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Single Dose Bioequivalence Study of Two Brands of Olanzapine 10 mg Tablets in Iranian Healthy Volunteers

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Key words
- olanzapine
- bioequivalence
- pharmacokinetics
- HPLC

Abstract

This single dose, randomized, open label, 2-period and crossover study in healthy Iranian adult volunteers was conducted to compare the bioavailability of 2 branded formulations of olanzapine 10 mg tablets. 24 volunteers received one tablet of each olanzapine 10 mg formulation. Drugs were administered after a 12 h overnight fast in each of 2 treatment days which separated by a 2-week washout period. Serial blood samples were collected over a period of 72 h. Plasma was analyzed using a validated high performance liquid chromatography method with ultraviolet detection in the range of 2–24 ng/mL with a lower limit of quantitation of 1.25 ng/mL. A non-compartmental method was employed to determine the pharmacokinetic properties (C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $T_{1/2}$) to test to bioequivalence. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were used to test the bioequivalence after log-transformation of plasma data. The mean (SD) C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the test formulation were 15.82 (3.15) ng/mL, 447.19 (100.64) ng.h/L and 570.75 (130.55) ng.h/L respectively. Corresponding values for the test formulation were 15.72 (4.25) ng/mL, 440.37 (98.75) ng.h/mL and 558.66 (129.57) ng.h/mL. For test formulation vs. the reference formulation, the 90% CIs of the least squares mean test/reference ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 97.6–110.0%, 96.4–109.4% and 97.3–109.2%. In these volunteers, based on the FDA regulatory definition, results from the pharmacokinetic analysis suggested that the test and reference formulations of olanzapine 10 mg tablets were bioequivalent.

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Introduction

Olanzapine (OZP, CAS Number: 132539-06-1) is an atypical antipsychotic drug showing high affinity for serotonin 5-HT2A/2C, dopamine, muscarinic M1–M5, histamine H1 and adrenergic alpha-1 receptors which is used to treat schizophrenia and related disorders. It is used either as a monotherapy or in combination with mood stabilizers for the treatment of acute mania in bipolar disorders. It is effective against both positive and negative symptoms of schizophrenia, which is an additional advantage compared to classical antipsychotics such as phenothiazines and butyrophenones [1–7]. Following oral administration, OZP is about 93% plasma protein bound, mainly to albumin and α-acid glycoprotein. It has an oral bioavailability of about 60% mainly due to hepatic first pass metabolism. OZP is well absorbed after oral administration and its absorption is not affected by food. After oral administration to healthy subjects, the mean terminal elimination half-life was 33 h. Approximately 57% of radiolabelled OZP is excreted in urine, principally as metabolites, about 7% is excreted unchanged in the urine after a single oral dose and around 30% is excreted in the feces [1, 4, 8–10]. Interchangeability between generic and innovator drug products and reducing pharmaceutical costs is a great goal and concern especially in developing countries. Bioequivalence is defined as the absence of a significant difference in the rate and extent of the active ingredient in pharmaceutical equivalents when administered at the same molar dose under similar conditions in an appropriately designed study [11]. The present study was undertaken to determine and compare the pharmacokinetic properties of one generic formulation manufactured in Iran (test) with a branded innovator formulation (reference) of OZP 10 mg tablets in Iranian subjects to establish their bioequivalence.

Materials and Methods

Materials

Acetonitrile, hexane and dichloromethane were HPLC grade and purchased from Merck Company (Darmstadt, Germany). Clozapine was provided form Fluka Chemica (Milano, Italy). Phosphoric acid, KH_2PO_4 and Triethanolamine were obtained from Merck Company (Darmstadt, Germany). Test formulation was Olanzapine 10 mg tablet (Exir, Boroujerd, Iran, batch number 275) and the reference formulation was Zyprexa10 mg tablet (Lilly, France, batch number A089301).

Dissolution test

The dissolution of the 2 formulations was assessed using USP apparatus II (Erweka DT6R) (900 ml HCl at 37 °C, 100 rpm). Each sample solution was filtered, and the drug release was determined spectrophotometerically at 258.8 nm (Shimadzu 160, Kyoto, Japan). According to drug monograph, each tablet should release at least 80% of its content in 30 min. The mean dissolution values at each time interval were used to calculate the difference factor (f_1) and similarity factor (f_2) using the standard mathematical equations [11].

