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

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ชื่อวิทยานิพนธ์	การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบ (Ketipinor®) เทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทยสุขภาพปกติ
ผู้เขียน	นางสาวจารุวรรณ ประดับแสง
สาขาวิชา	เภสัชวิทยา
ปีการศึกษา	2553

บทคัดย่อ

ควิไทอะปีน (quetiapine) เป็นยารักษาผู้ป่วยโรคทางจิตเวชกลุ่มใหม่ ซึ่งใช้ในการรักษาโรคจิตเภท (schizophrenia) วัตถุประสงค์ของการศึกษานี้คือเพื่อประเมินชีวสมมูลของยาควิไทอะปีนระหว่างยาสามัญ (Ketipinor®) เทียบกับยาต้นแบบ (Seroquel®) ชนิดเม็ด ขนาด 200 มก. โดยการรับประทาน รูปแบบการศึกษาเป็นแบบสุ่มไขว้สลับ ซึ่งเว้นระยะห่างของการให้ยาเป็นเวลา 2 สัปดาห์ในอาสาสมัครชายไทยสุขภาพปกติจำนวน 24 คน อาสาสมัครรับประทานยา Seroquel® หรือ Ketipinor® ขนาด 200 มก. ครั้งเดียว หลังจากงดอาหารและน้ำคืนก่อนการทดลองอย่างน้อย 8 ชั่วโมง เก็บตัวอย่างเลือดของอาสาสมัครก่อนรับประทานยา และหลังรับประทานยาที่เวลา 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 และ 48 ชั่วโมง นำพลาสมาที่แยกแล้วมาเก็บไว้ที่ -70°C จนกว่าจะนำมาวิเคราะห์ การวิเคราะห์หาระดับยาในพลาสมาใช้วิธีโครมาโตกราฟีชนิดของเหลวประสิทธิภาพสูงและตรวจวัดด้วยแมสสเปกโตรมิเตอร์ (LC-MS-MS) วิเคราะห์หาค่าพารามิเตอร์ทางเภสัชจลนศาสตร์โดยใช้แบบจำลองชนิด non-compartment ทดสอบความแตกต่างทางสถิติของค่าตัวแปรทางเภสัชจลนศาสตร์ด้วย two-way Analysis of Variance (ANOVA) ผลการทดลองไม่พบความแตกต่างอย่างมีนัยสำคัญของยาทั้งสอง การทดสอบ Power ของความเข้มข้นสูงสุดของยาในพลาสมา (C_{max}) พื้นที่ใต้กราฟที่แสดงความสัมพันธ์ระหว่างความเข้มข้นของยาในพลาสมากับเวลาในช่วง 48 ชั่วโมง (AUC_{0-48}) และที่เวลาอนันต์ ($AUC_{0-\infty}$) มีค่ามากกว่า 80% อาการข้างเคียงที่พบโดยทั่วไปคือ อาการง่วงนอนมากผิดปกติ ภายหลังจากการได้รับยาสามัญและยาต้นแบบ ไม่มีอาสาสมัครถอนตัวออกจากการศึกษา การพิจารณาชีวสมมูลของตำรับยาโดยการเปรียบเทียบค่าเฉลี่ยของความเชื่อมั่นที่ 90% ของอัตราส่วน (ยาทดสอบ/ยาต้นแบบ) ของ C_{max}, AUC_{0-48} และ$AUC_{0-\infty}$ ในรูปลอการึทึม มีค่าเท่ากับ 80.75-102.60%, 91.32-108.42% และ 88.47-106.77% ตามลำดับ ค่าที่ได้อยู่ในช่วง 80-125% ซึ่งอยู่ในเกณฑ์ที่ยอมรับได้โดยสำนักงานคณะกรรมการอาหารและยาของประเทศไทย ดังนั้นจึงสรุปได้ว่ายา Ketipinor® และ Seroquel® ที่ใช้

ในการศึกษาครั้งนี้มีชีวสมมูลกันทั้งอัตราเร็วและปริมาณการดูดซึม

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ABSTRACT

Quetiapine is an atypical antipsychotic drug which is used in the treatment of schizophrenia. The aim of this study was to evaluate the bioequivalence of a generic quetiapine (Ketipinor®) and the innovator preparation (Seroquel®) 200-mg tablet. Twenty-four healthy Thai male volunteers were enrolled in the study and were given a single oral dose, randomized, two-period, two-sequence crossover design with 2 weeks washout period. A single dose of 200-mg quetiapine was orally administered after an overnight fasting for at least 8 hr. Blood samples were collected at 0 (pre dose) and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 hr post dose. The plasma samples were separated and stored at -70 °C until analysis. The plasma quetiapine concentrations were determined by using a liquid chromatography tandem mass spectrometric method (LC-MS-MS). A non-compartment model was used for the analysis of pharmacokinetic parameters. The comparative bioequivalence between the two products were estimated by the Analysis of Variance (ANOVA) for two-way crossover design. There were no significant effects of formulation, sequence and period on this study. The power of test for C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ were more than 80%. The most commonly reported adverse event was somnolence after drug administration of both test and reference formulations. No subjects withdrew from the study. The 90% CI of logarithmically (ln)-transformed of the ratios (Test/Reference) of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ were 80.75-102.60%, 91.32-108.42% and 88.47-106.77%, respectively, which were within the acceptable range of the Thai FDA criteria, i.e. 80-125%. Therefore, it was concluded that Ketipinor® and Seroquel® were bioequivalent in terms of their rates and extents of absorption.

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Charuwan Pradabsang

CONTENTS

LIST OF TABLES

LIST OF TABLES (Continued)

LIST OF FIGURES

LIST OF FIGURES (Continued)

LIST OF FIGURES (Continued)

LIST OF ABBREVIATIONS AND SYMBOLS

%	=	Percentage
µg	=	Microgram
µL	=	Microlitre
®	=	Trade name
°C	=	Degree Celsius
ALP	=	Alkaline phosphatase
ANOVA	=	Analysis of Variance
AUC	=	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	=	Area under the plasma concentration-time curve from zero to infinity
AUC_{0-t}	=	Area under the plasma concentration-time curve from zero to last point
BMI	=	Body mass index
BUN	=	Blood urea nitrogen
CI	=	Confidence interval
CL/F	=	Clearance
CLO	=	Clozapine
cm	=	Centimeter
C_{max}	=	Maximum concentration
Cr	=	Creatinine
CV	=	Coefficient of variation
DBI	=	Direct bilirubin
df	=	Degree of freedom
E	=	Eosinophil
FBS	=	Fasting blood sugar
FDA	=	Food and drug administration
hr	=	Hour

LIST OF ABBREVIATIONS AND SYMBOLS (Continued)

Hb	=	Hemoeglobin
Hct	=	Hematocrit
HPLC	=	High Performance Liquid Chromatography
i.e.	=	Id est = That is
IS	=	Internal standard
kg	=	Kilogram
L	=	Litre
LC-MS-MS	=	Liquid chromatography tandem mass spectrometry
LLOQ	=	Lower limit of quantitation
Lymph	=	Lymphocyte
m	=	Meter
min	=	Minute
mL	=	Milliliter
MS	=	Mean of square
ng	=	Nanogram
No.	=	Number
P	=	*p*-value
PMN	=	Polymorphonuclear neutrophils
QC	=	Quality control
QUE	=	Quetiapine
r^2	=	Correlation coefficient
RSD	=	Relative standard deviation
SD	=	Standard deviation
SGOT	=	Serum glutamic oxaloacetic transaminase
SGPT	=	Serum glutamic pyruvic transaminase
SS	=	Sum of square
$T_{1/2}$	=	Half-life
TBL	=	Total bilirubin

LIST OF ABBREVIATIONS AND SYMBOLS (Continued)

T_{max}	=	Time to maximum concentration
UV	=	Ultraviolet
v/v/v	=	Volume by volume by volume
V/F	=	Volume of distribution
WBC	=	White blood cell

CHAPTER 1

INTRODUCTION

In Thailand, it is estimated that the consumption of drugs is as high as 25-80 billion baht per year. The consumption of innovator drugs is one third of the total drug consumption. In general, generic drug are less expensive than their innovator counterparts because generic drugs do not have to duplicate the cost of research and marketing conducted by the original manufacturer. The difference of the prices of generic and innovator drugs in Thailand is very high. The generic substitutions in hospitals cause substantial decrease in drug expenditures of 216.6 million baht (Tantivess *et al*., 2002).

The generic drug products come from multi-source of manufacturers and generally cheaper than the original ones, the bioequivalent tests are required to ensure that they can be used as substitutes and provide the same therapeutic effects. The important of generic drugs in healthcare, it is imperative that pharmaceutical quality and *in vivo* performance of generic drugs be reliably assessed. Because generic drugs would be interchanged with innovator products in the market place, it must be demonstrated that the safety and efficacy of generics are comparable to the safety and efficacy of the corresponding innovator drugs. Assessment of interchangeability between the generic and the innovator product is carried out by a study of "*in vivo* equivalence" or " bioequivalence " (Midha and McKay, 2009).

Bioequivalence study is based on the administration of two drug formulations in the same dose under similar experimental conditions. Bioequivalence is concerned with the comparison of the bioavailabilities of drug from two formulations of that drug and is usually assessed by measures obtained from the respective plasma concentration and time curves. Drug should be considered bioequivalent if their rate and extent of absorption are not significantly different. The pharmacokinetic parameters of interest are the observed area under the plasma concentration-time curve (AUC), the peak plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}) (Thailand FDA, 2005). Bioequivalence based on test/reference comparisons of pharmacokinetic measures serves two purposes. The first is to act as a surrogate for therapeutic equivalence. The second is to provide *in vivo* evidence of pharmaceutical quality. The overall

objective of bioequivalence is to ensure that generic formulations have similar efficacy and safety characteristics to the corresponding brand formulations.

Schizophrenia is a chronic illness, and the best known psychotic illness. The most patients are taking medications for a lifetime (Prior *et al.,* 1999). Schizophrenia affects 1 percent of the population, and in the United State there are over 300,000 acute schizophrenic episodes annually. Between 25 and 50 percent of schizophrenia patients attempt suicide, and 10 percent eventually succeed, contributing to a mortality rate eight times greater than that of the general population. The direct and indirect costs of schizophrenia in the United State alone are estimated to be in the tens of billions of dollars every year. Schizophrenia by definition is a disturbance that must last for 6 months or longer, including at least 1 month of delusion, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. Positive symptoms include hallucinations (auditory, visual, olfactory, gustatory and tactile), delusion (referential, somatic, religious or grandiose), thought disorder (tangentiality, derailment, circumstantiality), and bizarre behavior (clothing, appearance, aggression, repetitive actions). Negative symptoms include alogia (dysfunction of communication), affective blunting or flattening, asociality (reduced social drive and interaction), anhedonia (reduced ability to experience pleasure) and avolition (reduced desire, motivation, or persistence) (Stahl, 2008).

Antipsychotic drugs are classified into two groups, typical and atypical. Typical or conventional antipsychotic drugs include chlorpromazine, thioxanthenes, haloperidol, loxapine and molindone (มานิต, 2545). They could reduce positive symptoms, but negative symptoms are resisted. The extrapyramidal side effects have been a highly limiting factor of drug use. The new drugs or atypical antipsychotic drugs have a variety of structures and include clozapine, quetiapine, risperidone, olanzapine, ziprasidone, loxapine, molindone, pimozide and aripiprazole (มาโนช, 2547; Katzung, 2007). Atypical antipsychotics have a low incidence of extrapyramidal side effects and tardive dyskinesias compared to typical antipsychotic drugs (Barrett *et al.,* 2007).

Quetiapine is an atypical antipsychotic drug with a dibenzothiazepine structure similar to clozapine (Bellomarino *et al*., 2009). It is an antagonist with binding at neurotransmitter receptors, including 5-HT_{1A}, 5-HT_{2A}, D_1 and D_2, histamine (H_1) receptor, alpha-1 and alpha-2 adrenergic receptor (Moor and Jefferson, 2004). Quetiapine (Seroquel®) was released in the United States in 1998. Like clozapine, the drug appears to have low affinity for D_1 and D_2

receptors but relatively high affinity for D_4 receptors and 5-HT_2 receptors. Clozapine, olanzapine, and quetiapine all seem to have more pronounced effects on mesolimbic dopamine activity than on nigrostriatal pathways, a pheonomenon that accounts for their low tendency to produce extrapyramidal symptoms. Quetiapine does not appear to have very significant anticholinergic or antihistaminic effects, but it does block α_1-adrenergic receptors to some extent (Schatzberg *et al.,* 2005). It was not associated with sustained increases in plasma prolactin at any dose (King *et al.,* 1998). Quetiapine is an effective to reduce positive symptoms and treat negative symptoms with less extrapyramidal side effects. It has markedly improved the quality of life in many schizophrenic patients (Sachse *et al*., 2006). The advantages of the therapeutic profile of quetiapine have led to increasing use in the clinical practice, which encourages the development of new pharmaceutical preparations (Barrett *et al.,* 2007). Adding quetiapine to a mood stabilizer such as lithium is more effective in treating bipolar disorder than using lithium alone. There are unpublished, presented data suggesting quetiapine at dosages of 300-600 mg/day is an effective treatment for the anxiety component of bipolar depression. However, quetiapine seems to have good antidepressant properties in bipolar depression as well. Very preliminary work suggests that quetiapine may be a useful maintenance treatment in bipolar disorder. Further clinical trials in patients with bipolar depression and patients with mania led the FDA to approve additional indications for quetiapine's use in the acute and treatment of bipolar disorder.

The aim of this study was to investigate the bioequivalence between the generic drug, Ketipinor®, and innovator drug, Seroquel® 200 mg given orally in healthy Thai male volunteers. The result of this study may serve to facilitate selecting and prescribing of quetiapine and to ensure that the patients will receive qualified medical treatment with lower cost.

CHAPTER 2

LITERATURE REVIEWS

2.1 Quetiapine

Quetiapine (Seroquel®) is an atypical antipsychotic drug. It is a clozapine-like dibenzothiazepine compound (Atanasov *et al.,*2008). The chemical designation is 2-[2-(4-dibenzo [b,f][1,4] thiazepine-11-yl-l-piperazinyl)ethoxy]ethanol fumarate (2:1 salt). Its molecular formula is $C_{21}H_{25}N_3O_2S$ (Figure 1) and its molecular weight is 833.11 (Hendrickson, 2006)

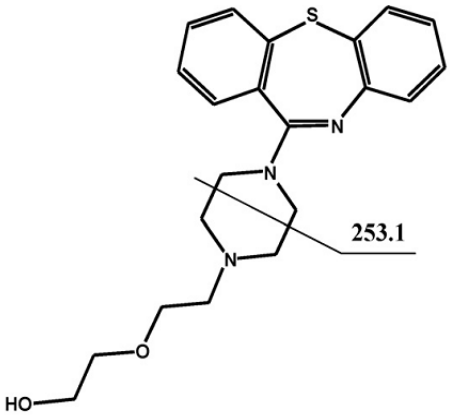


Figure 1. Structure formula of quetiapine (Barrett *et al.,* 2007)

Physical Properties

Ionization constant	:	pKa1 = 6.83 in phosphate buffer at 22°C
		pKa2 = 3.32 in formic buffer at 22°C
Melting point	:	172 - 174°C
Solubility	:	very slightly soluble in ether, slightly soluble in water and soluble in 0.1 N HCl
Storage	:	15 - 30°C

Composition

Quetiapine is available in 5 strengths containing 25, 100, 200 and 300 mg per tablet (Figure 2).

