BIOMOLECULES & THERAPEUTICS

Original Article
Biomol Ther 19(3), 364-370 (2011)

Effects of Curcumin on the Pharmacokinetics of Loratadine in Rats: Possible Role of CYP3A4 and P-glycoprotein Inhibition by Curcumin

Cheng Li[1,4], Byung-Chul Choi[2], Dong-Ki Kim[3] and Jun-Shik Choi[1,*]

[1]College of Pharmacy, [3]College of Dentistry, Chosun University, Gwangju 501-759,
[2]Health Insurance Review and Assessment Service, Seoul, Republic of Korea
[4]College of Pharmacy, Yanbian University, Jilin, 133000, China

Abstract

The purpose of this study was to investigate the effects of curcumin on the pharmacokinetics of loratadine in rats. The effect of curcumin on P-glycoprotein (P-gp) and cytochrome P450 (CYP) 3A4 activity was evaluated. Pharmacokinetic parameters of loratadine were also determined after oral and intravenous administration in the presence or absence of curcumin. Curcumin inhibited CYP3A4 activity with an IC50 value of 2.71 μM and the relative cellular uptake of rhodamine-123 was comparable. Compared to the oral control group, curcumin significantly increased the area under the plasma concentration-time curve and the peak plasma concentration by 39.4-66.7% and 34.2-61.5%. Curcumin also significantly increased the absolute bioavailability of loratadine by 40.0-66.1% compared to the oral control group. Consequently, the relative bioavailability of loratadine was increased by 1.39- to 1.67-fold. In contrast, curcumin had no effect on any pharmacokinetic parameters of loratadine given intravenously, implying that the enhanced oral bioavailability may be mainly due to increased intestinal absorption caused via P-gp and CYP3A4 inhibition by curcumin rather than to reduced renal and hepatic elimination of loratadine. Curcumin enhanced the oral bioavailability of loratadine in this study. The enhanced bioavailability of loratadine might be mainly attributed to enhanced absorption in the gastrointestinal tract via the inhibition of P-gp and reduced first-pass metabolism of loratadine via the inhibition of the CYP3A subfamily in the small intestine and/or in the liver by curcumin.

Key Words: Loratadine, Curcumin, Pharmacokinetics, CYP3A4, P-gp, Rats

INTRODUCTION

Antihistamines effectively inhibit histamine-mediated symptoms, such as sneezing and nasal discharge, because they have the ability to block histamine (H_1) receptors (Tarnasky and Van Arsdel, 1990; Wang *et al.*, 2001). Loratadine is a widely prescribed, non-sedating antihistamine with selective peripheral histamine H_1-receptor antagonist activity that is not associated with performance impairment and has an excellent safety record (Bradley and Nicholson, 1987; Ramaekers *et al.*, 1992; Kay *et al.*, 1997; Philpot, 2000; Prenner *et al.*, 2000). Loratadine is orally administered and is used to treat allergy symptoms, including sneezing, watery eyes, and runny nose. It is also used to treat skin hives and itching in people with chronic skin reactions. It has been widely used due to its efficacy in the treatment of allergic symptoms and lack of significant central and autonomic nervous side effects such as sedation and anticholinergic properties (Clissold *et al.*, 1989).

Loratadine undergoes extensive first-pass metabolism in the liver (Hilbert *et al.*, 1987) and CYP3A4 enzymes are responsible for the metabolism of loratadine (Yumibe *et al.*, 1996). Loratadine is also a substrate of P-gp (Wang *et al.*, 2001). Since P-gp is co-localized with CYP3A4 in the small intestine, P-gp and CYP3A4 may act synergistically in absorption and first-pass metabolism of drugs, respectively (Pichard *et al.*, 1990; Wacher *et al.*,1998; Ito *et al.*, 1999).

Curcumin is the major yellow pigment in turmeric, curry, and mustard and has been widely used in cosmetics and drugs (Govindarajan, 1980). Studies on the chemopreventive efficacy of curcumin have shown that it possesses both antiinitiating and antipromoting activities in several experimental systems (Huang *et al.*, 1994; Deshpande *et al.*, 1998). There are also reports that curcumin inhibits carcinogenesis in various tissues, including skin (Huang *et al.*, 1997), colorectal (Rao *et al.*, 1995), oral (Tanaka *et al.*, 1994), forestomach (Singh *et al.*, 1998) and mammary (Singletary *et al.*, 1998) cancers. *In*

www.biomolther.org

Open Access **DOI: 10.4062/biomolther.2011.19.3.364**

pISSN: 1976-9148 eISSN: 2005-4483

Received Sep 20, 2010 **Revised** Dec 31, 2010 **Accepted** Jan 23, 2011

***Corresponding Author**
E-mail: jsachoi@chosun.ac.kr
Tel: +82 62-230-6365, Fax: +82 62-222-5414

vitro and animal studies have suggested that curcumin may have antitumor (Aggarwal and Shishodia, 2006; Choi *et al.*, 2006), antioxidant, antiarthritic, anti-amyloid, anti-ischemic (Shukla *et al.*, 2008) and anti-inflammatory properties (Srivastava *et al.*, 1995).

