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Bioequivalence of a Generic Quetiapine (Ketipinor®) in Healthy Male Volunteers

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Abstract

Quetiapine is an atypical antipsychotic indicated for the treatment of schizophrenia and related psychoses. Uses of generic drugs are essential due to economic reason. Interchangeability of drugs is determined by bioequivalence studies. We aim to study the bioequivalence of a generic quetiapine (Ketipinor®, Orion Corporation, Finland) and the innovator product (Seroquel®, AstraZeneca, UK). The study was a randomized, two-way crossover design with a two-week washout period in 24 healthy Thai male volunteers. After a single 200-mg oral dosing, serial blood samples were collected at appropriate interval up to 48 h. Plasma quetiapine concentrations were determined by using a validated LC-MS/MS method. Pharmacokinetic parameters were estimated using the WinNonlin® software with non-compartment model analysis. The mean ± SD of maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve from 0 to 48 h ($AUC_{0\text{-}last}$) and the area under the plasma concentration-time curve from 0 to infinity ($AUC_{0\text{-}\infty}$) of Ketipinor® v.s. Seroquel® were 632.27 ± 304.43 v.s. 638.83 ± 214.49 ng/ml; 2,625.21 ± 972.14 v.s. 2,511.82 ± 704.21 ng.h/ml and 2,640.25 ± 979.10 v.s. 2,526.45 ± 704.37 ng.h/ml, respectively. The time to reach C_{max} (T_{max}) of Ketipinor® and Seroquel® were 1.34 ± 1.11 and 1.01 ± 0.63 h., respectively. The T_{max} of Ketipinor® was within the acceptance range of ±20% of the median T_{max} of the reference product. The 90% confidence interval of the ratios of the log-transformed data of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ were 80.75 - 102.60%, 91.32 - 108.42% and 88.47 - 106.77%, respectively, which were within the acceptance range of 80.00 - 125.00%. Power of the test for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ were 92.16%, 96.34% and 95.96%, respectively. In conclusion, Ketipinor® was bioequivalent to Seroquel® in terms of both the rate and extent of absorption under fasting condition.

Keywords: Bioequivalence; Ketipinor®; Pharmacokinetics; Quetiapine; Seroquel®

Introduction

Quetiapine is an atypical antipsychotic indicated for the treatment of schizophrenia and related psychoses [1,13]. It is an antagonist at multiple neurotransmitter receptors, including 5-HT_{1A}, 5-HT_{2A}, D_1 and D_2, histamine (H_1) receptors, α_1- and α_2-adrenergic receptors [7,11,16]. Antagonism of 5-HT_2 receptors in the mesocortical area is a proposed mechanism of the antipsychotic action. 5-HT_2 receptor blockade may enhance dopaminergic transmission, thereby relieving negative symptoms [14]. Its low level of D_2 occupancy may account for its very low risk of extrapyramidal side effects (EPS) and prolactin elevation [6]. Antagonistic effect on the H_1 receptor is responsible for the sedative effect of the drug.

Quetiapine is rapidly absorbed in the gastrointestinal tract, and its absorption is unaffected by food [9]. The peak plasma concentration is reached within 1 to 2 hours [15,17] and has linear pharmacokinetics [9]. The relative bioavailability from orally administered tablets compared with a solution was almost complete [9]. Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg. About 83% of quetiapine is bound to plasma protein at therapeutic concentration [3]. Quetiapine is mainly metabolized by hepatic cytochrome P450 (CYP) 3A4 [8] and at least 11 metabolites formed through hepatic oxidation have been identified [9]. Only 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine metabolites are considered to be active but its concentration is lower than 10% of the initial quetiapine amount [4]. CYP3A4 was demonstrated to be responsible for sulfoxidation, N-and O-desalkylation of quetiapine, and partially responsible for 7-hydroxylation. CYP2D6 played a minor role in the metabolism of quetiapine as CYP3A4 contributed for 89% of the overall metabolism [12]. The mean terminal half-life for 375 mg/day is 6.9 hours. Approximately 73% of the oral dose is excreted in the urine and 21% in faeces. The unchanged quetiapine in urine and faeces are less than 1% [4,9]. Quetiapine has been increasingly used instead of the classical antipsychotic drugs due to its lower extrapyramidal side effects. However, the innovator product is still too expensive for most patients. Use of generic drugs is essential due to economic reason. Interchangeability of drugs is determined by bioequivalence studies comparing the plasma concentration versus time curves for the generic and the innovator products. They are considered bioequivalent when the rate and extent of bioavailability of the active ingredient in the two products are not significant differently under suitable test conditions. In order to prevent the distribution of substandard products, bioequivalence studies are prerequisite for registration. Therefore, Ketipinor®, a new generic formulation, is needed for bioequivalence testing. Our objective was to perform the bioequivalence study of a generic quetiapine (Ketipinor®, as the test formulation) and the innovator product (Seroquel®, as the reference formulation) when given as a single 200 mg oral dose.

