Bioequivalence Study of the Generic Quetiapine (Quantia 200®) and the Innovator Preparation (Seroquel®) 200 mg Given Orally in Healthy Thai Male Volunteers

การศึกษาชีวสมมูลของยา quetiapine ที่ผลิตในประเทศ (Quantia 200®) เทียบกับยาต้นแบบ(Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทยสุขภาพปกติ

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ABSTRACT

Quetiapine is an atypical antipsychotic which has been used for the treatment of schizophrenia. The purpose of this study was to evaluate the bioequivalence of two formulations of quetiapine, i.e. the generic (Quantia 200®) and the innovator products (Seroquel®), in 24 healthy Thai male volunteers following a single 200-mg oral dose. The study was a randomized, two-period, two-sequence crossover design with a two-week washout period. After dosing, serial blood samples were collected at 0, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr. The plasma quetiapine concentrations were determined by HPLC method. The comparative bioequivalence between the two formulations were determined by the two-way ANOVA. No significant effect of formulation, sequence or period was observed in this study. The 90% CI for the ln-transformed ratio of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ were 98.21-124.37%, 94.43-117.03% and 94.77-116.61%, respectively. All of the pharmacokinetic parameters were within the acceptable range of 80-125%. Therefore, it was concluded that Quantia 200® was bioequivalent to Seroquel® in their rates and extents of absorption.

Key words: quetiapine, bioequivalence, Seroquel®, Quantia200®

คำสำคัญ: ควิไทอะปีน, ชีวสมมูล, ซีโรเควล®, ควานเทีย 200®

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บทคัดย่อ

ควิไทอะปีน (quetiapine) เป็นยารักษาโรคทางจิตเวช ซึ่งใช้สำหรับรักษาโรคจิตเภท การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาชีวสมมูลของยาควิไทอะปีนที่ผลิตในประเทศไทย (Quantia 200®) เทียบกับยาต้นแบบที่ผลิตจากต่างประเทศ (Seroquel®) ขนาด 200 มิลลิกรัม ในอาสาสมัครชายไทยสุขภาพปกติจำนวน 24 คน โดยรับประทานยาเม็ดควิไทอะปีนขนาด 200 มก. ครั้งเดียว การศึกษาเป็นแบบสุ่มสลับ 2 ระยะ โดยเว้นระยะห่างกัน 2 สัปดาห์ หลังจากให้ยาเก็บตัวอย่างเลือดของอาสาสมัครที่เวลา 0, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 และ 48 ชั่วโมง วิเคราะห์หาระดับยาในพลาสมาโดยใช้วิธีทาง HPLC ทดสอบความแตกต่างทางสถิติของค่าตัวแปรทางเภสัชจลนศาสตร์ด้วย two-way ANOVA ผลการทดลองไม่พบความแตกต่างอย่างมีนัยสำคัญของยาทั้งสองและ 90% CI ของอัตราส่วน C_{max}, AUC_{0-48} และ $AUC_{0-\infty}$ ในรูปลอการิทึมมีค่าเท่ากับ 98.21-124.37%, 94.43-117.03% และ 94.77-116.61% ตามลำดับ ค่าที่ได้เหล่านี้อยู่ในช่วง 80-125% ซึ่งอยู่ในเกณฑ์ที่ยอมรับ ดังนั้นจึงสรุปได้ว่ายาควิไทอะปีนที่ผลิตจากสองบริษัทที่ใช้ในการศึกษาครั้งนี้มีชีวสมมูลกันทั้งในด้านอัตราเร็วและปริมาณยาที่มีการดูดซึม

Introduction

Bioequivalence study is basically a comparative bioavailability of drug significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study (Chen *et al*., 2001). Thus, two products are bioequivalent if their rate and extent of absorption are the same. The generic substitution can help our country to save the health care budget and to strengthen our health care system.

Schizophrenia is the most common psychotic disorder that is among the world's top ten causes of long-term disability (Mueser and McGurk, 2004). It is a severe and chronic mental illness, associated with high prevalence about 0.5–1% of the population (Dargham and Laruelle, 2005; Jablensky, 1997). In Thailand, the incidence of schizophrenia was 293.2 cases per year per 100,000 population. Siriwanarangsun *et al*. (2003) found that the lifetime prevalence and point prevalence of schizophrenia were 1.17 and 0.59, respectively.