Appiah-Opong *et al.* (2008) reported that curcumin inhibits human CYP3A4, 2C9 and 2D6, while Thapliyal and Maru, (2001) found that curcumin inhibits human CYP1A1, 1A2 and 2B1. Thus, the inhibitory effects of curcumin against human CYP enzymes remain somewhat controversial. Curcumin is an inhibitor of P-gp in the KB/MDR cell line (Efferth *et al.*, 2002), but the inhibitory effect of curcumin against P-gp is ambiguous elsewhere. Therefore, we re-evaluated the inhibition of CYP enzyme activity and P-gp activity by curcumin using CYP inhibition assays and rhodamine-123 retention assays in P-gp-overexpressing MCF-7/ADR cells.

Loratadine and curcumin interact with CYP enzymes and P-gp, and the tremendous increase in the use of health supplements may result in curcumin being taken concomitantly with loratadine to treat dermatological or allergic diseases as a combination therapy. It is important to assess the potential pharmacokinetic interactions after the concurrent use of loratadine and curcumin or curcumin-containing dietary supplements in order to assure the effectiveness and safety of drug therapy. However, the possible effects of curcumin on the bioavailability and pharmacokinetics of loratadine have not been reported. Since loratadine and curcumin share the same CYP3A4-directed metabolic pathways, metabolism of loratadine may be competitively inhibited by curcumin. The aim of the current study was therefore to investigate the possible effects of curcumin on the pharmacokinetics of loratadine after oral and intravenous administration in rats.

MATERIALS AND METHODS

Chemicals and apparatus

Loratadine, curcumin and propranolol [an internal standard in high performance liquid chromatographic (HPLC) analysis of loratadine] were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Acetonitrile, methanol, diethyl ether were obtained from Merck Co. (Darmstadt, Germany). Other chemicals for this study were of reagent grade or HPLC grade.

The apparatus used in this study was a high-performance liquid chromatograph equipped with a Waters 1515 isocratic HPLC Pump, a Waters 717 plus autosampler and a Waters™ 474 scanning fluorescence detector (Waters Co., Milford, MA, USA), an HPLC column temperature controller (Phenomenex Inc., CA, USA), a Bransonic® ultrasonic cleaner (Branson Ultrasonic Co., Danbury, CT, USA), a vortex-mixer (Scientific Industries Co., NY, USA), and a high-speed microcentrifuge (Hitachi Co., Tokyo, Japan).

Animal experiments

Male Sprague-Dawley rats, 7-8 weeks old (270-300 g), were purchased from Dae Han Laboratory Animal Research Co. (Choongbuk, Republic of Korea) and were given free access to commercial rat chow diet (No. 322-7-1, Superfeed Co., Gangwon, Republic of Korea) and tap water *ad libitum.* The animals were housed (four or five per cage) in laminar flow cages maintained at 22 ± 2°C and 50-60% relative humidity under a 12:12 h light-dark cycle. The experiments began after acclimation to these conditions for at least one week. The experiments were carried out in accordance with the "Guiding Principles in the Use of Animals in Toxicology" adopted by the Society of Toxicology (USA) in July 1989 and revised in March 1999. The Animal Care Committee of Chosun University (Gwangju, Republic of Korea) approved the design and the conduct of this study.

The rats were fasted for at least 24 h prior to beginning the experiments and had free access to tap water. Each animal was lightly anaesthetized with ether, and the femoral artery and vein were cannulated using polyethylene tubing (SP45, I.D. 0.58 mm, O.D. 0.96 mm; Natsume Seisakusho Co. LTD., Tokyo, Japan) for blood sampling and intravenous administration.

Oral and intravenous administration of loratadine

The rats were divided into seven groups (n=6, each): the oral group (4.0 mg · kg^{-1} of loratadine dissolved in water, homogenized at 36°C for 30 min) without (control) or with 0.5 mg · kg^{-1}, 2.0 mg · kg^{-1} or 8.0 mg · kg^{-1} of oral curcumin; the intravenous group (1.0 mg · kg^{-1} of loratadine, dissolved in 0.9% NaCl solution, homogenized at 36°C for 30 min) without (control) or with 2.0 mg · kg^{-1} or 8.0 mg · kg^{-1} of oral curcumin. Oral loratadine was administered intragastrically using a feeding tube, and curcumin was intragastrically administered 30 min before administration of loratadine. Loratadine for intravenous administration was injected through the femoral vein within 0.5 min.

Blood samples (0.35 ml) were collected into heparinized tubes via the femoral artery at 0 (as a control), 0.017 (at the end of infusion), 0.1, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after intravenous infusion, and 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h after oral administration. Blood samples were immediately centrifuged for 3 min at 13,000 rpm and 0.2-ml aliquots of plasma were stored in a −40°C freezer until HPLC analysis of loratadine. Approximately 0.9 ml of whole blood collected from untreated rats was infused via the femoral artery at 0.5, 2, 4 and 8 h to replace the blood lost due to blood sampling.