Study design

24 healthy Iranian male volunteers aged between 20–33 years (24.6±3.1 years) and weighed from 60 to 89 kg (71.7±7.7 kg) were enrolled in the study and informed consent was obtained. The study was approved by the Ethics Committee of Tabriz University of Medical Sciences prior to commencing and was performed in accordance with the principles of the World Medical Association's Declaration of Helsinki and its amendments. Subjects underwent screening examinations that included a medical history and physical examination. Volunteers received a single 10 mg OZP tablet of the test or reference formulation along with 200 mL of water. Serial venous blood samples (7 mL) for the determination of plasma OZP concentrations were obtained from forearm vein before dosing and at 0.5, 1, 1.5, 2, 3, 6, 8, 10, 12, 24, 48 and 72 h after dosing in each period. Samples were collected in heparinized tube which contained 50 µL acid ascorbic 10% as antioxidant. The 2-week washout period between studies were chosen based on a reported $T_{1/2}$ for OZP. Serum was separated by centrifugation with 5000 rpm and stored at −20 °C until analysis. Frozen plasma was thawed at room temperature and then 50 µL of clozapine (as internal standard) solution (3750 ng/mL) and 8 mL of extracting solution (hexane 85: dichloromethane 15) were added to 2 mL of plasma. After mixing for 5 min, the solution was centrifuged at 5000 rpm for 5 min. 350 µL of KH_2PO_4 0.2 M (pH 2.8) was added to organic supernatant. After mixing for 1 min, mixture was centrifuged for further 5 min. Then upper organic phase was withdrawn and 200 µL of hydrophilic phase was injected into the column [12]. Investigation of long-term freezer stability (−20 °C) revealed that olanzapine was stable in plasma during storage time.

HPLC method

The liquid chromatographic system (Beckman, USA) used for the evaluation of OZP in human plasma, was a modified and validated method previously reported by Dusci, et al. [12]. All plasma samples of a given volunteer collected in the 2 treatment periods were measured in the same chromatographic run (analytical own control). Each run had a separate daily calibration and contained quality control samples (QC) at 4 concentration levels. There was no rationale for sample re-analysis in the present study. However, since the use of calibration standards and QC samples during validation may not mimic the actual study samples, accuracy of incurred samples were measured by reanalysis of study samples in separate runs at different days. Totally about 10% of samples around C_{max} and in the elimination phase were reanalyzed. For more than 85% of repeats the concentration obtained for the initial analysis and the concentration obtained by re-analysis were within 20% of their mean. Chromatographic separation was performed using a Shimpack CLC C8 5 µm (250×4.5 mm) (Shimadzu, Columbia, MD). The mobile phase consisted of H_2O (containing 0.25% phosphoric acid and 0.05% triethylamine, pH adjusted to 2.6): acetonitrile (86:14 v/v %), eluted at a flow rate of 1.5 mL/min. The ultraviolet detector set at 254 nm. In this condition retention time for OZP and clozapine (internal standard) were 3.9 min and 8.5 min respectively. The method was validated in terms of selectivity, linearity, precision, accuracy and recovery. The average extraction recovery was determined by comparing the peak area obtained from the serum sample with the peak area obtained by the direct injection of pure drug standard solution at 3 varied (4, 12, and 24 ng/mL) quality control (QC) levels. The procedure was repeated on the same day and between 3 consecutive days on the same QC samples. The precision and accuracy of the method were assessed in plasma by replicate analysis of QC samples against calibration standards. The peak area was measured for calculation of the ratio of OZP to IS, and the concentrations were estimated [8, 13–17]. Representative chromatograms of a typical blank plasma sample, IS and olanzapine (in concentrations of 1.25 and 4 ng/ml) was illustrated in **Fig. 1**.

Pharmacokinetic and statistical analysis

Plasma concentration-time profiles were generated for each volunteer and then mean values were determined. Individual pharmacokinetic parameters were assessed by a non-compartmental method. C_{max} and T_{max} were obtained by direct assessment of individual plasma concentration- time profiles. The AUC_{0-t} was calculated using the linear trapezoidal method. The terminal elimination constant (K_e) was estimated from the natural logarithm-transformed plasma concentration- time curve using linear regression, and the $T_{1/2}$ was calculated as $\ln 2/K_e$. The $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-t} and the ratio of the last measured plasma concentration of the last blood sampling time and K_e [18–21]. Statistical comparisons between pharmacokinetic parameters of the 2 products were analyzed using 2-way

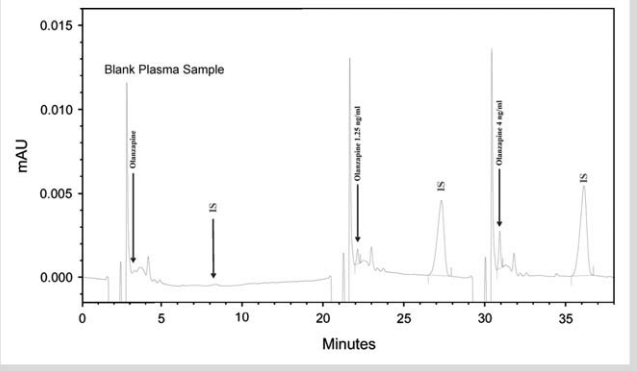

Fig. 1 Representative chromatogram of a typical blank plasma sample and blank plasma spiked by olanzapine and internal standard.