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Materials and Methods

Drug formulations

Test product: Ketipinor® 200 mg tablet, manufactured by Orion Corporation, Finland. Batch number: 1267850, Mfg. Date: 07-2008, Exp. Date: 07-2011.

Reference product: Seroquel® 200 mg tablet, manufactured by AstraZeneca, Macclesfield, Cheshire SK10 2NA, UK. Batch number: FM034, Mfg. Date: 08-2008, Exp. Date: 08-2011.

Chemicals and reagents

Quetiapine fumarate was obtained from Toronto Research Chemical Inc., Canada and clozapine from Sigma (Schnelldorf, Germany). All chemicals used in the study were an analytical and/or HPLC grade

Instrumentation

Mass spectrometry: Mass spectrometry was performed using a Quattro micro™ triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an ESI source. The specific precursor-to-ion transitions monitored were *m/z* 384.2 → 253.1 for quetiapine and *m/z* 327.2 → 270.3 for clozapine. The dwell times used were 0.1 and 0.2 s, respectively. Collision-induced dissociation (CID) was carried out using 2.5 x 10^{-3} mbar argon. The collision energy was 25 eV for both compounds. The cone voltage was set at an optimized value (30 kV) in the positive-ion mode. The capillary voltage was 2.0 kV and the entrance and exit energies of the collision cell were set at 1 and 3 V, respectively Nitrogen was used as desolvation (400 L/h) and cone (40 L/h) gas. The source and desolvation temperature were optimized and kept at 100˚ and 400˚C, respectively.

Liquid chromatography

A Waters 2695 liquid chromatography (Waters, Milford, USA) with an Atlantis C18 column (100 mm x 3.0 mm, 3 µm) (Waters, Manchester, UK) and Pelliguard LC-18 (20 mm x 4 mm) guard column was used for the separation of quetiapine and clozapine. The mobile phase was a mixture of acetonitrile-methanol-0.01 M ammonium acetate (31:19:50, V/V/V); pH was adjusted with acetic acid (pH 3.5). The flow rate was set at 0.4 mL/min.

Subjects

24 healthy Thai male volunteers, age between 20 and 45 years with body mass index between 18–25 kg/m^2. All volunteers were in good health on the basis of their medical history, physical examination, routine blood chemistry and hematology.

Experimental design

An open-label, randomized, single-dose, 2-period crossover design with a 2-week washout period was used in the study. This study was conducted in accordance to the revised Declaration of Helsinki for biomedical research involving human subjects (World Medical Association Declaration of Helsinki, 2000) and the rules of Good Clinical Practice. All volunteers were given a detailed explanation of the purpose, protocol and risk of the study, and each volunteer gave written informed consent. The protocol was approved by Thailand's Food and Drug Administration (registration number 1003.7/1105) and the Ethics Committee, Faculty of Science, Prince of Songkla University, Thailand (registration number 51/15-4).

Drug administration

The 24 volunteers were randomly assigned to one of the two sequence groups. During the first period, 12 volunteers from Group I received a single 200 mg tablet of Seroquel® while 12 volunteers from Group II received the same dose of Ketipinor®. During the second period, the procedure was repeated on the groups in reverse.