HPLC assay

The plasma concentrations of loratadine were determined by the HPLC assay modified from the methods of Yin *et al.* (2003) and Amini and Ahmadiani (2004). Briefly, 50 μl of propranolol (0.21 μg · ml^{-1}, as the internal standard), 50 μl of 2 N sodium hydroxide solution and 1.1 ml of diethyl ether were added to 0.2 ml of the plasma samples. The mixture was then stirred for 3 min and centrifuged at 13,000 rpm for 10 min. 1.0 ml of the organic layer was transferred to a clean test tube and evaporated at 35°C under a stream of nitrogen. The residue was dissolved in 150 μl of the mobile phase and centrifuged at 13,000 rpm for 5 min. A 70-μl aliquot of the supernatant was injected into the HPLC system. Fluorescence detection was performed at excitation and emission wavelengths of 290 and 460 nm. The stationary phase was a Kromasil KR 100-5C_8 column (150×4.60 mm, 5 μm, EKA chemicals, Sweden) and the mobile phase was methanol/acetonitrile/0.05 M KH_2PO_4 (3:30:67, v/v/v, pH 2.0 adjusted with phosphoric acid). The retention times at a flow rate of 1.2 ml · min^{-1} was as follows: internal standard at 4.49 min and loratadine at 11.86 min. The calibration curves of loratadine were linear within the range of 10-500 ng · ml^{-1}. The coefficients of variation were less than 13.3% for loratadine.

CYP 3A4 inhibition assay

The assay of inhibition of human CYP3A4 enzyme activity was performed in a multiwell plate using a CYP inhibition assay kit (GENTEST, Woburn, MA) as described previously (Crespi *et al*., 1997). Briefly, human CYP enzyme was obtained from baculovirus-infected insect cells. CYP substrate (7-BFC for CYP3A4) was incubated with or without test compounds in buffer containing the enzyme/substrate with 1 pmol of P450 enzyme and a NADPH-generating system (1.3 mM NADP, 3.54 mM glucose 6-phosphate, 0.4 U/ml glucose 6-phosphate dehydrogenase and 3.3 mM $MgCl_2$) in potassium phosphate buffer (pH 7.4). Reactions were terminated by adding stop solution after 45-min incubation. Metabolite concentrations were measured by spectrofluorometer (Molecular Device, Sunnyvale, CA) at an excitation wavelength of 409 nm and an emission wavelength of 530 nm. Positive control (1 μM ketoconazole for CYP3A4) was run on the same plate and produced 99% inhibition. All experiments were performed in duplicate, and the results are expressed as the percent of inhibition.

Rhodamine-123 retention assay

The procedures used for the Rho-123 retention assay were similar to a previously reported method (Han *et al*., 2008). MCF-7/ADR cells were seeded in 24-well plates. At 80% confluence, the cells were incubated in FBS-free DMEM for 18 h. The culture medium was then changed to Hanks' balanced salt solution and the cells were incubated at 37°C for 30 min. After incubation of the cells with 20 μM rhodamine-123 in the presence of curcumin (0, 1, 3 and 10 μM) for 90 min, the medium was completely removed. The cells were then washed three times with ice-cold phosphate buffer (pH 7.0) and lysed in lysis buffer. The rhodamine-123 fluorescence in the cell lysates was measured using excitation and emission wavelengths of 480 and 540 nm, respectively. Fluorescence values were normalized to the total protein content of each sample and presented as the ratio to control.

Pharmacokinetic analysis

The plasma concentration data were analyzed using a non-compartmental method on WinNonlin software version 4.1 (Pharsight Co., Mountain View, CA, USA). The elimination rate constant (K_{el}) was calculated by the log-linear regression of loratadine concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$. The peak concentration (C_{max}) and time to reach the peak concentration (T_{max}) of loratadine in the plasma were obtained by visual inspection of the data in the concentration-time curve. The area under the plasma concentration-time curve (AUC_{0-t}) from time zero to the time of the last measured concentration (C_{last}) was calculated using the linear trapezoidal rule. The AUC zero to infinity ($AUC_{0-\infty}$) was obtained by adding AUC_{0-t} and the extrapolated area was determined by C_{last}/K_{el}. The total body clearance for the i.v. route (CL_t) was calculated from D/AUC, where D is the dose of loratadine. The mean residence time (MRT) was calculated by dividing the first moment of AUC ($AUMC_{0-\infty}$) by $AUC_{0-\infty}$. The apparent volume of distribution at steady state (V_{dss}) was estimated by the product of $MRT_{i.v.}$ and CL_t after i.v. dosing. The bioavailability (A.B.) of loratadine was calculated by $AUC_{oral}/AUC_{iv} \times Dose_{iv}/Dose_{oral} \times 100$, and the

