Biomolecules & Therapeutics, **17(2)**, 205-210 (2009)
www.biomolther.org

ISSN: 1976-9148(print)/2005-4483(online)
DOI: 10.4062/biomolther.2009.17.2.205

Effects of Hydrocortisone on the Pharmacokinetics of Loratadine after Oral and Intravenous Loratadine Administration to Rats

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(Received January 16, 2009; Revised April 14, 2009; Accepted April 20, 2009)

Abstract − The present study investigated the effects of hydrocortisone on the pharmacokinetics of loratadine in rats after intravenous and oral administration. A single dose of loratadine was administered either orally (4 mg/kg) or intravenously (1 mg/kg) with or without oral hydrocortisone (0.3 or 1.0 mg/kg). Compared to the control group (without hydrocortisone), after oral administration of loratadine, the area under the plasma concentration-time curve (AUC) was significantly increased by 30.2-81.7% in the presence of hydrocortisone ($p < 0.05$). The peak plasma concentration (C_{max}) was significantly increased by 68.4% in the presence of 1.0 mg/kg hydrocortisone after oral administration of loratadine ($p < 0.05$). Hydrocortisone (1.0 mg/kg) significantly increased the terminal plasma half-life ($t_{1/2}$) of loratadine by 20.8% ($p < 0.05$). Consequently, the relative bioavailability of loratadine was increased by 1.30- to 1.82-fold. In contrast, oral hydrocortisone had no effects on any pharmacokinetic parameters of loratadine given intravenously. This suggests that hydrocortisone may improve the oral bioavailability of loratadine by reducing first-pass metabolism of loratadine, most likely mediated by P-gp and/or CYP3A4 in the intestine and/or liver. In conclusion, hydrocortisone significantly enhanced the bioavailability of orally administered loratadine in rats, which may have been due to inhibition of both CYP 3A4-mediated metabolism and P-gp in the intestine and/or liver by the presence of hydrocortisone.

Keywords: Loratadine, Hydrocortisone, Pharmacokinetics, CYP3A4, P-glycoprotein

INTRODUCTION

Antihistamines are effective for inhibiting histamine-mediated symptoms, such as sneezing and nasal discharge, because they can block histamine H_1- receptors (Tarnasky and Van Arsdel, 1990; Wang *et al*., 2001). Loratadine is a widely prescribed, non-sedating, anti-histamine with selective peripheral histamine H_1-receptor antagonist activity that is not associated with performance impairment and has an excellent safety record (Ramaekers *et al*., 1992; Philpot, 2000; Prenner *et al*., 2000). Loratadine is orally administered and is used to treat the symptoms of allergies, including sneezing, watery eyes and runny nose. It is also used to treat skin hives and itching for people with chronic skin reactions. It is widely used due to its efficacy for treating allergic symptoms without significant central or autonomic nervous system side effects, such as sedation or anti-cholinergic properties (Clissold *et al*., 1989).

Loratadine undergoes extensive first-pass metabolism in the liver to form its major metabolite desloratadine, which also possesses anti-histamine activity and is subject to further metabolism (Hilbert *et al*., 1987). Desloratadine has greater pharmacological potency than its parent drug (Kreutner *et al*., 2000; Henz, 2001). The CYP3A4 and CYP2D6 enzymes metabolize loratadine to desloratadine (Yumibe *et al*., 1996). Loratadine is also a substrate for P-glycoprotein (P-gp) (Wang *et al*., 2001). Because P-gp is co-localized with CYP3A4 in the small intestine, P-gp and CYP3A4 may act synergistically for the absorption and first-pass metabolism of drugs, respectively (Pichard *et al*., 1990; Wacher *et al*., 1998; Ito *et al*., 1999).

Hydrocortisone is a natural corticosteroid produced by the adrenal glands. Corticosteroids have potent anti-inflammatory properties and are used for a wide variety of in-

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flammatory conditions, such as arthritis, colitis, asthma, bronchitis, certain skin rashes and allergic or inflammatory conditions of the nose, skin and eyes. Hydrocortisone is primarily metabolized by CYP3A4 (El-Sankary *et al*., 2000; Gibson *et al*., 2002). Previous studies have found that many substrates for CYP3A4 are also substrates for P-gp, suggesting synergistic effects for CYP3A4-mediated metabolism and P-gp mediated secretion in the gut after oral administration (Zhang *et al*., 1998; Benet *et al*., 2003). Hydrocortisone is also known to be a substrate for P-gp (Nakayama *et al*., 1999; Yates *et al*., 2003).