Figure 2. Tablets-25, 100, 200 and 300 mg of quetiapine

2.1.1 Mechanism action of atypical antipsychotic drugs

Schizophrenia is a severe mental illness that affect 1% of the world's population. It is a very expansive illness because it usually affects people when they are young and it has a chronic course throughout the rest of their lives. Approximately 10% of all people with schizophrenia which the mortality is secondary to suicide (Kay *et al*., 2000). Most people with schizophrenia experience multiple hospitalizations and account for about 40% of hospital beds occupied (Goldman, 2000). Men and women have the same lifetime risk of schizophrenia, but in women, schizophrenia develops several years later, often from ages 25 to 35. The mean age for female with schizophrenia is 25 years with a range of 15-30 years being the most common. Women may be diagnosed with schizophrenia though menopause as well. Women with schizophrenia have fewer hospital stays and better social functioning than men with

schizophrenia. For male with schizophrenia, the mean age is 20 years with a range of 10-24 years (Ebert *et al*., 2000).

Dysfunction of central dopaminergic neurotransmission has been implicated in the pathogenesis of schizophrenia. Increased dopamine release in the mesolimbic dopaminergic pathway has also been associated with the pathogenesis of positive symptoms (delusion, hallucinations, bizarre behavior, and thought disorder). Decreased dopaminergic transmission in the mesocortical pathway is believed to modulate the negative symptoms of schizophrenia (affective flattening, anhedonia, avolition, alogia, and asociality). The negative symptoms are mostly closely related to dopamine receptor hypofunction in the prefrontal cortex (Crismon and Dorson, 2002).

Atypical antipsychotic drugs are now prescribed more commonly than typical antipsychotic drugs in many areas of the world, there continues to regard the cost-effectiveness and the clinical superiority of atypical antipsychotic drugs. Atypical antipsychotic drugs are low incidence of extrapyramidal side effects and tardive dyskinesias in human compared to typical antipsychotic drugs. They do not elevate serum prolactin levels and induce catalepsy in rodents (Csernansky and Lauriello, 2004). While risperidone, olanzapine and quetiapine are associated with a lower risk of extrapyramidal side effects, tardive dyskinesia and hyperprolactinemia than typical antipsychotic (Kasper *et al.,* 2001).

Quetiapine is an antipsychotic agent which interacts with a broad range of neurotransmitter receptors, including 5-HT_{1A}, 5-HT_{2A}, D_1 and D_2, histamine (H_1) receptor, alpha-1 and alpha-2 adrenergic receptor (Cutler *et al*., 2002). The efficacy of quetiapine in schizophrenia is mediated by a combination of 5-HT_{2A} and D_2 receptors (Kundlik *et al.,* 2009). It is combinated of receptor antagonism with a higher selectivity for 5-HT_{2A} than D_2 receptors (Ozkan *et al.,* 2006). This profile contrasts with its relatively weak affinity for other subclasses of the serotonin receptor family (Goldstein, 1999). Quetiapine also has strong affinity for adrenergic alpha-1 receptors. This antagonism may relate to its propensity to induce orthostatic hypotension. Additionally, quetiapine has strong antagonism at histamine type1 (H_1) receptors are associated with sedative effect. Weight gain during quetiapine therapy may also emanate from H_1 receptor antagonism. However, this structure activity relationship is less clear than the association between

H_1 antagonism which is associated sedation. Affinity of quetiapine for human neurotransmitter receptors were shown in Table 1.

Table 1. Affinity of quetiapine for human neurotransmitter receptors

Receptor binding profile	5-HT_{1A}	5-HT_{2A}	D_1	D_2	Histamine H_1	adrenergic α_1	adrenergic α_2
Ki (nM) (Davis *et al.,* 2002)	230	220	1,300	531	8.7	15	1,000
IC_{50} (nM) (AstraZeneca, 2006)	717	148	1,268	329	30	94	271

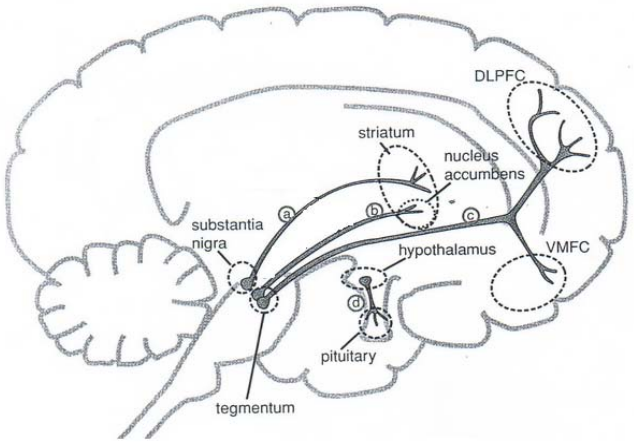
Antipsychotics have been characterized by their tightness of binding to the dopamine receptor. Typical antipsychotics bind more tightly than dopamine itself to the dopamine D_2 receptor, with dissociation constants that are lower than that of dopamine. The newer, atypical antipsychotics such as quetiapine, clozapine, and olanzapine all bind more loosely than dopamine to the dopamine D_2 receptor. Conventionals, such as haloperidol and chlorpromazine are tightly bound; and olanzapine and ziprasidone are somewhere in between (Ciraulo *et al.,* 2006). For instance, radioactive haloperidol, chlorpromazine, and raclopride all dissociate very slowly over a 30-minute time span, while radioactive quetiapine and clozapine dissociate rapidly, in less than 60 seconds. Conversely, the occupation of D_2 by clozapine or quetiapine has mostly disappeared after 24 hours (Seeman, 2002).

Quetiapine has high affinity for 5-HT_2 receptors. It blocks of postsynaptic dopamine type 2 receptors in the mesolimbic system reduces excessive dopaminergic activity and alleviates the positive symptoms of schizophrenia. The mesocortical tract is responsible for higher order thinking and executive functions dopamine hypofunctioning in this area may be responsible negative symptoms and cognitive dysfunction. The nigrostriatal pathway modulate body movement. Typical antipsychotics induce blockade of the dopamine pathway in the tuberoinfundibular area of the anterior pituitary leads to hyperprolactinemia. However, in the case of quetiapine is simultaneous inhibition of 5-HT_{2A} receptors, so serotonin can no longer stimulate prolactin release.

Quetiapine has a higher affinity for 5-HT_2 than dopamine D_2 receptors. It has the lowest D_2 receptor binding at clinical dose of 300–600 mg/day, D_2 binding range from 0% to 27%. Even at 800 mg/day, only 30% of D_2 receptors are occupied at the same daily doses, 45% to 90% of 5-HT_{2A} receptors are occupied. (Crismon and Dorson, 2002). Kapur *et al.* (2000) found that quetiapine led to transiently high D_2 occupancy of 58% to 64% during the first 2 to 3 hours, which decrease to minimal levels by 12 hours. This suggests that transient D_2 occupancy may be sufficient for an antipsychotic effect. Like clozapine, its low level of D_2 occupancy may account for its very low risk of EPS and prolactin elevation. This may also explain why doses of 150–300 mg/day show questionable efficacy (Small *et al*., 1997) since the dose of quetiapine required to reach a peak occupancy of 60% would be 600–800 mg/day or above. Akdede *et al*. (2005) suggests that quetiapine improves specific areas of neurocognitive function and suppresses positive and negative symptoms of schizophrenia, without an increase in motor side effects.

2.1.2 Relationship between dopaminergic and serotonergic pathway

The neuroanatomy of dopamine neuronal pathways in the brain can explain the symptoms of schizophrenia as well as the therapeutic effects and side effects of antipsychotic drugs. Four dopamine pathways in the brain as shown in Figure 3 play a role in the pathophysiology of schizophrenia.



(a): nigrostrital dopamine pathway;
(b): mesolimbic dopamine pathway;
(c): mesocortical dopamine pathway;
(d): tuberoinfundibular dopamine pathway

Figure 3. Four dopamine pathways in the brain (Stahl, 2008)

Nigrostriatal Dopamine Pathway

The nigrostriatal dopamine pathway, which projects from the substantia nigra to the basal ganglia or striatum, which consists of the caudate nucleus, globus pallidus and putamen. This pathway is a part of the extrapyramidal nervous system and controls motor function and movement. Deficiencies in dopamine in this pathway cause movement disorders, including Parkinson's disease, characterized by rigidity, akinesia/bradykinesia (i.e., lack of movement or slowing of movement), and tremor (Stahl, 2008). Blockade of D_2 receptors in this pathway causes the drug-induced movement disorders EPS and, eventually, tardive dyskinesia. Dopamine deficiency as well as receptor blockade in this pathway can also cause akathisia and dystonia (Stahl, 2003).

Mesolimbic Dopamine Pathway

The mesolimbic dopamine pathway projects from the midbrain ventral tegmental area of the brainstem to axon terminals in one of the limbic areas of the brain, namely the nucleus accumbens in the ventral striatum. This pathway is thought to have an important role in many behaviors such as pleasurable sensations, the powerful euphoria of drug of abuse, as well as delusions and hallucinations of psychosis. The mesolimbic dopamine pathway is also important for motivation, pleasure, and reward. Mesolimbic dopamine hypothesis of positive symptoms of schizophrenia is believed that it is hyperactivity specifically in this particular dopamine pathway that mediates the positive symptoms of psychois (Stahl, 2008).

Quetiapine has effects on mesolimbic dopamine activity than on nigrostriatal pathways, a pheonomenon that accounts for their low tendency to produce EPS. Like other atypical agents, quetiapine appears to have high affinity for 5-HT_2 receptors. It blocks of dopamine receptors in the mesolimbic pathway because hyperactivity in this location is responsible for positive symptoms. Blockade of the remaining dopamine pathway causes adverse effects rather than a therapeutic benefit.

Mesocortical Dopamine Pathway

The mesocortical dopamine pathway projects from the the midbrain ventral tegmental area but sends its axons to areas of the prefrontal cortex, where they may have a role in

mediating cognitive symptoms (dorsolateral prefrontal cortex) and affective symptoms (ventromedial prefrontal cortex) of schizophrenia (Stahl, 2008). This is believed to modulate the negative symptoms of schizophrenia such as affective, flattening, anhedonia, avolition, alogia, and asociality (Shiloh *et al.,* 2006). Dopamine function in schizophrenia may be more complicated than just "too high" in mesolimbic areas and "too low" in mesocortical areas. However, since dopamine receptor blockade in this pathway would theoretically lead to a worsening of negative and cognitive symptoms. In other words, an agent would have to decrease dopamine in the mesolimbic pathway to alleviate positive symptoms but increase it in the mesocortical pathway to treat negative and cognitive symptoms (Stahl, 2003).

Tuberoinfundibular Dopamine Pathway

The dopamine neurons that project from the hypothalamus to the anterior pituitary are known as the tuberinfundibular dopamine pathway. Normally, dopamine inhibits prolactin secretion into the circulation. If the functioning of tuberinfundibular dopamine neurons is disrupted by lesions or drugs, prolactin levels can rise. Elevated prolactin levels are associated with galactorrhea (breast secretions), amenorrhea (loss of ovulation and menstrual periods), and other problems such as sexual dysfunction (Stahl, 2008). Problems can occur after treatment with a conventional antipsychotic drugs that D_2 receptors are blocked, dopamine can no longer inhibit prolactin release, so prolactin levels rise. However, in the case of atypical antipsychotic drugs have relatively high affinities for 5-HT_{2A} receptors. Physiologically, 5-HT_{2A} receptors occur on the cell bodies and terminal axon fibers of dopamine neurons in the frontal cortex, basal ganglia and tuberinfundibular system. Serotonin inhibits the release of dopamine into the synapse. Blockade of these receptors by atypical antipsychotic drugs prevent serotonin from exerting its inhibitory effect and increases dopaminergic activity in the frontal cortex, basal ganglia and tuberinfundibular system (Wright, 2006).

Serotonergic pathway

Serotonin has importance influences on dopamine, but that influence is quite different in each of the four dopamine pathway. Serotonin inhibits dopamine release from

dopaminergic axon terminals in the various dopamine pathways, but the degree of control differs from one dopamine pathway to another (Stahl, 2000).

Serotonin neurons from the brainstem raphe innervate the dopamine cell bodies in the substantia nigra and also project to the basal ganglia, where serotonin axon terminal are in close proximity to dopamine axon terminal. In both area, serotonin interacts with postsynaptic 5-HT_{2A} receptors on the dopamine neuron, and this inhibits dopamine release. Thus in the nigrostriatal dopamine pathway, serotonin exerts powerful control over dopamine release because it occurs at two levels. At the level of serotonergic innervation of the substantia nigra, axon terminals arriving from the raphe synapse on cell bodies and dendrites of dopaminergic cells. As has been reviewed elsewhere, most atypical antipsychotic drugs are characterized by having relatively higher affinities for 5-HT_{2A} receptors than for D_2 receptors (Csernansky and Lauriello, 2004). Blocking 5-HT_{2A} receptors should promote dopamine release. When dopamine release is enhanced by quetiapine (second-generation atypical antipsychotic drug) via blockade of 5-HT_{2A} receptors, this allows the extra dopamine to compete with the quetiapine to reverse the blockade of D_2 receptors. This leads to a reduction or even an absence of EPS and tardive dyskinesia, because there is a reduction of D_2 receptor blockade in this pathway. 5-HT_{2A} receptors in other brain regions (i.e. mesocortical dopamine pathway and dopaminergic neurons of the mesolimbic pathway). This may result in a decreased firing rate of these neurons, and enhancement of the potential antipsychotic effects of a drug. The drug's capacity to block postsynaptic D_2 receptors in the mesolimbic pathway thereby alleviating positive symptoms of schizophrenia is usually considered to be as good as that of typical antipsychotic drugs. Blockade of 5-HT_{2A} receptors in the mesocortical pathway which is believed to modulate the negative symptoms of schizophrenia. 5-HT_{2A} receptor blockade may enhance dopaminergic transmission, thereby relieving negative symptom (Koda-Kimble *et al*., 2001). The beneficial roles of atypical antipsychotic drugs were shown in Figure 4.

D_2 receptor blockade may have a beneficial outcome in one pathway but it may cause problems in another (Table 2).

Table 2. Dopaminergic tracts and effects of dopamine antagonists (Stahl, 2008).

