ISSN: 0975-0851
Journal of Bioequivalence & Bioavailability

OPEN ACCESS Freely available online

Research Article

# Bioequivalence Study of Quetiapine 25 mg Tablets in Healthy Thai Volunteers under Fasting Conditions

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## ABSTRACT

A comparative randomized, single-dose, two-way crossover, open-label study was carried out to assess bioequivalence and tolerability of test (Quapine®) and reference (Seroquel®) products of quetiapine 25 mg tablets in healthy Thai volunteers. Forty-four male and female subjects were enrolled in the study. Blood samples were collected at predefined time points over 48 hours after oral administration. Plasma concentrations of quetiapine were determined using a validated Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS). The pharmacokinetic parameters were calculated for the test and reference products using non-compartmental analysis. Bioequivalence between the products was determined by calculating 90% Confidence Intervals (CIs) for the geometric least squares mean ratio of log-transformed primary parameters ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and $C_{max}$) between the test and reference products. The 90% CIs were 96.08%-108.33% for $AUC_{0\text{-tlast}}$, 96.21%-108.31% for $AUC_{0\text{-}\infty}$ and 96.52%-121.09% for $C_{max}$ which were within the bioequivalence criteria of 80.00%-125.00%. The analysis of variance did not show any significant difference between the two formulations. Both formulations were generally well tolerated in Thai subjects. The incidence of adverse events after receiving the test and reference products was similar. Therefore, they can be used interchangeably, and the same efficacy and safety can be anticipated.

**Keywords:** Quetiapine; Bioequivalence; Pharmacokinetics; Antipsychotic

## INTRODUCTION

Quetiapine is an atypical antipsychotic drug with dibenzothiazepine structure (Figure 1). It is indicated for the treatment of acute schizophrenia. It has the efficacy by improving positive and negative symptoms as well as cognitive functions of patients [1]. It is also effective against manic and depressive episodes associated with dipolar disorder [2,3]. The mechanisms of antipsychotic effects are not well understood but generally explained by antagonism at both serotonin 5-$HT_2$ and dopamine $D_2$ receptors. As quetiapine has relative lower binding affinity for $D_2$ receptors compared with 5-$HT_2$ receptor, a lower risk of extrapyramidal symptoms is anticipated than typical antipsychotics [4,5].

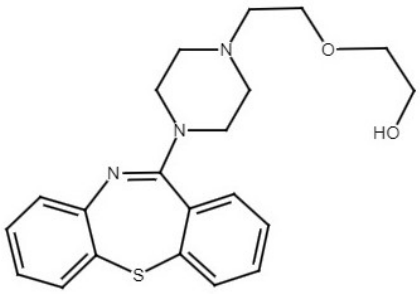


**Figure 1:** Chemical structure of Quetiapine.

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**Received:** 05-Jul-2022, Manuscript No. JBB-22-17308; **Editor assigned:** 08-Jul-2022, PreQC No. JBB-22-17308 (PQ); **Reviewed:** 22-Jul-2022, QC No. JBB-22-17308; **Revised:** 29-Jul-2022, Manuscript No. JBB-22-17308 (R); **Published:** 05-Aug-2022, DOI:10.35248/0975-0851.22.14.478.

**Citation:** Yoosakul E, Khaowroongrueng V, Vattanarongkup J, Seeduang C, Suthepakul N, Karachot B, et al. (2022) Bioequivalence Study of Quetiapine 25 mg Tablets in Healthy Thai Volunteers under Fasting Conditions. J Bioequiv Availab. 14:478.

The pharmacokinetics of quetiapine is linear within the clinical dose range. Quetiapine is well absorbed with achieved maximum plasma concentration within 2 hours following oral administration. The bioavailability of quetiapine is slightly affected by food consumption as evident from the increased rate and extent of absorption. However, quetiapine can be administered with or without food due to clinical irrelevance [6]. Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg and is eliminated with a mean terminal half-life of approximately 7 hours [7]. Although quetiapine is extensively metabolized by the liver, the pharmacokinetics appears to be insignificantly different in patients with hepatic impairment when compared with healthy subjects suggesting that dose adjustment may not be required [8]. Additionally, the dosage of quetiapine should be adjusted in the individual patient based on the clinical response and tolerability [7,9].

The Government Pharmaceutical Organization (GPO), Thailand had developed the generic quetiapine 25 mg tablets (Quapine®) to serve as a low-cost alternative product for physicians and patients without compromising quality and safety. Although Quetiapine is available in 25, 100, and 200 mg tablets as registered trademark in Thailand, Seroquel®, it is justifiable to conduct bioequivalence study at 25 mg tablets and biowaiver of higher strengths is acceptable due to safety concerns [10-12]. Therefore, a randomized, single-dose, two-way crossover, open-label study was conducted to demonstrate the equivalence in biopharmaceutics quality between two quetiapine 25 mg tablets formulations.