ANOVA with $p<0.05$ for statistical significance to assess the effect of formulation, periods, sequence, subjects within sequence. The 90% Confidence Intervals (CI) of the geometric means of the individual test/reference (T/R) ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were obtained to assume bioequivalence between the products based on regulatory requirements [11,19,22–24].

As proposed by the FDA, if the parametric 90% CIs fell within a predetermined range of 80–25%, the 2 formulations were concluded to meet the regulatory criteria for bioequivalence.

Results and Discussion

In vitro drug dissolution data generated from dissolution testing experiments showed that 97.6% and 99.8% of active substance was released during the first 20 min from test and reference formulations respectively, which are more than accepted value mentioned in drug monograph.

Moreover the difference factor of 4.52 (acceptable limit 0–15) and the similarity factor of 61.53 (acceptable limit 50–100) were calculated.

For construction of the calibration curve for in vivo study, olanzapine concentrations of 2, 4, 8, 12, 16 and 24 ng/mL in plasma were used. The mean of regression correlation coefficients (r^2) of the calibration curves was 0.998±0.005. The lower limit of quantitation (LLOQ) of OZP in plasma was 1.25 ng/mL. The recovery of the method was between 82.84% and 84.78% (**Table 1**). The intra-day and inter-day precision and accuracy are shown in **Table 2**. The precision values were all <15%. The accuracy was between 101.31% and 112.13%. Technically, the assay for the determination of OZP from human plasma in this study was a highly reproducible, sensitive and accurate method. Generally in single dose studies the highest marketed strength can be administered [25]. Therefore in the present study 10 mg olanzapine was taken by volunteers and drowsiness was the only observed side effect. The mean plasma concentration-time curves after administration of single oral doses of the 2 formulations of OZP 10 mg tablets are illustrated in **Fig. 2**.

The sampling schedule should cover the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure. This is achieved if AUC_{0-t} covers at least 80% of $AUC_{0-\infty}$ in more than 80% of the observations [26] which is met by our obtained results. In order to reliably estimate the terminal elimination rate constant at least 3–4 samples should be obtained during the terminal log-linear phase [25]. However it is assumed that absorption will be completed in most subjects within 72 h and normally any unabsorbed remnant of the dosage form or the drug would be eliminated from the body. Therefore effects of the dosage form itself are expected to be completed within this period. Hence, according to guidelines, for oral products with a long half-life drug, it will not be necessary to sample for more than 72 h post-dose, regardless of the half-life [26–29]. For this reason in the current study truncated AUCs at 72 h was used for comparison of extent of exposure. The obtained mean (SD) T_{max} for test and reference formulations were 5.17 (1.31) and 6.25 (1.22) h respectively and 6 samples were taken after C_{max}. The mean (SD) C_{max} for the test and reference formulations were 15.82 (3.15) and 15.72 (4.25) ng/mL, respectively. The AUC_{0-t} for the 2 formulations were 447.19 (100.64) and 440.37 (98.75) ng.h/mL, and the $AUC_{0-\infty}$ were 570.75 (130.55) and 558.66 (129.57) ng.h/mL (**Table 3**). In a similar study by Elshafeey et al., the mean C_{max} was found to be 13.07 ng/mL. The AUC_{0-t} and $AUC_{0-\infty}$ in their investigation were reported as 363.38 ng.h/mL and 466.87 ng.h/mL respectively [30].

The 90% CIs for the ratios of C_{max} (97.6–110.0), AUC_{0-t} (96.4–109.4) and $AUC_{0-\infty}$ (97.3–109.2) were within the acceptance range for bioequivalence and met the predetermined criterion for regulatory bioequivalence (**Table 4**). No product, period and group effects were found on ANOVA of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Several analytical methods have been reported for determination of olanzapine in biological fluids and pharmaceutical preparations including liquid chromatography (LC)-tandem mass spectrometry (MS), LC-atmospheric pressure ionization MS, gas chromatography-MS and electrophoresis [13,14,31–33]. However the most widely used method for the assay of OZP in biological samples and pharmaceuticals seems to be liquid

Table 1 Extraction recovery of olanzapine from different QC.

