Bioequivalence evaluation of two dosage forms of olanzapine 10 mg formulations in healthy volunteers

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Abstract

Two bioequivalence studies were carried out in healthy volunteers in order to determine the rate and extent of absorption of two dosage forms (film-coated tablet and orodispersible tablet) of oral olanzapine (CAS 132539-06-1) 10 mg test formulations and the respective brand formulations as reference. Twenty and twenty-six subjects were administered olanzapine film-coated tablet or orodispersible tablet of test and reference formulations in an open-label, randomised, fasting, two-period, two-sequence, crossover study. Blood samples were taken before and within 240 h after drug administration. Plasma concentrations were determined by LC/MS/MS. Log-transformed AUC and Cmax values were tested for bioequivalence based on the ratios of the geometric means (test/reference). tmax was analysed nonparametrically. The 90% confidence intervals of the geometric mean values for the test/reference ratios for AUC₀⁻,t and Cmax were within the bioequivalence acceptance range of 80–125%. It may be therefore concluded that the test formulations of olanzapine 10 mg film-coated tablet and orodispersible tablet are bioequivalent to the reference products and can be prescribed interchangeably.

Key words

- Atypical antipsychotic
- Bioequivalence
- CAS 132539-06-1
- Healthy volunteers
- Olanzapine, tablet
- Pharmacokinetics

Arzneimittelforschung 2011;61(2):75–79

1. Introduction

Olanzapine (CAS 132539-06-1) is an atypical antipsychotic medicine that belongs to the thienobenzodiazepine class, acting as a multireceptor antagonist which presents high affinity for several serotonin, muscarinic, histamine (H₁) and adrenergic (α₂) receptors. Atypical antipsychotics have proven to be at least as effective as conventional agents and better tolerated [1]. Their common feature is the low propensity for extrapyramidal symptoms when compared to classical antipsychotics [2].

Olanzapine is indicated for the treatment of schizophrenia, for the treatment of moderate to severe manic episode and, in patients whose manic episode responded to olanzapine treatment, it is indicated for the prevention of recurrence in patients with bipolar disorder.

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 h [3]. Olanzapine is metabolized in the liver. The major circulating metabolite is 10-N-glucuronide. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites. The predominant pharmacologic activity is from the parent drug. The plasma protein binding of olanzapine is about 93% over the concentration range of 7 to 1000 ng/ml [3].

The plasma half-life of olanzapine is 30 h (ranges from 21 to 54 h) and the apparent plasma clearance is 25 L/h (ranges from 12 to 47 L/h) [4].

According to the European Guideline [5] two products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent/alternatives and their bioavailabilities are similar. Plasma concentration profiles and the derived pharmacokinetic data are used to assess the rate and extent of absorption and to evaluate the bioequivalence of the tested products.
The aim of the two studies here reported was to compare the rate and extent of absorption of two generic olanzapine 10 mg oral formulations (film-coated tablet (FCT) and orodispersible tablet (ODT)) with those of the reference product of the corresponding dosage form, in a single-dose, two-period, two-sequence, crossover randomised study in healthy volunteers. As secondary objective the tolerability of both formulations was assessed.

The design, methodology and statistical considerations were almost identical in both studies. Therefore, unless otherwise stated, all reported data refer to the common aspects of both protocols.

2. Subjects and methods

2.1 Study subjects

Subjects included in both studies were healthy male and female volunteers, non-smokers. In the olanzapine FCT study, participants ranged from 21 to 35 years of age (mean ± SD; 26.9 ± 4.2), weighed 74.0 ± 7.7 kg (64 ± 8.30), averaged 151.0 ± 178.5 cm in height (168.5 ± 7.6), and had a body mass index (BMI) of 29.0 ± 24.6 kg/m² (22.5 ± 1.5). In the olanzapine ODT study, subjects aged 18–43 (29.96 ± 6.81) years had a weight between 44.70 and 80.60 (66.94 ± 9.88) kg, a height between 155.0 and 206.0 (169.8 ± 10.01) cm and a BMI between 18.60 and 27.10 (23.14 ± 2.56) kg/m².