Blood sample collection

Serial blood samples (5 ml) were collected via the heparinized cannula at 0 (predose) and at 0.25, 0.5, 0.75, 1.00, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 24.0 and 48.0 hours (post-dose). The samples were centrifuged and the plasma was collected and stored at –70°C until subsequent analysis.

Assay of plasma quetiapine

The plasma quetiapine concentrations were measured by a validated LC/MS-MS method modified from the method of Barrett et al. [5]. Solid phase extraction (SPE) was used for sample pretreatment. Oasis HLB (hydrophilic-lipophilic balance) cartridges (30 mg, 1 mL) from Waters (USA) were activated with 2 mL of MeOH and conditioned with 3 mL H_2O. The plasma sample (0.5mL) was spiked with 50µL of Working Internal Standard solution, alkalinized with 200µL of 0.4 M NaOH, and vortex-mixed. The mixture was loaded on the prepared cartridges. The cartridge was washed with 3mL H_2O, and the analyte was eluted with 200µL of mobile phase. A 20µL aliquote was then injected onto the HPLC system with MS/MS detection.

Stock standard and internal standard solution

The stock standard solution (quetiapine) and internal standard solution (clozapine) at a concentration of 10µg/ml and 1µg/ml, respectively, were prepared by dissolving in MeOH/H_2O (70:30, v/v). Working standard solution used to prepare a calibration curve was prepared daily by diluting the stock solution with blank plasma.

Validation procedure

The validation method used in the study was conducted under the guidance of the US-FDA, 2002.

Subject monitoring

During the study period, vital signs were monitored by medical doctors. Side effects of the drugs were closely observed and recorded.

Pharmacokinetic analysis

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

Statistical analysis

An analysis of variance (ANOVA) was used to determine the difference of the pharmacokinetic parameters, i.e. C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$. The evaluation criteria was based on the statistical results of 90% confidence intervals (CI) for the difference in the means of the ln-

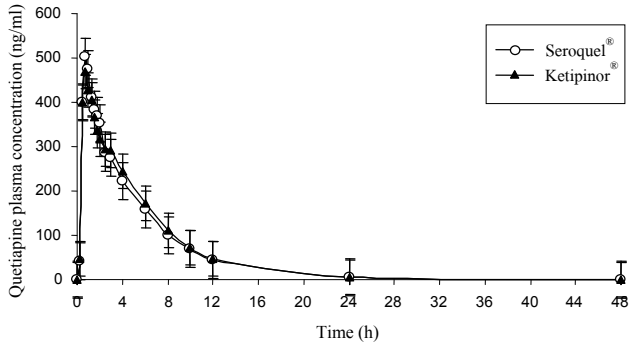

Figure 1: Plasma concentration-time curves after a single oral dose of 200 mg of Seroquel® and Ketipinor® in the 24 volunteers.

transformed data. 90% CI was calculated using the following equation:

$$\text{Confidence interval} = D \pm t0.10, \nu \sqrt{EMS(2 / n)}$$

Where Δ is a difference in means of the ln-transformed pharmacokinetic parameters (C_{max} or $AUC_{0\text{-last}}$ or $AUC_{0\text{-}\infty}$) between the test and the reference products, ***t0.10, ν*** is the tabulated 2-tail t value for a 90% CI, *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. Statistical analysis was performed using Statistical Package for Science (SPSS 17.0 for Window, SPSS Inc., Chicago)

Bioequivalence evaluation

Bioequivalence between the test and reference products would be concluded if the 90% CI of the ratios of the ln-transformed of the pharmacokinetics parameters, i.e. C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$, fell within the bioequivalence range of 80.00 to 125.00 (Asian Guidelines*, 2007, Thai FDA*, 2005, US FDA, 2001). (* both guidelines are based on US FDA Guidelines).

