

Comparative Bioavailability of Two Quetiapine Formulations in Healthy Volunteers after a Single Dose Administration

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Abstract

The study was performed to compare the bioavailability of two quetiapine 25 mg tablet formulations: the test formulation was quetiapine fumarate (kitapen®) manufactured by Cobalt Pharmaceuticals, Canada/ Arrow Farmacêutica Ltda* (Erowlabs). Seroquel® (quetiapine) from Astrazeneca Brazil was used as reference formulation. The study was conducted open with randomized two period crossover design and one week wash out period in 64 volunteers of both sexes. Plasma samples were obtained over a 48 hour interval. Quetiapine was analyzed by LC-MS-MS in the presence of quetiapine-D8 as internal standard. Plasma samples were obtained over a 48 hour interval. Quetiapine was analyzed by LC-MS-MS in the presence of quetiapine-D8 as internal standard. The mean ratio of parameters C_{max} and AUC_{0-t} and 90% confidence intervals of correspondents were calculated to determine the bioequivalence. The means AUC_{0-t} for test and reference formulation were 432.41 ng.h/mL and 412.20 ng.h/mL, for $AUC_{0-\infty}$ were 440.06 ng.h/mL and 418.90 ng.h/mL and, for C_{max} 126.94 ng/mL and 108.71 ng/mL, respectively. Geometric mean of quetiapine (kitapen®)/Seroquel® 25 mg individual percent ratio was 97.68% AUC_{0-t} , 97.47% for $AUC_{0-\infty}$ and 90.68% for C_{max} . The 90% confidence intervals were 92.67 – 102.96%, 92.53 – 102.67%, 83.37 – 98.64%, respectively. Since the 90% confidence intervals for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were within the 80 – 125% interval proposed by Food and Drug Administration, it was concluded that quetiapine (kitapen®) 25 mg tablet was bioequivalent to Seroquel® 25 mg tablet according to both the rate and extent of absorption.

Keywords: Bioavailability; Pharmacokinetics; Chromatography; Bioequivalence

Introduction

Quetiapine is an antipsychotic drug with a unique receptor-binding profile belonging to the same chemical class of the antipsychotic clozapine, the dibenzothiazepine derivatives and classified as an atypical or second generation antipsychotic [1,2]. This profile confers quetiapine a low risk of extrapyramidal effects and hiperprolactinemia [3].

Quetiapine is indicated for the treatment of schizophrenia and bipolar disorder. Schizophrenia is a common and serious mental disorder affecting around 0.7% of people at some point in their life. Its peak ages of onset are within the twenties; it is a chronic disabling disorder that affects young people and accounts for a disproportionate share of healthcare expenditures and loss of productivity [4]. Bipolar affective disorder, including the more classic form defined by the occurrence of manic or mixed episodes (bipolar I disorder) and the form defined by less severe hypomanic episodes (bipolar II disorder), is relatively common (combined lifetime incidence: approximately 3% to 5%), typically begins early in life (ie, before age 25), is associated with high rates of recurrence and chronicity, and results in significant morbidity. Due to these characteristics, bipolar affective disorder is one of the world's greatest public health problems [5-7].

Quetiapine is metabolized by the liver. Less than 1% excreted as unchanged drug. Approximately 73% of dose recovered in urine and 20% in feces. The mean terminal half-life for immediate-release is 6 h, for ER is 7 h, and for N-desalkyl quetiapine is 12 h. Quetiapine appears to be the major circulating species in plasma. Unlike other antipsychotics such as olanzapine no effect of cigarette smoking on quetiapine clearance was observed. The pharmacokinetics of quetiapine are linear, and do not differ between men and women [8-10].

In order to avoid adverse reactions and unnecessary risks to the

subjects, the study was conducted using the lowest dose (25 mg) of quetiapine, in compliance with the requirements of the Brazilian regulatory agency. It was taken into account that the pharmacokinetics of quetiapine is linear [8-10] and clinical trials must be carried out under conditions which ensure adequate safety of the subjects.

The objective of this study was to compare in healthy volunteers, the pharmacokinetics profiles and evaluate the bioequivalence of one test formulation of 25 mg tablet of quetiapine (kitapen®) manufactured by Cobalt Pharmaceuticals, Canada/ Arrow Farmacêutica Ltda* (Erowlabs). The test formulation was compared to 25 mg of quetiapine (Seroquel®) by Astrazeneca Brazil (reference formulation).