## MATERIALS AND METHODS

### Study products

The study products used in this study were quetiapine fumarate tablets equivalent to quetiapine 25 mg. Quapine® bearing lot no. S580231 manufactured by the Government Pharmaceutical Organization (GPO), Thailand was used as the test product and Seroquel® bearing lot no. 60021646 manufactured by AstraZeneca Pharmaceutical Co., Ltd., China was used as the reference product.

### Study subjects

The sample size was computed based on the maximum intra-subject variability for $C_{max}$ of quetiapine about 29%, T/R ratio at 95%, significance level at 5%, and bioequivalence limits of 80.00%-125.00% [13]. According to the calculation, the sample size of 36 study subjects were sufficient for establishing bioequivalence with the power greater than 80%. However, forty-four study subjects were enrolled in the study considering 20% dropouts and withdrawals.

The enrolled study subjects were healthy Thai males and females between 18 and 55 years of age with a Body Mass Index (BMI) between 18.0 kg/m$^2$ and 25.0 kg/m$^2$. The subjects were screened through medical history, physical and laboratory examinations. Female subjects were not pregnant or breastfeeding and were instructed to use non-hormonal birth control methods throughout the study. All study subjects were well informed and provided the written informed consent before participation in the study at International Bio Service Co., Ltd., Golden Jubilee Medical Center, Mahidol University, Thailand. They were randomly assigned to two groups, Test-Reference (TR) and Reference-Test (RT) in the two study periods according to the randomization schedule generated by SAS® version 9.3 (SAS Institute Inc., USA).

### Study design

This study was designed as a randomized, single-dose, two-way crossover, open-label study to determine the bioequivalence of two quetiapine 25 mg tablets formulations under fasting conditions. The study was conducted following the study protocol which was reviewed and approved by the Institute for the Development of Human Research Protections, Thailand. After an overnight fasting for at least 10 hours, one tablet of either the test or reference product was orally administered to each subject in sitting position with 240 mL of water as per the randomization schedule, followed by mouth and hand check to assess the dosing compliance. Then, they switched over to the other product in period II after 7-day washout period to complete the crossover design. All adverse events were monitored throughout the study for safety evaluation and the severity of the occurred adverse events was classified as mild, moderate and severe. A total of 23 blood samples were collected from each study subject at pre-dose and over 48 hours post-dose. At each time point, approximately 3 mL of blood was collected through an indwelling intravenous cannula in a forearm vein and transferred into a vacutainer containing Dipotassium Ethylenediaminetetraacetate ($K_2$EDTA) as the anticoagulant, and then centrifuged at 3000 ± 100 relative centrifugal force (rcf) for 5 minutes at 4°C to separate plasma. Each plasma sample was divided and stored in two separate aliquots for respective sample analysis, repeat analysis and incurred sample reanalysis at -55°C or colder until completion of analysis.

### Study sample analysis and incurred sample reanalysis

The plasma concentration of quetiapine was determined using a validated Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) method complying with the Principles of Good Laboratory Practice (GLP), European Medicines Agency guideline on the investigation of bioequivalence and in-house Standard Operating Procedures (SOPs) [10]. Quetiapine and internal standard, quetiapine-d8 were extracted from plasma by liquid-liquid extraction method using methyl-tert-butyl ether as an extraction solvent. The study samples of the same subject were analyzed in the same analytical run under the calibration range of 0.210 ng/mL-204.814 ng/mL.

The chromatographic separation was performed on Chromolith® HighResolution RP-18e 100-4.6 mm column maintained at 40°C. An isocratic mobile phase was composed of 10 mM ammonium formate at pH3 and methanol (10:90, v/v) and pumped into Nexera™ LC system (Shimadzu Corporation, Japan) at a flow rate of 1 mL/minute. The analyte and internal standard were detected by an electrospray ionization triple quadrupole mass spectrometer (TSQ Quantum Ultra, Thermo Fisher Scientific Inc., USA). The transition of precursor to product ion was monitored in positive mode at m/z 384.173 to 253.120 for quetiapine and m/z 392.236 to 258.130 for quetiapine-d8. Data analysis was performed using Xcalibur™ 3.0.63.3 and LCquan™ 2.9.0.34 (Thermo Fisher Scientific Inc., USA).