Results

Quetiapine and internal standard (clozapine) were clearly separated from the blank plasma with the retention time of 2.42 and 2.38 minutes, respectively (Figure not shown), indicating the selectivity/specificity of the analytical method. The lower limit of quantification with acceptable accuracy of 100.71% and precision of 7.48% was 0.70 ng/ml. The calibration curve of standard quetiapine was linear over the range of 0.70 - 1,600 ng/mL with the correlation coefficient of 0.9996. The intra-day accuracy ranged between 99.15 and 105.34% with a precision

Subject No.	C_{max} (ng/ml)	$AUC_{0\text{-last}}$ (ng/ml)	$AUC_{0\text{-}\infty}$ (ng/ml)	AUC extrapolated (%)	T_{max} (h)	$T_{1/2}$ (h)	Vd/F (L)	CL/F (L/h)
1	868.43	2861.14	2897.14	1.24	1.50	4.25	0.42	0.07
2	632.91	2738.75	2764.23	0.92	0.50	6.36	0.66	0.07
3	1060.34	2632.1	2650.97	0.71	0.50	3.42	0.370	0.08
4	554.54	1836.02	1846.72	0.58	0.50	3.60	0.56	0.11
5	351.58	1963.21	1971.87	0.44	1.50	5.29	0.77	0.10
6	393.3	2619.09	2621.57	0.10	0.50	4.64	0.51	0.08
7	523.55	1837.56	1857.16	1.06	0.75	3.70	0.58	0.11
8	868.32	3668.95	3687.59	0.51	2.00	2.92	0.23	0.05
9	887.34	3203.52	3218.99	0.48	0.75	3.02	0.27	0.06
10	631.48	1500.43	1508.78	0.55	0.75	6.07	1.16	0.13
11	1089.57	2658.70	2663.95	0.20	0.50	2.58	0.28	0.08
12	379.57	992.64	997.39	0.48	0.75	3.42	0.99	0.20
13	885.57	3173.09	3180.13	0.22	1.00	5.01	0.45	0.06
14	694.46	3103.81	3111.21	0.24	0.75	5.33	0.49	0.06
15	683.78	2766.5	2774.98	0.31	1.00	5.55	0.58	0.07
16	376.02	2316.01	2335.52	0.84	1.25	7.63	0.94	0.09
17	431.85	1742.22	1747.47	0.30	0.50	4.76	0.79	0.11
18	498.45	3713.2	3720.78	0.20	0.75	5.12	0.40	0.05
19	776.81	2673.57	2680.94	0.27	1.00	5.63	0.61	0.07
20	451.17	1755.85	1778.51	1.27	3.00	4.27	0.69	0.11
21	544.4	2763.70	2771.59	0.28	0.50	5.12	0.53	0.07
22	505.62	2301.01	2367.81	2.82	2.00	6.29	0.77	0.08
23	637.89	3471.6	3479.47	0.23	1.50	5.16	0.43	0.06
24	605.01	1991.04	1999.92	0.44	0.50	7.41	1.07	0.10
Mean	**638.83**	**2511.82**	**2526.45**	**0.61**	**-**	**4.86**	**0.60**	**0.09**
S.D.	**214.49**	**704.21**	**704.37**	**0.58**	**-**	**1.35**	**0.25**	**0.03**
Median	**-**	**-**	**-**	**-**	**0.75**	**-**	**-**	**-**
Max.	**-**	**-**	**-**	**-**	**3.0**	**-**	**-**	**-**
Min.	**-**	**-**	**-**	**-**	**0.5**	**-**	**-**	**-**

Table 1: Quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200 mg of Seroquel®.

(%CV) of 3.20 - 4.66%. The inter-day accuracy ranged between 97.25 - 103.30% with a precision (%CV) of 1.24 - 5.94%. All other validated parameters such as linearity, recovery of extraction, stabilities of the assay methods were all within the acceptance criteria as stated in the US-FDA guidance, 2002.

