A Retrospective, Open-Label Analysis of the Population Pharmacokinetics of a Single 10-mg Dose of Loratadine in Healthy White Jordanian Male Volunteers

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ABSTRACT

Background: Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H₁-receptor antagonist activity. Loratadine 10-mg tablets have been reported to be rapidly absorbed after once-daily administration for 10 days in healthy adult subjects, with a Tₘₐₓ of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. The t₁/₂ in normal adult subjects has been reported to be 8.4 hours (range, 3–20 hours) for loratadine and 28 hours for its metabolite.

Objective: The aim of this study was to determine the population pharmacokinetics of loratadine after oral administration.

Methods: A retrospective analysis was conducted of prior noncompartmental analysis results from healthy white Jordanian male subjects who participated in 2 pharmacokinetic studies. After a 10-hour overnight fast, a single 10-mg loratadine tablet was administered orally followed by 240 mL of water. Blood samples were collected before dosing and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dosing. Mean and population plasma level profiles were examined. The calculated primary and secondary pharmacokinetic parameters were Vd/F, kᵣ, absorption rate constant, lag time, distribution rate constant, redistribution rate constant, Tmax, and Cmax.

Results: A total of 72 healthy male subjects with a mean (SD) age of 23 (3.57) years participated in the 2 studies. The analytical method was linear over the concentration range from 0.10 to 20.00 ng/mL (r > 0.999). The lower limit of quantitation was 0.1 ng/mL with 95% accuracy. Precision, expressed as %CV, was 7.44%. Intraday accuracy ranged from 91.9% to 97.2% at high and low quality control levels, respectively. Interday accuracy ranged from 93.57% (%CV, 4.35%) to 98.78% (%CV, 5.78%), respectively. Population kᵣ, t₁/₂, absorption rate constant, and absorption t₁/₂ were 0.19 hour⁻¹, 3.65 hours, 1.31 hours⁻¹, and 0.53 hour, respectively. Distribution rate constant, redistribution rate constant, and lag time were 0.31 hour⁻¹, 0.02 hour⁻¹, and 0.32 hour, respectively. The noncompartmental estimate for Cmax was 3.02 ng/mL, which occurred at 1.30 hours, with a t₁/₂ of 5 hours and a kᵣ of 0.14 hour⁻¹. No adverse events were recorded during the study.

Conclusion: The population t₁/₂ for loratadine was 3.65 hours in this group of healthy white Jordanian male volunteers, shorter than that observed in previous research. (Clin Ther. 2010;32:391–395) © 2010 Excerpta Medica Inc.

Key words: population, pharmacokinetics, loratadine, half-life, HPLC-MS/MS.

INTRODUCTION

Loratadine is a long-acting tricyclic antihistamine with selective peripheral histamine H₁-receptor antagonist activity. Loratadine 10-mg tablets have been reported to be rapidly absorbed after once-daily administration for 10 days in healthy adult subjects, with a Tₘₐₓ of 1.3 hours for loratadine and 2.5 hours for its major active metabolite, descarboethoxyloratadine. The pharmacokinetics of loratadine and its metabolite are dose independent over the dose range from 10 to 40 mg.1–3 It has been reported that ~80% of the total loratadine dose is equally distributed between urine and feces in the form of metabolic products within 10 days.1–4 Exposure to the metabolite is greater than exposure to the parent compound. The t₁/₂ in normal adult subjects has been reported to be 8.4 hours (range, 3–20 hours) for loratadine and 28 hours for its
metabolite.\textsuperscript{1–3} Hilbert et al\textsuperscript{4} conducted a 3-way crossover study of loratadine in healthy volunteers and reported that the loratadine t\textsubscript{1/2} ranged from 4.2 to 36.3 hours. These authors used a radioimmunoassay with a lower limit of quantitation (LLOQ) of 0.3 ng/mL.

Variability in loratadine pharmacokinetic data has been observed in published studies of loratadine tablets and syrup, possibly because of the drug’s extensive first-pass metabolism.\textsuperscript{1–4} The authors of the present study have conducted unpublished pharmacokinetic research in humans after oral dosing of loratadine at the International Pharmaceutical Research Center (IPRC) in Amman, Jordan. In these studies, the calculated t\textsubscript{1/2} was observed to be shorter than that previously reported for this drug.

Through 2009, no detailed data analysis of loratadine on population pharmacokinetics has been published. This was confirmed by a search of MEDLINE using several combinations of the terms loratadine, pharmacokinetics, and population. The search covered up to 2009. The population pharmacokinetic approach is used to obtain integrated information on pharmacokinetics.\textsuperscript{5} It also allows the analysis of data from a variety of unbalanced designs, as well as data from studies that may otherwise be excluded because they do not lend themselves to the usual forms of pharmacokinetic analysis, such as concentration data obtained from pediatric and elderly patients, or data obtained from evaluation of the relationships between dose and concentration or efficacy and tolerability.

