EFFECT OF CYP2D6*10 ALLELE ON THE PHARMACOKINETICS OF LORATADINE IN CHINESE SUBJECTS

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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 interindividual variability in loratadine pharmacokinetics and the greater genetically determined variability of CYP2D6 activity than of 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 (n = 4); group II, heterozygous CYP2D6*10 (n = 6); and group III, homozygous CYP2D6*10 (n = 7) carriers. Each subject received a single oral dose of 20 mg of 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 high-performance liquid chromatography. In comparing homozygous CYP2D6*10 (group III) to heterozygous CYP2D6*10 (group II) to homozygous CYP2D6*1 (group I) subjects, loratadine oral clearanceance values were 7.17 ± 2.54 versus 11.06 ± 1.70 versus 14.59 ± 2.43 l/h/kg, respectively [one-way analysis of variance (ANOVA), p < 0.01], and the corresponding metabolic ratios [area under the plasma concentration-time curve (AUC)desloratadine/AUCloratadine] were 1.55 ± 0.73 versus 2.47 ± 0.46 versus 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.

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 interindividual variability. Previous studies in healthy white subjects showed that the disposition of loratadine varied 6- to 11-fold among individuals receiving equal doses (oral clearance ranged from 5.3 to 31.5 l/h/kg and elimination half-life ranged from 1.5 to 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 0.36–54.4) (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 in CYP3A4 (Yumibe et al., 1996). Genetic polymorphisms have been well documented for CYP2D6. The frequency of CYP2D6 poor metabolizer phenotype is much higher in white (7–10%) than in Asian populations (<1%) including Chinese, Japanese, and Koreans (Nakamura et al., 1985; Alvan et al., 1990; Sohn et al., 1991; Bertilsson L et al., 1992). Three mutated alleles, CYP2D6*3, CYP2D6*4, and CYP2D6*5, accounted for 93 to 98% of the poor metabolizers in white subjects (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 phenotype in Asian subjects is lower than that observed in white subjects. 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 white subjects (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, *2, and *3, have been identified to occur in white subjects at frequencies of 9%, 2.8%, and 2.2%, respectively, but are absent in Chinese subjects (Walker et al., 1998; Sata et al., 2000; van Schaik et al., 2001). Several Asian-specific alleles, i.e., CYP3A4*18, *19, *5, *6, *18, and *19, have also been reported in recent studies with frequencies of 1 to 3% (Dai et al., 2001; Hsieh et al., 2001). However, the in vivo functions of these alleles are uncertain at present (Eiselt et

ABBREVIATIONS: PCR, polymerase chain reaction; AUC, area under the plasma concentration-time curve; CL/F, apparent oral clearance; MR, metabolic ratio; CL, clearance.
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 of CYP3A4 in vivo, we hypothesized that the CYP2D6 polymorphisms may substantially contribute to the pharmacokinetic variability of loratadine in vivo. Since there is a high frequency of the 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 CYP2D6*10 allele.

Materials and 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 prestudy 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 ± S.D., 22.6 ± 1.4 years) and weight 55.3 to 70.6 kg (mean ± S.D., 60.9 ± 4.5 kg) were recruited from a pool of 65 subjects who underwent CYP2D6 genotype screening and were classified into three genotype groups: group I, homozygous CYP2D6*1/*1; group II, heterozygous CYP2D6*10/*1/*10 or *2/*10; and group III, homozygous CYP2D6*1/*10 carriers. Since CYP2D6*2 allele is not associated with decreased CYP2D6 activity as compared with CYP2D6*1 allele (Tateishi et al., 1999), subjects with CYP2D6*1/*10 and CYP2D6*2/*10 genotypes are combined into one group for this study. The demographic characteristics of the study subjects are shown in Table 1.

The subjects were all nonsmokers 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 2-week study period. 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, Valencia, CA). 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 (Johansson et al., 1994; Dahl et al., 1995; Garcia-Barcelo et al., 2000). The CYP2D6*5 allele was detected using long PCR with two primer sets, 2D6-F1-R and 2D6-F2-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. (1994).

