the control group (703.0 ± 125.6, 659.5 ± 102.4 and 187.9 ± 33.4 versus 102.5 ng/ml/h, respectively). Since the ratio of C_{max}/T_{max} could be used as an indicator for the rate of drug absorption (Anthony, 2004; Schmidt et al., 1998), these data showed that the average absorption rates of docetaxel in these three groups were higher than that of the control group. Accordingly, the increase in T_{max} was not due to the decreased intestinal absorption rate. Thus, in this study, our results indicated that the improved bioavailability of docetaxel was mainly achieved by increasing its net intestinal absorption, which resulted in a relatively longer time (T_{max}) taken to reach its maximum peak concentration (C_{max}).

Table 2
Pharmacokinetic parameters of docetaxel after oral administration of docetaxel (30 mg/kg) alone (control), in combination with curcumin pre-treatment (100 mg/kg), cyclosporine A (60 mg/kg), or ketoconazole (30 mg/kg) to the rats.

Parameters	Groups		
	Control	Cyclosporine A	Ketoconazole
AUC (ng h/ml)	282.6 ± 18.4	1987.5 ± 348.8**	854.3 ± 30.5*
C_{max} (ng/ml)	102.5 ± 11.5	964.5 ± 135.7**	257.4 ± 16.9*
T_{max} (h)	1.0 ± 0.0	1.5 ± 0.3	1.5 ± 0.2
$t_{1/2}$ (h)	2.3 ± 0.8	1.4 ± 0.4	1.9 ± 0.4
C_{max}/T_{max} (ng/ml/h)	102.5 ± 11.5	659.5 ± 102.4**	187.9 ± 33.4*
AB (%)	5.5	37.3**	16.1*

Each value represents the mean ± S.D. ($n = 5$).
* Significantly different compared with the control group ($p < 0.05$).
** Significantly different compared with the control group ($p < 0.01$).

At the dose level studied, the effect of cyclosporine A on the bioavailability of docetaxel in the rats was greater than that of ketoconazle. However, it cannot be concluded that the low oral bioavailability of docetaxel may be more dependent on the P-glycoprotein efflux pump in the intestinal mucosa than on intestinal metabolism by CYP3A. Cyclosporine A is a non-selective P-glycoprotein inhibitor and pharmacokinetic interactions occurred as a result of the concomitant inhibition of drug-metabolizing cytochrome P450 3A enzymes (Breedveld et al., 2006). The AUC of docetaxel enhanced by cyclosporine A showed no significant difference as compared to that of rats treated with curcumin for four consecutive days. However, with respect to its unintended toxic effects, curcumin is extremely safe and well tolerated. The tolerance of curcumin in a single oral dose up to 12 g appears to be excellent (Lao et al., 2006). Beside, recent exist on the anti-tumour activity effects of curcumin and docetaxel. It was reported that treatment with curcumin (500 mg/kg/day) resulted in a significant increase of anti-tumour activity compared with controls. There was also a significantly augmented tumour cell apoptosis with the curcumin (daily oral)/docetaxel (i.p. once weekly) combination group compared with docetaxel monotherapy animals (Lin et al., 2007). Thus, it was suggested that combining curcumin and docetaxel may actually be a superior therapeutic choice, since curcumin increases both the oral absorption and the cytotoxic effects of docetaxel.

Among the inhibitors tested in this study, curcumin and cyclosporine A acted as both P-gp and CYP3A inhibitors, but ketoconazole was only a CYP3A inhibitor. Thus, in order to differentiate between the degrees to which the P-gp efflux and CYP3A metabolism effect the bioavailability enhancement of docetaxel, a further study investigating the effects of other more specific P-gp inhibitors on the bioavailability of docetaxel will be carried out.

4. Conclusion

In conclusion, curcumin, in comparison to the currently marketed P-glycoprotein inhibitors CYP3A and CYP3A, is safe and possesses inherent anti-cancer properties, making it an ideal candidate for improving the oral bioavailability of docetaxel.

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