Quetiapine was approved by the U.S. Food and Drug Administration (U.S. FDA) on September, 1997 (Timothy and Kevin, 2000). It causes a much lower incidence of extrapyramidal symptoms than that of haloperidol and it does not cause siginifi- cant changes in hematological such as agranulocytosis (Mandrioli *et al*., 2002). So this medicine does not only help people live longer, but it also improves the quality of their lives because it can reduce positive symptoms and also alleviate negative symptoms with lower side effect.

Objective

This study was aimed at investigating the bioequivalence between the generic drug, Quantia 200®, and the innovator drug, Seroquel®, in healthy Thai male volunteers.

This study was approved by the Ethic Committee, Faculty of Science, Prince of Songkla University in December 2006.

Materials and Methods

Quetiapine formulations

Reference formulation: Seroquel® (AstraZeneca,UK) containing 200 mg quetiapine per tablet (Lot no. CT523, Mfg: 06/2005, Exp: 06/2008.)

Test formulation: Quantia 200® (Unison Laboratories Co., Ltd. Thailand) containing 200 mg quetiapine per tablet (Lot no.T02/6, Mfg: 9-2-06).

Volunteers

The subjects of this study were physically and mentally normal male volunteers, age 18 – 45 years old with body mass index 18-25 kg/m^2. All subjects were in good health on the basis of medical history and physical examination, routine blood test including CBC, FBS, BUN, Cr, SGOT(AST), SGPT(ALT), ALP, bilirubin, total protein and albumin. The subjects who have abnormal hematological, liver or kidney functions were excluded from this study. Subjects with known contraindication or hypersensitivity to antipsychotic drug were excluded as well as those with known history of alcoholism or drug abuse. Drinking of alcoholic beverages, coffee and tea were not allowed at least 1 month prior to and during the entire period of the study. After completing an explanation of the study, the written informed consents were obtained from all subjects.

Study design

The study was an open-labeled, randomized two-phase cross over designed with a 2 weeks washout period. During the first period, volunteers from group I received a single oral dose of 200 mg of Seroquel® (reference product) while volunteers from group II received a single 200 mg dose of Quantia200® (test product). During the second period, the procedure was repeated on the groups in reverse.

Sample collection

The drugs were administered to the volunteers in the morning, after an overnight fasting, with 200 ml of water. No food was taken at least 2 hours after ingestion of the drug.

Blood sample were collected at 0 (pre dose) and at 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hours post dose. The samples were centrifuged at 2,500 g and the plasma was collected and stored at -70°C until analysis.

Extraction procedure

The plasma quetiapine concentrations were measured by a HPLC method (modified from Mandrioli *et al*., 2002). Risperidone was used as an internal standard. Quetiapine was extracted by liquid-liquid extraction technique (modified from Avenoso *et al*., 2000). Human plasma was alkalinized with 1 ml of NaOH (2 M) and vortex-mixed for 20 seconds. 4 ml of diisopropylether-isoamylalcohol (99:1, v/v) was added and shaked for 5 minutes, the mixture was centrifuged at 2,500 g for 10 minutes. The organic phase (upper phase) was transferred to tubes containing 150 µl of KH_2PO_4 (0.1M, pH 2.2), mixed for 20 seconds and centrifuged at 2,500 g for 5 minutes. The upper organic layer was carefully aspirated and 1 ml of diethyl ether was added, vortex-mixed for 1 minute then shaked for 5 minutes and centrifuged at 2,500 g for 10 minutes. The upper ether phase was eliminated and a 70 µl aliquot of the remaining acid solution was injected into the HPLC system for analysis.

The mobile phase composed of 0.05 M potassiumdihydrogen phosphate (containing 11.5 mM triethylamine), acetronitrile and methanol in a 55: 18: 22 (v/v/v) ratio and adjusted to pH 2.5 with phosphoric acid. The mobile phase was freshly prepared daily. The flow rate was 0.7 ml/min. All analyses were performed at room temperature ($25^{\circ} \pm 1^{\circ}$C). The HPLC system consisted of Waters 2695 pump, autosampler (Waters Associates, Milford, MA, USA) and a Waters 2487 variable wavelength UV detector set at 225 nm. The column was reverse-phase Symmetry C8 (particle size 5 μm; column size 250 mm × 4.6 mm i.d.). A guard-pak precolumn module was used to obviate rapid column degeneration.