The plasma concentration-time curves after a single oral dose of 200 mg (200 mg/tablet)of Seroquel® and Ketipinor® in the 24 subjects are shown in Figure 1. Quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200 mg of Seroquel® and Ketipinor® are shown in Table 1 and Table 2, respectively. 2-way

Subject No.	C_{max} (ng/ml)	$AUC_{0\text{-last}}$ (ng/ml)	$AUC_{0\text{-}\alpha}$ (ng/ml)	AUC extrapolated (%)	T_{max} (h)	$T_{1/2}$ (h)	Vd/F (L)	CL/F (L/h)
1	856.94	2356.02	2362.49	0.27	1.25	6.22	0.76	0.08
2	875.39	2265.94	2280.10	0.62	0.50	3.43	0.43	0.09
3	840.11	3696.45	3724.08	0.74	1.00	3.36	0.26	0.05
4	432.69	2631.81	2646.80	0.57	0.75	5.47	0.60	0.08
5	494.32	1821.92	1827.88	0.33	0.75	5.66	0.89	0.11
6	238.63	2097.62	2103.26	0.27	0.75	5.50	0.75	0.10
7	610.9	2201.53	2207.99	0.29	0.75	5.70	0.75	0.09
8	431.64	2706.54	2712.34	0.21	3.00	4.93	0.53	0.07
9	641.20	3978.72	4022.41	1.09	4.00	3.41	0.24	0.05
10	595.4	1984.84	1987.69	0.14	0.50	4.57	0.66	0.10
11	726.20	2424.22	2430.96	0.28	0.50	5.19	0.62	0.08
12	192.13	893.50	903.24	1.08	0.75	8.43	2.69	0.22
13	278.33	1665.92	1672.78	0.41	4.00	5.49	0.95	0.12
14	422.38	2270.07	2275.18	0.22	1.75	4.75	0.60	0.09
15	1585.30	4506.01	4513.05	0.16	0.75	5.22	0.33	0.04
16	662.83	2170.06	2210.26	1.82	1.50	5.22	0.68	0.09
17	664.02	2963.26	2964.87	0.05	0.75	4.20	0.41	0.07
18	504.64	3722.96	3818.17	2.49	2.50	4.22	0.32	0.05
19	535.34	3103.09	3112.80	0.31	3.00	6.20	0.57	0.06
20	444.85	1272.01	1275.88	0.30	0.75	7.33	1.66	0.16
21	663.90	3348.58	3355.58	0.21	0.75	4.95	0.43	0.06
22	422.13	1297.86	1313.70	1.21	0.50	4.05	0.89	0.15
23	922.45	4412.69	4424.12	0.26	0.50	5.06	0.33	0.05
24	1132.80	3213.43	3220.30	0.21	0.75	5.11	0.46	0.06
Mean	**632.27**	**2625.21**	**2640.25**	**0.56**	**-**	**5.15**	**0.70**	**0.09**
S.D.	**304.43**	**972.14**	**979.10**	**0.59**	**-**	**1.17**	**0.52**	**0.04**
Median	**-**	**-**	**-**	**-**	**0.75**	**-**	**-**	**-**
Max.	**-**	**-**	**-**	**-**	**4.0**	**-**	**-**	**-**
Min.	**-**	**-**	**-**	**-**	**0.5**	**-**	**-**	**-**

Table 2: Quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200 mg of Ketipinor®.

Dependent variable	Source of variation	df	Sum of squares	Mean squares	F_{stat}	*P*- values
C_{max}	Subject*Sequence	22	5.189	0.236	2..213	0.034*
	Period	1	0.238	0.238	2.229	0.150
	Drug	1	0.106	0.106	0.997	0.329
	Error	22	2.345	0.107		
	Total	48	1,958.545			
$AUC_{0\text{-last}}$	Subject*Sequence	22	4.416	0.201	3.662	0.002*
	Period	1	0.023	0.023	0.417	0.525
	Drug	1	0.000	0.000	0.006	0.941
	Error	22	1.206	0.055		
	Total	48	2,920.980			
$AUC_{0\text{-}\infty}$	Subject*Sequence	22	4.674	0.212	3.215	0.004*
	Period	1	0.048	0.048	0.733	0.401
	Drug	1	0.010	0.010	0.148	0.704
	Error	22	1.454	0.066		
	Total	48	2,917.259			

Table 3: Two-way ANOVA studies of natural log-transformed data of ratio of C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ of Seroquel® and Ketipinor®.

