Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products of agomelatine in Chinese subjects

Fang Tang, Rui Zhou, Zeneng Cheng, Guoping Yang, Aiqiao Chen, Zhi Liu, Hongyi Tan, Shuang Yang, Sanwang Li, Lingli Mu, Peng Yu

Received 30 June 2015; received in revised form 20 August 2015; accepted 12 October 2015

Abstract  The aim of this study was to apply the reference-scaled average bioequivalence (RSABE) approach to evaluate the bioequivalence of 2 formulations of agomelatine, and to investigate the pharmacokinetic properties of agomelatine in Chinese healthy male subjects. This was performed in a single-dose, randomized-sequence, open-label, four-way crossover study with a one-day washout period between doses. Healthy Chinese males were randomly assigned to receive 25 mg of either the test or reference formulation. The formulations were considered bioequivalent if 90% confidence intervals (CIs) for the log-transformed ratios and ratio of geometric means (GMR) of AUC and $C_{\text{max}}$ of agomelatine were within the predetermined bioequivalence range based on RSABE method. Results showed that both of the 90% CIs for the log-transformed ratios of $C_{\text{max}}$ and AUC of 7-desmethyl-agomelatine and 3-hydroxy-agomelatine were within the predetermined bioequivalence range. The 90% CIs for natural log-transformed ratios of $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ of agomelatine (104.42–139.86, 101.33–123.83 and 97.90–117.94) were within the RSABE acceptance limits, and 3-hydroxy-agomelatine (105.55–125.23, 102.36–111.50 and 101.62–110.64) were within the FDA bioequivalence definition intervals (0.80–1.25 for AUC and...
1. Introduction

Agomelatine is a novel antidepressant for use in the European Union. It is thought to act through a combination of antagonist activity at serotonin 5-HT2C receptors and agonist activity at melatonergic MT1/MT2 receptors. As such, its pharmacology is unique among licensed antidepressant drugs. In patients with major depression, agomelatine is as effective as paroxetine, setraline, venlafaxine and fluoxetine, with a lower relapse rate (23.9%) than placebo (50.0%). Agomelatine improves sleep quality and reduced waking after sleep onset in depressed patients. At a therapeutic dose (25 mg once daily), agomelatine preserves vigilance and memory in healthy volunteers. Due to the risk of common liver enzyme elevation and rare serious liver complications, routine laboratory monitoring of liver function is recommended periodically throughout treatment.

The existing data on agomelatine metabolism, bioavailability and pharmacokinetics in Caucasians indicate that the absorption of agomelatine is rapid, with the median $T_{\text{max}}$ 0.75–1.5 h and almost complete with at least 80% intestinal absorption. However, the absolute oral bioavailability of this drug is low (approximately 3%–4%) and highly variable (estimated to 104%). These properties are attributed to the extensive first pass metabolism of agomelatine.

A systemically active generic drug is considered to be bioequivalent to the reference-listed drug if the rate and extent of absorption of the two products do not show a significant difference. The US Food and Drug Administration (FDA) uses peak drug concentrations ($C_{\text{max}}$) in plasma or other appropriate biological fluid as an index of drug rate of absorption and the area under the drug plasma concentration versus time curve (AUC) as an index of a drug’s extent of absorption. Due to the highly variable features (highly variable drugs are defined as those for which within-subject variability [CV(%)] in bioequivalence measures is 30% or greater), a standard number of subjects (e.g., 18–24) may not be able to demonstrate the bioequivalence of generic products or their corresponding reference product using a two-way crossover design. Although agomelatine pilot data are published for Caucasians, they may not be applicable to the bioequivalence in other populations due to ethnic differences. Pei et al. investigated the intra-subject CV of agomelatine in healthy Chinese volunteers. Results showed notable intra-subject variability in $AUC_{0-24}$ (CV = 43.52%) and $C_{\text{max}}$ (CV = 78.34%). Wang et al. evaluated the inter- and intra-individual variability in AUC and $C_{\text{max}}$ of agomelatine tablets in Chinese healthy male subjects and found inter-individual CVs of $C_{\text{max}}$, $AUC_{0-2}$ and $AUC_{0-\infty}$ to be 102.20%, 131.74% and 130.59%, respectively. The intra-individual CVs of $C_{\text{max}}$, $AUC_{0-2}$, and $AUC_{0-\infty}$ were 84.34%, 49.61% and 50.83%, respectively. In preliminary experiments with a four-way crossover method, the within-subjects variability of AUC and $C_{\text{max}}$ of agomelatine were 53% and 70%, respectively. Comparable values for 3-hydroxy-agomelagatine were 21.2% and 37.8%, and for 7-desmethyl-agomelatine were 42.6% and 61.4%. These results showed that although the within-subject CV of agomelatine could be reduced with a four-way crossover method, it was still difficult to evaluate the bioequivalence. Song et al. found no differences in agomelatine pharmacokinetics between the rs2069514 GG homozygotes ($n = 35$) and the rs2069514 AG allele ($n = 35$) in all subjects, suggesting that the rs762551, rs2470890 and rs2472304 genetic polymorphisms might be associated with the marked inter-individual variability of agomelatine.