Method validation

Method validation procedures were carried out according to Thai FDA guideline (2006).

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters, namely; maximum plasma concentration (C_{max}), time point of maximum plasma concentration (T_{max}), area under the plasma concentration-time curve from 0 h to the last measurable concentration (AUC_{0-t}), area under the plasma concentration–time curve from 0 h to infinity ($AUC_{0-\infty}$), and half-life of drug elimination during the terminal phase ($T_{1/2}$) were computed for the test drug using WinNonlin® Professional Software Version 1.1 (Pharsight, Mountain View, CA) by non-compartment model.

Statistical comparison between pharmacokinetic parameters (C_{max}, AUC_{0-48} and $AUC_{0-\infty}$) of the two products, after ln-transformed, were analyzed using two-way ANOVA.

The 90% CI for the C_{max} and AUC of the ratio of the test and reference products were estimated using the following equation:

$$90\%\ \text{C.I} = \Delta \pm t_{0.10,\,\nu}\sqrt{EMS(2/n)}$$

Where Δ is a difference in means of ln-transformed of pharmacokinetic parameters (C_{max} or AUC_{0-48} or $AUC_{0-\infty}$) between the test product and the reference, $t_{0.10}$, ν is the tabulated two-tail t value for a 90% confidence interval, ν is a degree of freedom of the error mean square obtained from the ANOVA table, EMS is the error mean square from the ANOVA table and n is the number of subjects. Antilogarithm of the calculated confidence interval will yield an exact confidence interval for the ratio.

Bioequivalence will be concluded if the 90% confidence interval fell within the bioequivalence range of 80.0–125.0% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Results

Subjects

Twenty four healthy Thai male volunteers were enrolled in the study. The mean ± SD of age, weight, height and BMI of the subjects were 21.08 ± 5.06 years, 64.02 ± 6.09 kg, 172.50 ± 5.28 m and 21.41 ± 2.24 kg/m^2, respectively. All subjects were healthy on the basis of medical history, physical, hematological and biochemical investigations. None was withdrawn from this study.

Method validation

Specificity: Quetiapine and internal standard (risperidone) were clearly separated from the plasma with the retention time of 6.091 and 8.612 minutes, respectively. Both peaks were clearly separated and no interference from endogenous substances was observed.

LLOQ: defined as the lowest concentration on the standard curve that can be analyzed with acceptable accuracy of 109.68% and precision of 2.45%, was 9 ng/ml.

Calibration curve: calibration curve of standard quetiapine was linear over the range of 9-1,737 ng/ml. The regression equation for the calibration curve of peak area ratio of quetiapine and internal standard (y) versus plasma quetiapine concentration (x) was y = 0.0118x-0.0338. The correlation coefficient of calibration curve was 0.9997

Precision and accuracy: for this method were controlled by calculating the intra-day and inter-day at three concentrations (13, 347 and 1,042 ng/ml) in five replicates. The intra-day accuracy ranged between 87.48-100.77% with a precision (%CV) of 1.71-5.79%. The inter-day accuracy ranged between 99.61-102.40% with a precision (%CV) of 2.92-8.31%.

Recovery: Mean extraction recoveries of quetiapine at concentrations 13, 347 and 1,042 ng/ml were 99.17, 90.38 and 94.09%, respectively, and the extraction recovery of the IS was 101.90%.

Stability: quetiapine was stable in freeze and thaw stability test. The percent change for quetiapine concentrations were 1.38, 7.42 and 4.10 %, at the concentrations of 13, 347 and 1,042 ng/ml, respectively.

At room temperature, quetiapine was found to be stable for 6 h (short term). The percent change at the concentrations of 13, 347 and 1,042 ng/ml were 7.57, 6.94 and 3.32 %, respectively.

Quetiapine was stable at -70°C for 1 month (long term) with 4.11, 8.68 and 10.91 % change at the concentrations of 13, 347 and 1,042 ng/ml, respectively.

Quetiapine was evaluated by leaving the samples in the autosampler for 6 h before injection. The quantitative results indicated that quetiapine was stable in the autosampler up to at least 6 h with 0, 2.74 and 1.58 % change at the concentrations of 13, 347 and 1,042 ng/ml, respectively.