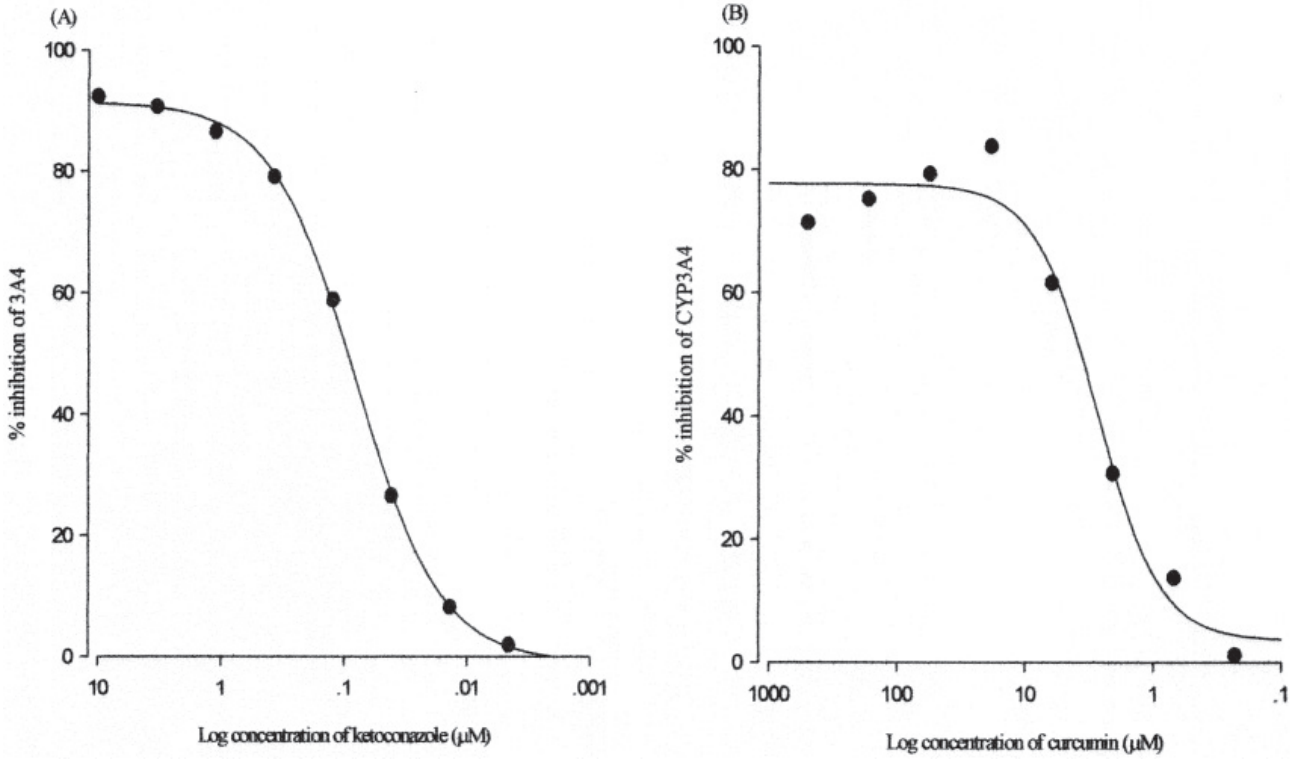

Fig. 1. Inhibitory effect of ketoconazole (A) and curcumin (B) on CYP3A4 activity. All experiments were performed in duplicate, and results are expressed as the percent of inhibition. The IC_{50} value of curcumin on CYP3A4 activity is 2.71 μM.

relative bioavailability (R.B.) was calculated by ($AUC_{with\ curcumin}$/$AUC_{control}$)×100

Statistical analysis

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

RESULTS

Inhibition of CYP3A4

The inhibitory effect of curcumin on CYP3A4 activity is shown in Fig. 1. The IC_{50} of curcumin on CYP3A4 activity was 2.71 μM. Higher concentrations of curcumin inhibited CYP3A4 enzyme activity in a concentration- dependent manner.

Rhodamine-123 retention assay

As shown in Fig. 2, accumulation of rhodamine-123, a P-gp substrate, was reduced in MCF-7/ADR cells overexpressing P-gp compared to that in MCF-7 cells lacking P-gp. The concurrent use of curcumin enhanced the cellular uptake of rhodamine 123 in a concentration dependent manner and showed statistically significant (p<0.01) increase at the concentration range of 10 μM. This result suggests that curcumin significantly inhibits P-gp activity.

Effects of curcumin on the plasma concentrations after oral administration

The plasma concentration-time profiles of loratadine in the

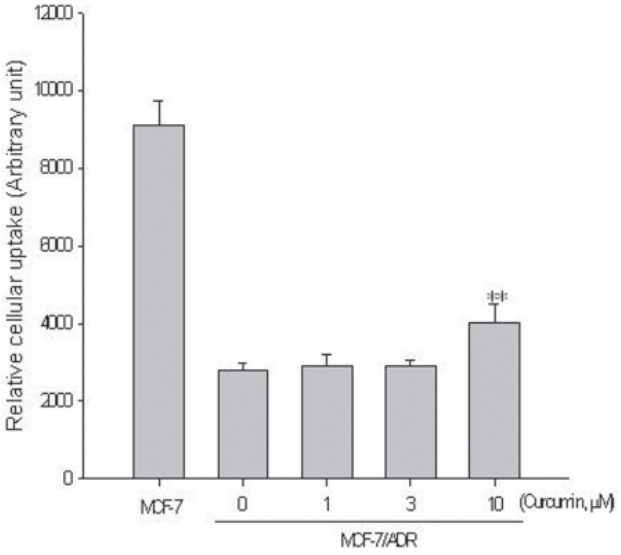

Fig. 2. Rhodamine-123 retention. MCF-7/ADR cells were preincubated with curcumin for 30 min. After incubation of MCF-7/ADR cells with 20 μM R-123 for 90 min, the R-123 fluorescence values in cell lysates were measured using excitation and emission wavelengths of 480 and 540 nm, respectively. The values were divided by the total protein content of each sample. Data represents mean ± SD of 6 separate samples (significant versus the control MCF-7 cells, ***p*<0.01).

