Effect of *CYP2D6*10 allele on the pharmacokinetics of loratadine in Chinese subjects

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Running title: loratadine and CYP2D6 polymorphism

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Number of text pages: 15
Number of figures: 2
Number of tables: 2
Number of references: 34
Number of words: Abstract (245), Introduction (512), Discussion (703)
ABSTRACT

Loratadine is known to be a substrate for both CYP3A4 and CYP2D6 based on a previous in vitro study. In view of the large inter-individual variability in loratadine pharmacokinetics and the greater genetically-determined variability of CYP2D6 activity than CYP3A4 in vivo, we hypothesized that CYP2D6 polymorphisms may contribute to the pharmacokinetic variability of loratadine. The purpose of this study was to evaluate the effect of CYP2D6 genotype (specifically the CYP2D6*10 allele) on the pharmacokinetics of loratadine in Chinese subjects. Three groups of healthy male Chinese subjects were enrolled: group I, homozygous CYP2D6*1 (*1/*1, n=4); group II, heterozygous CYP2D6*10 (*1/*10 or *2/*10, n=6); and group III, homozygous CYP2D6*10 (*10/*10, n=7) carriers. Each subject received a single oral dose of 20 mg loratadine under fasting conditions. Multiple blood samples were collected over 48 h, and the plasma concentrations of loratadine and its metabolite desloratadine were determined by HPLC. In comparing homozygous CYP2D6*10 (group III) to heterozygous CYP2D6*10 (group II) to homozygous CYP2D6*1 (group I) subjects, loratadine oral clearance values were 7.17 ± 2.54 vs 11.06 ± 1.70 vs 14.59 ± 2.43 L/h/kg respectively (one-way ANOVA, p<0.01), and the corresponding metabolic ratios (AUCdesloratadine/AUCloratadine) were 1.55 ± 0.73 vs 2.47 ± 0.46 vs 3.32 ± 0.49 respectively (one-way ANOVA, p<0.05), indicating a gene-dose effect. The results demonstrated that CYP2D6 polymorphism prevalent in the Chinese population significantly affected loratadine pharmacokinetics.
INTRODUCTION

Loratadine, a long-acting tricyclic antihistamine, undergoes extensive first-pass metabolism in the liver to form its major metabolite desloratadine, which also possesses antihistamine activity and is subject to further metabolism (Katchen et al., 1985). The pharmacokinetics of loratadine manifest large inter-individual variability. Previous studies in healthy Caucasian subjects showed that the disposition of loratadine varied 6-11 fold among individuals receiving equal doses (oral clearance ranged from 5.3-31.5 L/h/kg and elimination half-life ranged from 1.5-16.6 h) (Radwanski et al., 1987; Matzke et al., 1990). The variability has recently been shown to be even greater in Chinese subjects, using the metabolic ratio of desloratadine to loratadine (range 0.36 to 54.4) (Zhang et al., 2003).

The metabolism of loratadine to desloratadine is mediated via CYP3A4, and to a lesser extent via CYP2D6, based on a previous in vitro study (Yumibe et al., 1996). However, by incubating loratadine with various cDNA-expressed human microsomes, the catalytic formation rate was shown to be approximately 5-fold greater in cDNA-expressed CYP2D6 than CYP3A4 (Yumibe et al., 1996). Genetic polymorphisms have been well documented for CYP2D6. The frequency of CYP2D6 poor metabolizer (PM) phenotype is much higher in Caucasians (7-10%) than in Asian populations (<1%) including Chinese, Japanese and Koreans (Alvan et al., 1990; Bertilsson L et al., 1992; Nakamura et al., 1985; Sohn et al., 1991). Three mutated alleles, CYP2D6*3, CYP2D6*4 and
*CYP2D6*5 accounted for 93-98% of the PMs in Caucasians (Gaedigk et al., 1999), but in Asian subjects *CYP2D6*3 and *CYP2D6*4 are mostly absent and the frequency of the *CYP2D6*5 allele is only about 5%. On the other hand, the mean CYP2D6 activity of the so-called extensive metabolizer (EM) phenotype in Asian subjects is lower than that observed in Caucasians. This has been shown to be due to the high frequency of the *CYP2D6*10 allele (C100>T mutation resulting in a Pro34→Ser amino acid substitution and the formation of an unstable enzyme with decreased CYP2D6 activity) which occurs in approximately 50% of Asian subjects but is extremely uncommon in Caucasians (Wang et al., 1993; Johansson et al., 1994).

