Bioequivalence Evaluation of Two Levetiracetam Tablet Formulations after Single Oral Administration in Healthy Male
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ABSTRACT

Purpose: The aim of this study was to assess the bioequivalence of two tablet formulations (test and reference) of 500 mg levetiracetam, anti-epilepsy drug.

Methods: The bioequivalence was evaluated by two period crossover design with 1 week washout period. In 21 healthy volunteers, after a single oral dose of 500 mg levetiracetam per subject, plasma samples, obtained over 24 h, were analyzed by a validated high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay. The pharmacokinetic parameters were calculated by noncompartmental analysis using plasma concentration. Analysis of variance was used for comparison of mean plasma concentration and 90% confidence intervals for \( A_{UC,\text{test}} \) and \( A_{UC,\text{ref}} \) were calculated.

Results: The geometric mean of \( A_{UC,\text{test}} \) was 114.73 vs. 113.001 mg/mL (test vs. reference), and the geometric means of the \( C_{\text{max,ref}} \) were 16,759 vs. 16,566 ng/mL (test vs. reference). The geometric mean ratio of the test formulations to reference formulations for \( A_{UC,\text{test}} \) and \( C_{\text{max,ref}} \) were 1.013 and 1.015, respectively, and the 90% CIs for \( A_{UC,\text{test}} \) and \( C_{\text{max,ref}} \) were 0.991–1.028 and 0.992–1.038, respectively, satisfying the bioequivalence criteria of both the European Committee for Proprietary Medicinal Products and the US Food and Drug Administration Guidelines.

RESULTS

1. Chromatograms

2. Chromatogram Conditions

- HPLC: Silversun semi-prep (Shimadzu, Japan)
- Detectors: UV detector and MS detector
- Column: TSK-GEL ODS-50m (150 mm, 3.9 μm, 5 μm particle size, 3 cm)
- Mobile phase: Acetonitrile-water-acetic acid (1:1:0.1, v/v/v) in 20 min
- Flow rate: 1.0 mL/min
- MS/MS conditions: Positive ion detection, Q3 mode
Levetiracetam: m/z 171.2 → 20.2
Internal standard: m/z 171.2 → 20.2

3. Extraction of mirodenafil from Plasma

4. Pharmacokinetic Analysis

- Noncompartmental pharmacokinetic parameters:
  - Area under the curve (AUC): from 0 to infinity
  - Cmax: from plasma concentration-time profile
  - tmax: linear trapezoidal rule

5. Statistical Analysis of Data

- Software: Excel 2007 (version 1.19)
- Analysis of variance was performed
- log-transformed \( A_{UC,\text{test}} \) and \( C_{\text{max,ref}} \) were calculated.

6. Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Reference drug (111215_Intra_1day_1.rdb)</th>
<th>Test drug (111216_Selec&amp;ME_1 Blank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (μg/mL-h)</td>
<td>114.001</td>
<td>114.73</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>16.566</td>
<td>16.759</td>
</tr>
<tr>
<td>tmax (hr)</td>
<td>0.04 ± 0.12</td>
<td>0.09 ± 0.04</td>
</tr>
</tbody>
</table>

*Geometric mean

Mean ± SD

The values were calculated on the basis of log-transformed \( A_{UC,\text{test}} \) and \( C_{\text{max,ref}} \) data.

CONCLUSION

These results indicate that the two formulations of levetiracetam 500 mg tablets are bioequivalent in terms of maximum exposure and extent of drug absorption and, thus, may be prescribed interchangeably.