The bioequivalence study of olanzapine FCT was conducted in the Clinical Pharmacology Unit of Hospital Clínico de Barcelona, Spain; while the bioequivalence between olanzapine ODT formulations was carried out in Laboratorio de análisis Dr. Echevarne Phase I Unit, Hospital Dos de Maig, Barcelona, Spain. Both clinical trials were registered in the EudraCT database (EudraCT numbers: 2005-004411-34 for the olanzapine FCT bioequivalence study and 2007-002444-25 for the olanzapine ODT).

Prior to the study, the volunteers were informed about the nature, purpose, risks and discomforts that could arise from their participation and about their right to withdraw at any time. Subjects documented their willingness to participate by signing the informed consent form. Study protocols and information given to trial subjects were approved by an independent ethics committee (IEC); the one of the Hospital Clínico de Barcelona (Barcelona, Spain) evaluated the FCT study and the Hospital de l’Hospitalet (Consorti Sanitari Integral) IEC (L’Hospitalet de Llobregat, Spain) evaluated the ODT bioequivalence study. Both studies were performed in accordance with the Helsinki Declaration (revised version of Edinburgh 2000) and the provisions of Good Clinical Practice [6].

Within 21 days before the first study drug administration, study participants were screened for suitability by means of their clinical history, medical examination (including vital signs), 12-lead electrocardiogram, laboratory tests, serology and drugs of abuse. A urine pregnancy test was performed on all women participants. Subjects were excluded if they had taken an investigational product in another clinical trial in the previous 3 months, had a history of psychiatric disease or history of gastrointestinal, liver or kidney disease that could affect drug bioavailability, history or presence of clinically significant allergies, those with intake of excessive alcohol, regular intake of any medication in the previous 30 days before starting the study, were pregnant or breastfeeding.

2.2 Drug products

Olanzapine 10 mg film-coated tablet test formulation manufactured by Laboratorios Lesvi, S.L. (Sant Joan Despí, Barcelona, Spain) (batch GAL0522; expiry 06/2006). Olanzapine 10 mg film-coated tablet reference formulation (batch A122457; expiry 06/2006). The reference formulation was obtained from a local pharmacy.

Olanzapine 10 mg orodispersible tablet test formulation manufactured by Laboratorios Lesvi, S.L. (Sant Joan Despí, Barcelona, Spain) (batch GAL07173C; expiry 10/2007). Olanzapine 10 mg orodispersible tablet reference formulation (batch A198455A; expiry 08/2009). The reference formulation was obtained from a local pharmacy.

2.3 Study design

Design of both studies was the standard one for the comparison of two formulations: it was an open-label, randomised, fasting, two-period, two-sequence, crossover trial, comparing the bioavailability of generic and brand name formulations of olanzapine 10 mg, either film-coated tablet or orodispersible tablet.

On the morning of phase one, after fasting during the previous night (at least 10 h), each volunteer received one 10 mg olanzapine (FCT or ODT) test formulation or the reference one according to the randomisation scheme. After a wash-out period of 3 weeks, volunteers received the alternate product. FCT were administered with 150 ml of water, while ODT were to be totally dissolved in the mouth without water right after opening the blister. Standard meals were served at appropriate times after drug intake (+4 h, +6 h, +9 h, +12 h and +2 h, +5 h, +9 h, +12 h; ODT and FCT study, respectively).

Serial blood samples (8 ml) were obtained at pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240 h post-dosing.

Blood samples were collected in tubes containing heparin lithium and centrifuged at 3000 r.p.m. for 10 min at +4 °C. Plasma was aliquoted protected from light into two polypropylene tubes, into which ascorbic acid solution was added in order to prevent oxidation. Then samples were shaken to homogenise and stored frozen at −75 °C until assayed.