Stock solutions of quetiapine (43 μg/ml) and IS (10 μg/ml) were found to be stable in methanol for at least 14 days at -70°C with 0.79 and 0.2% for quetiapine and IS, respectively.

Bioequivalence evaluation

Mean quetiapine plasma concentra-tion-time profiles after test and reference formulations administration to 24 healthy Thai male volunteers are shown in Fig.1. The pharmacokinetic parameters between the test and reference formulations are presented in Table 1.

The mean extrapolate portion of the plasma concentration-time curves of Quantia 200® and Seroquel® were 6.55 and 6.58%, respectively, which were less than the acceptable value of 20%.

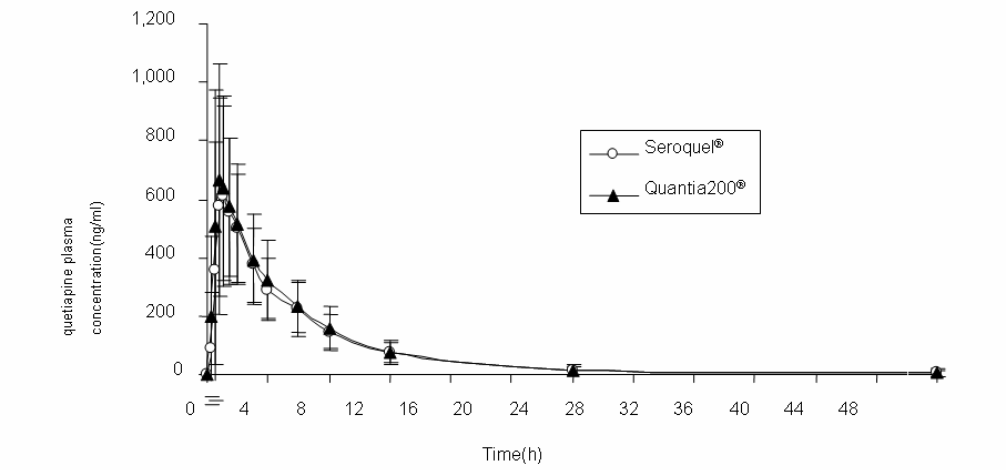

Figure 1 Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Quantia 200® in the 24 subjects

The results of two-way ANOVA test of the ln-transformed data of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ of quetiapine have shown that C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ of Quantia200® were not significantly different from the reference drug (Seroquel®).

Bioequivalence analysis has shown that the 90% CI of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ for ratios of Quantia 200® and Seroquel® were 98.21-124.37, 94.43-117.03 and 94.77-116.61%, respectively. These values fell within the acceptable range for bioequivalence of the Thai FDA criteria, i.e. 80-125%.

Adverse effect

All subjects were somnolence within 1 h after taking 200 mg of Seroquel® and Quantia 200®. Other adverse effects were orthostatic hypotension and agitation These adverse effects were subsided within 1 day and were not serious.

Discussion

The mean quetiapine plasma concentration time profiles after an oral administration of a single dose of the test and reference formulations were comparable and exhibited closely similar pattern. The results have shown that the mean and standard deviations of these parameters of the two formulations were similar, indicating that the pharmacokinetics of quetiapine in the two formulations is similar. After a single oral administration, the drug was rapidly absorbed and reached C_{max} at 1.08 and 1.10 h for the test and reference formulations, respectively. Mean peak of quetiapine levels of the test and reference formulation were 889.60 and 811.34 ng/ml,

Table 1 Phamacokinetic parameters (mean ± SD) and 90% CI for quetiapine, after the administration of single oral dose of 200-mg of Quantia 200® and Seroquel® to 24

Pharmacokinetic parameters	Quantia 200®	Seroquel®	90% CI
AUC_{0-48} (ng h/ml)	3,754.41 ± 1,453.00	3,520.00 ± 1,229.61	**94.43-117.03**
$AUC_{0-\infty}$(ng h/ml)	4,015.35 ± 1,528.25	3,769.45 ± 1,296.69	**94.77-116.61**
C_{max}(ng/ml)	886.60 ± 356.50	811.34 ± 323.37	**98.21-124.37**
T_{max} (h)	1.08 ± 0.78	1.10 ± 0.79	-
$T_{1/2}$(h)	5.26 ± 2.63	5.53 ± 2.83	-
CL (L/h)	58.86 ± 28.55	60.30 ± 22.64	-
Vz/f (L)	384.62 ±122.78	437.59 ± 191.42	-
AUC extrapolated (%)	6.55 ± 4.55	6.58 ± 4.68	-

