Pharmacokinetics of loratadine and its active metabolite descarboethoxyloratadine in healthy Chinese subjects[1]

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ABSTRACT

AIM: To investigate the pharmacokinetics of loratadine (LOR) and its active metabolite descarboethoxyloratadine (DCL) in healthy Chinese subjects. **METHODS:** Twenty healthy Chinese male subjects received a single oral dose of LOR 20 mg. A sensitive liquid chromatography-tandem mass spectrometry method (LC/MS/MS) was used for the determination of LOR and DCL in plasma. **RESULTS:** Mean maximum concentration (c_{max}) was found (17 ± 14) μg/L for LOR at 1.2 h and (16 ± 9) μg/L for DCL at 1.5 h. Mean area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was (47 ± 49) μg·h·L^{-1} for LOR and (181 ± 122) μg·h·L^{-1} for DCL, respectively. The apparent elimination half-life ($T_{1/2}$) of LOR was (6 ± 4) h, and that of DCL was (13.4 ± 2.6) h. The ratios of AUC_{DCL}/ AUC_{LOR} ranged from 0.36 to 54.5. **CONCLUSION:** LOR was rapidly absorbed and transformed to DCL. AUC of the parent drug was extremely variable, while AUC of the active metabolite DCL was moderately variable after an oral dose of LOR to Chinese subjects.

INTRODUCTION

Loratadine (LOR) is an orally active H_1 receptor antagonist. It has been widely used because of its efficacy in treating allergic disorders without significant central and autonomic nervous side effects such as sedation and anticholinergic properties[1]. Metabolic studies in man have demonstrated that this drug is rapidly absorbed but undergoes extensive first-pass metabolism. Descarboethoxyloratadine (DCL) is one of the main products of LOR metabolic transformation and has more pharmacological potencies than its parent drug[2,3].

CYP3A4 and CYP2D6 enzymes are responsible for the metabolism of LOR to DCL[4]. Pharmacokinetic studies of LOR and DCL in Caucasian have been reported[5-10]. However, no such reports in Chinese subjects have been found in the literature.

The current study was undertaken to evaluate the pharmacokinetics of LOR and its active metabolite DCL in plasma of healthy Chinese subjects using a liquid chromatography-tandem mass spectrometry method (LC/MS/MS).
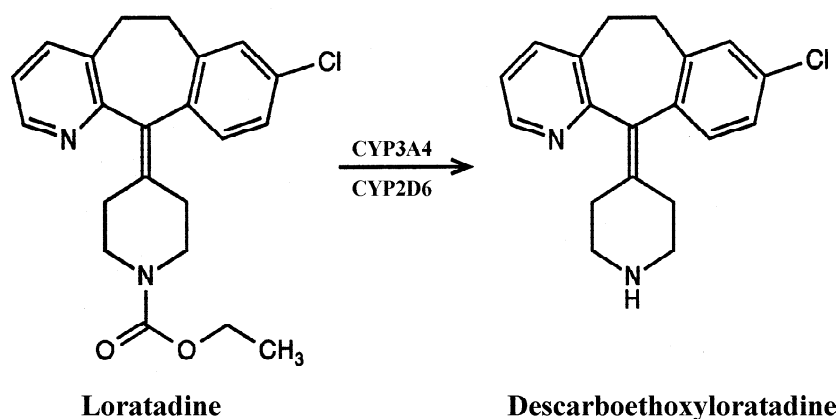
MATERIALS AND METHODS

Study design

Subjects Twenty healthy Chinese male subjects ranging in age from 21 to 24 a (22.5 a± 0.9 a), in weight from 55 to 73 kg (64.3 kg±0.8 kg), and in height from 168 to 185 cm (174 cm±5 cm) were enrolled in the

Loratadine   **Descarboethoxyloratadine**

study. Before enrollment, each subject was determined to be in good health through medical history, physical examination, electrocardiagrams (ECG), and routine laboratory tests. No medication was used for at least two weeks before the study and alcohol was forbidden within 72 h prior to drug administration. The study protocol followed the guidelines of the Helsinki Declaration (current revision) and was approved by the local Independent Ethic Committee. Written informed consent was obtained from each subject before the study.

Dosing procedure All participants were admitted to the Clinical Research Unit (People's Hospital of Liaoning Province) 12 h prior to drug administration. Following an overnight fast for at least 10 h, each subject received two tablets of Claritin (Schering-Plough, Shanghai) containing loratadine 20 mg with 240 mL mineral water and continued fasting for 2 h.