The topic of bioequivalence evaluation of highly variable drugs is one that has been intensely debated in many recent articles, conferences and meetings. The FDA observed that studies of highly variable drugs generally used more subjects than studies of lower variability. For the highly variable drug agomelatine, excessively large sample sizes would be required by a standard bioequivalence study, but the FDA discourages unnecessary human testing. These observations raise questions about the appropriate sample sizes for bioequivalence studies of drug products for which high variability does not appear to impact safety and efficacy. An additional concern is that the large sample sizes needed for bioequivalence studies of highly variable drugs may deter the development of new generic products. A final concern is that a highly variable reference product may not be shown to be bioequivalent to itself in a crossover study using a relatively modest number of subjects (e.g., 18–40). The commonly-accepted method for statistical analysis of bioequivalence data is the average bioequivalence (ABE) approach. Bioequivalence is established when the difference between the logarithmic means occur between preset regulatory limits, as shown below:

$$(\mu_T - \mu_R)^2 \leq \theta \lambda^2$$

where $\mu_T$ is the population average response of the log-transformed measure for the test (T) formulation, $\mu_R$ is the population average response of the log-transformed measure for the reference (R) formulation, and $\theta \lambda$ is equal to ln 1.25. So the limits are:

$$\ln 0.8 \leq (\mu_T - \mu_R) \leq \ln 1.25$$

On one hand, only the average means of main pharmacokinetic parameters (e.g., AUC and $C_{\text{max}}$) are taken into consideration in ABE method, and the individual variations of pharmacokinetic parameters are not considered. Thus, the two formulations showed ABE does not guarantee individuals’ bioequivalence (IBE). On another hand, the bioequivalence criteria for the ABE method are identical for both low variability and high variability drugs.

For a time, the FDA worked toward implementing an individual bioequivalence (IBE) approach for studies submitted to New Drug Applications (NDAs) and Abbreviated New Drug Application (ANDAs, for generic drugs). It was argued that requiring drug products to meet an IBE rather than an ABE standard would improve formulation switchability. The proposed criteria for acceptable IBE included the comparison of test and reference means, comparison of within-subject variances, assessment of subject-by-formulation interactions, and ability to scale the bioequivalence limits if within-subject variability of the reference

The RSABE approach was successful in evaluating the bioequivalence of these two formulations.
product exceeded predetermined values. Under IBE, the inequality used to determine if two products are bioequivalent is as follows:

\[
\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} + \sigma_D^2 + (\sigma_{WR}^2 - \sigma_{W0}^2) \leq \theta_I
\]  

(3)

where \( \sigma_D^2 \) is the population subject-by-formulation interaction variance components, \( \sigma_{WR}^2 \) is the population within-subject variance of the test formulation, \( \sigma_{W0}^2 \) is the population within-subject variance of the reference formulation, and \( \theta_I \) is the bioequivalence limit for IBE. From 1999 to 2001, at the FDA’s request, the pharmaceutical industry applied the IBE study design and analysis to NDAs and ANDAs for modified-release drug products. The IBE was used to evaluate the bioequivalence of modified-release drug products because it was thought that, due to the relative complexity of modified-release formulations, the likelihood was greatest of detecting subject-by-formulation interactions with these types of drug products. However, analysis of these data failed to detect the presence of clinically significant subject-by-formulation interactions.

To lower the sample size required for bioequivalence studies of highly variable drugs, the FDA and European Medicines Agency (EMA) have recommended the RSABE approach, whereby the bioequivalence acceptance limits are scaled to the variability of a reference product. The RSABE for both AUC and \( C_{max} \) is evaluated as below:

\[
\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \theta_S
\]  

(4)

where \( \mu_T \) is the population average response of the log-transformed measure for the test (T) formulation, \( \mu_R \) is the population average response of the log-transformed measure for the reference (R) formulation, and \( \sigma_{WR}^2 \) is the population within-subject variance of the reference formulation, \( \theta_S = \frac{\ln(1.25)^2}{\sigma_{W0}^2} \) is the bioequivalence limits, and \( \sigma_{W0}^2 \) is a predetermined constant set by the regulatory agency.