Loratadine Pharmacokinetic Study. After an overnight fast of 10 h, subject received a single oral dose of 20 mg of loratadine (two 10-mg Claritine tablets; Schering-Plough Labo N.V., Heist-op-den-Berg, Belgium) with 240 ml of water. Standardized meals were served 4 and 10 h after dosing. Venous blood samples were collected at predose (0 h) and at 0.33, 0.67, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 h postdosing. All blood samples were collected in lithium heparin tubes and centrifuged immediately. Separated plasma samples were stored at −80°C until analysis.

### TABLE 1

| Demographic characteristics and CYP2D6 genotypes of the study subjects |
|-----------------|-------------------|-------------------|
| Age (yr)        | Weight (kg)       | Genotype          |
| 22.5 ± 1.9      | 59.7 ± 4.0        | *1/*1, n = 4      |
| 22.0 ± 0.9      | 62.7 ± 4.4        | *1/*10, n = 4     |
| 23.1 ± 1.4      | 60.0 ± 5.1        | *1/*10, n = 7     |

### Determination of Loratadine and Its Metabolite in Plasma.
Plasma concentrations of loratadine and desloratadine were determined by a high-performance liquid chromatography 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 interday assay was <3.3%, 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 noncompartmental method (Gibaldi and Perrier, 1982), with the aid of WinNonlin (version 2.1; Pharsight, Mountain View, CA). Peak plasma concentrations (Cmax) of loratadine and desloratadine were obtained directly from the observed concentration-time data. The terminal elimination rate constant (λ2) was estimated by linear regression of the terminal portion of the concentration-time curve, and the elimination half-life (t1/2) was calculated as 0.693/λ2. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule and was 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 AUCdesloratadine to AUCloratadine.

### Statistical Analysis.
All data from the study were expressed as mean ± S.D. 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 analysis of variance with Scheffe’s multiple comparison tests. The relationship between the number of CYP2D6*10 alleles versus loratadine CL/F or MR was assessed using the Spearman rank correlation coefficient (r). 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., Chicago, IL).

### 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 Fig. 1, A and B, respectively. The plasma concentrations of loratadine were much higher in the homozygous CYP2D6*10 group, compared with the other two groups. In homozygous CYP2D6*10 carriers (group III), the values for the AUC of loratadine were 75.5% and 123.6% higher (p < 0.05), and CL/F was 35.2% and 50.9% lower (p < 0.01) compared with the heterozygous CYP2D6*10 (group II) and homozygous CYP2D6*1 (group I) subjects, respectively (Table 2). The elimination half-life (t1/2) 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 (Fig. 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 analysis of variance). When comparing group III (homozygous CYP2D6*10) to group II (heterozygous CYP2D6*10) subjects, the AUC values for the AUC of the terminal portion of the concentration-time curve, and the elimination half-life (t1/2) was calculated as 0.693/λ2. The area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule and was 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 AUCdesloratadine to AUCloratadine.
CYP2D6*10 or group I (homozygous CYP2D6*1) subjects, the 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 Fig. 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 = −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 with 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

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

![Fig. 2. A, relationship between loratadine oral clearance and the number of CYP2D6*10 alleles (r = −0.84, p < 0.001). B, relationship between loratadine metabolic ratio and the number of CYP2D6*10 alleles (r = −0.80, p < 0.001).](image)

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Homozygous CYP2D6*1 (Group I, n = 4)</th>
<th>Heterozygous CYP2D6*10 (Group II, n = 6)</th>
<th>Homozygous CYP2D6*10 (Group III, n = 7)</th>
<th>Multiple Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loratadine</strong></td>
<td></td>
<td></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>
<td>14.65 ± 7.71</td>
<td>N.S.</td>
</tr>
<tr>
<td>AUC (ng · h/ml)</td>
<td>23.40 ± 3.11</td>
<td>29.81 ± 6.88</td>
<td>52.31 ± 18.81</td>
<td>N.S.</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>
<td>10.32 ± 9.30</td>
<td>N.S.</td>
</tr>
<tr>
<td>CL/F (l/h/kg)</td>
<td>14.59 ± 2.43</td>
<td>11.06 ± 1.70</td>
<td>7.17 ± 2.54</td>
<td>N.S.</td>
</tr>
<tr>
<td><strong>Desloratadine</strong></td>
<td></td>
<td></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>
<td>7.07 ± 2.96</td>
<td>N.S.</td>
</tr>
<tr>
<td>AUC (ng · h/ml)</td>
<td>78.15 ± 14.95</td>
<td>84.94 ± 11.56</td>
<td>94.39 ± 29.42</td>
<td>N.S.</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>
<td>1.55 ± 0.73</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

C<sub>max</sub>, peak plasma concentration; t<sub>1/2</sub>, terminal elimination half-life.