2.4 Analysis of plasma samples

Concentrations of olanzapine in plasma samples were analysed using a validated method involving liquid chromatography tandem mass spectrometry with triple quadrupole in Laboratory de análisis Dr. Echevarne, Barcelona, Spain. Calibration curves were linear in the range of 0.1–100 ng/ml with a coefficient of correlation of r ≥ 0.9995 and a lower limit of quantification of 0.1 ng/ml. Recovery of olanzapine ranged from 79.67 to 87.73%. Intr-assay precision (expressed as a coefficient of variation) was ≤ 10.15%; and inter-assay variability was ≤ 11.99%. The stability evaluation showed that olanzapine was stable in plasma for 102 days when stored at −75 °C. The study was conducted in compliance with the principles of Good Laboratory Practice.

Olanzapine and the internal standard (clonazepam) were isolated from 0.5 ml plasma samples by solid-phase extraction procedure (Oasis extraction cartridges).

Aliquots of plasma extracts (10 μl) were subjected to LC/MS/MS on an API 3000 system with Turbon ionspray probe using a Kromasil 100 C18, 150 × 4 mm, 5 μm column and a mobile phase of 0.01 M ammonium acetate/acetonitrile (25:75, v/v) eluted at a flow rate of 1 ml/min. The mass spectrometry em...
2.5 Pharmacokinetic analysis

The pharmacokinetic parameters were estimated according to a non-compartmental approach using the drug concentration profiles and the actual sampling times with WinNonlin software (WinNonlin Professional, ver 5.0.1 and 5.2, Pharsight Corporation). Concentration values below the limit of quantification that occurred before or after $C_{\text{max}}$ were set to zero. Area under the plasma concentration-time curve from zero to the last measurable concentration ($AUC_{0-\infty}$) was calculated with the mixed model log-trapezoidal rule. Area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) was estimated by extrapolating to infinity $AUC_{0-\infty}$. The extrapolation to infinity was performed by regression with the last log-transformed data to estimate the terminal area by means of the line which maximized the coefficient of determination ($R^2$). The maximum plasma concentration ($C_{\text{max}}$) and the time of the peak concentration ($t_{\text{max}}$) were directly derived from the plasma concentration-time curve. The terminal rate constant ($\lambda_\text{z}$) was obtained as the slope of the log-linear regression analysis on data points on the terminal log-linear phase. The terminal half-life ($t_{1/2}$) was estimated as $t_{1/2} = \ln(2)/\lambda_\text{z}$.

Geometric mean ratios and 90% confidence intervals for $AUC_{0-\infty}$ and $C_{\text{max}}$ were used in the determination of bioequivalence.

2.6 Statistical analysis

Sample size was calculated based on observed data [7] from the Food and Drug Administration that indicated a $C_{\text{max}}$ coefficient of variation of a maximum of 20%, derived from the residual variability obtained in the analysis of variance (ANOVA) after log-transformation.

Two different approaches were considered in both studies. For the olanzapine FCT study 20 subjects were sufficient to achieve a power of 80% according to Chow and Liu [8] formula, while according to Zhang’s approach [9] for the olanzapine ODT study a total of 26 subjects were required to achieve a power of 80%. The probability of type I error was set at 5%.

For the purpose of bioequivalence analysis, log-transformed $AUC_{0-\infty}$ and $C_{\text{max}}$ were considered as the primary variables and log-transformed $AUC_{0-\infty}$ was considered a supportive parameter. $t_{\text{max}}$ was calculated as a secondary parameter.

An analysis of variance was performed in order to evaluate treatment, sequence and period effects. The fixed factors included were the treatment received, the period and the sequence. Subject (nested within sequence) was included as a random effect.

The bioequivalence assessment was done using a parametric approximation for $AUC_{0-\infty}$, $AUC_{0-\infty}$, and $C_{\text{max}}$ after logarithmic transformation. For each parameter, a 90% parametric confidence interval was defined for the ratio test/reference using the residual variability obtained from the ANOVA. Additionally, the parametric Schuirmann’s approach [10] by means of a two one-sided t-test was also calculated. $t_{\text{max}}$ was analysed non-parametrically by means of Hauschke method [11] using BIOEQV 6.2 [12]. The statistical significance was established at $p \leq 0.05$ for all statistical tests.