Therefore, the objective of the present study was to determine the population pharmacokinetics of loratadine by simultaneous data-fitting of prior noncompartmental analysis results from 72 subjects who participated in 2 pharmacokinetic studies. The parameters k\textsubscript{e}, T\textsubscript{max}, and C\textsubscript{max} were compared with the population analysis.

SUBJECTS AND METHODS
Healthy white Jordanian male subjects gave written informed consent to participate in the 2 studies before screening. The studies were approved by the Institutional Review Board at IPRC and were performed in accordance with the Good Clinical Practice guideline and the Declaration of Helsinki.

Subjects
Male volunteers included in the 2 pharmacokinetic studies were within 15% of their ideal body weight and were judged to be healthy based on medical history, physical examination, complete blood count, serum chemistry, and lack of hepatic, renal, respiratory, cardiac, or gastrointestinal conditions. In both studies, no subjects took any medication, including over-the-counter drugs, for 7 days before the study. Subjects were negative for HIV, hepatitis B and C viruses, and the presence of illegal drugs. The subjects did not participate in any other clinical study, donate blood, or require hospitalization within 3 months before initiation of both studies. The subjects were under continuous medical observation by the investigators and attending physicians during both studies.

Follow-up medical testing (vital signs, physical examination, ECG, biochemistry, hematology, and urinalysis) was conducted on all volunteers at discharge from both studies, and the subjects were questioned about adverse events by the investigators.

Drugs and Reagents
Loratadine 10-mg tablets (batch #00A1101, expiration date, January 2003; batch #32007, expiration date, April 2003\textsuperscript{*}) were purchased from local suppliers. Chemicals and reagents (eg, acetonitrile, methanol, formic acid) were all analytical grade for HPLC use. Water was purified using a Milli-Q integral water purification system (Millipore S.A.S., Molshiem, France). Six batches of lithium heparin plasma were obtained from healthy blood donors who were HIV and hepatitis B and C negative.

Experimental and Assay Procedures
In both studies, after a 10-hour overnight fast, a single 10-mg loratadine tablet was administered orally followed by 240 mL of water. Blood samples (7 mL) were collected in heparinized tubes from an indwelling catheter in the antecubital vein of the forearm before dosing and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours after dosing. Blood samples were centrifuged for 5 minutes at 1789 g and stored at –20°C until analysis.

Plasma samples were analyzed at IPRC using a validated HPLC-MS/MS method.\textsuperscript{6} The method was modified by readjusting the mobile phase composition, and consisted of liquid–liquid extraction and separation on a reverse-phase C\textsubscript{18} analytical column. Electrospray ionization in the positive mode was used to ionize the analytes. Chromatograms were extracted at 383.11 >
337.20 m/z. The HPLC-MS/MS method was validated according to the US Food and Drug Administration’s bioanalytic method validation guidance.7

Data Analysis

A 2-compartment model was employed for population data-fitting using 6 parameters: Vd/F, k, absorption rate constant (k01), lag time, distribution rate constant (k12), and redistribution rate constant (k21). A modified Gauss-Marquardt algorithm was used under uniform weighting and the Marquardt algorithm converged after 12 iterations. In addition, a noncompartmental analysis was performed for each subject, and the parameters k, Tmax, and Cmax were reported for comparisons.

Model Building

The criteria used for model building included examination of the fitted curves, improvement in objective function, improvement in residual plots, and statistical tests including the Akaike criterion, the Schwarz criterion, and the log-likelihood test.8–10 No further assumptions were used.

Population and Noncompartmental Analysis

In this retrospective analysis of prior noncompartmental analysis results, simultaneous data-fitting was conducted using Kinetta version 4.1 (Thermo Electron Corporation, Waltham, Massachusetts). Kinetta is a software package for population pharmacokinetic analysis that uses an expectation-maximization (EM) algorithm to conduct nonlinear mixed-effect model analysis. The EM algorithm is an iterative procedure developed for finding maximum likelihood estimates for incomplete data. This is a 2-step algorithm comprised of an E-step (expectation) and an M-step (maximization). The E-step uses current values for parameter estimates to obtain the expectation of individual parameters conditioned by the observed data vector. The M-step obtains the maximum likelihood posterior population mean and variance together with the residual error variance, given the individual parameter values. Further applications of this algorithm are possible in linear mixed-effect models with fewer assumptions in the variance models and either maximum likelihood or restricted maximum likelihood estimation.