Dopamine pathway	**Origin**	**Innervation**	**Function**	**Dopamine antagonist effect**
Nigrostriatal (a)	Substantia nigra	Caudate nucleus and putamen	Extrapyramidal system and movement	Movement disorders
Mesolimbic (b)	Midbrain ventral tegmental area	Limbic system	Emotional and motivational behavior	Relief of psychosis
Mesocortical (c)	Midbrain ventral tegmental area	Prefrontal cortex	Cognition, communication, social function, response to stress	Relief of psychosis
Tuberoinfun-dibular (d)	Hypothalamus	Pituitary gland	Regulates prolactin release	Increase prolactin

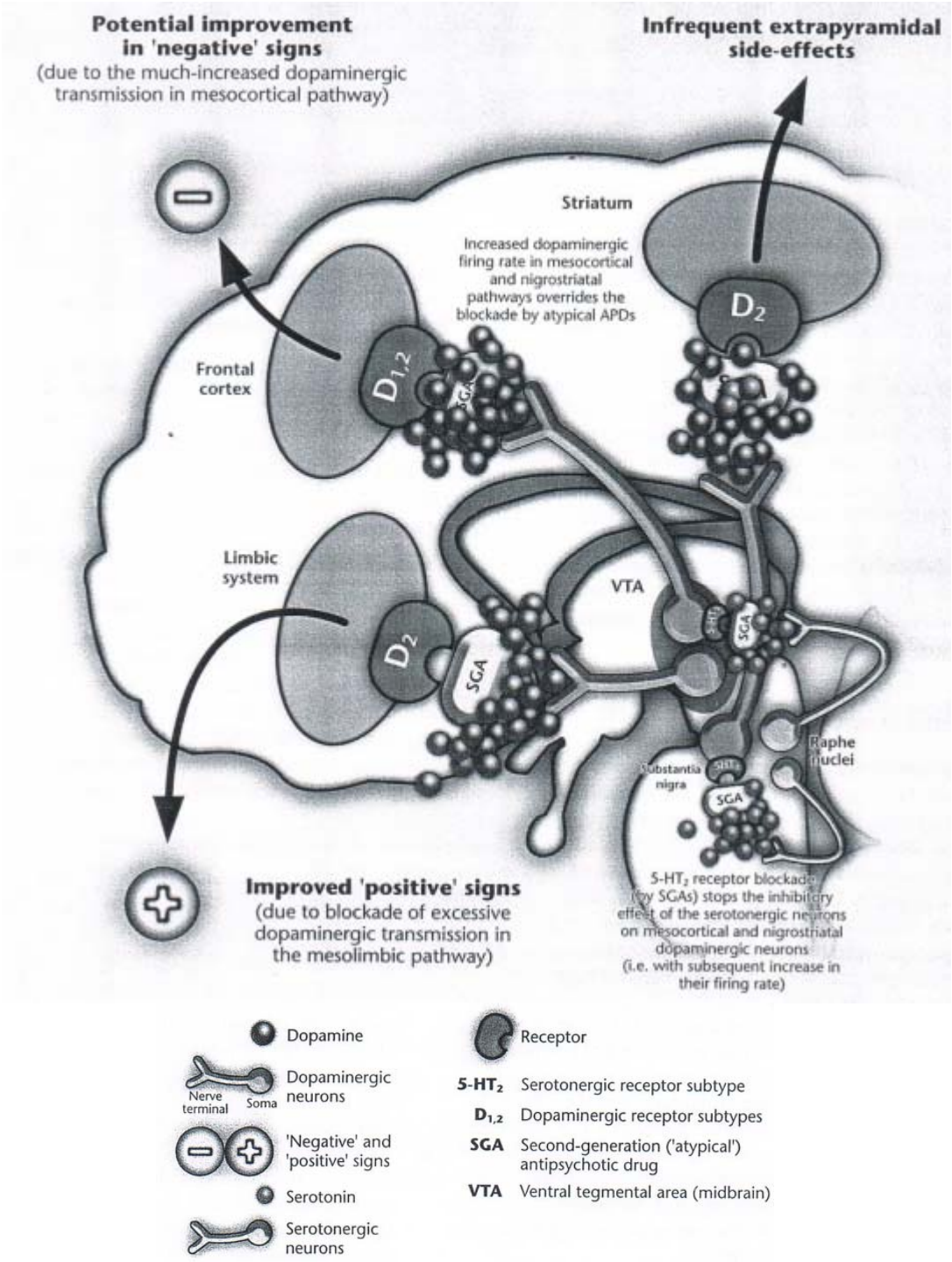


Figure 4. Mechanism of action of atypical antipsychotic drugs (Shiloh *et al.,* 2006)

2.1.3 Pharmacokinetic of quetiapine

Absorption: Quetiapine is rapidly absorbed in the gastrointestinal tract, and its absorption is unaffected by food (DeVane and Nemeroff, 2001). The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15% respectively (AstraZeneca, 2006; Kundlik *et al.,* 2009). Peak plasma concentrations are reached in 1 to 2 hours (Sadock and Sadock, 2001). They reach peak plasma levels 1.5 hours after oral administration and have linear pharmacokinetics (Ozkan, *et al.,* 2006). Quetiapine is rapidly absorbed after oral administration with maximum observed plasma concentration time (t_{max}) of 1 to 1.5 hours in case of 25 mg dose and C_{max} of 53-117 ng/ml (Atanasov *et al.,* 2008). Jaskiw *et al*. (2004) assess the pharmacokinetics in 12 elderly patients (age 63 to 85 years) with selected psychotic disorders. Under steady-state conditions, they found that quetiapine was rapidly absorbed after oral administration, with T_{max} ranging from 0.5 to 3 hours at the 100 mg dose (day 15) and from 1 to 3 hours at the 250 mg dose (day 23). These results indicated that the pharmacokinetics of quetiapine were linear in the elderly population. Quetiapine should be start at lower doses and titrated at a relatively slower rate in patients $\geq$65 years. When study in twenty-one Chinese suffering from schizophrenia who were given quetiapine 25 mg to control the schizophrenia symptoms. After 4 days, all patients reached the dose of 200 mg twice daily. quetiapine is rapidly absorbed with a mean T_{max} about 2 h (Li *et al*., 2004).

The absolute bioavailability is unknown, but the relative bioavailability from orally administered tablets compared with a solution was nearly complete (DeVane and Nemeroff, 2001). Therefore the tablet formulation is 100% bioavailable relative to solution.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10 ± 4 L/kg. About 83% of quetiapine bound to plasma proteins at therapeutic concentrations (AstraZeneca, 2006). *In vitro*, quetiapine does not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine (AstraZeneca, 2006; Kundlik *et al.,* 2009). After the dose reached 200 mg twice daily, the main V/F is 672 L (Li *et al*., 2004), which indicates quetiapine widely distributed throughout the body. Quetiapine passes the human placenta (Karch, 2002) but that the blood-placental barrier partially limits the transplacental transfer of quetiapine (Rahi *et al*., 2007).

Metabolism: Quetiapine is metabolized to a parent compound in the liver by cytochrome P450 isoenzyme 3A4 (Davis *et al.,* 2010). Quetiapine is metabolized *in vivo* include oxidation of the alkyl side chain, sulfoxidation, oxidation of the hydroxyl group to the carboxylic acid, hydroxylation of dibenzothiazepine ring, O-desalkylation, N-desalkylation and phase II conjugation (Atanasov *et al.,* 2008). The human plasma metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid. Because both metabolites are pharmacologically inactive (AstraZeneca, 2006; Kundlik *et al.,* 2009). The major metabolites of quetiapine are sulfoxide and carboxylic acid (c.a. 30% of quetiapine amount) (Atanasov *et al.,* 2008). Quetiapine is mainly metabolized in the liver and least 11 metabolites formed through hepatic oxidation have been identified (DeVane and Nemeroff, 2001). Only 7-hydroxy-quetiapine and 7-hydroxy-N-desalkyl-quetiapine metabolites are considered to be active but in plasma is lower than 10% of the initial quetiapine amount (Atanasov *et al.,* 2008). DeVane and Nemeroff (2001) reported that metabolism of quetiapine is mainly catalyzed by CYP3A4. CYP3A4 has been 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 while CYP3A4 contributes for 89% of the overall metabolism (Hasselstrom and Linnet, 2006) and may also play a role in the 7-hydroxylation pathway (Grimm *et al*., 1997). *In vivo*, quetiapine sulfoxide (QTP-SF) is the major inactive metabolite. 7-hydroxy-quetiapine (QTP-OH) and 7-hydroxy-N-desalkyl-quetiapine (QTP-ND) are active metabolites. *In vitro*, quetiapine has no effect on activity by CYP 1A2, 2C9, 2C19, 2D6 and 3A4 at clinically relevant concentrations. The metabolic profile of quetiapine was shown in Figure 5.

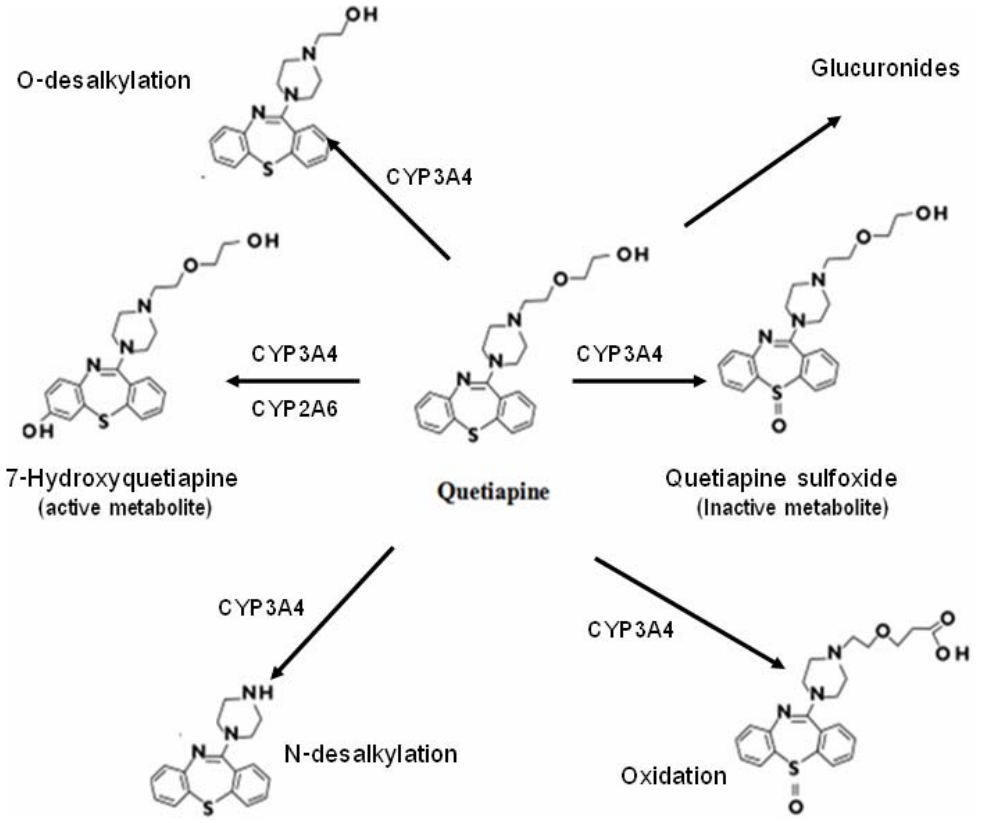


Figure 5. Metabolic profile of quetiapine (Wrighton and Thummel *et al*., 2000)

Excretion of quetiapine: Quetiapine is mainly metabolized by liver with a mean terminal half-life of about 6 hours. The quetiapine is eliminated with a mean terminal haif-life for 375 mg/day is 6.9 hours (Ozkan *et al.,* 2006). Approximately 73% in urine and 21% in faces are eliminated of quetiapine. The unchanged quetiapine in urine and feces are less than 1% of the administered oral dose (DeVane and Nemeroff, 2001; Atanasov *et al.,* 2008).

2.1.4 Dosage and administration

Quetiapine is initiated at a staring dose of 25 mg twice a day and then increased on day 2 to 50 mg twice a day, on day 3 to 100 mg in the morning and 200 mg in the evening. Most people receiving maximum benefit at 300-500 mg/day (Sadock and Sadock, 2001). Quetiapine is titrated, according to clinical response and tolerability within the effective range of 150-750 mg/day (Thyrum *et al.,* 2000). A slower titration and lower daily doses may be warranted for elderly patients and patients with hepatic disease which should be started on 25 mg/day and

increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient (AstraZeneca, 2006).

2.1.5 Therapeutic efficacy

Schizophrenia: The pivotal product registration trials and early trials of quetiapine (Arvanitis and Miller, 1997; Small *et al*., 1997; Copolov *et al*., 2000) indicated that quetiapine is an efficacious antipsychotic for the treatment of schizophrenia.

Arvanitis and Miller (1997) reported a multiple fixed-dose, placebo- controlled, double-blind study of quetiapine in comparison with haloperidol and placebo in acutely exacerbated patients with chronic schizophrenia. Quetiapine is administered in five doses: 75, 150, 300, 600 and 750 mg/day. Haloperidol is given at 12 mg/day. The study design has slightly more than 50 patients in each group. Quetiapine is well tolerated and clinically effective in the treatment of schizophrenia. Doses ranging from 150 to 750 mg/day are superior to placebo and comparable with haloperidol in reducing positive symptoms and dose of 300 mg/day is superior to placebo and comparable with haloperidol in reducing negative symptoms.

Small *et al*. (1997) studied in 286 patients hospitalized with chronic or subchronic schizophrenia (DSM-III-R) evaluated quetiapine at high dose ($>$ 250 mg but $\leq$ 750 mg), low doses ($\leq$ 250 mg) or placebo. Only the higher dose was related to significantly greater improvement when compared to placebo, suggesting that the effective dose is greater than 250 mg. Thus a randomized to short-term (6-week) trials compare quetiapine and placebo using quetiapine dosages of either 250 mg/day or 750 mg/day.

Copolov *et al*. (2000) studied in 448 acutely psychotic patients by comparing the efficacy of quetiapine (mean dose 455 mg/day) and haloperidol (mean dose 8 mg/day). This study found similar efficacy for the two agents.

Subsequent studies helped refine quetiapine dosing strategies. Clinicians are now using high doses of quetiapine that are, on average, more consistent with those used in recent studies. Emsley *et al*. (2000) studied a fixed-dose comparison of quetiapine at 600 mg/day with 20 mg/day of haloperidol in patients only partially responsive or non-responsive to a trial of fluphenazine (20 mg/day). There is a non-significant trend toward an advantage for quetiapine.

Quetiapine's efficacy with respect to typical antipsychotic drugs, most studies comparing quetiapine with haloperidol reports that the agent has similar efficacy in treating schizophrenia.

Pae *et al.* (2007) compared a rapid titration strategy (beginning 200 mg on day 1, 400 mg on day 2, 600 mg on day 3, and 800 mg on day 4) with a more conventional dosing strategy (50 mg on day 1, 100 mg on day 2, and increased in 100 mg/day increments to reach 400 mg on day 5). The two groups fared equally well in terms of tolerability and effectiveness during this 14-day study.

Several studies, comparisons between quetiapine and other atypical antipsychotic drugs.

Mullen *et al*. (2001) compared quetiapine (mean dose 254 mg/day) to risperidone (mean dose 4.4 mg/day) in an open-label study in 728 outpatients who were having their medications changed. The result indicates that the two drugs are similar in efficacy and tolerability.

Zhong *et al.* (2006) reported on an 8-week comparative in the efficacy and tolerability of quetiapine and risperidone in the treatment of schizophrenia. The average quetiapine dosage is 525 mg/day and the average risperidone dosage is 5.2 mg/day. The agents prove similar in efficacy. Another study comparing quetiapine and risperidone, reported better efficacy with risperidone (Potkin *et al.,* 2006).

Mania: Quetiapine has been found to be efficacious in the treatment of acute mania. In short-term placebo-controlled trials, quetiapine as a monotherapy reduced symptoms of mania as well as monotherapy in bipolar depression (Calabrese *et al*., 2005). The superior efficacy of quetiapine in combination with lithium or divalproex compared with lithium or divalproex alone in acute mania has been established in a large study (Sachs *et al*., 2004). McIntyre *et al*. (2005) studied in patients (n=302) with bipolar I disorder (manic episode) was up to 800 mg/day leading to a response rate between 42.6% to 55.7% in the quetiapine groups at day 21.

Bipolar: Quetiapine is effective treatment of schizophrenia or bipolar disorder for children. It is well tolerated and effective in reducing manic symptoms in adult and adolescent patients with acute bipolar mania and improved for use in adults for this indication.