Bioequivalence assessment was based on a predefined acceptance criterion of 80—125% for the ratio test/reference and its 90% confidence interval for the log-transformed data of $AUC_{0-\infty}$, $AUC_{0-\infty}$ and $C_{\text{max}}$. Acceptance range for un-transformed $t_{\text{max}}$ was 70—130%.

3. Results

3.1 Study population

In the FCT study 20 subjects were included. Two of them dropped out for personal reasons during the wash-out period, being replaced for two eligible volunteers assigned to the same treatment sequence and who received both doses of study medication (test and reference). In order to ensure a total of 20 completing subjects, one additional subject was enrolled as a volunteer informed about the possibility that he may have to drop out from the study. However, this participant took only one dose (period 1) as the twenty subjects previously included completed both periods of the study and it was considered unnecessary to subject the volunteer to the dose of period 2. Blood concentrations of olanzapine were not determined for the three subjects that were replaced.

The 23 subjects (12 male/11 female) exposed at least to one dose of study medication were included in the safety analysis; and the 20 participants (10 male/10 female) who stayed on till the end of the study were included in the pharmacokinetic analysis.

26 subjects were enrolled in the ODT study. One participant revoked consent before taking period 1 study medication and was replaced. This subject was not included in any analysis. Safety and pharmacokinetic data were obtained from the 26 subjects (14 male/12 female) who completed both study periods.

3.2 Safety

The tolerability profile of the drugs was expected as per the investigator’s brochure and the summary of product characteristics. In the FCT study a total of 105 adverse events (AE) occurred, 53 after the reference formulation dose and 52 after the test medication. The most observed AE was somnolence (43 cases; observed in all volunteers), followed by dizziness (16), headache (11) and cold (5). Relationship with study medication was assessed as probable or possible in most observations (82). Sixty-one AE were of mild intensity and 44 were assessed as being moderate.

A total of 131 AE occurred in the ODT study. Seventy AE occurred after one single dose of the reference formulation, and 61 after one single dose of the test formulation. The most frequently reported AE was somnolence (51), followed by dizziness, headache, dry mouth, limb discomfort, constipation and orthostatic hypotension. Most of AE (119/131) were assessed as being related to the investigational medicinal product and were of mild (61/131), moderate (51/131), and severe (19/131) intensity. Most AE of severe intensity were somnolence (16).

No serious AE occurred and no AE resulted in withdrawal in any of both studies. The safety profile was similar for the test and reference formulations and it was consistent with the summary of product characteristics [3, 13].
3.3 Drug concentration

Plots of the mean plasma olanzapine concentration versus time profiles of volunteers over the 240-h sampling period after administration of the generic and brand formulations are shown in Fig. 1 (FCT) and 2 (ODT). Plasma profiles of test and reference were very similar for both, the FCT and the ODT formulations.

Table 1 presents the mean values and standard deviations for \( \text{AUC}_{0-\infty}, \text{C}_{\text{max}} \) and \( \text{AUC}_{0-\text{inf}}; t_{\text{max}} \) is presented with the median and the range. The parameters \( \text{AUC}_{0-\infty} \) and \( \text{AUC}_{0-\text{inf}} \) indicate the extent of absorption of the drug, while \( t_{\text{max}} \) and \( \text{C}_{\text{max}} \) are influenced by the rate of absorption. The mean \( \text{AUC}_{0-\text{inf}} \) value of test FCT was 967.853 h·ng/ml (SD 276.464 h·ng/ml), mean \( \text{AUC}_{0-\text{inf}} \) of the reference formulation was 890.717 h·ng/ml (SD 265.026 h·ng/ml). \( \text{C}_{\text{max}} \) was 30.747 ± 7.443 ng/ml (mean ± SD) for the test formulation and 27.975 ± 6.141 ng/ml for the reference formulation.