Under this model, the implied limits (which represent FDA’s desired consumer risk model) on \( \mu_T - \mu_R \) are:

\[- \left( \ln 1.25 \frac{\sigma_{WR}}{\sigma_{W0}} \right) \leq \mu_T - \mu_R \leq \ln 1.25 \frac{\sigma_{WR}}{\sigma_{W0}} \]  

(5)

If \( \sigma_{WR} = \sigma_{W0} \), the implied limits are equal to the standard unscaled bioequivalence limits of \( -\ln 1.25 \) (0.80–1.25). If \( \sigma_{WR} > \sigma_{W0} \), the implied limits are wider than the standard limits. If \( \sigma_{WR} < \sigma_{W0} \), the implied limits are narrower than the standard limits.

The Agency has determined that it is acceptable for the implied limits to be wider than the standard limits only when \( \sigma_{WR} \) is large (as for highly variable drugs). The mixed scaling model is as shown below.

\[
T \text{ and } R \text{ are considered bioequivalent if:}
\]

\[
\frac{(\mu_T - \mu_R)^2}{\sigma_{W0}^2} \leq \frac{(\ln 1.25)^2}{\sigma_{W0}^2} \quad \text{if} \quad \sigma_{WR} \leq \sigma_{W0}
\]  

(6)

and if:

\[
\frac{(\mu_T - \mu_R)^2}{\sigma_{WR}^2} \leq \frac{(\ln 1.25)^2}{\sigma_{W0}^2} \quad \text{if} \quad \sigma_{WR} \geq \sigma_{W0}
\]  

(7)

The FDA sets the value of \( \sigma_{W0} \) at 0.25. Formulations were considered bioequivalent if the 90% CIs for the log-transformed ratios and ratio of geometric means (GMR) of AUC and \( C_{max} \) of agomelatine were within the predetermined bioequivalence range based on RSABE method. Both the 90% CIs
for the log-transformed ratios of AUC and $C_{\text{max}}$ of 7-desmethyl-agomelatine and 3-hydroxy-agomelatine were within the bioequivalence range of ABE method. The sample size was calculated by the within-subject variability (37.8%) of 3-hydroxy-agomelatine from pre-experiment as follows:

$$n = \left(\frac{t_\alpha + t_\beta}{\sigma_\alpha/\delta}\right)^2$$

(8)

where $t_\alpha$ is $t$ value of the $\alpha$ inspection standards, $t_\beta$ is the type II error rate, $\delta$ is the requirements of discrimination, and $\sigma_\alpha$ is the within-subject variability. As $t_\alpha = 1.6449$, $t_\beta = 1.2816$, $\delta = 0.2$, $\sigma_\alpha = 0.378$, the sample size used was $n = 31$.

Based on the above, a minimum of 32 subjects were required. Taking into account the test management and lost cases, 44 subjects were enrolled in the four-way crossover study.

Forty-four healthy Chinese male volunteers aged 18–40 years with body mass indices (BMI) between 19 and 25 kg/m$^2$ were assessed for inclusion in the study. As females can be influenced by additional variables such as menstruation and pregnancy, the guidelines of the Chinese State Food and Drug Administration (SFDA) generally recommend selecting healthy males for bioequivalence studies. Subjects were judged to be eligible for the study when no clinically significant abnormal findings existed on a complete medical examination. The exam included medical history, physical examination, 12-lead electrocardiogram, hematology, blood biochemistry and urinalysis.

### 2.3. Blood sampling

Blood samples (5 mL) were collected from a suitable forearm vein into anticoagulant tube by an indwelling catheter at the following time point: 0 (before administration), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0 and 8.0 h after drug administration. After washout and administration of the alternate formulation, blood samples were drawn and analyzed in the same way.

### 2.4. Tolerability assessments

Subjects were carefully monitored by vital signs (sitting blood pressure, heart rate, breathing rate, and oral body temperature), clinical laboratory tests (hematology, blood biochemistry, and urinalysis), 12-lead ECGs, and physical examinations at baseline and at the end of each study period. National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 was used to describe and grade all toxicities and adverse events. The relationship of adverse events to study drug was documented by the investigator as unrelated or unlikely, possibly, probably, or definitely related.