Pini *et al*. (2006) evaluated the efficacy and tolerability of quetiapine in the acute and maintenance phase of bipolar disorder. Quetiapine has been found to be effective as adjunctive therapy in combination with lithium or valproate, significantly superior to placebo, and equal to lithium or haloperidol as monotherapy.

DelBello *et al.* (2007) reported the effectiveness and tolerability of quetiapine for the treatment of adolescents at high risk for developing bipolar I disorder in twenty adolescents who showed subsyndromal symptoms and were at risk for bipolar disorder but who did not actually meet diagnostic threshold criteria for a bipolar diagnosis.

Depression: Doree *et al*. (2007) reported that in a pilot study (n=20) and patients are randomised to either lithium (600 mg/day) or quetiapine (400 mg/day). Quetiapine is an effective augmenting agent for major depression.

Calabrese *et al.* (2005) and Thase *et al.* (2006) have studied quetiapine in patients with bipolar depression. Calabrese *et al.* (2005) compared two dosages of quetiapine (600 and 300 mg/day) and placebo in 8-week trial. Both dosages were efficacious, with improvements observed across the full range of depressive and anxiety symptoms. In a subsequent similar study of the same two dosages of quetiapine (600 and 300 mg/day; Thase *et al.* 2006), quetiapine is again compared with placebo in 8-week trial in patients with bipolar depression. Both dosages show efficacy across a broad range of depressive symptoms. Two studies led to FDA approval of quetiapine for treating bipolar depression.

Dementia: Quetiapine is tolerated at mean dosage of 100 mg/day. Zhong *et al*. (2007) reported a 10-week study comparing two dosages of quetiapine (100 mg/day and 200 mg/day) versus placebo. The results of this study suggest that quetiapine 100 mg/day is not efficacious, but quetiapine 200 mg/day is effective and well-tolerated for treating agitation associated with dementia.

2.1.6 Efficacy of short-term and long-term treatment

Quetiapine has established efficacy and good tolerability in the short-term and long-term treatment in schizophrenia. An analysis of open-label extension studies found that patients continue to improve when treated long term with quetiapine (Kasper *et al*., 2004).

In elderly, Tariot *et al*. (2000) studied in 184 elderly patients are 98 women and 86 men (≥65 years of age) with psychotic disorders long-term (52-week). They found that quetiapine is effective, good tolerated, safety, and clinical benefit in elderly.

Judit (2005) studied in open-label 35 hospitalised patients with psychosis, who received quetiapine at dose up to 1,600 mg/day in a 4-week acute phase, were followed for up to 14 months as outpatients. The results at the end of the 4-week hospitalization period, showed that overall 94.3% of patients experience improvements in symptoms, with 37.1% very much improve and 20% minimally improve. Among the 12 patients receiving > 800 mg/day, 83% are very much improved and no increase in extrapyramidal symptoms or other adverse events is observed at dose above 800 mg/day. These results indicate that short-term quetiapine therapy at dose up to 1600 mg/day with maintenance doses up to 1,000 mg/day, may be an effective and good tolerated treatment for patients with psychosis.

2.1.7 Side effects

The most common side effects of quetiapine, compared with placebo are somnolence and dizziness. Quetiapine can produce orthostatic hypotention in about 7% of patients and 1% may experience frank syncope rapid titration of the dose (Schatzberg *et al*., 2005).

AstraZeneca (2006) reported the side effects of quetiapine as follows:

Somnolence: Somnolence is a common side effect of quetiapine. It occurs early in treatment and generally decreases over time. Somnolence is a problem for many patients. It may also cause patients to stop taking their medication because sedation is generally a poorly tolerated side effect. Somnolence is experienced by at last 18% of patients taking quetiapine in 6-week clinical trials, but our experience is that as many as 50% of patients complain of somnolence when the dosage is increased above 400 mg/day (Schatzberg *et al*., 2005).

EPS: Quetiapine has no greater propensity to cause EPS than placebo (King *et al.,* 1998). As with olanzapine, there have been rare reports of tardive dyskinesia. Although no clear estimates of the frequency of tardive dyskinesia with quetiapine are available (Schatzberg *et al*., 2005).

Weight gain: Atypical antipsychotics include aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone increase weight gain and metabolic

disturbances (Brooke *et al.,* 2009). Quetiapine is associated with weight gain seems to be less than that seen with olanzapine and clozapine but more than that seen with ziprasidone and risperidone (Schatzberg *et al*., 2005). Brecher *et al*. (2000) reported open-label extention studies of patients with schizophrenia who received quetiapine for up to 18 months. Patients have on average a 1.74 kg increase over their baseline weight. During acute therapy in placebo-controlled schizophrenia clinical trials, mean weight gain in patients taking quetiapine is 2.3 kg when compared to a mean weight gain of 0.1 kg in patients taking placebo.

Seizure: There have been occasional reports of seizures in patients administered quetiapine, althought the frequency is no greater than that observed in patients administered placebo in controlled clinical trials.

Priapism: There have been very rare reports of priapism in patients administered quetiapine. While a causal relationship to use of seroquel® has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Pais and Ayvazian (2001) reported a first case of priapism occurring after an overdose of quetiapine. This case is a 45-year-old man with a history of depression and bipolar disorder who has ingested quetiapine 25-mg tablets.

Prolactin level: Two side effect characteristics that distinguish quetiapine from other atypical antipsychotic drugs and from tyical antipsychotic drugs are its low rates of prolactin elevation and low rates of EPS. Consistently, quetiapine is associated with a low risk of increasing prolactin levels (Small *et al.,* 1997; Zhong *et al.,* 2006). Flischhacker *et al*. (1996) found that substitution of quetiapine is associated with a reduction in mean serum prolactin levels, whereas haloperidol is associated with an increased mean prolactin level. The mean level in the haloperidol group is significantly higher than that in the quetiapine group ($P < 0.01$). Stevens *et al*. (2005) studied in 70 male youths, 50 males treated with risperidone and 20 males treated with quetiapine in a cross-sectional retrospective medical. Serum prolactin levels were drawn according to a protocol, after at least 6 weeks of treatment. They reported that prolactin is above the upper limit of normal for 68% of the patients on risperidone and 20% of the patients on quetiapine. Both risperidone and quetiapine produce dose-related increases in serum prolactin levels. No correlation has been found between duration of treatment and prolactin levels.

Impotence: Sexual dysfunction is commom in patients from schizophrenia which associated with antipsychotic treatment. Abnormal ejaculation and amenorrhea have been reported in pivotal trials to occur in less than 0.1% of patients. In over 2,000 patients treated with quetiapine, menstrual change occurs in less than 1% (Conley and Kelly, 2004).

Abnormality of thyroid hormone levels are a concern that emanated from early trials of quetiapine. Kelly and Conley (2006) reported in a randomized, 12 weeks in a double-blind trial of risperidone (4 mg/day), quetiapine (400 mg/day) and fluphenazine (12.5 mg/day) in 27 people with schizophrenia. 78% of patients on fluphenazine reported sexual dysfunction, 42% on risperidone and 50% on quetiapine. Quetiapine has some benefits as compared risperidone normalization of prolactin levels and regarding sexual function. This no longer appears to be a clinically meaningful risk, and recent studies have not shown any consistent evidence of thyroid dysfunction with quetiapine use.

Ocular change: The potential of quetiapine to induce cataracts is still unknown and the relationship of antipsychotic therapy in general to cataract formation is unclear. The development of cataracts has been in association with quetiapine treatment preclinical studies of dog, but a causal relation has not been established in humans. Post-marketing experience has not detected an increase in incidence of cataracts with quetiapine compared with other antipsychotics, however, cataracts are more common in schizophrenia in general compared with the general population (Hales and Yudofsky, 2004).

Cardiovascular effects: As predicted with alpha-1 antagonism, quetiapine may induce orthostatic hypotention associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Syncope was reported in 1% of the patients treat with quetiapine, compared with 0.2% on placebo. This risk is minimized by limiting the initial dose to 25 mg twice daily (bid).

Hepatic effects: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported in patients taking quetiapine in premarketing evaluation. The proportions of patients with transaminase elevations of >3 times the upper limit were 6% for quetiapine compared 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of >3 times the upper limit were 1% for both quetiapine and

placebo. And in bipolar depression trial, the proportions of patients with transaminase elevations of >3 times the upper limit were 1% for quetiapine compared 2% for placebo.

Table 3. Comparative side-effect profile of quetiapine versus risperidone: adverse effects present in ≥5% of patients in an 8-week study (Schatzberg and Nemeroff, 2009)

	Quetiapine (N=338; Median Dosage, 525 mg/day)	Risperidone (N=335; Median Dosage, 5.2 mg/day)
Adverse effects	N (%)	N (%)
Somnolence	89 (26.3)	66 (19.7)
Headache	51 (15.1)	56 (16.7)
Weight gain	48 (14.2)	45 (13.4)
Dizziness	48 (14.2)	32 (9.6)
Dry mouth	41 (12.1)	17 (5.1)
Dyspepsia	22 (5.6)	26 (7.8)
Nausea	21 (6.2)	22 (6.6)
Pain	21 (6.2)	24 (6.6)
Asthenia	17 (5.0)	14 (4.2)
Agitation	17 (5.0)	10 (3.0)
Pharyngitis	15 (4.4)	24 (7.2)
Akathisia	13 (3.8)	28 (8.4)
Vomiting	13 (3.8)	18 (5.4)
Dystonia	1 (0.3)	18 (5.4)

Source. Adapted from Zhong *et al*., 2006. The results from a clinical trial of 8 weeks' duration in schizophrenic patients received an average quetiapine dosage of 525 mg/day (Table 3). This study, quetiapine was generally well tolerated and the most commonly reported sied effects were somnolence (26% of patients), headache (15%), weight gain (14%), dizziness (14%), and dry mouth (12%).

McIntyre *et al*. (2005) studied in 302 bipolar patients, randomized, 12 weeks double-blind treatment with quetiapine, haloperidol or placebo. The most commonly adverse event with quetiapine was somnolence (12.7%), insomnia (19.6%) and EPS-related.

King *et al*. (1998) studied in 618 patients by comparing bid and three time daily (tid) dosage regimens of quetiapine in a 6-week, double-blind, randomized, multi-centre, parallel-group study with quetiapine 225 mg bid (n=209) and 150 mg tid (n=209) or comparator dose of 25 mg bid groups (n=200). The results found that quetiapine is generally well tolerated. The 225 mg bid and 150 mg tid groups are not difference in the tolerability profile and the majority of these events are apparently independent of the dose prescribed (Table 4).

Table 4. Adverse events in three treatment groups (adapted from King *et al*., 1998)

	25 mg bid (n = 200)		**150 mg tid (n = 209)**		**225 mg bid (n = 209)**	
Adverse event	**Number of patients**	**%**	**Number of patients**	**%**	**Number of patients**	**%**
Somnolence	17	8	29	14	27	13
Insomnia	19	9	16	8	20	10
Dry mouth	6	3	10	5	16	8
Dizziness	4	2	12	6	11	6
Asthenia	3	1	7	3	9	5
Postural hypotension	10	5	12	6	8	4
Anxiety	8	4	13	6	8	4
Agitation	11	5	8	4	6	3
Headache	10	5	10	5	5	3

2.1.8 Drug interaction

Quetiapine is primarily metabolized by cytochrome P450 (CYP) 3A4. Although genetic variations are not clearly described for the CYP3A4. Drug interactions with inhibitors and inducers of CYP3A4 are likely to be clinically significant. When coadministered with inducers or inhibitors (psychotropic or non-psychotropic medications or substances) of CYP enzymes, antipsychotic plasma levels may be reduced or increased, respectively, as a result of drug

interaction. This can result in a reduced effectiveness of the antipsychotic, or an increased risk of adverse events, respectively. The anticonvulsants carbamazepine and phenytoin are common of CYP3A4 inducers, and quetiapine doses may need to be increased due to accelerated drug clearance. Protease inhibitors (ritonavir, indinavir, and atazanavir), antifungal agents (ketaconazole), macrolides (troleandomycin, erythromycin), and nefazadone are potent inhibitors of CYP3A4 (Conley and Kelly, 2007) and their use requires caution when they are coadministered with quetiapine, while they are used, doses of quetiapine should be lowered.

Ketoconazole: In a multiple dose trial in 12 healthy volunteers to assess the pharmacokinetics of quetiapine coadministered before and during treatment with ketoconazole. The result found that it increases mean quetiapine C_{max} and AUC of 235% and 522%, respectively, with corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increases from 2.61 to 6.76 hours, but the mean T_{max} is unchanged. In the clinical study found that ketoconazole increases mean quetiapine plasma by 3.35-folds and decreases its clearance by 84% (Grimm *et al*., 2005).

Erythromycin: Li *et al*. (2005) studied the effects of erythromycin on metabolism of quetiapine in Chinese patients suffering from schizophrenia, 19 patients completed the study. The first period (day 1-8) multiple and rising dose received twice daily (25-200 mg bid by day 4) and remained at 200 mg bid on day 5-7 of quetiapine. During the second period (day 9-12), fixed dose of quetiapine (200 mg twice daily) and erythromycin (500 mg, three times daily) were co-administered to the subjects. The results found that erythromycin increases the quetiapine C_{max}, AUC, $T_{1/2}$ by 68%, 129% and 92% respectively. It decreases clearance 52%. Erythromycin has a noticeable effect on the metabolism of quetiapine. When quetiapine is co-administered with CYP3A4 inhibitors such as erythromycin, the dosing regimen should be modified according to quetiapine serum concentrations.

Cimetidine: Strakowski *et al*. (2002) studied the effects of multiple doses of cimetidine (CYP 3A4 inhibitor) on the steady-state pharmacokinetics of quetiapine in 13 patients with selected psychotic disoders. Quetiapine was maintained at 150 mg three times daily and cimetidine 400 mg. The results found that a 20% decrease in the mean oral clearance and a slight increase in quetiapine plasma levels after cimetidine coadministration.

Fluoxetine: Potkin *et al*. (2002) investigated in 26 patients with schizophrenia in a multi-center, two period, multiple doses, open label randomized trial. Patients were treated with 300 mg twice daily dose of quetiapine for at least 7 days and received fluoxetine 60 mg or imipramine 75 mg for 8 days. The results found that coadministration of quetiapine with fluoxetine leads to an increase in $AUC_{0–12\ h}$ of 12% and C_{max} of 26%; these increases are deemed statistically significant, although not clinically significant, and result in no adverse events.

Imipramine: It does not affect the pharmacokinetics of quetiapine (Potkin *et al*., 2002)**.**

Divalproex: Co-administration of quetiapine (150 mg bid) and divaproex (500 mg bid) increase the mean maximum plasma concentration of quetiapine at steady state by 17% without changing the mean oral clearance (AstraZeneca, 2006).

Phenytoin: Phenytoin is a potent CYP3A4 inducer that is co-administered with quetiapine may result in an decreases mean plasma levels of quetiapine. Wong *et al*. (2001) studied the effects of concomitant phenytoin administration on the steady-state pharmacokinetics of quetiapine. The quetiapine geometric mean $AUC_{0–8h}$, C_{max}, and C_{min}, are reduced to 19%, 27%, and 12% of their former values, respectively, after the administration of phenytoin. Quetiapine CL/f increased more than 5-fold after phenytoin co-administration. This study demonstrates that the potent CYP450 inducer, phenytoin causes 5-fold increase in the clearance of quetiapine and suggests that dosage adjustment of quetiapine may be necessary when the two drugs are given concurrently.