- N.S., not significant
- p < 0.005
- p < 0.05
- p < 0.01

![Figure 1](image)

![Figure 2](image)
testosterone 6β-hydroxylation, a CYP3A-mediated reaction (Yumibe et al., 1996), suggesting that loratadine is metabolized to desloratadine primarily by CYP3A. However, the same authors also showed that the formation rate of desloratadine was almost 5-fold greater in cDNA-expressed CYP2D6 than in CYP3A4 (Yumibe et al., 1996). Since these data were obtained from in vitro studies that do not necessarily reflect in vivo conditions, the relative contribution of CYP2D6 versus CYP3A4 toward the metabolism of loratadine in vivo needs 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 and Belpaire, 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 white subjects) cannot be directly extrapolated to in vivo situations, especially in different populations. This may be particularly important for CYP2D6, which manifests large interethnic 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 (Wang 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.

Whereas 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, since the majority of loratadine (60–70%) has been reported to be converted to desloratadine 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 interrelationship 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 under Appendix). 2) Loratadine may have been metabolized via CYP2D6 to a metabolite other than desloratadine. This is consistent with the observation that coadministration 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 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 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 in vivo involvement of CYP3A4 in loratadine metabolism. However, these studies were conducted in U.S. 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 has 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 the CYP2D6 genotype could influence the pharmacokinetics of drugs for which CYP2D6 is not the primary pathway of elimination.

Acknowledgments. We thank Evelyn Chau and Emily Poon for their valuable technical assistance in this investigation.

Appendix

Assuming a parent drug (i.e., loratadine) and its metabolite (i.e., desloratadine) follows a one-compartment model, their pharmacokinetic process can be described as shown in Scheme 1. The corresponding plasma concentrations of the parent drug and metabolite can be described by eqs. 1 and 2, respectively:

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

\[
\text{Metabolite } C_{m(t)} = \frac{F \cdot D \cdot k_d \cdot k_i}{V_2 \cdot (k_e - k_d)} \left( \frac{e^{-k_{d\text{me}} t} - e^{-k_{d\text{me}} t}}{k_e - k_{d\text{me}}} - \frac{e^{-k_{e\text{me}} t} - e^{-k_{e\text{me}} t}}{k_e - k_{e\text{me}}} \right) \quad (2)
\]

where

\[
k_i = k_e + k_f
\]

\[
F \text{ is the fraction of a given dose (D) absorbed, and } V_1 \text{ and } V_2 \text{ refer to the volume of distribution of the parent drug and metabolite, respectively. } k_d \text{ and } k_e \text{ are the absorption rate constant and total elimination rate constant of the parent drug, } k_i \text{ is the elimination rate constant associated with other pathways of the parent drug, } k_f \text{ is the formation rate constant of the metabolite, and } k_{d\text{me}} \text{ is the elimination rate constant of the metabolite.}

Integrating eqs. 1 and 2, the AUC of the parent drug (AUCp), metabolite (AUCm), and the metabolic ratio (AUCm/AUCp) are

\[
\text{AUC}_p = \int_0^\infty C_{p(t)} \, dt = \frac{F \cdot D}{k_e \cdot V_1} = \frac{F \cdot D}{CL} \quad (4)
\]

\[
\text{AUC}_m = \int_0^\infty C_{m(t)} \, dt = \frac{F \cdot D \cdot k_d \cdot k_i}{k_e \cdot k_{d\text{me}} \cdot V_2} = \frac{F \cdot D \cdot f_m}{CL_{\text{me}}} \quad (5)
\]

\[
\frac{\text{AUC}_m}{\text{AUC}_p} = \frac{f_m \cdot CL}{CL_{\text{me}}} \quad (6)
\]

where \(f_m = k_f/k_d\), which refers to the fraction of drug converted to the metabolite; CL represents the total systemic clearance of the parent drug.
drug; $\text{CL}_{\text{m}}$ is the formation clearance of the metabolite; and $\text{CL}_{\text{m(0)}}$ is the total elimination clearance of the metabolite.

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

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

**References**


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