To ensure the reliability and reproducibility of the data, incurred sample reanalysis was performed following EMA guideline on bioanalytical method validation [14]. The study samples having concentrations close to maximum plasma concentration ($C_{max}$) and in the elimination phase of each subject in each period were chosen and reanalyzed in separate analytical runs. The concentration from incurred samples was not used for pharmacokinetic calculation.

### Pharmacokinetic and statistical analysis

The pharmacokinetics parameters were computed using non-compartmental model of Phoenix WinNonlin software version 6.3 (Pharsight Corporation, USA). The maximum measured plasma concentration ($C_{max}$), area under the plasma concentration versus time curve from time zero to the last sampling time point ($AUC_{0\text{-}tlast}$) and area under the concentration versus time curve from time zero to time infinity ($AUC_{0\text{-}\infty}$) were considered as the primary pharmacokinetic parameters, while the time to achieve $C_{max}$ ($t_{max}$), elimination rate constant ($\lambda z$) and half-life ($t_{1/2}$) were considered as the secondary parameters.

The statistical analysis was carried out using PROC GLM SAS® version 9.3 (SAS Institute Inc., USA). The Analysis of Variance (ANOVA) was used to determine the effects of the formulation, period, and sequence on log-transformed primary parameters ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and $C_{max}$). The ANOVA model included sequence, formulation and period as fixed effects and subject (sequence) as a random effect. Sequence effect was tested using subject (sequence) as an error term. Two one-sided tests for bioequivalence were evaluated by considering the 90% Confidence Intervals (CIs) for the ratio of geometric least squares mean (test/reference) of log-transformed primary parameters. The median $t_{max}$ of the test and reference products were compared using Wilcoxon signed rank test. All statistical calculations were performed at a significance level of 5% ($\alpha$=0.05).

## RESULTS

### Demographic characteristics of study subjects

Forty-four healthy Thai male and female study subjects were enrolled and randomly divided into TR and RT group equally. The mean ± SD of age, height, weight and BMI of enrolled study subjects at screening were 30.57 ± 7.33 years, 1.63 ± 0.07 m, 57.78 ± 8.41 kg and 21.57 ± 2.16 kg/$m^2$ , respectively. Two study subjects were withdrawn by the clinical investigator in period I and two study subjects were withdrawn in period II due to the adverse events. Therefore, forty study subjects completed the study and their plasma concentration data were used for pharmacokinetic and statistical analysis.

### Study sample analysis and incurred sample reanalysis

All study samples from 44 study subjects were completely analyzed. The correlation coefficient of each analytical run constructed from 8 calibration standards was more than 0.99. Four levels of quality control samples were used to demonstrate the precision and accuracy in each analytical run. The inter-day Coefficient of Variation (CV) and accuracy of quality control samples ranged from 2.0%-2.9% and 98.7%-101.3%, respectively. A total of 190 samples were chosen to establish the reproducibility of the analytical data *via* incurred sample reanalysis, and 96.8% of them had percent difference between the original and reanalyzed concentrations less than ± 20%

### Pharmacokinetic and statistical analysis

The data obtained from 40 study subjects who completed the entire study were used for pharmacokinetic and statistical analysis. The mean plasma concentration-time profiles of quetiapine after administration of the test and reference products are shown in Figure 2 and the mean ± SD values of pharmacokinetic parameters of two formulations are represented in Table 1. Quetiapine was rapidly absorbed and reached the maximum plasma concentration around 80 ng/mL within one hour after administration.

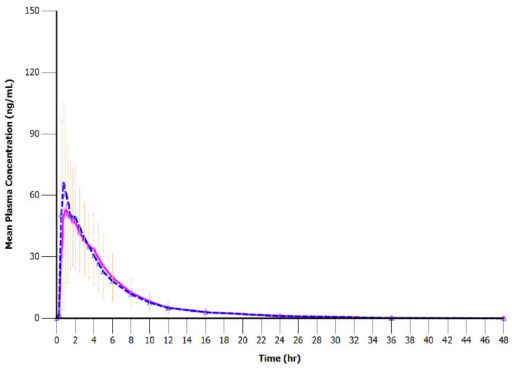


**Figure 2:** Mean plasma concentration-time profiles of quetiapine after oral administration of the test and reference products. Note: (—) R;(---) T.