Thioridazine: It significantly increases the oral clearance of quetiapine and, consequently, doses of quetiapine may need to be increased during co-administration with thioridazine to achieve the necessary control of psychotic symptoms (Potkin *et al*., 2002).

Carbamazepine: This drug decreases quetiapine plasma C_{max} by 80% and increased its clearance 7.5-fold. Co-administration of carbamazepine decreases in the steady-state plasma concentrations of quetiapine. These results demonstrate that co-administration of quetiapine with a potent CYP3A4 inducer can lead to a increase in quetiapine metabolism and, potentially, a loss of clinical efficacy (Grimm *et al*., 2005).

Lithium: Concomitant administration of quetiapine (250 tree times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a three times daily) of quetiapine to subjects with selected psychotic disorders has no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediates metabolism of antipyrine (AstraZeneca, 2006).

2.1.9 Overdose

In clinical trial, reported in acute overdoses of up to 30 grams of quetiapine. Patients who overdose experienced no adverse reactions. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported side effects are drowsiness, sedation, tachycardia, and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. One case, involving an estimated overdose of 9600 mg, is associated with hypokalemia (AstraZeneca, 2006). Quetiapine in overdose is limited, estimated doses of up to 20 grams of quetiapine have been taken, no fatalities have been reported and patients recover without sequelae. In post-marketing experience, there have been cases of coma and death in patients taking a quetiapine overdose. The lowest reported dose associated with coma has been in patients who took 5 grams and had a full recovery within 3 days. The lowest reported dose associated with a death was in patients who took 10.8 g.

Hunfeld *et al*. (2006) studied in 21 intoxication with quetiapine case. They found that the ingested doses range from 1,200- 18,000 mg, the blood concentrations ranged from 1.1 – 8.8 mg/L with a lag time of 1 – 26.2 hours. The most frequent findings are somnolence and tachycardia. Severity of intoxication is not associated with a higher amount of quetiapine intake. No fatalities occurred.

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drugs involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, monitoring and support of the cardiovascular system (AstraZeneca, 2006).

2.1.10 Special patient populations (Cutler *et al*., 2002)

Adolescents: Although there have been no randomized, double-blind studies of quetiapine in children, results of a pilot study in adolescents (aged 12.3-15.9 years) suggest that the dose requirements and clinical responses to quetiapine in this population are not significantly different from those in adult patients with psychotic disorders.

The Elderly: Like other antipsychotic agents, quetiapine should be used with caution in elderly patients, particularly during the initiation of therapy. Dosing should begin at 25 mg/d, increasing by 25 mg/d until an effective dose is reached. Because of the reduced clearance of quetiapine in the elderly, the optimal dose is likely to be lower in this population than in younger patients. This is illustrated by the results of an open-label trial in 18 elderly patients in which the median dose of quetiapine is 138 mg/d. Consequently, the recommended initial target dose in elderly patients is 100 mg/d.

Renal and Hepatic Impairment: Dose adjustment of quetiapine is not required in patients with renal impairment. However, because quetiapine is metabolized in the liver, slower dose titration may be desirable in patients with hepatic impairment. Also, depending on individual clinical response and tolerance, the daily therapeutic dose may be lower in patients with hepatic impairment. In these patients, therapy should be started at 25 mg/d and increased by 25 to 50 mg/d to an appropriate dose. Quetiapine is excreted in the kidneys and is not affected by gender or smoking status (Thyrum *et al.,* 2000).

Pregnancy: Quetiapine is a Pregnancy Category C drug and should be used during pregnancy only if the potential benefits outweigh the potential risk to the fetus. Quetiapine has been found in the breast milk of animals administered the drug and women receiving quetiapine should not breast-feed. McKenna *et al*. (2005) studied a sample of pregnant women treated with atypical antipsychotics. Thirty-six women treated with quetiapine. There are no statistically significant difference in any of the pregnancy outcomes of interest between the exposed and comparison groups are not significantly different, with the exceptions of the rate of low birth weight, which is 10% in exposed babies versus 2% in the comparison group (*P=0.05*), and the rate of therapeutic abortion, which is 9.9% in exposed women versus 1.3% in the comparison group (*P=0.003*). These results suggest that atypical antipsychotics do not appear to be associated with an increased risk for major malformations.

Mood and Affective Disorders: Clinicians are increasingly using atypical antipsychotic agents in patients with mood and affective disorders, and quetiapine has shown potential benefit in this population. Patients with acute psychotic mania appear to require and tolerate higher doses of quetiapine and these antipsychotic medications than patients with stable depression or bipolar.

2.2 Cytochrome P450 (CYP450)

Metabolism is the biotransformation of a drug to another chemical and a less lipid-soluble form that is more easily excreted. The major of metabolic processing is done by a group of enzyme (i.e. cytochrome P450 (CYP)) located in microsomes of the endoplasmic reticulum of hepatic cells. There are four main types of metabolic reactions include oxidation, reduction, and hydrolysis (phase I), and conjugation (phase II). Many drugs alter the activities of these metabolic processes by either stimulating catabolic enzymes or inhibiting, and many drug-drug interactions (Shiloh *et al.,* 2006)

Phase I (biotransformation reactions) usually occur in the first step and introduce or presents a functional group on the drug molecule. Phase I metabolism includes oxidation, reduction, hydrolysis and hydration reaction. The main function of phase I is to prepare the compound for phase II metabolism. The phase I reactions serve to introduce a suitable functional group into the drug molecule, thereby changing the drug to a more polar form and hence making it more readily excretable. In most cases, the final product contains a chemically reactive functional group, such as -OH, -NH2, -SH, -COOH, etc.

Phase II (conjugation reactions) involves coupling the drug to endogenous substances, such as glucuronic acid, glycine, glutathione or glutamine is usually inactive metabolites (Prior *et al*., 1999), water-soluble and easily excreted. The major conjugation reactions include glucuronidation, sulphation, acetylation, methylation, amino acid conjugation and glutathione conjugation. Glucuronidation and sulphate conjugations are very common phase II reactions that result in water-soluble metabolites rapidly excreted in bile and/or urine.

Phase I metabolism is dominated by the mixed-function oxidase system. The mixed-function oxidase (MFOs) are structural enzymes which constitute an electron transport

system that requires reduced NADPH ($NADPH_2$), molecular oxygen, CYP P450, NADPH- CYP P450 reductase, and phospholipids.

CYP450 is a haem-containing enzyme, or haemoprotein, with ferric protoporphyrin IX as the prosthetic group. The haem is non-covalently bound with apoprotein. It is the terminal oxidase component of an electron transfer system that is responsible for the oxidation reactions of several drugs. The haemoprotein serves as both, the oxygen- and substrate-binding locus for the MFO reactions. The CYP450, in conjunction with the associated flavoprotein reductase and NADPH- CYP450 reductase, is necessary for the catalytic reactions of the MFO.

NADPH-CYP450 reductase is a flavin-containing enzyme consisting of one mole of flavin adenine dinucleotide (FAD) and one mole of flavin mononucleotide (FMN) per mole of apoprotein. The enzyme exists in close association with cytochrome P450 in the endoplasmic reticulum membrane. NADPH- CYP450 reductase is responsible for transferring reducing equivalents from NADPH + H^+ to CYP450.

The fatty acid composition of the phospholipids is critical in determining functional reconstitution of MFO activity. These lipids may be required for substrate binding, facilitation of electron transfer or providing a template for the interaction of cytochrome P450 and NADPH-cytochrome P450 reductase molecules.

Catalytic Cycle of CYP450

Cytochrome P450 acts as a terminal oxidase in the oxidation reactions. Such reactions all involve reduced nicotinamide adenine dinucleotide phosphate (NADPH), molecular oxygen, mixed function oxidase and one or more of a group of CYP450 haemoproteins (Figure 6). The cycle involves six steps:

1. Binding of the substrate to the oxidized (Fe^{3+}, ferric) CYP450

The formation of the enzyme-substrate complex at CYP450 is the triggering event for the mono-oxygenation process. Substrate binding causes a dissociation or weakening of the sixth ligand of the haem iron and this shifts the spin equilibrium toward the high spin state (activated state).

2. Reduction of ferric CYP450-substrate complex

The electrons from NADPH + H^+ are transferred by the NADPH CYP450 reductase to CYP450. NADH can also serve as an electron donor, although with much lower efficiency.

3. Binding of molecular oxygen to the binary ferrous CYP450- substrate adduct

This step involves the addition of oxygen to the reduced cytochrome. The addition of oxygen to CYP450 is reversible and carbon monoxide can compete for the oxygen-binding site, thereby inhibiting mono-oxygenase reactions.

4. Electron rearrangement

The oxygen of oxyferrocytochrome P450-substrate complex is activated prior to addition to the substrate. An electron from the ferrous iron of the haem is transferred to the oxygen to oxygen to from the oxyanionferricytochrome P450-substrate complex.

5. Introduction of the second electron

The oxyferrocytochrome P450-substrate complex accepts an electron from reduced NADPH-cytochrome P450 reductase, or from ferrocytochrome b_5.

6. Oxygen insertion and product release

The oxygen atom is transferred to the substrate, resulting in the release of product from the enzyme complex. The CYP450 is then restored to its uncomplexed, low spin ferric state.

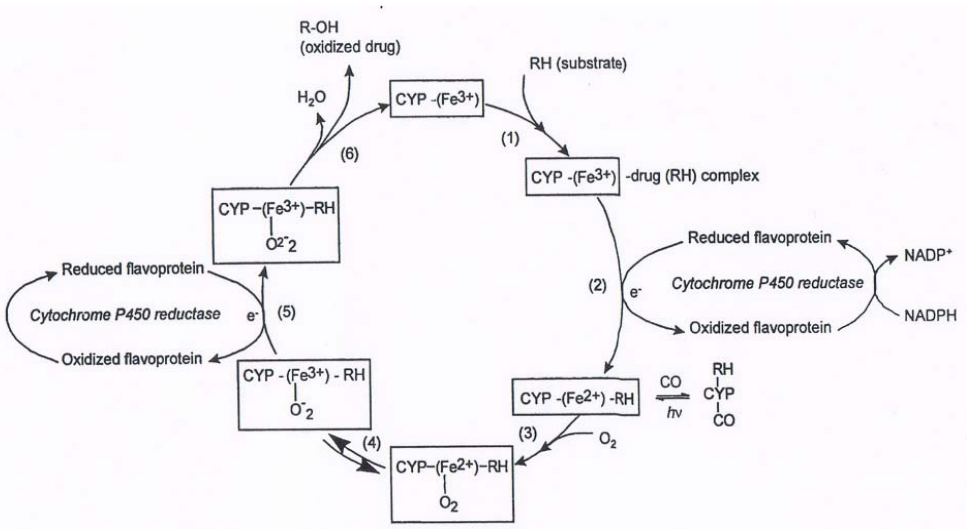


Figure 6. Catalytic cycle of CYP450. RH: drug substrate; ROH : oxidized product (Katzung *et al.,* 2009).

Drug metabolism occurs mainly in the liver, with additional contributions by the kidney, blood, brain, gastrointestinal tract, skin and other tissues. Phase I group, oxidative reactions are the most important and are mediated by a large family of heme-containing enzymes called the CYP450 system (Prior *et al*., 1999). The human CYP450 superfamily of enzymes is comprised of 18 families, 42 subfamilies, and 57 individual genes. CYP450 enzyme in the CYP1, CYP2, and CYP3 families are particularly important in the biotransformation of drug (Ioannides, 2008). Seventy-four CYP gene families have been described, of which three main such as CYP1, CYP2, and CYP3 are involved in drug metabolism in human liver. Different members of the family have distinct, but often overlapping, substrate specificities, with some enzyme acting on the same substrates as each other but at different rates (Rang *et al.,* 2007). The CYP3A subfamily is the most in the human liver; it accounts for about 60% of total CYP450. The CYP3A4 is the most important isozyme, an enzyme with very broad substrate specificity. It is responsible for the metabolism of a large number of therapeutically important drugs. These include the corticosteroids cortisol and prednisolone, the antifungals ketoconazole; the antineoplastic agents cyclophosphamide and etoposide; the macrolide antibiotics erythromycin and triacetyloleandomycin; and sex hormones testosterone. High level of CYP3A4 are found in the small intestine, and several of its substrates undergo significant first-pass metabolism not only in the liver but also in the gut. CYP3A5 appears to be expressed in the liver about 25% of adults. It is expressed in liver, gastrointestinal enteric, mucosa, lung, colon, esophagus, as well as a number of other tissues such as prostate and kidney (Nebert and Russell, 2002). CYP3A7 is only expressed in fetal liver. It appears to play a minor role in drug metabolism in adult population (Zhou *et al*., 2004). The CYP1A subfamily appears to contain two members in human, namely CYP1A1, and CYP1A2. CYP1A1 metabolises polycyclic aromatic hydrocarbons, but is not involved in drug oxidation. It is expressed at only very low levels in human liver and is essentially an extrahepatic enzyme (Ioannides, 2008). The CYP1A1 and CYP1A2 enzyme are about 70% identical in amino acid sequences. CYP1A1 and CYP1A2 enzyme play critical roles in the metabolic activation of carcinogen activation. The CYP2 family is to be the largest and most diverse of the CYP450 families. It is divided into 5 subfamilies, i.e. 2A, 2B, 2C, 2D and 2E. The CYP2D subfamily exhibits pharmacogenetic polymorphism. CYP2D6 is of great interest because of its large number of substrates (30-50 drugs) and its genetic polymorphism. It metabolises over

50 clinically used drugs, most of them acting on the central nervous system or on the heart. The drug interacting as substrates with CYP2D6 represented a fraction of about 15% of all drugs, next to subfamilies CYP3A (36%) and CYP2C (25%). CYP2E, besides oxidizing ethanol, is involved in the biotransformation of small spectrum of drugs including halothane, isoflurane, the xanthines caffeine and theophylline, and the antiepileptic agent ethosuximide.

CYP450 isoenzyme are to be responsible for most (90%) of the metabolism used drugs including CYP1, CYP2 and CYP3 in human. The six isoforms, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 are involved in the metabolism of a large proportion of drugs. The activity of these enzyme is modulated by genetic and other factors including age, ethnic origin, gender, diet, consumption of alcohol or tobacco, and pathological conditions (Boxtel *et al.,* 2008). Genetic polymorphisms, which simply mean that some of the population have a variant of the isoenzyme with different (usually poor) activity. Approximately 5% to 10% of Caucasians are poor metabolizers via CYP2D6, while approximately 20% of Japanese and Chinese are poor metabolizers via the CYP 2C19 (Sharif, 2003). Poor metabolism will increase the bioavailability of some drugs, increasing their likelihood of side effect.

2.2.1 Enzyme induction

The cytochrome P450 enzymes can be induced. Induction causes the liver to produce a greater amount of the enzyme, which can increase elimination and reduce plasma levels of a second drug or its metabolites. If a reduction in a drug's plasma level decreases its clinical effectiveness, the dose of the affected drug should be increased to achieve the same serum concentration (Marangell *et al.,* 2002). Increased levels of enzyme in an eliminating organ, such as the liver, generally results in an increase in the intrinsic metabolic clearance, increased excretion and reduced area under the concentration(AUC)-time profile (Wrighton and Thummel., 2000). The effects of inducers tend to be delayed for days to weeks because this process involves enzyme synthesis.