The individual parameters in the model were estimated assuming that they had known prior and residual error distributions. Then, posterior population mean and variance were computed. The evaluation graphs in the software enabled evaluation of the distribution of computed parameters and the residual error, weighting schemes, and prediction of the individual and population profiles, with the option to display the CI. We estimated the expected individual parameters given the population’s estimated values, and then computed the appropriate statistical tests to evaluate the distribution properties of the differences between the expected and observed data.

RESULTS

Seventy-two healthy male subjects (36 in each of the 2 studies) with a mean (SD) age of 23 (3.57) years were included in this analysis. The analytical method was linear over the concentration range from 0.10 to 20.00 ng/mL (r > 0.999). The LLOQ was 0.1 ng/mL with 95% accuracy. Precision, expressed as %CV, was 7.44%. Intraday accuracy ranged from 91.9% to 97.2% at high and low quality control levels, respectively. Interday accuracy ranged from 93.57% (%CV, 4.35%) to 98.78% (%CV, 5.78%).

None of the subjects had clinically relevant changes in vital signs after administration of the study drug. No adverse events were recorded during the studies.

Population and noncompartmental parameter estimates are summarized in the Table. Mean and popula-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Value</th>
<th>Noncompartmental Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ke, h⁻¹</td>
<td>0.19 (72)</td>
<td>0.14 (44)</td>
</tr>
<tr>
<td>t1/2, h*</td>
<td>3.65</td>
<td>5.0</td>
</tr>
<tr>
<td>k12, h⁻¹</td>
<td>0.31 (241)</td>
<td>–</td>
</tr>
<tr>
<td>k21, h⁻¹</td>
<td>0.02 (81)</td>
<td>–</td>
</tr>
<tr>
<td>Cmax, ng/mL</td>
<td>–</td>
<td>3.02 (96)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>–</td>
<td>1.30 (55)</td>
</tr>
<tr>
<td>Vd/F, L</td>
<td>2147 (0.03)</td>
<td>–</td>
</tr>
<tr>
<td>k01, h⁻¹</td>
<td>1.31 (116)</td>
<td>–</td>
</tr>
<tr>
<td>Absorption</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>t1/2, h*</td>
<td>0.53</td>
<td>–</td>
</tr>
<tr>
<td>Lag time, h</td>
<td>0.32 (19)</td>
<td>–</td>
</tr>
</tbody>
</table>

k12 = distribution rate constant; k21 = redistribution rate constant; k01 = absorption rate constant.

* t1/2 values were calculated using the formula: 0.693/k.

† Cmax and Tmax values were determined directly from each subject profile.
DISCUSSION

The population pharmacokinetics of loratadine were evaluated by simultaneous fitting of data from 72 healthy white Jordanian men who participated in 2 pharmacokinetic studies. The goodness-of-fit figures suggest that residuals were of random and homogeneous dis-

![Figure](image_url)

Figure. (A) Mean plasma concentration–time curve and (B) output curve of all individual data for plasma concentrations (Kinetica version 4.1, Thermo Electron Corporation, Waltham, Massachusetts) after 10-mg oral dose in healthy white Jordanian male volunteers (N = 72).
tribution up to the C\textsubscript{max} of 3.02 ng/mL. Calculated and observed points were well correlated with each other up to the C\textsubscript{max}. This indicates acceptable data-fitting and model choice. The large V\textsubscript{d}/F indicates wide tissue distribution, which again supports the choice of a 2-compartment model.

As shown in the table, the estimates of all parameters were in agreement with the noncompartmental analysis results presented. The variability, as indicated by population %CV, was generally >30%. The t\textsubscript{1/2} for loratadine ranged from 3.65 to 5 hours, shorter than the 7.8 to 11 hours previously reported in other studies.\textsuperscript{1–4}

However, the large k\textsubscript{01} and small lag-time estimates were in agreement with the small T\textsubscript{max} value, which was similar to the previously reported T\textsubscript{max} of 1.5 hours.\textsuperscript{1–4}

A limitation of this study is that population parameter estimates were limited to white Jordanian male volunteers. More volunteers from different national groups should be included to account for possible ethnic differences in future studies.

**CONCLUSION**
In the present study conducted in healthy white Jordanian male volunteers, the population t\textsubscript{1/2} for loratadine was found to be 3.65 hours, which was shorter than that observed in previous research.

**ACKNOWLEDGMENTS**
The authors wish to thank the staff pharmacists, chemists, nurses, and technicians at IPRC for their help and cooperation. The authors have indicated that they have no conflicts of interest regarding the content of this article.

**REFERENCES**


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