It is likely that loratadine and hydrocortisone will be co-administered as a combination therapy for patients with dermatological or allergic diseases. Previous reports have indicated pharmacokinetic interactions between loratadine and other drugs, such as cimetidine, clarithromycin and ketoconazole (Carr *et al*., 1998; Kosoglou *et al*., 2000). These significantly increased the AUC and C_{max} of loratadine in rats by inhibition of CYP3A4 and P-gp. Given that loratadine and hydrocortisone can both interact with CYP3A4 and P-gp, there is a high probability for an interaction between these 2 drugs. However, there are few reports for the possible interactions between loratadine and hydrocortisone *in vivo.*

Because loratadine and hydrocortisone share the same CYP3A4-directed metabolic pathways, the metabolism of loratadine may be competitively inhibited by hydrocortisone. Thus, the aim of the current study was to investigate the possible effects of oral hydrocortisone on the pharmacokinetics of loratadine in rats after oral and intravenous administrations of loratadine.

MATERIALS AND METHODS

Chemicals and equipments

Loratadine, hydrocortisone and propranolol (an internal standard) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Acetonitrile, methanol, diethyl ether were obtained from Merck Co. (Darmstadt, Germany). Other chemicals were of reagent grade or HPLC grade. The apparatus used in this study was: high-performance liquid chromatography 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); HPLC column temperature controller (Phenomenex Inc., CA, USA); Bransonic® ultrasonic cleaner (Branson Ultrasonic Co., Danbury, CT, USA); vortex-mixer (Scientific Industries Co., NY, USA); high-speed microcentrifuge (Hitachi Co., Tokyo, Japan).

Animal experiments and drug administration

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 (4 or 5 per cage) in laminar flow cages maintained at 22 ± 2°C, 50-60% relative humidity. The experiments began after acclimation to these conditions for at least 1 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.

The rats were divided into 6 groups (n=6 per group): 3 oral groups (4 mg/kg of loratadine dissolved in water, homogenized at 36°C for 30 min) (1) without (control) or with (2) 0.3 mg/kg or (3) 1.0 mg/kg of oral hydrocortisone, and 3 intravenous groups (1 mg/kg of loratadine, dissolved in 0.9% NaCl solution, homogenized at 36°C for 30 min) (4) without (control) or with (5) 0.3 mg/kg or (6) 1.0 mg/kg of oral hydrocortisone. Oral loratadine and hydrocortisone were administered by intragastric feeding tube; hydrocortisone was administered 30 min before oral administration of loratadine. Loratadine for intravenous administration was injected through the femoral vein within 0.5 min. Blood samples (0.5 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, 3, 4, 8, 12 and 24 h after intravenous infusion, and at 0.1, 0.25, 0.5, 1, 2, 3, 4, 8, 12 and 24 h for the oral study. Blood samples were immediately centrifuged for 5 min at 13,000 rpm and 0.25 ml aliquots of plasma were stored in a −40°C freezer until HPLC analysis for loratadine. Approximately 1.2 ml of whole blood collected from untreated rats was infused via the femoral artery at 0.25, 1, 3 and 8 h to replace the blood loss due to blood sampling.

HPLC analysis

Plasma concentrations of loratadine were determined by an HPLC assay modified from the methods of Yin *et al*.