Methods

Study protocol

The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guideline, and informed consent was obtained from participants prior to study commencement. The clinical part of the study was conducted at Scentryphar Clinical Research (Campinas City, São Paulo, Brazil) and the bioanalytical

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part at Nucleus of Bioequivalence and Clinical Research/NUBEC (São Paulo, Brazil).

Subjects

Sixty four healthy volunteers of both sexes (32 males and 32 females) who were between the ages of 18 and 48 (mean \pm SEM: 30.84 \pm 8.03 years), who had heights between 144.00 cm and 182.00 cm (165.00 \pm 0.08 cm), and who weighed between 49.10 kg and 88.00 kg (66.19 \pm 9.45 kg) and within 15% of their ideal body weight were enrolled in the study. Subjects were judged eligible for enrolment in this study if they were in compliance with all the inclusion and exclusion criteria described in the protocol.

All the subjects provided written informed consent to participate after explaining the nature and purpose of the study. The study protocol was approved by the University of Campinas/Unicamp with the ethical principles described in the Declaration of Helsinki, guidelines for International Conference on Harmonization-Good clinical practices (ICH-GCP).

All volunteers were healthy as assessed by physical examination, ECG, and the following laboratory tests: blood glucose, urea, creatinine, AST, ALT, alkaline phosphatase, Gamma GT, total bilirubin, albumin and total protein, triglycerides, total cholesterol, hemoglobin, hematocrit, total and differential white cell counts and routine urine. All subjects were negative for HIV, HBV (except for serological scare) and HCV.

Drug products

The test formulation employed was quetiapine (kitapen®) 25 mg tablet (lot number ZA77) and the reference formulation was: Seroquel® 25 mg tablet (lot number 80915).

Study design

The study was performed to compare the bioavailability of two quetiapine 25 mg tablet formulations under fasting conditions: the test formulation was *fumarato de quetiapina* (kitapen®). Seroquel® from Astrazeneca Brazil was used as reference formulation. The formulation was tested for bioequivalence for the first time.

The study was conducted in an open randomized 2 period crossover balanced design with a 1 week wash out period between the doses. During each period, the volunteers were hospitalized at 8:00 pm having already had a normal evening meal, and after an overnight fast they received at 7:00 am a single 25 mg tablet quetiapine dose of either formulation. Water (200 mL) was given immediately after drug administration. All volunteers were then fasted 05 hours following the drug administration, after which a standard lunch was consumed and an evening meal was provided 10 hours after dosing. No other food was permitted during the "in-house" period. Liquid consumption was permitted ad libitum after lunch but xanthine-containing drinks including tea, coffee and cola were avoided. Systolic and Diastolic arterial pressure (measured on invasively with a sphygmomanometer automatic by Omron equipment), heart rate and temperature were recorded just before and hourly after drug administration.

Blood samples (06 mL) from a suitable antecubital vein were collected into EDTA containing tubes before and 0.10, 0.20, 0.30, 0.40, 0.50, 1.00, 1.10, 1.20, 1.40, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00, 48.00 hours after administration of each quetiapine 25 mg tablet.

Drug analysis

Blood samples were cooled in a bath and centrifuged at 3.000 rpm for at least 10 min at approximately 4°C. At least 3mL of plasma were dispensed into polypropylene tubes. Sample tubes were frozen at -20°C, and maintained to that temperature until analysis. All samples from a single volunteer were analyzed on the same day in order to avoid inter assay variation.

Plasma concentrations of quetiapine were determined by the HPLC coupled with tandem mass spectrometry (LC/MS/MS), in positive ion electrospray ionization mode, using a multiple monitoring (MRM) method and isotopic labeled quetiapine-D8 as internal standard (IS). The transitions used were 384.6 \rightarrow 253.0 for quetiapine and 392.6 \rightarrow 253.0 for IS. This apparatus consisted of a Shimadzu LC-10ADvp pump, an on line SPE system - Prospekt-2™ Spark Holland and Micromass QuattroLC triple-quadrupole mass spectrometer. The analytes were extracted automatically from plasma using on line solid phase extraction, with Hysphere HD C18 cartridges. The method was validated for selectivity, linearity, precision, accuracy, extraction recovery and stability.

The analytical column was a Chromolith-RP18, 100 x 4.6 mm, 5 μ (Merck). The mobile phase used, in isocratic mode, was a mixture of acetonitrile, methanol and water (30:20:50 v/v), containing 20 mM acetic acid.