Although CYP3A4 activity varies considerably between individuals, polymorphisms for this isozyme have not been well characterized and current data are inconsistent. A number of variant alleles, such as *CYP3A4*1B, *1B* and *3* have been identified to occur in Caucasian at frequencies of 9%, 2.8% and 2.2% respectively, but are absent in Chinese subjects (Walker et al., 1998; Sata et al., 2000; Ven Schaik et al., 2001). Several Asian-specific alleles, i.e. *CYP3A4*4, *5*, *6*, *18* and *19* have also been reported in recent studies with frequencies of 1-3% (Hsieh et al., 2001; Dai et al., 2001). However, the in vivo functions of these alleles are uncertain at present (Eiselt et al., 2001). Based on current information, the clinical importance of CYP3A4 polymorphism is not likely for the majority of the general population.

In view of the greater polymorphic variability of CYP2D6 activity than CYP3A4 in vivo, we hypothesized that the CYP2D6 polymorphisms may substantially contribute to the
pharmacokinetic variability of loratadine \textit{in vivo}. Since there is high frequency of the \textit{CYP2D6*10} allele as well as larger variability of loratadine metabolic ratio observed in Chinese populations, we carried out this study to investigate whether the variability in loratadine pharmacokinetics is related to \textit{CYP2D6*10} allele.
METHODS

Subjects

The study protocol was approved by the local Clinical Research Ethics Committee. Written informed consent was obtained from each subject before participating in the study.

All subjects underwent a pre-study genotype screening for CYP2D6. Those who had CYP2D6*5 allele or CYP2D6 duplicated gene copies were excluded since the number of such carriers was too small to form separate groups. Seventeen healthy male Chinese subjects aged 21 to 26 years (mean ± SD, 22.6 ± 1.4 years) weight 55.3 to 70.6 kg (mean ± SD, 60.9 ± 4.5 kg) were recruited from a pool of 65 subjects who underwent CYP2D6 genotype screening, and classified into three genotype groups: Group I, homozygous CYP2D6*1 (*1/*1); Group II, heterozygous CYP2D6*10 (*1/*10 or *2/*10); and Group III, homozygous CYP2D6*10 (*10/*10) carriers. Since CYP2D6*2 allele is not associated with decreased CYP2D6 activity as compared to CYP2D6*1 allele (Tateishi T et al., 1999), subjects with CYP2D6*1/*10 and CYP2D6*2/*10 genotypes are combined in one group for this study. The demographic characteristics of the study subjects are shown in Table 1.

The subjects were all non-smokers and in good health as determined from their medical history, physical examination, ECG evaluation and routine laboratory tests (blood
chemistry, hematology and urine analysis). All subjects were required not to take any prescription or nonprescription medication 2 weeks before and throughout the study. They were instructed to abstain from grapefruit, grapefruit juice, herbal dietary supplements, and caffeine-containing beverages including coffee and green tea 3 days before the study and during the study period.

**CYP2D6 genotyping**

A 10-ml blood sample was obtained from each subject and DNA was isolated using an extraction kit (QIAamp Blood Mini Kit, Qiagen). The following CYP2D6 alleles were identified using polymerase chain reaction (PCR): \( CYP2D6^*1, *2, *5, *10A \) and \( *10B \). These mutated alleles \( (*5, *10) \) and the wild-type \( (*1, *2) \) constituted the predominant alleles in the Chinese population based on the previous studies reported in the literature (Dahl et al., 1995; Johansson et al., 1994; Garcia-Barcelo et al., 2000). The \( CYP2D6^*5 \) allele was detected using long PCR with two primer sets, 2D6-F/-R and 2D6*5-F/-R, as described previously (Steen et al., 1995). The \( CYP2D6^*10 \) allele was identified with use of a two-step PCR analysis according to the method by Johansson et al (Johansson et al., 1994).