### 2.5. Pharmacokinetic evaluations

An LC–MS/MS validated method for the simultaneous determinations of agomelatine, 3-hydroxy-agomelatine and 7-desmethyl-agomelatine concentrations in human plasma. The analytes were quantified by use of phenacetin as the internal standard. The plasma sample clean-up procedure was performed by liquid-liquid extraction. Aliquots (5 μL) were injected onto the analytical column (Phenomenex ODS3, 150 mm x 4.6 mm, 5 μm, USA). The mobile phase consisted of methanol and formic acid aqueous solution (20%) within 5 mmol/L ammonium formate (70:30, v/v) was delivered with a flow rate of 0.8 mL/min, with a run time of approximately 7 min. Positively charged ions, created at atmospheric pressure, were transferred to an Agilent 6460 triple-quadrupole LC–MS (Agilent, USA). The transitions for agomelatine were selected from $m/z$ 244.1 → 185.1, 3-hydroxy-agomelatine from $m/z$ 260.1 → 201.1, 7-desmethyl-agomelatine from $m/z$ 230.1 → 171.1, and the internal standard from $m/z$ 180.1 → 110.1.

### 2.6. Pharmacokinetic analysis

A non-compartmental analysis was used to determine the pharmacokinetic parameters using WinNonlin 6.1. $C_{\text{max}}$ and $T_{\text{max}}$ were obtained directly from the plasma concentration-time curves. The $AUC_{0-\infty}$ was calculated according to the trapezoidal rule. $AUC_{0-\infty}$ was calculated as follows:

$$AUC_{0-\infty} = AUC_{0-t} + C_t/k_e$$

(9)

where $C_t$ was the last measured concentration at time $t$, and $k_e$ was the terminal elimination rate constant estimated by log-linear regression analysis of data visually assessed to be a terminal log-linear phase. At least 3 points were used for estimation of $k_e$. The apparent terminal elimination $t_{1/2}$ was calculated as follows:

$$t_{1/2} = 0.693/k_e$$

(10)

Intra-individual variability for the considered pharmacokinetic parameters was assessed by CV(%).
2.7. Statistical analysis

To test the bioequivalence of the formulations, ANOVA was performed on log-transformed \( C_{\text{max}}, \) AUC\(_{0,\infty}\), and AUC\(_{0,\text{max}}\). The nonparametric signed rank test was used to complete the \( T_{\text{max}} \) for the 2 formulations. \( P \leq 0.05 \) was considered statistically significant. The ratios of the log-transformed \( C_{\text{max}}, \) AUC\(_{0,\infty}\), and AUC\(_{0,\text{max}}\) of parent agomelatine, 3-hydroxy-agomelatine and 7-desmethyl-agomelatine for both formulations were calculated, and 90% CIs were obtained. The probability of exceeding the limits of acceptance was obtained by two 1-side \( t \) tests. The 2 formulations were considered bioequivalent if the 90% CIs of the parent agomelatine of two formulations ratios of AUC and \( C_{\text{max}} \) were within the limits according to RSABE method shows below:

Bioequivalence limits, upper, lower = \( e^{\pm 2.2768\times \text{min} / \text{max}} \) \( \times 1.33 \) (11)

For 3-hydroxy-agomelatine and 7-desmethyl-agomelatine, the test/reference ratios of AUC were within the predetermined bioequivalence range of 0.80 to 1.25 and \( C_{\text{max}} \) ratios were within 0.75–1.33, according to the guidelines of the SFDA of the China.

The bioequivalence assessment of the parent drug agomelatine was an essential goal of the present study. Evaluation of the bioequivalence of the two metabolites was considered as possibly supportive evidence for the bioequivalence of the parent drug.

3. Results

A total of 44 male subjects were enrolled in the study. Index, mean (range): age, 22.8 (2.5) years (range, 19–28 years); height, 170 (10) cm (range, 157–181 cm); weight, 60.5 (6.3) kg (range, 51–74 kg); BMI, 20.7 (1.6) kg/m\(^2\) (range, 19.0–24.0 kg/m\(^2\)). Each subject received the test formulation and the reference formulation and 1.22 [0.86] h for the reference formulation (\( P<0.05 \) by Mann–Whitney \( U \) test). For the metabolite 3-hydroxy-agomelatine and 7-desmethyl-agomelatine, no period, formulation, or sequence effects were observed for any pharmacokinetic properties by ANOVA, and there were no significant differences between the two formulations in AUC\(_{0,\infty}\). C\(_{\text{max}}\) by two 1-side \( t \) test or in \( T_{\text{max}} \) by Mann–Whitney \( U \) test.