Pharmacokinetic analysis and statistical analysis

The first-order terminal elimination rate constant (Ke) was estimated by linear regression from the points describing the elimination phase on a log-linear plot, using the software SAS® Institute (Version 9.1.3). Elimination half-life (T_{1/2}) was derived from this rate constant (T_{1/2} = ln (2)/Ke). The maximum observed plasma concentration (C_{max}) and the time taken to achieve this concentration (T_{max}) were obtained directly from the curves. The areas under the quetiapine metabolite plasma concentration versus time curves from 0 to 48 hours (AUC_{0-48h}) were calculated by applying the linear trapezoidal rule. Extrapolation of these areas to infinity (AUC_{0-∞}) was done by adding the value C₄₈/Ke to the calculated AUC_{0-48h} (where C₄₈=plasma concentration calculated from the log-linear regression equation obtained for the estimation of Ke 48 hours after dose).

The bioequivalence between both formulations was assessed by calculating individual C_{max}, AUC_{0-48h}, AUC_{0-∞} and C_{max}/AUC_{0-48h} ratios (test/reference) together with their mean and 90% confidence intervals (CI) after log transformation of the data. The inclusion of the 90% CI for the ratio in the 80% to 125% range was analyzed by nonparametric (SAS® Institute Version 9.1.3) and parametric (ANOVA) methods.

Results

Tolerability analysis

Quetiapine was well tolerated at the administered dose. All the biochemical parameters did not any clinical relevant alterations. No adverse effects serious were either reported or observed.

Method validation

The calibration curves were linear in the ranges of 0.2 – 200 ng/mL (R² \geq 0,99) by using least square linear regression analysis with a weight factor of 1/x. The precision and accuracy were obtained by the analysis of tree batches of QC samples (LLOQ, low, medium and High QCs)

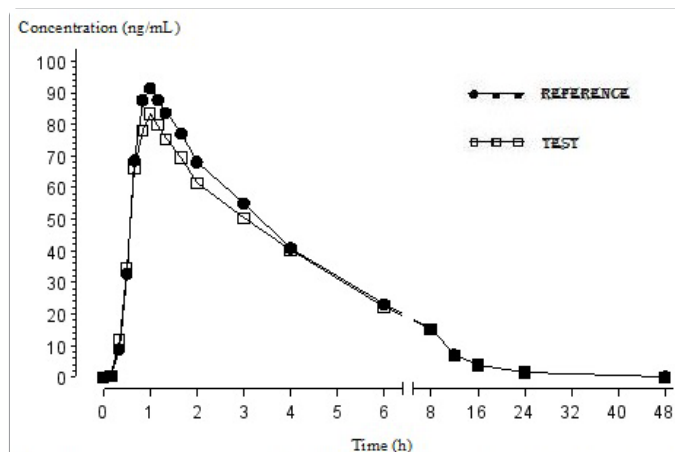


Figure 1: Mean plasma concentration-time profile of quetiapine over the first 48 h after oral administration of the test and reference formulation.

and the intra and inter day RSDs were no more than 8.3%, indicating acceptable precision and accuracy of the present method.

The extraction recoveries of quetiapine and IS from human plasma were $75.70 \pm 3.92\%$ and $79.74 \pm 4.00\%$, respectively.

The stability of stock solutions of quetiapine and IS were assessed and found stable at room temperature for 6 h and at 4°C for 60 days. The analytes in plasma stored at room temperature for 6 h, at 4°C for 7 days, at -20°C for 100 days and during the three freeze and thaw cycles indicated the good stability of quetiapine and IS during the study.

Pharmacokinetic and statistical analysis

The mean (\pm SD) plasma concentration time profile of the 2

formulations, shown in Figure 1, was similar and super imposable.

Central and dispersion measures for all pharmacokinetic parameters for both formulations are shown in Table 1 and Table 2. From this, the mean values of C_{max} were found to be $126.94 (\pm 67.80)$ standard deviations [SD] ng/mL for the reference product and $108.71 (\pm 41.63)$ ng/mL for the locally manufactured (test) product. For T_{max} (h), the mean values were found to be similar for both the reference and local product and the value was 5.52 (5.38) h. The mean values of AUC_{0-48} were found to be $432.41 (\pm 259.23)$ ng.h/mL for reference and $412.20 (\pm 217.26)$ ng.h/mL for local product. The mean $AUC_{0-\infty}$ were found to be $440.06 (\pm 260.24)$ ng.h/mL and $418.90 (\pm 218.22)$ ng.h/mL for the reference and locally manufactured product, respectively.

Table 3 presents the ratios and the respective confidence intervals for bioequivalence analysis.