**Loratadine pharmacokinetic study**

After an overnight fast of 10 h, subject received a single oral dose of 20 mg loratadine (2×10 mg Clarityne tablet, Schering-Plough Labo N.V.) with 240 ml of water. Standardized meals were served 4 and 10 h after dosing. Venous blood samples were
collected at pre-dose (0 h) and at 0.33, 0.67, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48 h post dosing. All blood samples were collected in lithium heparin tubes and centrifuged immediately. Separated plasma samples were stored at –80°C until analysis.

**Determination of loratadine and its metabolite in plasma**

Plasma concentrations of loratadine and desloratadine were determined by an HPLC method developed in our laboratory (Yin et al., 2003). Briefly, both loratadine and desloratadine together with their internal standard (propranolol hydrochloride) were extracted from plasma using a two-step liquid-liquid extraction with toluene. The analytes were then separated on a C18 column with a gradient mobile phase consisting of methanol-acetonitrile-phosphate buffer. Fluorescence detection was performed at an excitation wavelength of 290 nm and an emission wavelength of 480 nm. The coefficient of variation of intra- and inter-day assay was <8.3%, with accuracy ranging from 98.3% to 105.7%. The lower limit of quantification was 0.5 ng/ml for both loratadine and desloratadine.

**Pharmacokinetic Analysis**

Pharmacokinetic parameters of loratadine and desloratadine were calculated using the non-compartmental method (Gibaldi and Perrier 1982), with the aid of WinNolin program (version 2.1, Pharsight Corp.). Peak plasma concentrations (Cmax) of loratadine and desloratadine were obtained directly from the observed concentration-time data. The terminal elimination rate constant (λZ) was estimated by linear regression of the terminal
portion of the concentration-time curve, and the elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_Z$. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule, and extrapolated to infinity. The apparent oral clearance (CL/F) of loratadine was calculated as Dose/AUC, and its metabolic ratio (MR) was calculated as the ratio of AUC_{desloratadine} to AUC_{loratadine}.

**Statistical Analysis**

All data from the study were expressed as mean ± SD. To evaluate the effect of CYP2D6 genotype on the pharmacokinetics of loratadine, the pharmacokinetic parameters of loratadine and desloratadine among different genotype groups were compared using one-way ANOVA with Scheffe’s multiple comparison tests. The relationship between the number of $CYP2D6^{*10}$ allele versus loratadine CL/F or MR was assessed using Spearman’s rank correlation coefficient ($r_s$). A $p$ value of <0.05 was considered statistically significant for all tests. All analyses were performed with the SPSS software (version 11.5, SPSS Inc.).
RESULTS

All subjects completed the study without clinically important adverse effects. The mean plasma concentration-time profiles of loratadine and desloratadine in relation to different CYP2D6 genotypes are shown in Figure 1A and 1B, respectively. The plasma concentrations of loratadine were much higher in the homozygous CYP2D6*10 group compared to the other two groups. In homozygous CYP2D6*10 carriers (group III), the values for the area under the plasma concentration-time curve (AUC) of loratadine were 75.5% and 123.6% higher (p<0.05) and apparent oral clearance (CL/F) 35.2% and 50.9% lower (p<0.01) compared to the heterozygous CYP2D6*10 (group II) and homozygous CYP2D6*1 (group I) subjects respectively (Table 2). The elimination half-life (t_{1/2}) of loratadine also tended to be greater in the homozygous CYP2D6*10 group (10.32 versus 4.12 and 4.11 h), however, the difference was not statistically significant, possibly due to the large variations among homozygous CYP2D6*10 subjects as well as the small number of subjects included (Table 2).

Loratadine oral clearance tended to be lower in heterozygous CYP2D6*10 (group II) subjects than in homozygous CYP2D6*1 subjects (Group I), but this difference did not reach statistical significance (p=0.085). No significant differences were observed in the other pharmacokinetic parameters of loratadine between these two groups.