3.4. Bioequivalence evaluation

The 90% CIs of the ratios (T/R) for the log-transformed AUC\(_{0,\infty}\), AUC\(_{0,\text{max}}\), and AUC\(_{0,\infty}\) C\(_{\text{max}}\) are listed in Table 3. There were no significant differences between the test and reference formulations. The 90%
According to US FDA guidelines\textsuperscript{35}, only the parent compound is generally recommended for bioequivalence studies. However, when a metabolite contributes meaningfully to the drug’s pharmacologic effects or when a parent compound is difficult to analyze in plasma, metabolite quantification is also recommended. Although the pharmacokinetic parameters of agomelatine itself are the most essential criteria for bioequivalence evaluation, 3-hydroxy-agomelatine and 7-desmethyl-agomelatine were assessed in the present study to provide supporting evidence.

The median values of $T_{\text{max}}$ for 3-hydroxy-agomelatine and 7-desmethyl-agomelatine confirmed the rapid disappearance of the parent compound which was comparable between the two formulations.

The FDA has recommended the RSABE approach to evaluate the bioequivalence of highly variable drugs (e.g., agomelatine). Accordingly, the acceptance limits for such a study is to be scaled to the variability of the reference formulation. In the present study, we used the RSABE approach to assess the bioequivalence of two formulations of parent compounds for the first time in Chinese healthy male subjects. The standard criteria were used to evaluate the bioequivalence of the test formulation and the reference formulation, along with studies of the metabolites 3-hydroxy-agomelatine and 7-desmethyl-agomelatine.

The aim of this study was to apply the RSABE approach to evaluate the bioequivalence of 2 formulations of agomelatine, a drug with highly variable kinetics, and to investigate the pharmacokinetic properties of agomelatine in Chinese healthy male subjects. There are a few reports in the literature on the pharmacokinetics of agomelatine in Chinese population. Pei et al.\textsuperscript{14} investigated the CV(%) of agomelatine in 16 Chinese healthy male volunteers and showed significant ethnic differences between Chinese and Caucasian subjects in $C_{\text{max}}$ and AUC\textsubscript{0–t}, whereas no ethnic differences in $T_{\text{max}}$ or $t_{1/2}$ were found. Less obvious first-pass effects in Chinese subjects may partially account for why both $C_{\text{max}}$ and AUC of Chinese males were much higher than those of Caucasian males. In this study, the mean (SD) agomelatine and its metabolites AUC\textsubscript{0–t}, $T_{\text{max}}$, and $C_{\text{max}}$ for Chinese subjects (summarized in Table 3) are presented for the first time.

The 90% CIs of the test/reference ratios of $C_{\text{max}}$, AUC\textsubscript{0–t}, AUC\textsubscript{0–∞} for agomelatine (104.42–139.86, 101.33–123.83, and 97.90–117.94, respectively) were within the RSABE acceptance limits (8.99%–204.13%, 59.48%–170.99%, 61.38%–162.91% for $C_{\text{max}}$, AUC\textsubscript{0–t} and AUC\textsubscript{0–∞}, respectively). The metabolites 3-hydroxy-agomelatine and 7-desmethyl-agomelatine were within the predetermined regulatory 90% CI ranges for bioequivalence (80%–125% for AUC\textsubscript{0–t} and AUC\textsubscript{0–∞}, 75–133% for $C_{\text{max}}$ for the T/R ratio).