respectively. Plasma quetiapine level then gradually declined, with the mean $T_{1/2}$ of 5.26 and 5.53 h for Quantia200® and Seroquel®, respectively. The pharmacokinetic parameters in these healthy Thai volunteers were similar to the previously studies. (Davis *et al*., 1999; Thyrum *et al*., 2000; Wong *et al*., 2001; Jaskiw *et al*., 2004; Li *et al*., 2004; Li *et al*., 2005; Grimm *et al*., 2005). These results have also shown that quetiapine is rapidly absorbed with T_{max} of 0.5-2 h.

The $T_{1/2}$ of Quantia 200® (5.26 h) was similar to Seroquel® (5.53 h). $T_{1/2}$ of both formulations were markedly varied among individuals, between 1-11 h. This range of $T_{1/2}$ is similar to that of Li *et al*. (2004) who reports that $T_{1/2}$ can be varied between 5-10 h. The longer $T_{1/2}$ and significantly deviates from the common range may be resulted from the lower activity of CYP3A4. Li *et al*. (2004) reported that genetic polymorphism of *CYP* is the main factor for individual difference of metabolism for quetiapine and its metabolites. The activity of CYP3A4 is considered to be the major metabolizing enzyme for quetiapine (DeVane and Nemeroff, 2001).

A high inter-individual variation in plasma concentration was also observed by Davis *et al*. (1999) and Li *et al*. (2004) who reported that % CV of C_{max} and AUC were about 40% and more than 50%, respectively. In the present study, the plasma concentrations of quetiapine were varied and the % CV of C_{max} and AUC were similar to the above reports. The high variation of pharmacokinetic parameters of individual is mainly due to difference in metabolism and uniform of products.

In addition, many subjects showed double peaks of quetiapine after receiving Quantia 200® and Seroquel®. The rationale for the double peaks phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling or uniformity of the products (Shargel *et al*., 2005). In this study, double peaks were proposed to be due to difference in the enterohepatic circulation, similar to Granero and Amidon (2007) who suggested that enterohepatic circulation is a likely explanation for multiple peaks in ketoprofen plasma concentrations.

The results from the ANOVA study showed that formulation, sequence and period had no significant effect on C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ at the significant level of 0.05. The results showed that all the pharmacokinetic parameters of both products were similar. The 90% CI of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ for Quantia 200®/Seroquel® were 98.21-124.37%, 94.43-117.03% and 94.77-116.61%, respectively (Table1). These values were within the acceptable range of the Thai FDA criteria, i.e. 80-125%.

The power of the tests obtained from the present study for pharmacokinetic parameters C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ was found to be 92.1, 96.9 and 97.4%, respectively. Indicating that the sample size in this study was adequate based on the data for C_{max}, AUC_{0-48} and $AUC_{0-\infty}$, thus the power of the test was considered adequate in this study.

The adverse events associated with quetiapine were mild to moderate. In this study, somnolence was the dominant adverse event for both formulations. All subjects were somnolence (100%) within 1 h after taking the drug which is similar to the report of Thyrum *et al* (2000) and Grimm *et al*. (2005). Other adverse events were orthostatic hypotension and agitation. These manifestations were minor adverse events described for quetiapine. Antagonism at H_1 and adrenergic α_1-recepters, may explain the somnolence and orthostatic hypotension, respectively. (Jaskiw *et al*., 2004). No serious adverse events were observed during quetiapine treatment and no subject withdrew because of adverse events.

Conclusion

In conclusion, the bioequivalence study on Thai male volunteers, 200 mg quetiapine formulations in the form of tablet were assessed, and statistical comparison of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ obviously revealed no significant difference between Quantia 200® and Seroquel®. The 90% CI of the ratios of C_{max} (98.21-124.37%), AUC_{0-48} (94.43-117.03%) and $AUC_{0-\infty}$ (94.77-116.61%) values for the test and reference products are within the 80-125%, which is the acceptable range of the Thai FDA guidelines. Therefore, it was concluded that the two quetiapine formulations are bioequivalent in both the rate and extent of absorption.

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