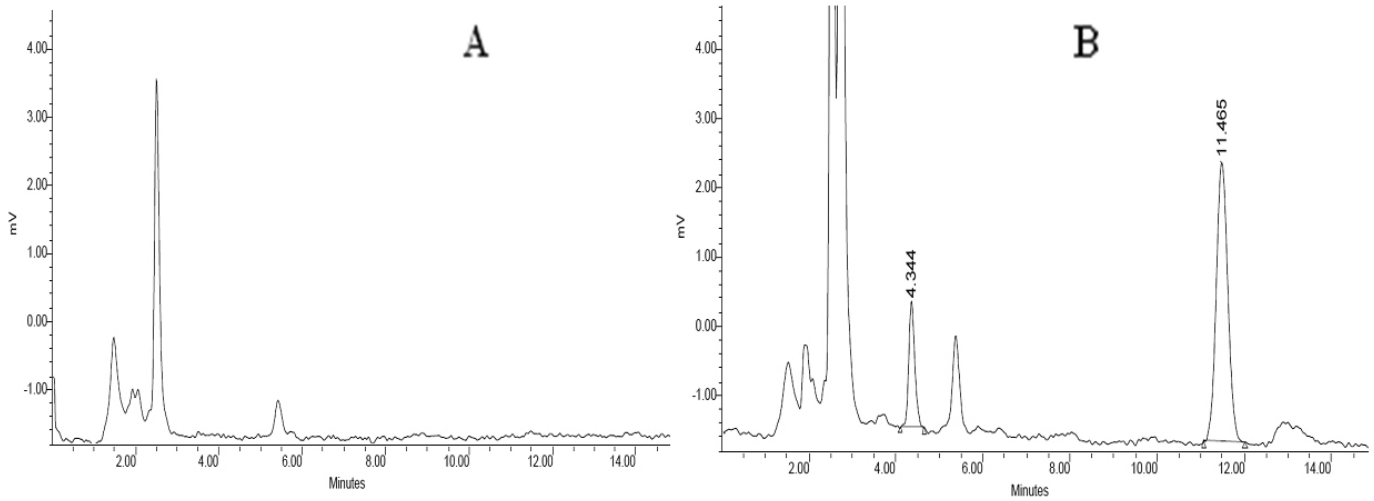

Fig. 1. Chromatograms of blank plasma (A) and plasma (B) spiked with propranolol (4.34 min) and loratadine (11.47 min).

and Amini *et al*. (Yin *et al*., 2003; Amini and Ahmadiani, 2004). Briefly, 50 μl of propranolol (0.21 μg/ml; used as internal standard), 50 μl 2 N sodium hydroxide solution and 1.1 ml diethyl ether were added to 0.25 ml of a plasma sample. The mixture was 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 used 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 were as follows: internal standard at 4.34 min and loratadine at 11.47 min (Fig. 1). The calibration curves for loratadine were linear within the range of 10-500 ng/ml (Fig. 2). The coefficients of variation were less than 13.3% for loratadine.

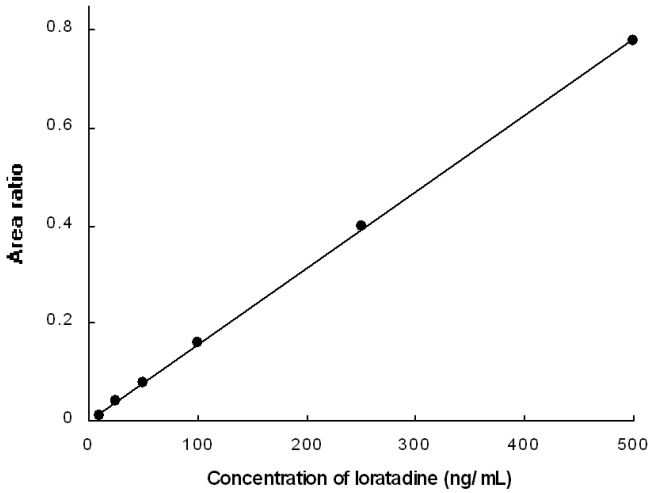

Fig. 2. Calibration curve of loratadine when spiked in rat's blank plasma within the range of 10-500 ng/ml, r=0.9997.

Pharmacokinetic analysis

The plasma concentration data were analyzed by a non-compartmental method using WinNonlin software version 4.1 (Pharsight Co., Mountain View, CA, USA). The elimination rate constant (K_{el}) was calculated by a log-linear regression of loratadine concentration 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 a visual inspection of the data from 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 determined by C_{last}/K_{el}. The relative bioavailability (R.B.) was calculated by $AUC_{with\ hydrocortisone}/AUC_{control} \times 100$.