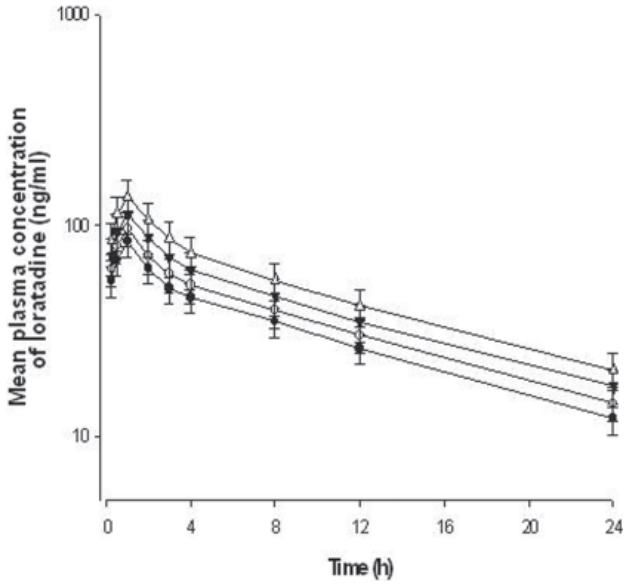

Fig. 3. Mean plasma concentration-time profiles of loratadine after oral administration of loratadine (4.0 mg • kg^{-1}) without (●) or with 0.5 mg · kg^{-1} (○) or 2.0 mg · kg^{-1} (▼) or 8.0 mg · kg^{-1} (△) of curcumin to rats. Bars represent the standard deviations (n=6).

Table 1. Mean (± S.D.) pharmacokinetic parameters of loratadine after its oral administration (4.0 mg · kg^{-1}) to rats in the presence and absence of curcumin

Parameters	Loratadine (Control)	Loratadine+Curcumin		
		0.5 mg · kg^{-1}	2.0 mg · kg^{-1}	8.0 mg · kg^{-1}
$AUC_{0-\infty}$ (ng·h·ml^{-1})	926 ± 167	1,079 ± 205	1,291 ± 258[a]	1,544 ± 324[b]
C_{max} (ng·ml^{-1})	84.2 ± 15.2	97.0 ± 18.4	113.0 ± 21.5[a]	136.0 ± 29.9[b]
T_{max} (h)	0.83 ± 0.26	0.92 ± 0.21	1.17 ± 0.41	1.33 ± 0.52
$t_{1/2}$ (h)	10.5 ± 1.9	10.8 ± 2.1	11.3 ± 2.2	11.5 ± 2.5
A.B. (%)	6.5 ± 1.2	7.6 ± 1.4	9.1 ± 1.8[a]	10.8 ± 2.3[b]
R.B. (%)	100	117	139	167

(Mean ± S.D., n = 6). [a]p<0.05, [b]p<0.01, significant difference compared to the control (given loratadine alone) group. $AUC_{0-\infty}$: area under the plasma concentration-time curve from 0 h to infinity, C_{max}: peak plasma concentration, T_{max}: time to reach peak plasma concentration, $t_{1/2}$: terminal half-life, A.B. (%): absolute bioavailability, R.B. (%): relative bioavailability.

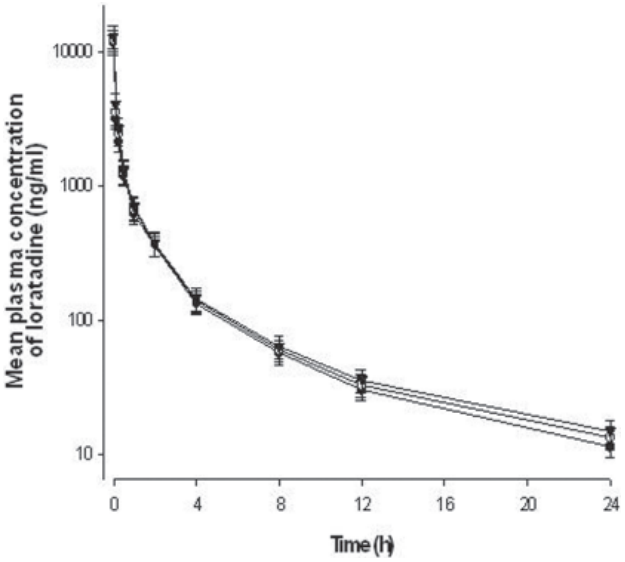

Fig. 4. Mean plasma concentration-time profiles of loratadine after i.v. administration of loratadine (1.0 mg · kg^{-1}) without (●) or with 2.0 mg · kg^{-1} (○) or 8.0 mg · kg^{-1} (▼) of curcumin to rats. Bars represent the standard deviations (n=6).

Table 2. Mean (± S.D.) pharmacokinetic parameters of loratadine after its intravenous administration (1.0 mg · kg^{-1}) to rats in the presence and absence of curcumin

Parameters	Loratadine (Control)	Loratadine+Curcumin	
		2.0 mg·kg^{-1}	8.0 mg·kg^{-1}
$AUC_{0-\infty}$ (ng·h·ml^{-1})	3,560 ± 641	3,841 ± 730	4,096 ± 819
CLt (ml·min^{-1}·kg^{-1})	271.7 ± 48.9	250.4 ± 47.6	234.2 ± 46.8
V_{dss} (L·kg^{-1})	17.6 ± 3.2	17.1 ± 3.3	16.4 ± 3.4
$t_{1/2}$ (h)	7.2 ± 1.3	7.7 ± 1.5	7.9 ± 1.6
MRT (h)	3.9 ± 0.7	4.1 ± 0.8	4.2 ± 0.9