Concentration (ng/ml)	4	12	24
Mean Recovery (%)	82.84	84.49	84.78
SD (ng/ml)	5.71	2.82	4.97
RSD	6.89	3.34	5.86

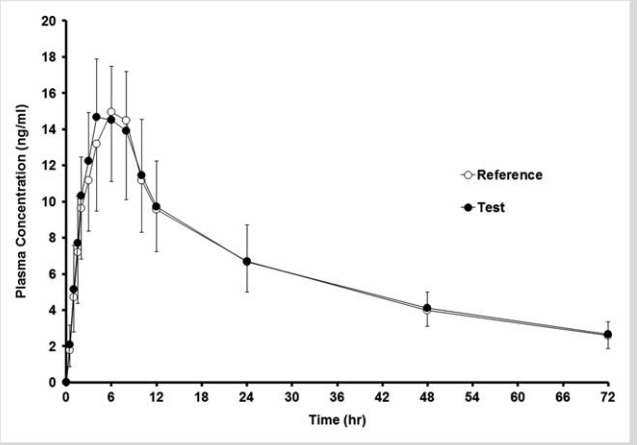

Fig. 2 Mean plasma concentration-time curve after administration of single doses of the test and reference formulations.

Table 2 Intra-day and Inter-day precision and accuracy obtained from 4 levels of QC samples.

Added concentration (ng/ml)	Intra-day				Inter-day			
	Mean (ng/ml)	SD (ng/ml)	CV (%)	Accuracy (%)	Mean (ng/ml)	SD (ng/ml)	CV (%)	Accuracy (%)
2	2.19	0.15	6.83	109.25	2.24	0.24	10.60	112.13
8	8.11	0.28	3.49	101.41	8.11	0.40	5.00	101.31
12	12.24	0.59	4.78	102.00	12.70	0.72	5.68	105.85
24	25.31	1.09	4.30	105.47	26.05	1.45	5.57	108.52

Parameter	Test			Reference		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC_{0-t} (ng.h/mL)	447.19	100.64	22.50	440.37	98.75	22.43
$AUC_{0-\infty}$ (ng.h/mL)	570.75	130.55	22.87	558.66	129.57	23.19
C_{max} (ng/mL)	15.82	3.15	19.91	15.72	4.25	27.08
T_{max} (h)	5.17	1.31	25.31	6.25	1.22	15.49
$T_{½}$ (h)	31.53	5.57	17.65	30.96	4.80	15.49

Table 3 Pharmacokinetic parameters for the test and reference preparations (10 mg OZP tablet) after oral administration to 24 healthy volunteers.

Pharmacokinetic parameter	ANOVA (P-value) Variation source			90% C.I. for the ratios
	Product	Group	Period	
C_{max}	0.8425	0.2431	0.1037	97.6–110.0
AUC_{0-t}	0.6629	0.2205	0.097	96.4–109.4
$AUC_{0-\infty}$	0.5337	0.1748	0.498	97.3–109.2

Table 4 The 90% CI for the ratios test/reference of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values.

chromatography with ultraviolet detection. In previous studies in which HPLC-UV method was used, the lowest LOQ and retention time were reported to be 1 ng/mL and 8 min respectively [8]. In the method used in this research LOQ was 1.25 ng/mL and retention time was 3.9 min. Therefore the present method was almost as sensitive as previously reported HPLC-UV method with 2-fold faster run time.

Evaluation of the bioequivalence of test and reference drugs is required to exclude any clinically important differences in the rate or extent of the drugs becomes available at the site of action. The FDA considers 2 drugs bioequivalent if they are pharmaceutically equivalent and their bioavailabilities are so similar that they are unlikely to produce clinically relevant differences in regard to efficacy. The pharmacokinetic parameters obtained with the test and reference formulations were not significantly different, which reflects the comparable pharmacokinetic characteristics of the 2 formulations.

Conclusion

Bioequivalence between the products was determined with 90% CIs for the ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values for the test and reference formulations using log-transformed data. The calculated 90% CIs for the ratios of mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the regulatory acceptance range for bioequivalence (80–125%). Therefore the present study suggests that the test formulation, 10 mg OZP tablet, was bioequivalent to the reference formulation, according to the FDA regulatory definition in this population of healthy adult male Iranian volunteers.

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Conflict of Interest

The authors indicate that they have no conflicts of interest in this report.

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