Statistical analysis

Results are given as means ± SD. Pharmacokinetic parameters were compared using one-way analysis of variance (ANOVA), followed by *a posteriori* testing using

Dunnett correction. p value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The mean plasma concentration-time profiles in rats for loratadine after oral administration (4 mg/kg) in the presence or absence of oral hydrocortisone (0.3 or 1.0 mg/kg) are shown in Fig. 3. The pharmacokinetic parameters for loratadine are summarized in Table I. Compared to the control group (without hydrocortisone), after oral administration of loratadine, the area under the plasma concentration-time curve (AUC) was significantly increased by 30.2-81.7% in the presence of hydrocortisone ($p < 0.05$).

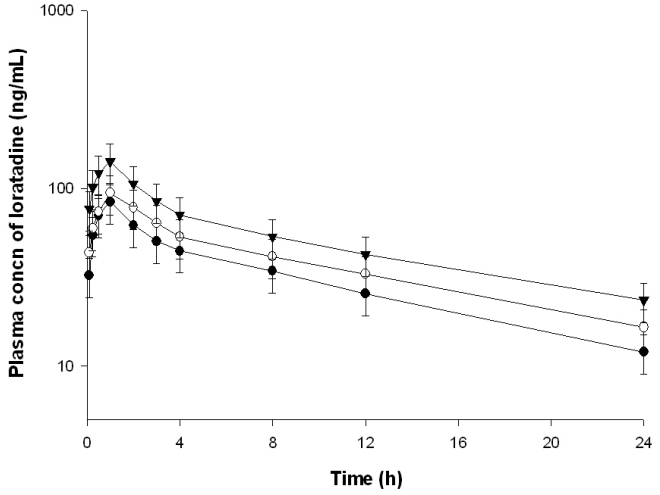

Fig. 3. Mean plasma concentration-time profiles of loratadine after oral administration (4 mg/kg) to rats with or without oral hydrocortisone (Mean ± S.D., n=6). ●: Control (loratadine 4 mg/kg), ○: with 0.3 mg/kg oral hydrocortisone, ▼: with 1.0 mg/kg oral hydrocortisone.

Table I. Pharmacokinetic parameters of loratadine after oral administration (4 mg/kg) to rats with or without oral hydrocortisone

Parameters	Loratadine (4 mg/kg)	With hydrocortisone	
		0.3 mg/kg	1.0 mg/kg
AUC (ng·h/ml)	924.2 ± 166.4	1,203.2 ± 240.6*	1,679.0 ± 369.4*
C_{max} (ng/ml)	84.2 ± 15.2	94.1 ± 24.8	141.8 ± 39.2*
T_{max} (h)	1.0 ± 0.5	0.8 ± 0.3	0.8 ± 0.3
$t_{1/2}$ (h)	10.6 ± 1.7	11.9 ± 2.4	12.8 ± 2.5*
R.B. (%)	100	130	182

Results are Means ± S.D., n=6. *$p < 0.05$ compared to the control (without hydrocortisone). AUC: area under the plasma concentration-time curve from 0 h to infinity, C_{max}: peak plasma concentration, T_{max}: time to reach C_{max}, $t_{1/2}$: terminal plasma half-life, R.B.: relative bioavailability.

The peak plasma concentration (C_{max}) was significantly increased by 68.4% in the presence of 1.0 mg/kg hydrocortisone after oral administration of loratadine ($p < 0.05$). Hydrocortisone (1.0 mg/kg) significantly increased the terminal plasma half-life ($t_{1/2}$) of loratadine by 20.8% ($p < 0.05$). Consequently, the relative bioavailability of loratadine was increased by 1.30- to 1.82-fold. However, there was no significant change for the time to reach the peak plasma concentration (T_{max}) of loratadine in the presence of hydrocortisone after oral administration.

The pharmacokinetic profiles for loratadine were also evaluated after intravenous administration (1 mg/kg) in the presence or absence of oral hydrocortisone (0.3 mg/kg and 1.0 mg/kg) as shown in Fig. 4. As summarized in Table II, hydrocortisone had no significant effects on the pharmacokinetic parameters for intravenous loratadine, although it had a significant effect on the bioavailability of lor-