There were also no significant differences in the plasma concentrations or pharmacokinetic parameters of desloratadine among the three genotype groups (Figure
1B, Table 2). The AUC values of desloratadine were similar, with mean values of 78.15 ± 14.95, 84.94 ± 11.56 and 94.39 ± 29.42 ng•h/ml in the homozygous *CYP2D6*1, heterozygous *CYP2D6*10 and homozygous *CYP2D6*10 groups, respectively (p>0.05, one-way ANOVA). When comparing group III (homozygous *CYP2D6*10) to group II (heterozygous *CYP2D6*10) or group I (homozygous *CYP2D6*1) subjects, the metabolic ratio (MR) values of loratadine were lowered by 37.2% (p<0.05) and 114.2% (p<0.01) respectively.

The effects of the number of *CYP2D6*10 alleles in relation to the individual loratadine CL/F and MR values are shown in Figure 2. Despite some overlap between values shown in the three groups, significant correlations between the number of *CYP2D6*10 alleles versus loratadine CL/F or MR were observed indicating a gene-dose effect (Spearman correlation coefficient $r_s = -0.84$ and $-0.80$ respectively, both $p<0.001$).
DISCUSSION

In this study, the metabolic ratio of loratadine was significantly decreased in subjects with *CYP2D6*/*10/*10 genotype in comparison to the wild-type or heterozygotes of *CYP2D6*/*10. These results suggest the presence of CYP2D6 genotype-dependent pharmacokinetics of loratadine in Chinese subjects.

To our knowledge, this is the first report on CYP2D6 genotype-dependent pharmacokinetics of loratadine in humans. Previous *in vitro* study on loratadine metabolism demonstrated that desloratadine formation in human liver microsomes was highly correlated with testosterone 6β-hydroxylation, a CYP3A-mediated reaction (Yumibe et al., 1996), suggesting that loratadine is metabolized to desloratdine primarily by CYP3A. However, the same authors also showed that the formation rate of desloratadine was almost 5-fold greater in c-DNA expressed CYP2D6 than CYP3A4 (Yumibe et al., 1996). Since these data were obtained from *in vitro* studies which do not necessarily reflect *in vivo* conditions, the relative contribution of CYP2D6 versus CYP3A4 towards the metabolism of loratadine *in vivo* need to be clarified and determined in human subjects.

A similar observation on the relationship of *CYP2D6*/*10 genotype to the pharmacokinetics of another drug (haloperidol) has also been reported in Asian subjects (Mihara et al., 1999; Roh et al., 2001), despite *in vitro* studies indicating CYP3A4 rather than CYP2D6 as the main isozyme involved in biotransformation of the drug (Fang et al.,
1997; Pan et al., 1999). Thus our present study together with the previous work (Mihara et al., 1999; Roh et al., 2001) suggest that the data from in vitro studies (presumably from pooled liver microsomes of Caucasians) cannot be directly extrapolated to in vivo situations, especially in different populations. This may be particularly important for CYP2D6, which manifests large inter-ethnic differences in its polymorphisms with a higher frequency of CYP2D6*10 mutant alleles in Chinese subjects.

Loratadine has also been shown to be a substrate of P-glycoprotein (Wand et al., 2001). Thus the variability in loratadine oral clearance could be influenced not only by its metabolic pathway but also by absorption or transport via P-glycoprotein. In our study, we have observed a significant effect of CYP2D6 genotype on loratadine oral clearance and its metabolic ratio (AUCdesloratadine/AUCloratadine). Based on the metabolic kinetics, the metabolic ratio is directly proportional to the formation clearance and inversely proportional to the elimination clearance of the metabolite (representing enzyme activity), and should not be affected by drug absorption (see Appendix). Thus the observed consistent relationship between CYP2D6 genotype versus loratadine oral clearance or metabolic ratio indicates that the variability in the oral clearance is largely related to metabolic activity which is CYP2D6*10 genotype dependent.