The mean \( \text{AUC}_{0-\text{inf}} \) value of test orodispersible tablets was 761.307 h·ng/ml (SD 328.759 h·ng/ml), being slightly higher than that of the reference formulation which was 731.497 h·ng/ml (SD 233.823 h·ng/ml). \( \text{C}_{\text{max}} \) was 21.354 ± 9.983 ng/ml (mean ± SD) for the test formulation and 19.813 ± 5.775 ng/ml for the reference formulation. The percentage AUC extrapolated was less than 20% in both studies, indicating that the sampling schedule was long enough.

3.4 Bioequivalence evaluation

The ANOVA model showed no statistically significant sequence effect in any of the FCT and the ODT formulations in the \( \text{AUC}_{0-\text{inf}}, \text{AUC}_{0-\text{t}}, \text{C}_{\text{max}} \) (logarithmic and un-transformed values), indicating that there was no carryover effect. Less than expected intrasubject variability was observed for log-transformed \( \text{C}_{\text{max}} \) in the FCT and ODT studies (10.5% and 16.95%, respectively).

The 90% confidence interval for the ratio of the logarithmically transformed values of primary variables (\( \text{AUC}_{0-\text{inf}}, \text{AUC}_{0-\text{t}}, \text{C}_{\text{max}} \)) laid between the predefined range of 80–125%. \( \text{AUC}_{0-\text{inf}} \) and \( t_{\text{max}} \) were also within the acceptance bioequivalence limits (80–125% and 70–130%, respectively). Results are presented in Table 2.
Table 1: Un-transformed descriptive data of pharmacokinetic parameters of generic (Test) and brand name (Reference) olanzapine.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Olanzapine film-coated tablets</th>
<th>Olanzapine orodispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (h · ng/ml)</td>
<td>967.833 (276.646)</td>
<td>890.717 (265.626)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>39.747 (7.443)</td>
<td>37.975 (6.141)</td>
</tr>
<tr>
<td>AUCA&lt;sub&gt;0-∞&lt;/sub&gt; (h · ng/ml)</td>
<td>988.652 (287.313)</td>
<td>914.138 (291.548)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>4.00 (1.00–5.00)</td>
<td>4.00 (3.00–7.00)</td>
</tr>
</tbody>
</table>

1) Pharmacokinetic parameters are given as mean (SD). Median and range for t<sub>max</sub>.

Table 2: Bioequivalence assessment summary.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Olanzapine film-coated tablets</th>
<th>Olanzapine orodispersible tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T/R ratio (%)</td>
<td>90 % CI (%)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (h · ng/ml)</td>
<td>109.16</td>
<td>99.96–119.22</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>109.59</td>
<td>103.48–116.06</td>
</tr>
<tr>
<td>AUCA&lt;sub&gt;0-∞&lt;/sub&gt; (h · ng/ml)</td>
<td>108.79</td>
<td>95.59–118.85</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>88.4</td>
<td>75.2–100.0</td>
</tr>
</tbody>
</table>

1) Log-transformed data. 2) Hauschke’s non-parametric ratio and 90 % confidence interval.

4. Discussion

Based upon the 90 % confidence interval for the ratio of geometric means (test/reference) of logarithmically transformed AUC<sub>0-∞</sub> and C<sub>max</sub> bioequivalence can concluded for the two olanzapine 10 mg film-coated tablet formulations (test and reference) as well as for the two olanzapine 10 mg orodispersible tablet formulations. The 90 % confidence intervals for the ratio of AUC<sub>0-∞</sub> and t<sub>max</sub> were also within the bioequivalence limits. Based on the study data, it can be confirmed that drug exposure between brand and generic formulation is comparable. Considering that the observed plasma concentration of test and reference formulations are essentially similar, the generic formulations are expected to produce the same therapeutic response as the brand name formulations and they can be used interchangeably in clinical practice.

Conflict of Interest

All authors of the article declare no conflict of interests.

References