**Table 1:** Pharmacokinetic parameters of quetiapine for the test and reference products.

| Parameters | Mean ± SD (N=40) | |
|---|---|---|
| | Test product | Reference product |
| $AUC_{0\text{-}tlast}$ (ng.h/mL) | 317.4 ± 131.5 | 311.0 ± 137.3 |
| $AUC_{0\text{-}\infty}$ (ng.h/mL) | 321.4 ± 131.7 | 314.6 ± 137.5 |
| $C_{max}$ (ng/mL) | 85.0 ± 36.2 | 78.8 ± 37.2 |
| $t_{max}$ (h, in median (min,max)) | 0.75 (0.50-5.00) | 1.00 (0.50-4.50) |
| $\lambda z$ (1/h) | 0.13 ± 0.03 | 0.14 ± 0.03 |
| $t_{1/2}$ (h) | 0.99 ± 0.01 | 0.99 ± 0.01 |
| %AUC extrapolation | 1.43 ± 0.82 | 1.37 ± 0.84 |

The results of ANOVA (Table 2) showed no significant effects of period, formulation and sequence on log-transformed $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ ($p>0.05$). The 90% CIs for the ratio of the geometric least squares mean ratio of log-transformed $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ were within the bioequivalence criteria of 80.00%-125.00%. Wilcoxon signed rank test showed significant difference in median $t_{max}$ between the two formulations ($p<0.05$). However, there was no effect on the bioequivalence of this study since test and reference products of this study were not rapid-release claimed product of which the statistical analysis of $t_{max}$ was necessary for bioequivalence consideration.

### Tolerability

With concerning to the safety of study subjects, adverse events were closely monitored and recorded throughout the study. The list of adverse events after receiving the test and reference products are shown in Table 3. Total twenty-four adverse events were reported in 18 study subjects. Twelve adverse events were reported in 10 study subjects who received the test product while 12 adverse events were reported in 12 study subjects who received the reference product. The frequently reported adverse events were asymptomatic hypotension and dizziness. There were 4 incidences of serious adverse events in this study including 2 incidences of syncope due to orthostatic hypotension and 2 incidences of acute dizziness with drowsiness and blurred vision. The study subjects who had serious adverse events were withdrawn and admitted to the hospital immediately; however, all of them could resolve completely. All adverse events were reported to the Institute for the Development of Human Research Protections, Thailand in a timely manner whereas the serious adverse events were reported within 7 days after occurrence.

**Table 2:** Statistical comparison of primary parameters between test and reference products.

| Parameters | Ratio (90% CI) | Power (%) | Intra-subject CV (%) | ANOVA (p-value) | | |
|---|---|---|---|---|---|---|
| | | | | Period | Formulation | Period |
| ln $AUC_{0\text{-tlast}}$ | 102.0 (96.08-108.33) | 100.0 | 16.0 | 0.8366 | 0.5772 | 0.8404 |
| ln $AUC_{0\text{-}\infty}$ | 102.1 (96.21-108.31) | 100.0 | 15.8 | 0.8318 | 0.5617 | 0.8319 |
| ln $C_{max}$ | 108.1 (96.52-121.09) | 94.4 | 30.8 | 0.9313 | 0.2537 | 0.9521 |

**Table 3:** List of adverse events.

| Adverse event | Incidence (N) | |
|---|---|---|
| | Test | Reference |
| Asymptomatic hypotension | 5 | 4 |
| Syncope | 1 | 1 |
| Vomiting | 1 | 0 |
| Nausea | 1 | 0 |
| Dizziness | 2 | 5 |
| Fever | 1 | 0 |
| Acute dizziness with drowsiness and blurred vision | 1 | 1 |
| Loose stool | 0 | 1 |
| Total | 12 | 12 |

## DISCUSSION

In the present study, bioequivalence of quetiapine 25 mg tablets formulations was evaluated under fasting condition as it is more sensitive to detect the difference between the test and reference formulations [10]. The bioequivalence of quetiapine 25 mg tablets was successfully demonstrated using the data from 40 healthy Thai subjects with the power greater than 90% for all primary pharmacokinetic parameters. The 90% CIs of the geometric least squares mean ratio between the formulations of log-transformed $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ met the standard bioequivalence criteria. The ANOVA did not show any significant effects of period, sequence and formulation on the primary pharmacokinetic parameters. Even though the results of Wilcoxon signed rank test showed the significant difference in median $t_{max}$ between the test and reference products of quetiapine, neither rapid onset of action nor time-dependent adverse effect has been claimed for quetiapine. Therefore, the insignificant difference in median $t_{max}$ may not be necessary for the conclusion on bioequivalence of quetiapine formulations [10].