(Mean ± S.D., n=6). $AUC_{0-\infty}$: area under the plasma concentration-time curve from 0 h to infinity, CL_t: total clearance, V_{dss}: volume of distribution, $t_{1/2}$: terminal half-life, MRT: mean residence time.

presence and absence of curcumin were characterized in rats and illustrated in Fig. 3. The mean pharmacokinetic parameters of loratadine are summarized in Table 1. As shown in Table 1, the presence of curcumin (2.0 or 8.0 mg · kg^{-1}) significantly altered the pharmacokinetic parameters of loratadine compared to those in the control group given loratadine alone. Curcumin significantly (2.0 mg · kg^{-1}, p<0.05; 8.0 mg · kg^{-1}, p<0.01) increased the $AUC_{0-\infty}$ of loratadine by 39.4-66.7%. The C_{max} was significantly (2.0 mg · kg^{-1}, p<0.05; 8.0 mg · kg^{-1}, p<0.01) increased by 34.2-61.5% in the presence of curcumin. The A.B. of loratadine was significantly increased 40.0-66.1% (2.0 mg · kg^{-1}, p<0.05; 8.0 mg · kg^{-1}, p<0.01) compared to that in the oral control group. Consequently, the R.B. of loratadine was increased by 1.39- to 1.67-fold. However, there were no significant changes in the T_{max} and the $t_{1/2}$ of loratadine in the presence of curcumin.

Effects of curcumin on the plasma concentrations after *i.v.* administration

The pharmacokinetic profiles of loratadine were also evaluated after its intravenous administration (1.0 mg · kg^{-1}) in the presence or absence of curcumin (2.0 or 8.0 mg · kg^{-1}) and illustrated in Fig. 4. As summarized in Table 2, curcumin had no effect on the pharmacokinetic parameters of intravenous loratadine although it had a significant effect on the bioavailability of loratadine given orally, suggesting that curcumin may be mainly due to increased intestinal absorption caused via P-gp and CYP3A4 inhibition rather than to reduced renal and hepatic elimination of loratadine.

DISCUSSION

With the great interest in herbal components as alternative medicines, much effort is currently being expended to identify natural compounds of plant origin that modulate P-gp and metabolic enzymes, however, there is far less information on the pharmacokinetic interactions between herbal components and medicines. More preclinical and clinical investigations on the herbal constituents-drug interaction should be performed to prevent potential adverse reactions or to utilize those interactions for a therapeutic benefit. Therefore, the present study evaluated the effect of curcumin, a naturally occurring flavonoid, on the pharmacokinetics of loratadine in rats to examine a potential drug interaction between curcumin and loratadine via the dual inhibition of CYP3A4 and P-gp.

Loratadine has low bioavailability because of poor solubility and first-pass metabolism in the liver and epithelial cells of the small intestine. Yumibe *et al.* (1996) reported that loratadine is metabolized by CYP 3A4 in both liver and small intestine. Since loratadine is also a substrate for the efflux pump, P-gp (Wang *et al.*, 2001), the oral bioavailability of loratadine might be affected by this transporter. P-gp co-localized with CYP3A4 may function synergistically in regulating the bioavailability of many orally administered compounds (Pichard *et al.*, 1990; Wacher *et al.*, 1998; Ito *et al.*, 1999). Based on their broad overlap in substrate specificities as well as their co-localization in the small intestine, which is the primary site of absorption for orally administered drugs, CYP3A4 and P-gp are recognized as a concerted barrier to drug absorption (Wolozin *et al.*, 2000; Cummins *et al.*, 2002). CYPs contribute significantly to first-pass metabolism and oral bioavailability of many drugs. The first-pass metabolism of compounds in the intestine limits the absorption of toxic xenobiotics and may ameliorate side effects. Moreover, induction or inhibition of intestinal CYPs may be responsible for significant drug-drug interactions when one agent decreases or increases the bioavailability and absorption rate constant of a concurrently administered drug (Kaminsky and Fasco, 1991).

As shown in Figs. 1 and 2, curcumin inhibited CYP3A4 and P-gp. In this study, the presence of curcumin increased the AUC and C_{max} of oral loratadine. Since curcumin acts as an inhibitor of efflux transporters, *i.e.*, P-gp, located in intestinal cells, the presence of curcumin might decrease the efflux of loratadine by this transporter in the intestine. The enhanced oral bioavailability of loratadine contributed to the competitive inhibition of loratadine metabolism by CYP 3A4 both in the liver and intestine. This result was consistent with previous studies showing that a single oral administration of cimeti-

dine, clarithromycin and ketoconazole significantly increased the AUC and C_{max} of loratadine in rats through inhibition of CYP3A4 (Carr *et al.*, 1998; Kosoglou *et al.*, 2000). These results are coincident with previous studies, in which CYP3A9 expressed in rat is corresponds to the ortholog of CYP3A4 in human (Kelly *et al.*, 1999). Therefore, rats are frequently used to evaluate the potential pharmacokinetic interactions mediated by CYP3A4, although there may be some difference in enzyme activity between rat and human (Cao *et al.*, 2006).