Whilst the loratadine clearance and metabolic ratio differ among different CYP2D6 genotypes, the plasma concentrations of desloratadine were not significantly different among the three groups, although there was a trend of increasing desloratadine concentrations in subjects with one or two CYP2D6*10 alleles. This is in contrast to our
expectation as majority of loratadine (60-70%) has been reported to be converted to desloratadine \textit{in vivo} (Katchen et al., 1985), and different metabolic activity should result in different desloratadine concentrations. We believe that the lack of significant difference in the concentrations of desloratadine among different CYP2D6 genotype groups could be attributed to the following reasons: (1) Desloratadine has been shown to be highly metabolized in the liver to form several hydroxylated metabolites, which in turn are glucuronidated (Geha and Meltzer 2001). The inter-relationship of the formation of desloratadine and its further metabolism could have resulted in the lack of difference in the plasma desloratadine concentrations among different CYP2D6 genotype groups. This has been confirmed by our additional pharmacokinetic simulation studies, which generated similar desloratadine concentrations when using variations in the formation rate (CYP2D6 activity) and elimination rate of desloratadine (using the equations shown in Appendix). (2) Loratadine may have been metabolized \textit{via} CYP2D6 to a metabolite other than desloratadine. This is consistent with the observation that co-administration of desloratadine with a potent inhibitor of CYP2D6 (fluoxetine) did not cause significant changes in the plasma concentrations of desloratadine (Gupta et al., 2004).

In this \textit{in vivo} study, we did not evaluate the effect of CYP3A4 polymorphisms, due to the relatively low prevalence of the mutant alleles in Chinese populations as well as their uncertain function \textit{in vivo}. Previous studies showed that CYP3A4 inhibitors such as clarithromycin (Carr et al., 1998), erythromycin (Brannan et al., 1995) and ketoconazole (Kosoglou et al., 2000) significantly increased the plasma concentrations of loratadine. These data indirectly suggested a significant \textit{in vivo} involvement of CYP3A4 in
loratadine metabolism. However, these studies were conducted in US populations in which the CYP2D6 genotypes of the study subjects were not specified, and the influence by CYP2D6 polymorphism in the presence of CYP3A4 inhibitors have not been studied. Further studies are needed to determine the contribution of CYP3A4 relative to CYP2D6 for loratadine in different ethnic groups with or without inhibitors.

In conclusion, the common CYP2D6 polymorphism present in Chinese populations significantly affected the pharmacokinetics of loratadine. Such observation indicates that CYP2D6 genotype could influence the pharmacokinetics of drugs for which CYP2D6 is not the primary pathway of elimination.
ACKNOWLEDGEMENT

We would like to thank Ms. Evelyn Chau and Ms. Emily Poon for their valuable technical assistance in this investigation.
REFERENCES


FOOTNOTES

This study was supported in part by grant ITS/174/00 from the Innovation and Technology Commission of the Government of Hong Kong SAR.

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LEGENDS FOR FIGURES

Figure 1 Mean plasma concentration-time profiles of loratadine (A) and desloratadine (B) after a single oral administration of 20 mg loratadine in subjects with different CYP2D6 genotypes.

Figure 2 (A) Relationship between loratadine oral clearance and the number of CYP2D6*10 alleles ($r_s=-0.84$, $p<0.001$)

(B) Relationship between loratadine metabolic ratio and the number of CYP2D6*10 alleles ($r_s=-0.80$, $p<0.001$)

n=0, 1 and 2 for homozygous CYP2D6*1, heterozygous CYP2D6*10 and homozygous CYP2D6*10 subjects respectively.
<table>
<thead>
<tr>
<th></th>
<th>Homozygous</th>
<th>Heterozygous</th>
<th>Homozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$CYP2D6^*1$</td>
<td>$CYP2D6^*10$</td>
<td>$CYP2D6^*10$</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>22.5 ± 1.9</td>
<td>22.0 ± 0.9</td>
<td>23.1 ± 1.4</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>59.7 ± 4.0</td>
<td>62.7 ± 4.4</td>
<td>60.0 ± 5.1</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>*1/*1, n=4</td>
<td>*1/*10, n=4</td>
<td>*10/*10, n=7</td>
</tr>
<tr>
<td></td>
<td>*2/*10, n=2</td>
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<td></td>
</tr>
</tbody>
</table>
Table II Pharmacokinetic parameters of loratadine and desloratadine in different CYP2D6 genotypes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Genotype group</th>
<th>Multiple comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Homozygous</td>
<td>Heterozygous</td>
</tr>
<tr>
<td></td>
<td>CYP2D6*1 (Group I, n=4)</td>
<td>CYP2D6*10 (Group II, n=6)</td>
</tr>
<tr>
<td>Loratadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>6.57 ± 3.10</td>
<td>9.06 ± 5.98</td>
</tr>
<tr>
<td>AUC (ng·h/ml)</td>
<td>23.40 ± 3.11</td>
<td>29.81 ± 6.88</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>4.11 ± 1.13</td>
<td>4.12 ± 1.59</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>14.59 ± 2.43</td>
<td>11.06 ± 1.70</td>
</tr>
<tr>
<td>Desloratadine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>5.12 ± 1.92</td>
<td>6.14 ± 1.60</td>
</tr>
<tr>
<td>AUC (ng·h/ml)</td>
<td>78.15 ± 14.95</td>
<td>84.94 ± 11.56</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;desloratadine&lt;/sub&gt;/AUC&lt;sub&gt;loratadine&lt;/sub&gt;</td>
<td>3.32 ± 0.49</td>
<td>2.47 ± 0.46</td>
</tr>
</tbody>
</table>