Induction of cytochrome activity occurs at the level of gene transcription. In the case of CYP1A1, inducing agents bind to cytosolic polycyclic aromatic hydrocarbon (Ah) receptors and are translocated into the nucleus. The transcriptional process include a sequence of events: ligand-dependent heterodimerisation between the Ah receptor and an Ah receptor nuclear

translocator, interaction of the heterodimer with a xenobiotic responsive enhancer, transmission of the induction signal from the enhancer to a CYP1A1 promotor, and alteration in chromatin structure. This is followed by subsequent transcription of the appropriate mRNA and translation of the corresponding proteins. Probably the most important drugs that act as inducers are ethanol, rifampin (a drug used to treat tuberculosis), the barbiturates (e.g., phenobarbital), and two antiepileptic drugs - phenytoin and carbamazepine. The inducers stimulate the transcription of genes encoding cytochrome P450 enzyme, and this result in increased messenger RNA and protein synthesis.

Many drugs and chemicals induce metabolism upon repeated administration or exposure. Enzyme induction is involved in the development of tolerance to some therapeutic agents. Exposure to many common environmental chemicals, including pollutants, cigarette smoke and dietary constituents, can induce xenobiotic metabolism (Kedderis, 1997). Barbiturates, carbamazepine, phenytoin, rifampin, dexamethasone, smoking, and chronic alcohol use induce CYP450 enzymes (Marangell *et al.,* 2002). The time course of enzyme induction onset and offset is closely related to the plasma concentration of the inducer, as well as the half-life of enzyme production and degradation (Gram, 1997). Enzyme inducing drugs with short half-lives (e.g. rifampicin) will induce metabolism more quickly than drugs with longer half-lives (e.g. phenytoin) because they reach steady-state concentrations more rapidly. Enzyme induction usually results in a reduced pharmacological effect of the induced drug but where active metabolites are responsible for a drug's effect the reverse may occur (Boxtel *et al.,* 2008).

In drug therapy, there are 2 major concerns related to CYP induction. First, induction will result in a reduction of pharmacological effects caused by increased drug metabolism. Secondly, induction may create an undesirable imbalance between toxification and detoxification. Induction of drug metabolizing enzymes may lead to a decrease in toxicity through acceleration of detoxification, or to an increase in toxicity caused by increased formation of reactive metabolites. Depending upon the delicate balance between detoxification and activation, induction can be a beneficial or harmful response (Lin and Lu, 1998).

Considering that cigarette smoke is a rich source of benzo[a]pyrene and that benzo[a]pyrene is a potent enzyme inducer, it might be inferred that tobacco smoke should induce drug metabolism (Gram, 1997).

2.2.2 Enzyme inhibition

Enzyme inhibition is an extremely common mechanism in the interaction between drugs. A number of drugs have the potential to inhibit microsomal enzymes. Inhibition of the metabolism of drugs may therefore result in exaggerated and prolonged responses, with an increase risk of toxicity. The onset of enzyme inhibition is usually more rapid than induction, occurring as soon as sufficient concentrations of the inhibitor appear in the liver. Thus for drugs with a short half-life, the effects may be seen within 24 hours of administration of the inhibiting agent. The effects are not seen until later for drug with a long half-life. The clinical significance of this type of interaction depends on various factors, including dosage (of both drugs), alterations in pharmacokinetic properties of the affected drug, such as half-life, and patient characteristics such as disease state. The combination of an enzyme inhibitor and a medication that is a substrate for that enzyme is not contraindicated, but the patient should be monitored for signs and symptoms related to increased substrate levels, and the substrate dose should be decreased if necessary (Marangell *et al.,* 2002).

Enzyme inhibitors are molecules that interact in some way with the enzyme to prevent it from working in the normal manner. There are a variety of types of inhibitors including: nonspecific, irreversible, reversible-competitive and noncompetitive. Certain drug substrates may inhibit CYP450 enzyme activity. A number of drugs have the capacity to bind the enzyme tightly forming an inactive complex which prevents the access of other agents (Boxtel *et al.,* 2008). Imidazole-containing drugs such as cimetidine and ketoconazole bind tightly to the heme iron of CYP450 and effectively reduce the metabolism of endogenous substrate or other coadministered drugs through competitive inhibition (Katzung, 2001). An inhibitor may or may not be metabolized by the enzyme that it inhibits. Known inhibitors of CYP3A are the macrolide antibiotics erythromycin and troleandromycin, the azole antifungals ketoconazole, itraconazole and fluconazole, the calcium channel entry blockers diltiazem and verapamil and the selective serotonin re-uptake inhibitors fluvoxamine and fluoxetine. It has been reported that grapefruit juice inhibits CYP3A4 in the bowel wall and in the liver. Concomitant ingestion of grapefruit juice with drugs that are a substrate for CYP3A4 reduces their first-pass metabolism, resulting in decreased clearance and increased plasma concentrations of the drugs. Among the drugs reported to be affected by grapefruit juice are the benzodiazepines, the dihydropyridine calcium channel

blockers, and the antihistamine terfenadine. All of these compounds are metabolized by CYP450 isoenzyme CYP3A4 (Friedericy and Bovill, 1998).

CYP450 enzymes 2C19 and 2D6 exhibit polymorphis. Persons who exhibit a genetic polymorphism that causes a large reduction in the amount of active enzyme are referred to as poor metabolizers and are at risk for increased drug levels, which may lead to toxicity. In contrast, some people have increased amounts of an enzyme. These individuals, referred to as ultrarapid metabolizers, may have reduced levels of drugs that are metabolized by the enzyme, resulting in decreased efficacy (Marangell *et al.,* 2002).

The three most important CYPs involved in atypical antipsychotic metabolism are CYP3A, CYP2D6 and CYP1A2. Metabolism of quetiapine was mainly catalyzed by CYP3A4 and minor role by CYP2D6 (Ciraulo *et al.,* 2006).

2.3 Bioavailability and Bioequivalence

Bioavailability is a pharmacokinetic term that defined the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of drug action (Chen *et al.,* 2001). However, drug concentrations cannot be directly measured at the site of action. Therefore, most bioavailability studies involve the determination of drug concentration in the blood or urine.

Bioequivalence (BE) is defined in the absence of a 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). Bioequivalence studies play an important role in the drug development process. Instead of repeating expensive clinical trials to establish the safety and efficacy of a new formulation, the pharmacokinetic characteristics of plasma or urine concentration-time curves are used to conclude that two drug formulations will provide similar pharmacologic effects (Ramirez *et al*., 2008).

Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety

profile after administration under the conditions specified in the labeling. In general, the FDA considers two products to be " therapeutic equivalents " if they meet the following criteria:

1. They are pharmaceutical equivalents.
2. They are bioequivalent (demonstrated either by a bioavailability measurement or an in vitro standard).
3. They are in compliance with compendial standards for strength, quality, purity and identity.
4. They are adequately labeled.
5. They have been manufactured in compliance with Good Manufacturing Practices (GMP)

2.4 Bioequivalence study

The concept of bioequivalence and approaches to its assessment were developed in various stages over the last 35 years (Midha and Mckay, 2009). Many drugs are marketed by more than one pharmaceutical manufacturer. The study of biopharmaceutics gives substantial evidence that the method of manufacture and the final formulation of the drug can markedly affect the bioavailability of the drug. Because of the plethora of drug products containing the same amount of active drug, physicians, pharmacists and others who prescribe, dispense or purchase drugs must select generic products that produce an equivalent therapeutic effect to the brand product. BE studies provide important information in the overall set of data that ensure the availability of safe and effective medicines to patients and practitioners.

The term bioequivalence refers to the comparison of bioavailability of different formulations, drug products or batches of the same drug product (Aulton, 2002). Bioequivalence drug products are pharmaceutical equivalent that have similar bioavailability (are not significantly different with respect to rate and extent of absorption) when given in the same molar dose and studied under similar experimental condition (Shargel and Yu, 1999). Thus two products are bioequivalence if their rate and extents of absorption are the same (Gelder *et al*., 1999).

The rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the

same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. Bioequivalence refers to equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations.

The rational for BE study is scientifically valid to assume that, if an active ingredient or therapeutic moiety of a test veterinary medicinal product reaches the systemic circulation with the same rate and extent as the active ingredient or therapeutic moiety of a reference veterinary medicinal product, the local availability (concentration is tissue) of the active ingredient or therapeutic moiety will be similar for the test and reference products. The similarity of availability at the site of action is the basis of concluding therapeutic equivalence of the products. Changes of inactive ingredients in a veterinary medicinal product or in the manufacturing process may have significant effects on bioavailability. The *in vivo* bioequivalence of a veterinary medicinal product is demonstrated if the rate and extent of absorption, as determined by comparison of measured parameters derived from relevant data (e.g. concentration of the active ingredient in the blood, urinary excretion rates or pharmacological effects) do not indicate a significant difference in the rate of extent of absorption from the reference material. When the aim of the trial is to demonstrate therapeutic equivalence, the clinician should be consulted to select the kinetic parameters which are to be analyzed and to qualify their acceptable limits of variation in clinical situations. In other words, the final decision that two or more veterinary medicinal products are bioequivalent should take into account not only the statistical significance of numerical values but also the medicinal significance of differences. An active ingredient which is absorbed from the test product at the same rate but to a greater extent than from the reference product is superavailable.

2.4.1 Methods for determining bioequivalence

BE may sometimes be demonstrated using an *in vitro* BE standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies (Hendrickson, 2006). The requirement could be either an *in vivo* or an *in vitro* investigation, as specified by the FDA. The types of BE requirements include the following:

1). An *in vivo* test in humans.

2). An *in vivo* test in animals that has been correlated with human *in vivo* data.

3). An *in vivo* test in animals that has not been correlated with human *in vivo* data.

4). An *in vitro* bioequivalence standard, i.e., an *in vitro* test that has been correlated with human *in vivo* bioavailability data.

5). A currently available *in vitro* test (usually a dissolution rate test) that has not been correlated with human *in vivo* bioavailability data.

2.4.2 BE study design

The study should be designed in such a way that the effects of formulation can be distinguished from other factors. When two formulations are compared, crossover designs are the primary statistical designs for bioavailability and BE studies. Such designs allow for comparison of individual treatments using withinsubject variation and thus increase the power of the study for a 2 ×2 crossover design with two treatments and two periods.

A single-dose BE study is generally performed in normal, healthy, adult volunteers. The subject population should be selected carefully, so that product formulations, and not intersubject variations, will be the only significant determinants of BE. A minimum of 12 subjects is recommended, although 18 to 24 subjects are used to increase the data base for statistical analysis. The test and the reference products are usually administered to the subjects in the fasting state (overnight fast for at least 10 hours, plus 2 to 4 hours after administration of the dose), unless some other approach is more appropriate for valid scientific reasons. These subjects should not take any other medication for one week prior to the study or during the study. The

bioavailability is determined by collection of either blood samples or urine samples over a period of time and measurement of the concentration of drug present in the samples. Generally, a crossover study design is used. Using this method, both the test and the reference products are compared in each subject, so that inter-subject variables, such as age, weight, differences in metabolism, etc., are minimized. Each subject thus acts as his own control. Also, with this design, subjects' daily variations are distributed equally among all dosage forms or drug products being tested.

The subjects are randomly selected for each group and the sequence of drug administration is randomly assigned. The administration of each product is followed by a sufficiently long period of time to ensure complete elimination of the drug (washout period) before the next administration. The washout period should be a minimum of 5 half-lives of the administered drug. A waiting period of one week between administrations is usually an adequate washout period of most drugs (Gelder *et al*., 1999). With a drug requiring a washout period of one week, a typical randomized two-way crossover BE study was shown in Table 5.

Table 5. Two-way crossover design

	Period I	Period II
Sequence I	R	T
Sequence II	T	R

R = reference drug; T = test drug

To avoid bias of the test results, each test subject is randomly assigned one of the two products for the first phase of the study. Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety or its metabolites as a function of time. The same procedure is then repeated (crossover) with the second product after an appropriate interval of time (washout period) (Aulton, 2002)

Sequential blood samples (about 12 to 18, including a pre-dose sample) shall be drawn at appropriate, specified, and carefully recorded times (to capture increasing and decreasing concentrations during the absorption, distribution and elimination phases). The collections are to continue for about three terminal drug half-lives in order to capture at least 80% of the total area. At least three to four samples need to be obtained from the terminal log-linear phase to derive an

acceptable estimate of the terminal constant from linear regression. For long half-life drugs, a truncated AUC (e.g. up to 72 hours) is generally considered adequate. Blood samples or the harvested plasma/serum should be analyzed for the administered drug or metabolites by means of a validated analytical method.

Westlake (1979) summarizes the selection of sampling times in BE studies with no universal rule is apparent and a pragmatic approach is usually taken. After a single dose of administration, a rule of thumb is that blood samples are drawn at several times during the absorption phase of the drug, then several times near the peak and at relatively fewer times in the elimination phase. Usually, 10-15 total sampling times are employed. For example, for a drug with a half-life of 4-5 hours, a typical sampling schedule might be 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15 and 24 hours following administration.

The standard *in vivo* BE study design is based on administration of the test and reference products on separate occasions to healthy subjects either in single or multiple doses, with random assignment to the two possible sequences of drug product administration (Hendrickson, 2006).

2.4.3 Duration of washout period

The administration of each product is followed by a sufficiently long period of time to ensure complete elimination of the drug (washout period) before the next administration. The washout period should be a minimum of 5 half-lives of the administered drug, to provide for 99.9% of the administered dose to be eliminated from the body. A waiting period of one week between administration is usually an adequate washout period of most drugs.

2.4.4 Reference and test product

Reference product: One lot should be selected from among three marketed lots of products already approved for which therapeutic efficacy and safety were established by clinical trials or BE was demonstrated by human studies. The reference product should show intermediate dissolution among the three lots under the most discriminative condition, where the difference in dissolution between the fastest and slowest lots is the largest**.**

Test product: These are products with different strengths from that of reference products. The test product should be manufactured in a production scale or 1/10 production scale or larger. The test product should be the same as the production lots in manufacturing method, quality and bioavailability. In the case of controlled release dosage forms, test products should not significantly differ from the reference product in shape of dosage form, density and release mechanism. The dissolution characteristics of the test product should be similar to those of the reference product.

2.4.5 Subject

The subject population for BE studies should be selected with the aim to minimize variability and permit detection of difference between pharmaceutical products. Therefore, the study should normally be performed with healthy volunteers. The inclusion/exclusion criteria should be clearly stated in the protocol. In general, subjects should be as follow: (Thai FDA, 2006)

- Age between 18 – 45 years old
- Weight within the normal range according to accepted normal values for the body mass index (BMI) 18 – 25 kg/m^2.
- Should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination
- Before and during of the study, subjects should preferable be non-smokers and without a history of alcohol or drug abuse.
- Subjects should preferably be non-smoker.
- Subjects should not take any other medication prior to the study or during the study.

2.4.6 Sample size for bioequivalence studies

According to the Committee for Proprietary Medicinal Products (CPMP) guidance, the number of subjects required is determined by the error variance associated with the primary characteristic to be studied (as estimated from a pilot experiment, from previous studies, or from published data), the significance level desired, by the expected deviation from the

reference product and by the required power. It should be calculated by appropriate methods and should not be less than 12.