In contrast to the oral pharmacokinetics of loratadine, the intravenous pharmacokinetics of loratadine was not affected by the concurrent use of curcumin. The total body clearance (CL_t) of loratadine tended to be decreased and the AUC of loratadine was increased, although these values were not statistically different from those in the control. The $t_{1/2}$ of loratadine was also increased but this was not significant. These results were consistent with the report by Li *et al.* (2008) in that roxithromycin did not significantly increase the AUC of intravenous loratadine, a substrate for P-gp and CYP3A4 in rats. Accordingly, while there was no significant change in the intravenous pharmacokinetics of loratadine, the enhanced oral bioavailability in the presence of curcumin may be mainly caused by increased intestinal absorption via P-gp inhibition by curcumin rather than by reduced renal elimination of loratadine.

In conclusions, curcumin significantly enhanced the oral bioavailability of loratadine in rats. The enhanced bioavailability of loratadine may be caused by inhibition of the CYP3A4-mediated metabolism of loratadine in the small intestine or in the liver and by inhibition of the P-gp efflux pump in the small intestine by curcumin. Therefore, concomitant use of curcumin or curcumin-containing dietary supplements with loratadine may require close monitoring for potential drug interactions.

REFERENCES

Aggarwal, B. B. and Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochem. Pharm.* **71**, 1397-1421.

Amini, H. and Ahmadiani, A. (2004). Rapid determination of loratadine in small volume plasma samples by high-performance liquid chromatography with fluorescence detection. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* **809**, 227-230.

Appiah-Opong, R., de Esch, I., Commandeur, J. N., Andarini, M. and Vermeulen, N. P. (2008). Structure-activity relationships for the inhibition of recombinant human cytochromes P450 by curcumin analogues. *Eur. J. Med. Chem.* **43**, 1621-1631.

Bradley, C. M. and Nicholson, A. N. (1987). Studies on the central effects of the H1-antagonist, loratadine. *Eur. J. Clin. Pharmacol.* **32**, 419-421.

Cao, X., Gibbs, S. T., Fang, L., Miller, H. A., Landowski, C. P., Shin, H. C., Lennernas, H., Zhong, Y., Amidon, G. L., Yu, L. X. and Sun, D. (2006). Why is it challenging to predict intestinal drug absorption and oral bioavailability in human using rat model. *Pharm. Res.* **23**, 1675-1686.

Carr, R. A., Edmonds, A., Shi, H., Locke, C. S., Gustavson, L. E., Craft, J. C., Harris, S. I. and Palmer, R. (1998). Steady-State Pharmacokinetics and Electrocardiographic Pharmacodynamics of Clarithromycin and Loratadine after Individual or Concomitant Administration. Antimicrob. *Agents. Chemother.* **42**, 1176-1180.

Choi, H., Chun, Y. S., Kim, S. W., Kim, M. S. and Park, J. W. (2006). Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: a mechanism of tumor growth inhibition. *Mol. Pharm.* **70**, 1664-1671.

Clissold, S. P., Sorkin, E. M. and Goa, K. L. (1989). Loratadine, a preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs* **37**, 42-57.

Crespi, C. L., Miller, V. P. and Penman, B. W. (1997). Microtiter plate assays for inhibition of human, drug-metabolizing cytochromes P450. *Anal. Biochem.* **248**, 188-190.

Cummins, C. L., Jacobsen, W. and Benet, L. Z. (2002). Unmasking the dynamic interplay between intestinal P-glycoprotein and CYP3A4. *J. Pharmacol. Exp. Ther.* **300**, 1036-1045.

Deshpande, S. S., Ingle, A. D. and Maru, G. B. (1998). Chemopreventive efficacy of curcumin-free aqueous turmeric extract in 7, 12-dimethylbenz [a] anthracene-induced rat mammary tumorigenesis. *Cancer Lett.* **123**, 35-40.

Efferth, T., Davey, M., Olbrich, A., Rücker, G., Gebhart, E. and Davey, R. (2002). Activity of drugs from traditional Chinese medicine toward sensitive and MDR1- or MRP1-overexpressing multidrug-resistant human CCRF-CEM leukemia cells. *Blood Cells Mol. Dis.* **28**, 160-168.

Govindarajan, V. S. (1980). Turmeric--chemistry, technology, and quality. *Crit. Rev. Food Sci. Nutr.* **12**, 199-301.

Han, C. Y., Cho, K. B., Choi, H. S., Han, H. K. and Kang, K. W. (2008). Role of FoxO1 activation in MDR1 expression in adriamycin-resistant breast cancer cells. *Carcinogenesis* **29**, 1837-1844.

Hilbert, J., Radwanski, E., Weglein, R., Luc, V., Perentesis, G., Symchowicz, S. and Zampaglione, N. (1987). Pharmacokinetics and dose proportionality of loratadine. *J. Clin. Pharmacol.* **27**, 694-698.

Huang, M. T., Lou, Y. R., Ma, W., Newmark, H. L., Reuhl, K. R. and Conney, A. H. (1994). Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. *Cancer Res.* **54**, 5841-5847.

Huang, M. T., Newmark, H. L. and Frenkel, K. (1997). Inhibitory effects of curcumin on tumorigenesis in mice. *J. Cell Biochem.* **27**, 26-34.

Ito, K., Kusuhara, H. and Sugiyama, Y. (1999). Effects of intestinal CYP3A4 and P-glycoprotein on oral drug absorption; theoretical approach. *Pharm. Res.* **16**, 225-231.

Kaminsky, L. S. and Fasco, M. J. (1991). Small intestinal cytochromes P450. *Crit. Rev. Toxicol.* **21**, 407-422.