The mean $AUC_{0\text{-}\infty}$ and $C_{max}$ of the reference formulation reported in Brazilian subjects were 440.06 ng.h/mL and 126.94 ng/mL, respectively which were higher than the values reported in Thai subjects. However, the intra-subject variability of $C_{max}$ observed in the present study was comparable to the previously reported value [13]. Another bioequivalence study conducted in Indonesian subjects demonstrated the mean $AUC_{0\text{-}\infty}$ and $C_{max}$ of the reference formulation at approximately 300 ng.h/mL and 75 ng/mL, respectively which were similar to those observed in Thai subjects [15]. The mean extrapolation of $AUC_{0\text{-tlast}}$ to infinity was less than 2% for both formulations suggesting that the $AUC_{0\text{-}\infty}$ was reliably estimated as the sampling time points covered more than 80% of the $AUC_{0\text{-}\infty}$. No significant amounts of drug were found in any pre-dose samples indicating sufficient washout of drug between study periods.

Most adverse events reported in the present studies had been previously reported for quetiapine. Common adverse events of quetiapine include dizziness, drowsiness, vomiting, dry mouth and constipation. These adverse events are associated with the blockade of Histaminic ($H_1$) and Muscarinic ($M_1$) receptor. In addition, the blockade of $\alpha_1$-adrenergic receptor can cause orthostatic hypotension which can lead to serious consequences [16]. Quetiapine is well tolerated during short-term and long-term use in adults [17]. However, the safety of patients should be closely monitored. In this study, the serious adverse events were reported and causality to the study drug was convinced. The incidence of serious adverse events after receiving the test and reference products was similar.

## CONCLUSION

The study successfully established bioequivalence between Quapine® and Seroquel®. The statistical comparison of $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and $C_{max}$ of the test and reference formulations indicated that there was no significant difference between two formulations in terms of rate and extent of absorption. The significant difference in $t_{max}$ between the formulations did not affect the conclusion on bioequivalence in this study. Both formulations were generally well tolerated in Thai subjects. The incidence of adverse events after receiving the test and reference products was similar. Therefore, they can be used interchangeably, and the same efficacy and safety can be anticipated.

## ACKNOWLEDGEMENT

This study was supported by the Government Pharmaceutical Organization (GPO), Thailand.

## REFERENCES

1. Cheer SM, Wagstaff AJ. Quetiapine. CNS Drugs. 2004;18(3):173-199.
2. Dando TM, Keating GM. Quetiapine. Drugs. 2005;65(17):2533-2551.
3. Sanford M, Keating GM. Quetiapine. CNS Drugs. 2012;26(5):435-460.

4. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: Insights from receptor-binding profiles. Mol Psychiatry. 2008;13(1):27-35.

5. Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: Preclinical studies, pharmacokinetics, drug interactions and dosing. J Clin Psychiatry. 2002;63(S1):5-11.

6. DeVane CL, Nemeroff CB. Clinical Pharmacokinetics of Quetiapine. Clin Pharmacokinet. 2001;40(7):509-522.

7. Product Monograph. Seroquel® Quetiapine fumarate immediate-release tablets, 25, 100, 200 and 300 Mg oral use professed antipsychotic agent. AstraZeneca Canada Inc. 2021.

8. Thyrum PT, James Wong Y, Yeh C. Single-dose pharmacokinetics of quetiapine in subjects with renal or hepatic impairment. Prog Neuro-Psychopharmacol Biol Psychiatry. 2000;24(4):521-533.

9. Cutler AJ, Goldstein JM, Tumas JA. Dosing and switching strategies for quetiapine fumarate. Clin Ther. 2002;24(2):209-222.

10. European Medicines Agency. Guideline on the investigation of bioequivalence. Committee for Medicinal Products for Human Use (CHMP), London. 2010.

11. U.S. Food and Drug Administration. Product-specific guidances for generic drug development: Guidance on Quetiapine Fumarate. Center for Drug Evaluation and Research (CDER), Silver Spring. 2008.

12. Brett J. Concerns about quetiapine. Aust Prescr. 2015;38(3):95-97.

13. Abib E, Duarte LF, Suenaga E, Cruz A, Nakaie C. Comparative bioavailability of two quetiapine formulations in healthy volunteers after a single dose administration. J Bioequiv Availab. 2011;3(8):178-181.

14. European Medicines Agency. Guideline on bioanalytical method validation. Committee for Medicinal Products for Human Use (CHMP), London. 2011.

15. Harahap Y, Prasaja B, Lusthom W, Yusvita L, Sinandang T, Hardiyanti H. A bioequivalence study of quetiapine 25 mg film-coated tablets in healthy Indonesian subjects. Int J Clin Pharmacol Ther. 2017;56(1):38-42.

16. Garver DL. Review of quetiapine side effects. J Clin Psychiatry. 2000;61(S8):31-35.

17. Dev V, Raniwalla J. Quetiapine. Drug Saf. 2000;23(4):295-307.