Discussion

Due to increasing use of quetiapine in the clinical practice, which encourages the development of new pharmaceutical preparations, there is an increasing demand for new analytical methods for determination of quetiapine. Several HPLC methods for the determination of quetiapine have been reported. None of these methods is sensitive enough for determination of the expected drug levels and some of them are timeconsuming and require complex sample pretreatment or long run times. The quantification of various drugs by chromatography with tandem mass spectrometry is becoming each more common time due to improvement in the sensitivity and the selectivity of this method [11-19]. With the advance of the chromatography the quality in the determination of the concentrations is more precise, getting a lower LOQ and better analysis of results. The analytical method presented here for the determination of quetiapine was analyzed by LC-MS-MS. No interferences from endogenous

Parameter (unit)	TEST		REFERENCE	
	Means (Median)	Standard Deviation (Amplitude)	Means (Median)	Standard Deviation (Amplitude)
AUC_{0-t} (ng.h/mL)	412.20	217.26	432.41	259.23
AUC_{0-inf} (ng.h/mL)	418.90	218.22	440.06	260.24
C_{max} (ng/mL)	108.71	41.63	126.94	67.80
T_{max} (median/amp) (h)	1.00	3.50	1.00	2.50
Kel (1/h)	0.14	0.05	0.14	0.05
$T_{1/2}$ (median/amp) (h)	5.38	7.19	5.52	17.07

Table 1: Mean pharmacokinetic parameters of quetiapine of test and reference formulation.

Parameter (unit)	TEST	REFERENCE
	Geometric Mean	Geometric Mean
AUC_{0-t} (ng.h/mL)	369.21	377.99
AUC_{0-inf} (ng.h/mL)	376.15	385.92
C_{max} (ng/mL)	101.06	11.45

Table 2: Geometric mean pharmacokinetic parameters of quetiapine of test and reference formulation.

Parameter	Ratio T/R (%)	Lower Limit (%)	Upper Limit (%)	Power (%)	Coefficient of Variation (%)
AUC_{0-t}	97.68	92.67	102.96	99.99	17.53
AUC_{0-inf}	97.47	92.53	102.67	99.99	17.30
C_{max}	90.68	83.37	98.64	79.29	28.34
T_{max} (dif) (h)	0.00	0.00	0.17	-	-

Table 3: Ratios means and the 90% geometric confidence interval of test and reference formulation.

plasma components or other sources were found and no “cross-talk” was observed in plasma samples. The assay showed good precision and accuracy. The analytical method has been proved useful for the investigation of the characteristics of quetiapine in human plasma in pharmacokinetic studies.

The bioavailability of a pharmaceutical form refers to the extent and speed of absorption of the active principle in contained it. Two pharmaceutical forms are said bioequivalent when administered to the same individual, in the same experimental conditions and at the same dose, they show no significant differences in relation to bioavailability. In this study two formulations of quetiapine had been evaluated. Washout period was adequate, there was no quantifiable concentration of the drugs in the second period of the study, indicating that there was no carryover effect from the first to the second period. The mean ratio of parameters C_{max} and AUC_{0-t} and 90% confidence intervals of correspondents were calculated to determine the bioequivalence. The means AUC_{0-t} for test and reference formulation were 432.41 ng.h/mL and 412.20 ng.h/mL, for $AUC_{0-\infty}$ were 440.06 ng.h/mL and 418.90 ng.h/mL and, for C_{max} 126.94 ng/mL and 108.71 ng/mL, respectively. The ratios were 97.68% for AUC_{0-t} , 97.47% for $AUC_{0-\infty}$ and 90.68% for C_{max} . The 90% confidence intervals were 92.67 – 102.96% for AUC_{0-t} , 92.53 – 102.67% for $AUC_{0-\infty}$ and 83.37 – 98.64% for C_{max} .

The AUC_{0-t} and $AUC_{0-\infty}$ are both recognized as an uncontaminated measurement of the extent of absorption. The present study showed that 90% CI of mean AUC_{0-t} and $AUC_{0-\infty}$ (after log-transformation of individual ratios) were included into the bioequivalence range (80-125%), consequently, the two formulations of quetiapine are equivalent for the extend of absorption.

The statistical comparison of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ clearly indicated no significant difference in the two formulations of quetiapine 25 mg tablet. 90% confidence intervals for the mean ratio (T/R) of C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were entirely within the US Food and Drug Administration acceptance range. Based on the pharmacokinetic and statistical results of this study, we can conclude that quetiapine 25 mg tablet (kitapen®, manufactured by Cobalt Pharmaceuticals, Canada/ Arrow Farmacêutica Ltda* (Erowlabs) is bioequivalent to Seroquel® 25 mg tablet (Astrazeneca, Brazil), and that then the test product can be considered interchangeable in medical practice.

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