Kay, G. G., Berman, B., Mockoviak, S. H., Morris, C. E., Reeves, D., Starbuck, V., Sukenik, E. and Harris, A. G. (1997). Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch. Intern. Med.* **57**, 2350-2356.

Kelly, P. A., Wang, H., Napoli, K. L., Kahan, B. D. and Strobel, H. W. (1999). Metabolism of cyclosporine by cytochromes P450 3A9 and 3A4. *Eur. J. Drug. Metab. Pharmacokinet.* **24**, 321-328.

Kosoglou, T., Salfi, M., Lim, J. M., Batra, V. K., Cayen, M. N. and Affrime, M. B. (2000). Evaluation of the pharmacokinetics and electrocardiographic pharmacodynamics of loratadine with concomitant administration of ketoconazole or cimetidine. *Br. J. Clin. Pharmacol.* **50**, 581-589.

Li, C., Kim, C. S., Yang, J. Y., Park, Y. J. and Choi, J. S. (2008). Effects of roxithromycin on the pharmacokinetics of loratadine after oral and intravenous administration of loratadine in rats. *Eur. J. Drug Metab. Pharmacokinet.* **33**, 231-236.

Philpot, E. E. (2000). Safety of second generation antihistamines. *Allerg. Asthma. Proc.* **21**, 15-19.

Pichard, L., Gillet, G., Fabre, I., Dalet-Beluche, I., Bonfils, C., Thenot, J. P. and Maurel, P. (1990). Identification of the rabbit and human cytochromes P-450IIIA as the major enzymes involved in the N-demethylation of diltiazem. *Drug Metab. Dispos.* **18**, 711-719.

Prenner, B. M., Capano, D. and Harris, A. G. (2000). Efficacy and tolerability of loratadine versus fexofenadine in the treatment of seasonal allergic rhinitis: adouble-blind comparison with crossover treatment of nonresponders. *Clin. Ther.* **22**, 760-769.

Ramaekers, J. G., Uiterwijk, M. M. and O'Hanlon, J. F. (1992). Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *Eur. J. Clin. Pharmacol.* **42**, 363-369.

Rao, C. V., Rivenson, A., Simi, B. and Reddy, B. S. (1995). Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. *Cancer Res.* **55**, 259-266.

Shukla, P. K., Khanna, V. K., Ali, M. M. and Khan, M. Y. (2008). An-

ti-ischemic effect of curcumin in rat brain. *Neurochem. Res.* **33**, 1036-1043.

Singh, S. V., Hu, X., Srivastava, S. K., Singh, M., Xia, H., Orchard, J. L. and Zaren, H. A. (1998). Mechanism of inhibition of benzo[a] pyrene-induced forestomach cancer in mice by dietary curcumin. *Carcinogenesis* **19**, 1357-1360.

Singletary, K., MacDonald, C., Iovinelli, M., Fisher, C. and Wallig, M. (1998). Effect of the beta-diketones diferuloylmethane (curcumin) and dibenzoylmethane on rat mammary DNA adducts and tumors induced by 7,12-dimethylbenz[a]anthracene. *Carcinogenesis* **19**, 1039-1043.

Srivastava, K. C., Bordia, A. and Verma, S. K. (1995). Curcumin, a major component of food spice turmeric (Curcuma longa) inhibits aggregation and alters eicosanoid metabolism in human blood platelets. Prostaglandins. *Leukot. Essent. Fatty Acids.* **52**, 223-227.

Tanaka, T., Makita, H., Ohnishi, M., Hirose, Y., Wang, A., Mori, H., Satoh, K., Hara, A. and Ogawa, H. (1994). Chemoprevention of 4-nitroquinoline 1-oxide-induced oral carcinogenesis by dietary curcumin and hesperidin: comparison with the protective effect of beta-carotene. *Cancer Res.* **54**, 4653-4659.

Tarnasky, P. R. and Van Arsdel, P. P. Jr. (1990). Antihistamine therapy in allergic rhinitis. *J. Fam. Prac.* **30**, 71-80.

Thapliyal, R. and Maru, G. B. (2001). Inhibition of cytochrome P450 isozymes by curcumins in vitro and in vivo. *Food Chem. Toxicol.* **39**, 541-547.

Wacher, V. J., Silverman, J. A., Zhang, Y. and Benet, L. Z. (1998). Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. *J. Pharm. Sci.* **87**, 1322-1330.

Wang, E. J., Casciano, C. N., Clement, R. P. and Johnson, W. W. (2001). Evaluation of the interaction of loratadine and desloratadine with P-glycoprotein. *Drug Metab. Dispos.* **29**, 1080-1083.

Wolozin, B., Kellman, W., Ruosseau, P., Celesia, G. G. and Siegel, G. (2000). Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch. Neurol.* **10**, 1439-1443.

Yin, O. Q., Shi, X. and Chow, M. S. (2003). Reliable and specific high-performance liquid chromatographic method for simultaneous determination of loratadine and its metabolite in human plasma. *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.* **796**, 165-172.

Yumibe, N., Huie, K., Chen, K. J., Snow, M., Clement, R. P. and Cayen, M. N. (1996). Identification of human liver cytochrome P450 enzymes that metabolize the nonsedating antihistamine loratadine. Formation of descarboethoxyloratadine by CYP3A4 and CYP2D6. *Biochem. Pharmacol.* **51**, 165-172.