C<sub>max</sub>: peak plasma concentration; AUC: area under the plasma concentration-time curve from time 0 to infinity; t<sub>1/2</sub>, terminal elimination half-life; CL/F: apparent oral clearance.
Figure 1B
Figure 2A

Oral clearance (L/h/kg) vs. Number of CYP2D6*10 allele
Figure 2B

Metabolic ratio (MR)

Number of CYP2D6*10 allele
APPENDIX

Assuming a parent drug (ie. loratadine) and its metabolite (ie. desloratadine) follows a one-compartment model, their pharmacokinetic process can be described as below:

\[
\text{Dose} \xrightarrow{k_a} V_1 \xrightarrow{k_f} k_e \rightarrow V_2 \xrightarrow{k_{me}}\]

The corresponding plasma concentrations of the parent drug and metabolite can be described by equation 1 and 2 respectively:

\[
P\text{arent drug } C_{p(t)} = \frac{F \cdot D \cdot k_a}{V_1 \cdot (k_a - k_e)} \cdot (e^{-k_p t} - e^{-k_a t}) \quad (1)
\]

\[
M\text{etabolite } C_{m(t)} = \frac{F \cdot D \cdot k_a \cdot k_f}{V_2 \cdot (k_a - k_e)} \cdot \left(\frac{e^{-k_m t} - e^{-k_f t}}{k_e - k_{me}} - \frac{e^{-k_{me} t} - e^{-k_e t}}{k_a - k_{me}}\right) \quad (2)
\]

where

\[
k_e = k_1 + k_f \quad (3)
\]

F is the fraction of a given dose (D) absorbed, and V_1 and V_2 refer to the volume of distribution of the parent drug and metabolite respectively. k_a and k_e are the absorption rate constant and total elimination rate constant of the parent drug; k_1 is elimination rate.
constant associated with other pathway of the parent drug; $k_f$ is the formation rate constant of the metabolite, and $k_{me}$ is the elimination rate constant of the metabolite.

Integrating equation 1 and 2, the area under the plasma concentration-time curve (AUC) of the parent drug ($AUC_p$), metabolite ($AUC_m$) and the metabolic ratio ($AUC_m/AUC_p$) are

$$AUC_p = \int_0^\infty C_{p(t)} \cdot dt = \frac{F \cdot D}{k_e \cdot V_1} = \frac{F \cdot D}{CL}$$

$$AUC_m = \int_0^\infty C_{m(t)} \cdot dt = \frac{F \cdot D \cdot k_f}{k_e \cdot k_{me} \cdot V_2} = \frac{F \cdot D \cdot f_m}{CL_{(m)}}$$

$$\frac{AUC_m}{AUC_p} = \frac{f_m \cdot CL}{CL_{(m)}} = \frac{CL_m}{CL_{(m)}}$$

where $f_m = k_f/k_e$, which refers to the fraction of drug converted to the metabolite; CL represents the total systemic clearance of the parent drug; $CL_m$ is the formation clearance of the metabolite; $CL_{(m)}$ is the total elimination clearance of the metabolite.

Thus, specifically for loratadine and desloratadine, the following relationship exists:

$$\frac{AUC_{desloratadine}}{AUC_{loratadine}} = \frac{\text{Formation clearance of desloratadine}}{\text{Total elimination clearance of desloratadine}}$$