Collection of blood sample Blood samples were collected into heparinized tubes prior to the drug administration and at 0.33, 0.67, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 24.0, and 36.0 h after medication. Blood was immediately centrifuged for 15 min, the plasma was separated and frozen at -20 °C until assay.

Analysis of plasma samples

LC/MS/MS system A liquid chromatographic-tandem mass spectrometric method was established to determine LOR and DCL simultaneously in plasma[11]. A Shimadzu LC-10AD pump (Kyoto, Japan) was used. Chromatography was performed on a Zorbax SB-C8 column (partical size 5 μm, 150 mm×4.6 mm ID, HP Company, USA), using a mobile phase of acetonitrile–water–formic acid (75:25:15, v:v:v), The flow rate was 0.5 mL/min. A Finnigan TSQ™ triple quadrupole mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) source (San Jose, CA, USA) was used for mass analysis and detection. Quantitation

was performed using selected reaction monitoring (SRM) of the transitions m/z 383.1 → m/z 336.8 for LOR, m/z 310.9 → m/z 258.6 for DCL, and m/z 256 → m/z 166 for the internal standard (diphenhydramine), respectively. The collision energies of 30, 30, and 25 V were used for LOR, DCL, and the internal standard, respectively.

Preparation of plasma sample for LC/MS/MS analysis To a 1.0 mL aliquot of plasma were added 1 mL of water, 100 μL of the internal standard (diphenhydramine hydrochloride 400 μg/L), and sodium carbonate 100 μL of 1.0 mol/L. The sample was vortex-mixed and then extracted with 3 mL of ether-hexane (15:10, V/V). The organic layer was separated and evaporated to dryness at 40 °C under a gentle stream of the nitrogen. The residue was dissolved in 100 μL of the mobile phase, and vortex mixed. A 20-μL aliquot of the solution was injected into the LC/MS/MS system.

Analytical performance The calibration curves of LOR and DCL were both linear up to 20 μg/L, with a lower limit of quantitation at 0.2 μg/L. The typical r value was 0.9992 for LOR and 0.9995 for DCL, respectively. The intra-run precision was <8.9 % for LOR and <6.5 % for DCL, the inter-run precision for LOR and DCL was <14.2 %. The accuracy was within 1.2 % for LOR and 4.6 % for DCL, respectively. During routine analysis, each analytical run included a set of calibration samples, a set of quality control (QC) samples in duplicate and the unknowns.

Pharmacokinetic analysis The noncompartmental analysis was used in the data processing of both LOR and DCL. C_{max} and T_{max} were determined by inspection of the plasma concentration-time curves. k_e was determined by liner regression of the terminal linear portion of the concentration-time curve, and $T_{1/2}$ was calculated as $\ln(2)/k_e$. AUC was calculated by linear

trapezoidal rule. CL/F of LOR was calculated as $D/AUC_{0-\infty}$, D was the dose of LOR. V_d/F was calculated as $D/(k_e \times AUC_{0-\infty})$. The ratio of AUC_{DCL}/AUC_{LOR} was calculated as ($AUC_{0-\infty}$ of LOR/$AUC_{0-\infty}$ of DCL)×1.25, where 1.25 was the correction factor of the unequal molar concentration.

RESULTS AND DISCUSSION

The mean plasma concentration-time curves of LOR and its active metabolite DCL were shown in Fig 1. Their mean pharmacokinetic parameters and ranges were given in Tab 1.
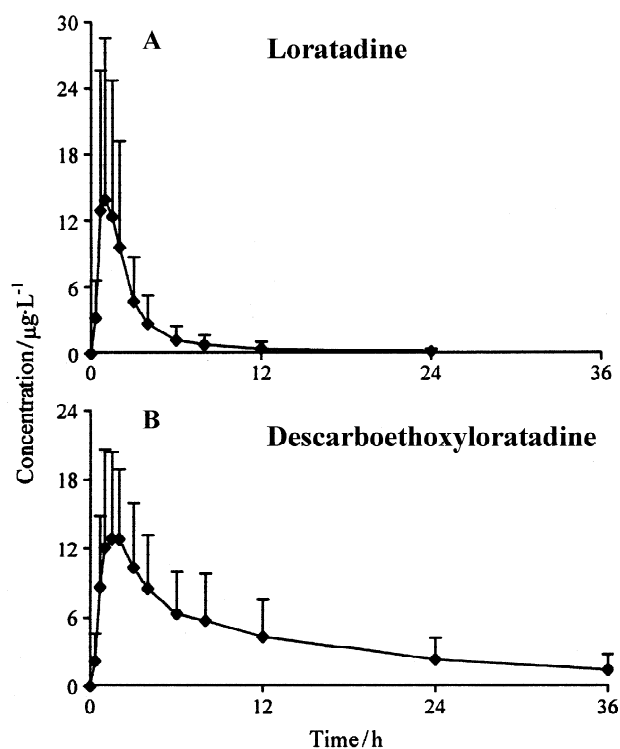