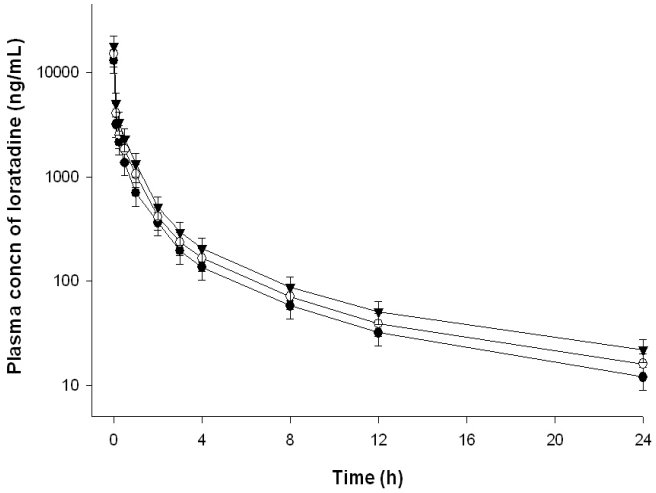

Fig. 4. Mean plasma concentration-time profiles of loratadine after intravenous administration (1 mg/kg) to rats with or without oral hydrocortisone (Mean ± S.D., n=6). ●: Control (loratadine 1 mg/kg), ○: with 0.3 mg/kg oral hydrocortisone, ▼: with 1.0 mg/kg oral hydrocortisone.

Table II. Pharmacokinetic parameters of loratadine after intravenous administration (1 mg/kg) to rats with or without oral hydrocortisone

Parameters	Loratadine (4 mg/kg)	With hydrocortisone	
		0.3 mg/kg	1.0 mg/kg
AUC (ng·h/ ml)	4,077 ± 933.9	5,126 ± 1,425.2	6,494 ± 1,728.7
CLt (ml/min·kg)	245.3 ± 57.2	195.1 ± 45.0	154.0 ± 43.9
$t_{1/2}$ (h)	6.0 ± 1.2	6.3 ± 1.5	6.6 ± 1.6

Results are Means ± S.D., n=6. AUC: area under the plasma concentration-time curve from 0 h to infinity, CL_t: total body clearance, $t_{1/2}$: terminal plasma half-life.

atadine given orally. This shows that hydrocortisone may improve the bioavailability of orally administered loratadine by increasing its absorption, or reducing its first-pass metabolism, in the intestine and liver.

Based on the broad overlap of their substrate specificities as well as their co-localizations in the small intestine, 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 enzymes 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).

It has been shown that loratadine is well absorbed, although it undergoes extensive first-pass metabolism in animals (Hilbert *et al*., 1987). Loratadine is a substrate for P-gp (Wang *et al*., 2001). As P-gp is co-localized with CYP3A4 in the small intestine and liver, P-gp and CYP3A4 can act synergistically during the absorption and first-pass metabolism of drugs (Pichard *et al*., 1990; Wacher *et al*., 1998; Ito *et al*., 1999). Hydrocortisone is also metabolized by CYP3A4 isoenzymes (El-Sankary *et al*., 2000; Gibson *et al*., 2002) and inhibits the efflux pump, P-gp (Nakayama *et al*., 1999; Yates *et al*., 2003). Thus, it might be expected that hydrocortisone would alter the absorption and metabolism of loratadine in rats.

The AUC was significantly increased by 30.2-81.7%, and the C_{max} was significantly increased by 68.4% in the presence of hydrocortisone after oral administration of loratadine. This resulted in a 1.30- to 1.82-fold increased relative bioavailability of loratadine. The enhanced bioavailability of loratidine may have been due to inhibition of both CYP 3A4-mediated metabolism and P-gp in the intestine and/or liver by the presence of hydrocortisone. This result was consistent with previous studies showing that single oral administration of cimetidine, clarithromycin or ketoconazole significantly increased the AUC and C_{max} of loratadine in rats by inhibition of CYP3A4 (Carr *et al*., 1998; Kosoglou *et al*., 2000). Overall, the presence of hydrocortisone significantly enhances the oral bioavailability of loratadine by increasing the intestinal absorption and reducing the first-pass metabolism of loratadine.

CONCLUSIONS

The presence of hydrocortisone significantly enhanced the bioavailability of orally administered loratadine in rats. The enhanced bioavailability of loratadine may be due to inhibition of both CYP 3A4-mediated metabolism and P-gp in the intestine and/or liver by the presence of hydrocortisone. If these results can be confirmed in clinical studies, the dosage of loratadine might be readjusted when used concomitantly with hydrocortisone for treatment of allergic diseases.

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