The equations for the approximate sample size calculation for the two one-sided '*t*' test is given below (Liu and Chow, 1992; Bolton, 1997)

$$n \geq [t_{\alpha,2n-2} + t_{\beta,2n-2}]^2 [CV/(\nabla - \theta)]^2$$

where

n = number of subjects per sequence

t = the appropriate value from the *t* distribution

α = the significant level (usually 0.10)

$1-\beta$ = the power (usually 0.80)

CV = coefficient of variation

∇ = the bioequivalence limit = $\pm$ 20%

θ = difference between product

2.4.7 Parameters for assessment and comparison of BE

Earlier it was argued that a bioequivalence study is a check on the similarity of the release characteristics of test and reference products. The amount of drug molecules released and speed of the release are therefore the most important parameters. In the *in-vivo* bioequivalence study, these characteristics are determined by measuring the following parameters:

2.4.7.1 The peak height concentration (C_{max}): C_{max} is the maximum drug concentration observed in the blood, plasma or serum following a dose of the drug. The C_{max} will usually occur at only a single time point, referred to as T_{max} . C_{max} will increase in the dose, as well as with an increase in the absorption rate. It determines the therapeutic efficacy and toxicity of the drug.

2.4.7.2 The time of peak concentration (T_{max}): The second parameter of importance in assessing the comparative bioavailability of two formulations is the time required to achieve the maximum level of drug in the blood. The T_{max} reflects the rate of the drug absorption. If changes in the rate of drug absorption will result in changes in the values of both C_{max} and T_{max}. Each product has its own characteristic rate of absorption. When the rate of absorption is

decreased, the C_{max} is lower and T_{max} is slower. If the doses of the drugs are the same and presumed completely absorbed, the AUC for each is essentially the same.

2.4.7.3 The area under the plasma concentration-time curve (AUC): AUC is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent dose of a drug, when fully absorbed, would produce the same AUC. Thus, two curves are alike in terms of peak height and time of peak.

C_{max} and T_{max} are measures of the rate of systemic availability, whereas the total AUC is a measure of its extent. The AUC is the most important parameter for the assessment of bioavailability or BE of a drug preparation. The AUC reflects the total amount of drug reaching the systemic circulation.

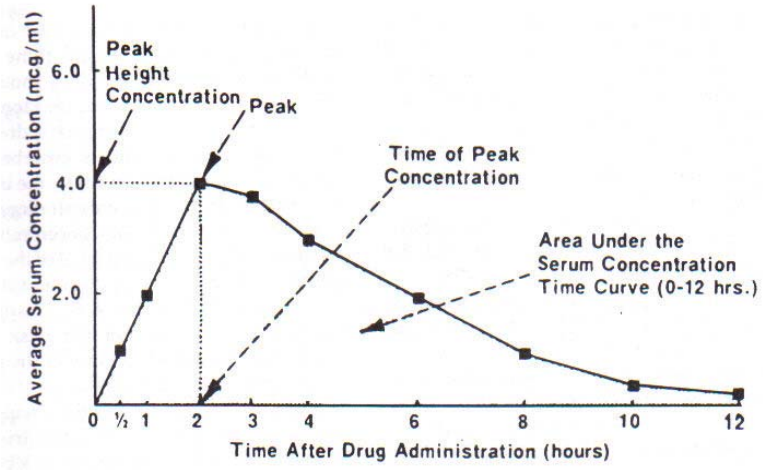


Figure 7. Serum concentration-time curve showing the parameters which are used to determine BE; peak height concentration (C_{max}), time of peak concentration (T_{max}), and area under the curve (AUC) (Aulton, 2002).

2.4.8 Evaluation of the data

Analytical method: The analytical method for measurement of the drug must be validated for accuracy, precision, sensitivity and specificity. Data should be presented in both tabulated and graphical form for evaluation. The plasma drug concentration versus time curve for each drug product and each subject should be available.

Analysis of Variance (ANOVA): Data from BE study are commonly evaluated by ANOVA. It is to be used to identify the source contributions by factors including subjects, period, formulation, and potential interactions. A Bioequivalent product should produce no significant difference in all pharmacokinetic parameters tested (Shargel and Yu, 1999). The geometric mean ratio together with the ANOVA residual mean error term are used to identify the statistical basis for the 90% confidence interval for the ratio of the population means (New Formulation/Original Formulation) of the identified metrics (e.g. AUC, C_{max}).

The statistical methodology for analyzing these BE studies is called the two one-sided test procedures. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly may be more bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products. Numerically, this is expressed as a limit of average test-product /reference-product.

Average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and C_{max}) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data are log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an ANOVA and calculating a 90% confidence interval for each pharmacokinetic parameter (C_{max} and AUC). The 90% confidence interval for both pharmacokinetic parameters, AUC and C_{max}, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when BE is demonstrated through comparative clinical trials, pharmacodynamic studies, or comparative *in vitro* methodology. Classically, the assessment of BE relies on the concept of average BE. Two drug products, a generic versus the innovator are considered to be bioequivalent if the calculated 90% confidence interval (90% CI)

for the ratio of the mean measures of bioavailability (AUC, C_{max}) lies between the predefined BE limits of 0.80-1.25 (Kytariolos *et al*., 2006). The FDA regulations state that "two formulations whose rate and extent of absorption differ by -20%/+25% or less are generally considered bioequivalent" (Benet, 1999; Chereson and Banakar, 2000).

Previous BE studies of some antipsychotics have been reported as shown in Table 6.

Table 6. BE studies of antipsychotics

Drug	Researcher	Year	Place	Dose	Study design	Subjects
Haloperidol	Midha *et al*.	1989	University of Saskatchewan, Canada	5-mg, tablet	Three-way crossover	28 healthy male
	Weringh *et al*.	1994	Haarlem Hospital, Netherlands	100-mg, injection	Open, randomized, crossover	15 schizophrenic patients
	Yun *et al*.	2005	Chungnam National University, Korea	5-mg, tablet	Single dose, two-way crossover	24 healthy volunteers
	Singh and Sharma	2005	India	5-mg, tablet	Two-way crossover, single blind, open label, two period	14 healthy male subjects

Table 6. BE studies of antipsychotics (continued)

Drug	Researcher	Year	Place	Dose	Study design	Subjects
Clozapine	Taesotikul *et al*.	2000	Chiang Mai University, Thailand	100-mg, tablet	Single dose, randomized, double blind, two-period crossover	12 healthy volunteers
	Lam *et al.*	2001	University of Texas, USA	100-mg, tablet	Randomized, crossover	16 Schizophrenia patients
	Tassaneeyakul *et al.*	2005	Khon Kaen University, Thailand	100-mg, tablet	Multiple dose,randomized, two-way crossover	18 male schizophrenia patients

Table 6. BE studies of antipsychotics (continued)

Drug	Researcher	Year	Place	Dose	Study design	Subjects
Risperidone	Gaete *et al.*	2003	Hoapital Clinico de la, Spain	1-mg, tablet	Single-dose, randomized, double- blind, two period	12 healthy volunteers
	Schaick *et al*.	2003	Johnson Pharmaceutical,Belgium	0.5-mg, tablet	Open-label, randomized, two-way crossover	37 healthy volunteers
	Mahatthanatrakul *et al.*	2008	Prince of Songkla University, Thailand	2-mg, tablet	Single-dose, Open-label randomized, two-sequence crossover	16 healthy volunteers

Table 6. BE studies of antipsychotics (continued)

Drug	Researcher	Year	Place	Dose	Study design	Subjects
Olanzapine	LI *et al.*	2006	Beijing Anding hospital, China	10-mg, tablet	Randomized, two-way crossover	22 male volunteers
Quetiapine	Mahatthanatrakul *et al.*	2008	Prince of Songkla University, Thailand	200-mg, tablet	Single-dose, randomized, double-blind, two period	24 healthy volunteers

CHAPTER 3

MATERIALS AND METHODS

3.1 Chemicals and reagents

The standard quetiapine fumarate was obtained from Harn Thai Pharma (2508) Co., Ltd., 2121 New Petchburi Road, Huaykwang district, Bangkok 10320, Thailand. The internal standard, clozapine, was purchased from Sigma.

The HPLC grade of acetronitrile and methanol were purchased from J.T Baker (Phillipsburg, NJ, USA). Potassium phosphate monobasic was obtained from Carlo Erba (Milan, Italy). Triethylamine and sodium hydroxide were purchased from Sigma-Aldrich (Milan, Italy). Diisopropyl ether and isoamyl alcohol were purchased from J.T Baker (Deventer, Netherlands). Water was deionized and purified by using a Milli-Q system (Millipore, Milford, MA, USA).

Blank human plasma was obtained from healthy volunteers.

3.2 Assay Methodology and Validation

3.2.1 Assay method description

A LC-MS/MS method was developed to determine the plasma concentration of quetiapine and validated according to the USFDA guidelines for bioanalytical method validation, USFDA, 2001.

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. 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 °C and 400°C, respectively. The system was controlled by Masslynx software.

Liquid chromatography

A Waters 2695 liquid chromatography (Waters, Milford, USA) with an Atlantis dC18 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). Before using, the mobile phase was degassed by vacuum filtration through a 0.45 µm filter. The flow rate was set at 0.4 mL/min.

Preparation of standard and quality control solutions

The stock standard solution of quetiapine (10 µg/mL) was prepared by dissolving accurately weighted quetiapine standard in MeOH/H_2O (70:30, v/v). The stock standard solution was then diluted with MeOH/H_2O (70:30, v/v) to achieve a working standard solution. The quality control (QC) working standard solution was prepared from quetiapine stock control solution. Blank plasma sample (9.9 mL) were spiked by working solutions (100 µL) to gain either the most concentrated calibration standard of quetiapine (S1) or quality control sample (QC1). All plasma samples were stored at -25 ± 5°C.

The remaining plasma calibration standards (S7-S2) were prepared from S1 by sequential dilutions with blank plasma directly before sample processing. The final concentrations of plasma calibration standards were 0.70, 10, 100, 200, 400, 800 and 1,600 ng/mL.

The stock internal standard solution was prepared by accurately weighting of clozapine (0.0080 g), which was dissolved in MeOH/H_2O (70:30, v/v). The working internal standard (WIS) was prepared by accurate dilution of stock internal standard with MeOH/H_2O (70:30, v/v) to get a final concentration of 1 µg/mL. Stock IS was stored at 4°C for 5 days. Volume of 50 µL WIS was added to 0.50 mL plasma samples.

Sample preparation

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 (0.5 mL) was spitked with 50 µL of Working Internal Standard solution, alkalinized with 200 µL of 0.4 M NaOH, and vortex-mixed. The mixture was loaded on the prepared cartridges. The cartridge was washed with 3 mL H_2O, and the analyte was eluted with 200 µL of mobile phase. A 20 µL aliquote was then injected into the HPLC system with MS/MS detection.

3.2.2 Validation procedure

Pre-study Phase Validation

1. Specificity

Specificity was evaluated by analyzing six blank plasma samples and looking for interfering peaks at the retention time of quetiapine and IS.

2. Lower limit of quantification (LLOQ)

The LLOQ of the assay was the smallest analytical concentration which give rise to peaks height with a signal to noise ratio of 5 times of the blank plasma. In addition, the analyte peak in LLOQ sample should be identifiable, discrete and reproducible with a precision of 20% and accuracy within 80-120%.

3. Linearity/standard calibration curve

Linearity was evaluated using freshly prepared dilution plasma samples in the 7 levels (0.7, 10, 100, 200, 400, 800 and 1,600 ng/mL). Samples were quantified using the ratio of peak area of quetiapine to that of IS as the assay parameter. Standard curves were calculated using weighted least square regression. The coefficient of determination (r^2) should be more than 0.99.

4. Accuracy and precision

Intraday accuracy and precision were evaluated by replicate analysis of quetiapine at different concentrations in human plasma. The run consisted of a calibration curve plus five replicates each of low (4 ng/mL), medium (600 ng/mL) and high (1,200 ng/mL) QC samples. The inter-day accuracy and precision were assessed in a similar manner by analysis of low, medium and high quality control samples for quetiapine on five separate occasions. A comparison was made between the experimental values obtained and actual values. The evaluation of precision was based on the criteria that, the coefficient of variation for each

concentration level should not be more than 15. Similarly, for accuracy, the mean value should not deviate by ±15 of the actual concentration.

Accuracy (%) = (estimated concentration / theoretical concentration) ×100

5. Recovery

The extraction efficiency of quetiapine from human plasma was evaluated by comparing the mean detector responses of five processed QC samples of low (4 ng/mL), medium (600 ng/mL) and high (1,200 ng/mL) concentrations to mean detector responses for five standard solutions of equivalent concentration. As per the acceptance criteria the recovery of the analyte need not be 100%, but the extent of recovery of an analyte and of internal standard should be consistent, precise and reproducible.

$$\text{Extraction Recovery (\%)} = \left[\frac{\text{Peak area of analyte from QC sample}}{\text{Peak area of analyte from un-extracted standard solution}} \right] \text{x } 100$$

6. Stability

6.1 freeze-thaw stability: Effect of three freeze and thaw cycles on stability of frozen plasma sample containing quetiapine was determined to establish the ruggedness of the method. Three aliquots each of low (4 ng/mL) and high (1,200 ng/mL) extracted quality control samples were stored at -70 °C and subjected to three freeze-thaw cycles. After the completion of third cycle the samples were processed, analyzed and results were compared with nominal values. The values were expected to fall within ±15% of the theoretical concentration.

6.2 Short-term stability: Six aliquots each of the low (4 ng/mL) and high (1,200 ng/mL) unprocessed QC samples were kept at room temperature for 2 and 6 hr in order to establish the short-term stability of quetiapine in human plasma. Thereafter, the samples were analyzed and the concentrations obtained were compared with the actual values of QC samples. Samples will be concluded stable if deviation of the stability samples is not more than ±15% of the actual value.

6.3 Long-term stability: To determine the long term stability of quetiapine in human plasma, three aliquots of each, low (4 ng/mL) and high (1,200 ng/mL) QC samples were kept in deep freezer at -70 °C for 14 and 60 days. The samples were analyzed and concentrations

obtained were compared with the nominal values of QC set and all values within ±15% of the actual value is qualified the test.

6.4 Post preparative stability (Auto-sampler stability): In order to establish the auto-sampler stability of quetiapine in human plasma matrix, three aliquots of low (4 ng/mL) and high (1,200 ng/mL) QC samples were stored at room temperature in auto-sampler for 8 hr. Thereafter, samples were reanalyzed and concentrations were compared with the actual values. The percentage deviation is calculated and stability is concluded if it is within ±15% of the actual value.

6.5 Stock solution stability: Quetiapine and IS were prepared by dissolving suitable amount of each pure substance in methanol kept at -20°C and -70°C for 14 days. Stock solutions were obtained by diluting with the mobile phase. Thereafter, the mean detector response of quetiapine and IS from three replicate chromatographic runs was compared to that of freshly prepared solutions of the same concentration. The samples qualified the criteria of stability if the deviation is within ± 2%.

Study Phase Validation

A calibration curve and a set of QC samples are recommended for each bioanalytical batch. The QC samples results must be in range at all concentration levels. The criteria for accepting in study runs (4 out of 6 QC results must be within 30% of their respective nominal values).

3.3 Clinical study methods

3.3.1 Sample size

The following example illustrates the calculation of sample size to achieve an 80% power at the 5% nominal level when $\theta = 5\%$. According to the current FDA guidelines, ∇ is usually set to be ±20% of the average reference bioavailability in most BE studies. CV is the coefficient of variation, which is the intra-subject variability expressed as percentage of the average reference bioavailability. The following illustrates the computation of sample size to achieve an 80% power at the 5% nominal level of θ. The sample size for each sequence group is approximately:

$$n \geq [t_{\alpha,2n-2} + t_{\beta,2n-2}]^2 [CV/(\nabla - \theta)]^2$$

$$n \geq [1.72 + 0.86]^2 [0.2/(0.2 - 0.05)]^2$$

$$n \geq [6.656][1.777] = 11.8 \approx 12$$

n = number of subjects per sequence

t = the appropriate value from the *t* distribution

α = the significant level (usually 0.10)

$1-\beta$ = the power (usually 0.80)

CV = coefficient of variation

∇ = the bioequivalence limit = $\pm$ 20%

θ = difference between products

Thus n = 12 per sequence or 24 subjects for 2 sequences. Anyway 24 subjects were used in this study in order to cover, if any, those subjects who might drop out from the study.