### 4. Discussion

According to US FDA guidelines\textsuperscript{35}, only the parent compound released from the formulation rather than the metabolite is generally recommended for bioequivalence studies. However, when a metabolite contributes meaningfully to the drug’s pharmacologic effects or when a parent compound is difficult to analyze in plasma, metabolite quantification is also recommended. Although the pharmacokinetic parameters of agomelatine itself are the most essential criteria for bioequivalence evaluation, 3-hydroxy-agomelatine and 7-desmethyl-agomelatine were assessed in the present study to provide supporting evidence.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Agomelatine</th>
<th>3-Hydroxy-agomelatine</th>
<th>7-Desmethyl-agomelatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0–t}$ (µg·h/L)</td>
<td>8.59 (10.17)</td>
<td>88.30 (31.81)</td>
<td>5.75 (2.64)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>54.1</td>
<td>14.4</td>
<td>24.2</td>
</tr>
<tr>
<td>$\text{AUC}_{0–∞}$ (µg·h/L)</td>
<td>8.72 (10.16)</td>
<td>89.78 (32.27)</td>
<td>6.16 (2.76)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>52.6</td>
<td>14.4</td>
<td>23.1</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg·h/L)</td>
<td>7.55 (10.11)</td>
<td>50.09 (25.45)</td>
<td>4.43 (3.04)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>84.4</td>
<td>43.9</td>
<td>53.5</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.14 (0.75)</td>
<td>1.13 (0.72)</td>
<td>1.07 (0.72)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.24 (1.40)</td>
<td>1.24 (0.24)</td>
<td>1.55 (1.97)</td>
</tr>
</tbody>
</table>

Data are expressed as Mean (SD), unless otherwise specified, $n=44$. The median values of $T_{\text{max}}$ for 3-hydroxy-agomelatine and 7-desmethyl-agomelatine confirmed the rapid disappearance of the parent compound which was comparable between the two formulations.

### Table 3

Comparison of 90% CIs of natural log(ln)-transformed parameters of agomelatine, 3-hydroxy-agomelatine and 7-desmethyl-agomelatine for a test or a reference formulation of agomelatine 25-mg tablet after a single 25-mg oral dose in healthy fasted Chinese adult males ($n=44$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Agomelatine</th>
<th>3-Hydroxy-agomelatine</th>
<th>7-Desmethyl-agomelatine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\ln C_{\text{max}}$</td>
<td>1.21</td>
<td>1.14</td>
<td>1.14</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–t}$</td>
<td>1.12</td>
<td>1.05</td>
<td>1.07</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–∞}$</td>
<td>1.07</td>
<td>1.05</td>
<td>1.06</td>
</tr>
<tr>
<td>3-Hydroxy-agomelatine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\ln C_{\text{max}}$</td>
<td>1.14</td>
<td>1.14</td>
<td>1.09</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–t}$</td>
<td>1.05</td>
<td>1.02</td>
<td>1.06</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–∞}$</td>
<td>1.05</td>
<td>1.02</td>
<td>1.06</td>
</tr>
<tr>
<td>7-Desmethyl-agomelatine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\ln C_{\text{max}}$</td>
<td>1.14</td>
<td>1.14</td>
<td>1.14</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–t}$</td>
<td>1.07</td>
<td>1.02</td>
<td>1.07</td>
</tr>
<tr>
<td>$\ln \text{AUC}_{0–∞}$</td>
<td>1.06</td>
<td>1.02</td>
<td>1.06</td>
</tr>
</tbody>
</table>

CIs for natural log-transformed ratios of $C_{\text{max}}$, AUC\textsubscript{0–t}, AUC\textsubscript{0–∞} of agomelatine (104.42–139.86, 101.33–123.83, and 97.90–117.94, respectively) were within the RSABE acceptance limits (8.99%–204.13%, 59.48%–170.99%, 61.38%–162.91% for $C_{\text{max}}$, AUC\textsubscript{0–t} and AUC\textsubscript{0–∞}, respectively). The metabolites 3-hydroxy-agomelatine and 7-desmethyl-agomelatine were within the predetermined regulatory 90% CI ranges for bioequivalence (80%–125% for AUC\textsubscript{0–t} and AUC\textsubscript{0–∞}, 75–133% for $C_{\text{max}}$ for the T/R ratio).

The median values of $T_{\text{max}}$ for 3-hydroxy-agomelatine and 7-desmethyl-agomelatine confirmed the rapid disappearance of the parent compound which was comparable between the two formulations.
The study present had several limitations that should be considered. The pharmacokinetic data of this study were obtained only from Chinese healthy males who were administered a single dose. Therefore, the pharmacokinetics might be different in other targeted populations or after other dosage regimens.

5. Conclusions

The RSABE approach was successfully applied to evaluate the bioequivalence of two formulations of the highly variable drug agomelatine in Chinese male volunteers. This study found that the test and reference formulations of agomelatine 25-mg tablet met the regulatory definition.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81102499), Hunan Science and Technology Project (No. 2011SK3261), the Fundamental Research Funds for the Central Universities of Central South University (No. 2014zzts313). The authors are also grateful for the support from Chongqing FuAn Pharmaceutical Group Qingyutang Pharmaceutical Co., Ltd.

References