Fig 1. The mean plasma concentration-time curves of LOR (A) and DCL (B) after a single oral dose of LOR 20 mg in Chinese subjects. *n*=20. Mean±SD.

It was reported that the rapid absorption of LOR and formation of DCL were consistent with the onset of action within 1 h and their pharmacokinetic profiles further support a once-a-day dosage regimen in clinical use[9]. In this study, T_{max} values of LOR and DCL were 1.2 h and 1.5 h, mean AUC value of the DCL was about 4 times of that of the parent drug. Compared with the parent drug, DCL had the long $T_{1/2}$. These results were in agreement with the data reported for Caucasian[8,9]. Recent studies have demonstrated that DCL exhibits

Tab 1. Pharmacokinetic parameters of LOR and DCL after a single oral dose of LOR 20 mg in Chinese subjects. *n*= 20. Mean±SD.

Parameters	LOR	DCL
$C_{max}/\mu g \cdot L^{-1}$	17±14	16±9
	(4.1-53.7)	(3.7-30.4)
T_{max}/h	1.2±0.6	1.5±0.5
	(0.7-2.0)	(0.7-4.0)
$AUC_{0-\infty}/\mu g \cdot h \cdot L^{-1}$	47±49	181±122
	(8.2-187.6)	(22.4-483.6)
$T_{1/2}/h$	6±4	13.4±2.6
	(1.5-15.8)	(7.8-18.2)
$CL/F(mL \cdot kg^{-1} \cdot min^{-1})$	229±118	
	(28.3-623.9)	
$V_d/F(L \cdot kg^{-1})$	74±30	
	(36.8-133.7)	
AUC_{DCL}/AUC_{LOR}		12±17
		(0.36-54.5)

qualitatively the similar pharmacodynamic activity to its parent drug, but is 2.5-4 times more potent orally[2,3]. Therefore, the active metabolite DCL plays an important role on the sustained effect after administration of LOR.

It was reported that $T_{1/2}$ of LOR was about 11 h and that of the active metabolite DCL was about 18 h in Caucasian[8]. While in our study, mean values of $T_{1/2}$ of LOR and DCL were only 5.9 h and 13.4 h, respectively. We also found that the AUC and C_{max} for both LOR and DCL in Chinese were higher than those reported in Caucasian[8,9]. In Caucasian treated with the same dose of LOR, the mean AUC value was 34.4 $\mu g \cdot h \cdot L^{-1}$ for LOR and 141.7 $\mu g \cdot h \cdot L^{-1}$ for DCL. The mean C_{max} value was 10.8 $\mu g/L$ for LOR and 9.9 $\mu g/L$ for DCL, respectively[8]. In this study, the mean AUC value was 47.3 $\mu g \cdot h \cdot L^{-1}$ for the parent drug and 181 $\mu g \cdot h \cdot L^{-1}$ for the active metabolite. The mean C_{max} values of LOR and DCL were 16.6 $\mu g/L$ and 15.6 $\mu g/L$. These results indicated that LOR might be faster eliminated in Chinese than in Caucasian. According to these pharmacokinetic results, it would be recommended for LOR to be taken twice daily at a lower dose in Chinese.

In the present study, the parameters such as AUC, C_{max}, and $T_{1/2}$ of LOR were found extremely variable and the transformation extent of LOR to DCL also exhibited significant inter-individual variability. The ratios of AUC_{DCL}/AUC_{LOR} ranged from 0.36 to 54.5.

The remarkable inter-individual variability of LOR may be mainly due to its first-pass metabolism, as we can see in Tab 1 that the parameters of DCL are less variable than LOR. The pharmacokinetics of DCL was studied when it was given directly in another study[12]. In that case, a smaller inter-individual variability of AUC for DCL was observed than in the present study.

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