Pharmacokinetic parameters	Ketipinor®	Seroquel®	90% CI of Test:Reference	Power (%)
C_{max} (ng/ml)	632.27 ± 304.43	638.83 ± 214.49	80.75 - 102.60	92.16
$AUC_{0\text{-}last}$ (ng.h/ml)	2625.21 ± 972.14	2511.82 ± 704.21	91.32 - 108.42	96.34
$AUC_{0\text{-}\infty}$ (ng.h/ml)	2640.25 ± 979.10	2526.45 ± 704.37	88.47 - 106.77	95.96
T_{max} (h)	1.34 ± 1.11	1.01 ± 0.63		
$T_{1/2}$ (h)	5.15 ± 1.17	4.86 ± 1.35		
CL (L/h)	0.09 ± 0.04	0.09 ± 0.03		
Vd/F (L)	0.70 ± 0.52	0.60 ± 0.25		
AUC extrapolated (%)	0.56 ± 0.59	0.61 ± 0.58		

Table 4: Pharmacokinetic parameters (mean ± SD) and 90% CI of the ratios of the natural Log-transformed of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ between Ketipinor® (test) and Seroquel® (ref.), after a single oral dose of 200-mg of Ketipinor® and Seroquel® in the 24 healthy volunteers.

ANOVA studies of the ln-transformed data of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ of Seroquel® and Ketipinor® are shown in Table 3. Subject within sequence had significant effect on all parameters while sequence did affect the $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$. The pharmacokinetic parameters (mean±SD) and 90% CI of the ratios of the ln-transformed of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ between Ketipinor® and Seroquel®, after a single oral dose of 200 mg of the drugs in the 24 healthy volunteers are shown in Table 4.

Both treatment groups were well tolerated to the medications. There was no serious side effect from the drugs and no one was withdrawn from the study. Adverse effects of Seroquel® and Ketipinor® found were somnolence (100% and 100%), orthostatic hypotension (8.34% and 8.34%), nasal congestion (8.34% and 8.34%) and myalgia (4.17% and 0%).

Discussion

All the validated analytical method of quetiapine used in this study was accurate, precise and rugged. 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 T_{max} of Ketipinor®, 0.5-4.0 h, was within the acceptance range of ±20% of the median T_{max} of the reference product, 0.5-3.0 h. Therefore, the time to reach maximum response of both formulations should not be significant different. The power of the test for C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ was 92.16%, 96.34% and 95.96%, respectively, which were much greater than 80.00%, indicating reliability of the test. As the extrapolated AUC from 48 h to infinity of both products were much less than 20% (Table 4), therefore the blood samples collection were adequate for the study.

The ANOVA results indicated that formulation and period had no statistically significant effect on C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ at the significant level of 0.05. However, the subject within sequence had significant effect on all the parameters indicating that there should be high interindividual variation in drug metabolism. Although CYP2D6 plays a minor role in metabolism of quetiapine [12], but genetic polymorphism of CYP2D6 might be the cause of the variation. Moreover there was no predose concentration observed. Therefore, the sequence effect did not impair the results. However, the 90% confidence interval of the ratios between the test and reference products of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ were 80.75 - 102.60%, 91.32 - 108.42% and 88.47 -106.77%, respectively, which were within the acceptance criteria for bioequivalence, indicating that both products were bioequivalent.

Conclusion

We have found that the generic quetiapine (Ketipinor®, manufactured by Orion Corporation, Finland) and the innovator product (Seroquel®, manufactured by AstraZeneca, UK) used in this study were bioequivalent in both the rate and extent of absorption under fasting condition. Because the 90% CI of the ratios between the test and the reference products of C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}\infty}$ were within the acceptance interval of 80 - 125%.

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