3.3.2 Subjects

The subjects in this study were physically and mentally normal male volunteers, 18 to 45 years old. All volunteers were screened for use of medication, cigarettes, alcoholic beverages, coffee and tea. After complete explanation of the study, the written informed consents were obtained from all subjects. The study protocol was approved by the Ethics Committee, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

3.3.3 Subject Selection Criteria

Inclusion criteria:

- Healthy Thai male volunteers with the ages range from 18 to 45 years old and body mass index between 18-25 kg/m^2.

- All subjects were in good health on the basis of medical history and physical examination, routine blood chemistry tests and complete blood count (CBC).

- The written informed consent.

Exclusion criteria:

- The subjects who have history of alcoholism or drug abuse.

- The subjects who have either abnormal blood chemistry or CBC would be excluded from this study.

- The subjects who have history of allergic disease.

- The subjects who have physiological conditions which affect bioavailability, e.g., GI, hepatic, or renal disease.

3.3.4 Study design

The BE of two formulations of quetiapine fumarate 200 mg was conducted using an experimental design of two-way crossover, two-period, two-sequence, and randomized study with a 2-week washout period. During the first period, volunteers from group I received a single 200-mg dose of Seroquel® (reference product) whereas volunteers from group II received a single 200-mg dose of Ketipinor® (test product). During the second period, the procedure was repeated on the groups in reverse.

3.3.5 Drug administration

During the first period, volunteers from group I received a single 200-mg dose of Seroquel® (reference product) tablet, was given orally with 240 mL of water after at least 10 hr of overnight fasting. No food was taken at least 4 hr after ingestion of the drug. While volunteers from group II received a single 200 mg dose of Ketipinor® (test product). During the second period, the procedure was repeated on the groups in reverse. Volunteers were not allowed to ingest any alcoholic drink and take medication for at least two weeks prior to and during the entire period of the study. Caffeine containing food and beverage were abstained at least two days prior to dosing until blood sample collection. After drug administration, the subjects were sat before 30 min and subsequently supine posture.

3.3.6 Blood sample collection

Each 5 ml of blood sample was collected from forearm vein at 0 (pre dose), 15, 30, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 48 hr post dose. The blood samples were centrifuged at 3,500 rpm for 15 min. The plasma samples were collected and stored at -70°C until analysis.

3.3.7 Subject monitoring

During the study period, vital signs were monitored every 2 hr after drug administration by medical doctors. Side effects of the drugs were monitored and recorded in the case report forms. Serious side effects, if happened, would be immediately managed by the medical doctors.

3.4 Pharmacokinetic parameters and statistical analysis

3.4.1 Definition and calculation

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

AUC_{0-t} was estimated according to the linear trapezoidal method. K_e was estimated from the natural logarithms of the observed plasma concentration of quetiapine during the terminal monoexponential phase of the concentration-time profile. $AUC_{0-\infty}$, $T_{1/2}$, CL/F, and Vd/F were calculated using the formulae:

$AUC_{0\rightarrow t}$; $AUC_{0\rightarrow last} = \sum \frac{(C_{n-1} + C_n)}{2}(t_n - t_{n-1})$; $n = 1, 2, 3, ...$

$AUC_{0-\infty} = AUC_{0-t} + C_{last}/ K_e$ (the ratio of the last quantifiable concentration over the elimination rate constant (C_t/ K_e))

$$K_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}$$

$T_{1/2} = 0.693/ K_e$

$CL/F = dose/ AUC_{0-\infty}$

$Vd/F = CL/F.K_e$

The comparison of the pharmacokinetic parameters and ANOVA for untransformed and log-transformed pharmacokinetic parameters: C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The

evaluation criteria was based on the statistical results of 90% CI for the difference in the means of the log-transformed data, at the 10% significance level, was calculated using the following equation (Bolton, 1997):

$$90\%\ CI \quad = \quad (X_T - X_R) \pm (t_{0.10,\ df} \times S.E.)$$

Where; $X_T - X_R$ is a difference in means of log transformed (ln) pharmacokinetic parameters (C_{max} or AUC_{0-48} or $AUC_{0-\infty}$) between the test product and the reference, $t_{0.10,\ \nu}$ is the tabulated two-tail t value for a 90% CI, df is a degree of freedom of the mean square error obtained from the ANOVA table, S.E. or $\sqrt{2MSE/n}$ 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.

BE will be concluded if the 90% CI fell within the bioequivalence range of 80.00–125.00% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

CHAPTER 4

RESULTS

Summary of validation

Pre-study Phase Validation

1. Specificity

Quetiapine and IS (clozapine) were clearly separated from the plasma with the retention time of 2.42 and 2.38 min, respectively. The chromatogram of blank plasma and the chromatograms of quetiapine and internal standard were shown in Figure 8 and 9, respectively. Both peaks were clearly separated and no interferences from endogenous substances were observed.

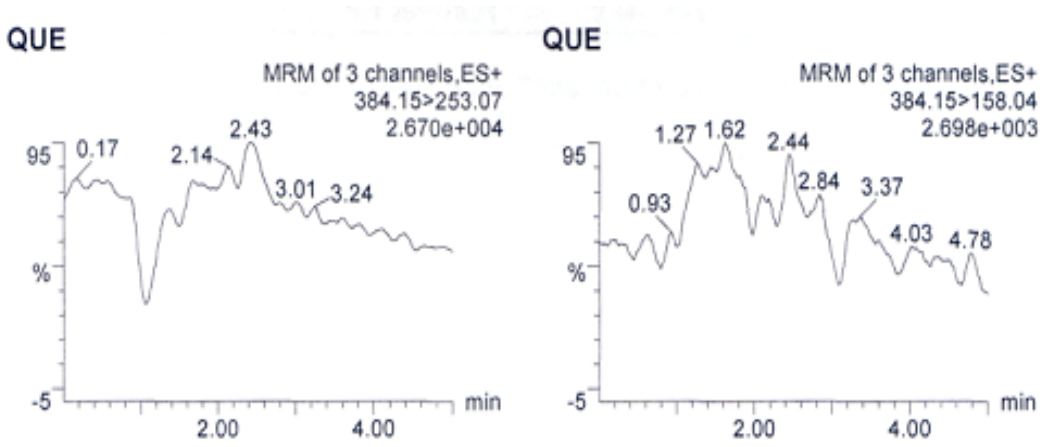


Figure 8. Chromatogram of blank plasma

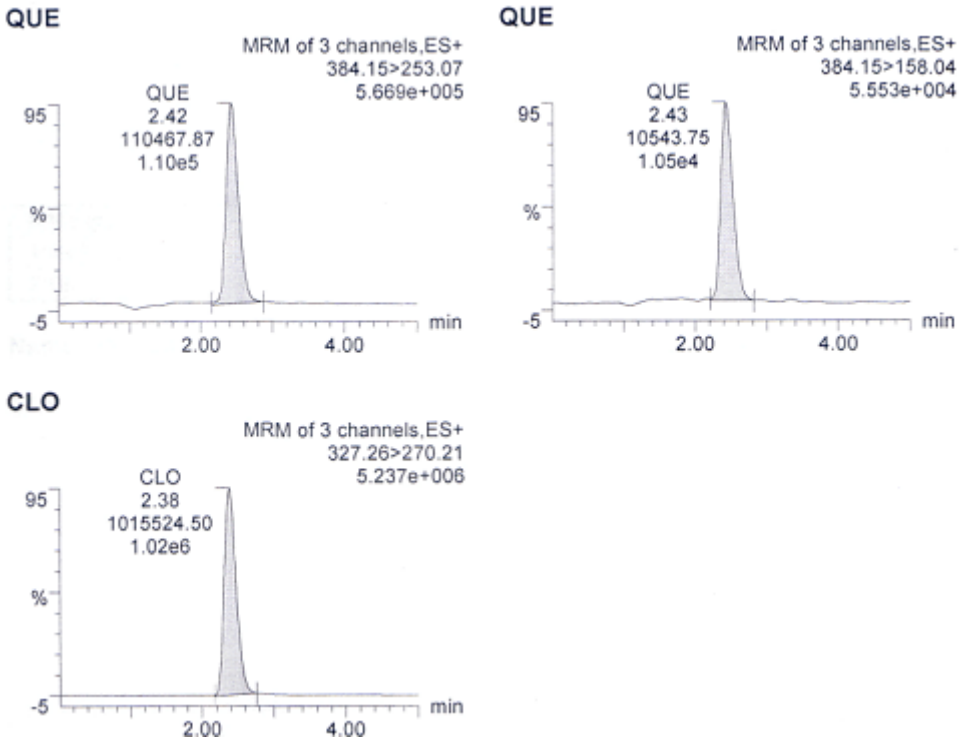


Figure 9. Chromatogram and retention times of quetiapine (QUE) and IS (clozapine, CLO)

2. Lower limit of quantitation (LLOQ)

LLOQ with acceptable accuracy of 100.71% and precision of 7.48 %, was 0.705 ng/mL (Table 7).

Table 7. LLOQ of quetiapine in plasma.

No.	Peak area		Peak area ratio	Concentration (ng/ml)
	Quetiapine	IS		
1	4,013	152,923	0.026	0.766
2	2,747	105,749	0.026	0.758
3	8,070	359,947	0.022	0.654
4	3,940	168,230	0.023	0.683
5	5,661	247,832	0.023	0.666
			Mean	**0.705**
			SD	**0.053**
			%CV	**7.48**
			%Accuracy	**100.71**

3. Calibration curve and linearity

The calibration curve of standard quetiapine was linear over the range of 0.70, 10, 100, 200, 400, 800 and 1,600 ng/mL (Figure 10 and Table 8). The regression equation for the calibration curve of peak area ratio of quetiapine and IS (y) versus plasma quetiapine concentration (x) was y = 3.20824x-0.661422. The correlation coefficient of calibration curve was 0.9996 (Figure 10).

Table 8. Calibration curve data of quetiapine in plasma.

No.	Concentration (ng/mL)	Peak area of quetiapine	Peak area of IS	Peak area ratio (%)
1	0.70	7,071	369,720	1.91
2	10	61,646	203,543	30.29
3	100	1,441,022	495,813	290.64
4	200	1,387,805	223,442	621.10
5	400	3,734,670	291,265	1282.22
6	800	7,107,435	275,496	2579.87
7	1,600	9,318,851	180,277	5169.20

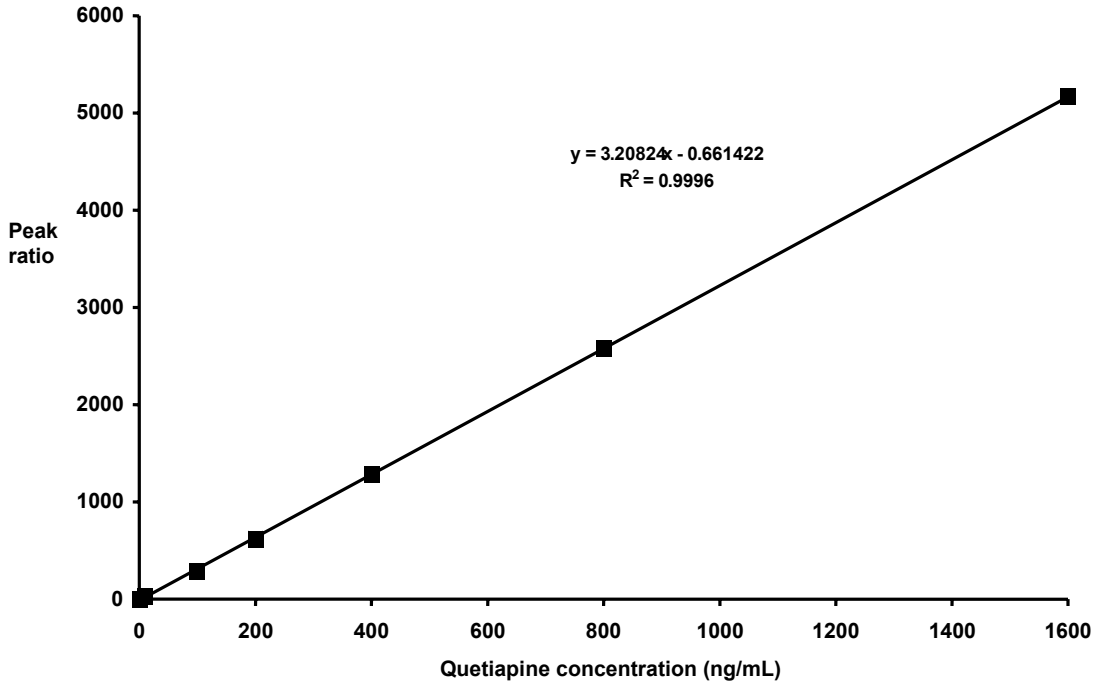


Figure 10. The calibration curve of standard quetiapine

4. Precision and accuracy

Precision and accuracy for this method were controlled by calculating the intra-day and inter-day at three concentrations (4, 600 and 1,200 ng/mL) in five replicates. As shown in Table 9 and 10, the intra-day accuracy ranged between 99.15 - 105.34% with a precision (%CV) of 3.20 - 4.66% (Table 9). The inter-day accuracy ranged between 97.25 - 103.30% with a precision (%CV) of 1.24 - 5.94% (Table 10).

5. Recovery

Mean extraction recoveries of quetiapine at concentrations 4, 600 and 1,200 ng/mL were 84.59, 107.48, and 101.11%, respectively, and the extraction recovery of the IS was 122.83% (Table 11).

Table 9. The intra-day variance of 3 quetiapine concentrations in plasma

Theoretical Conc. (ng/mL)	Calculated concentration (ng/mL)								
	1	2	3	4	5	Mean	SD	%CV	%Accuracy
4	3.73	3.86	3.94	4.09	4.20	3.97	0.19	4.66	99.15
600	646.57	613.78	632.67	657.12	609.97	632.02	20.38	3.22	105.34
1,200	1,247.29	1,174.14	1,234.27	1,282.04	1,221.32	1,231.81	39.39	3.20	102.65

Table 10. The inter-day variance of 3 quetiapine concentrations in plasma

Theoretical Conc. (ng/mL)	Calculated concentration (ng/mL)								
	Day 1	Day 2	Day 3	Day 4	Day 5	Mean	SD	%CV	%Accuracy
4	4.01	3.64	3.80	3.79	4.20	3.89	0.22	5.62	97.25
600	682.18	585.49	617.42	603.86	609.97	619.78	36.82	5.94	103.30
1,200	1,227.91	1,233.87	1,235.20	1,261.42	1,221.32	1,235.94	15.27	1.24	103.00

Table 11. Recovery of quetiapine and IS in plasma

Theoretical Conc. (ng/mL)	Calculated concentration (ng/mL)						Mean	SD	%CV	%Accuracy
	Sample	1	2	3	4	5				
	in plasma	3.266	3.385	3.332	3.492	3.782	3.45	0.20	5.87	86.29
Low	in mobile phase	4.117	4.139	4.000	3.993	4.152	4.08	0.08	1.90	102.01
(4)	% recovery	79.33	81.78	83.30	87.45	91.09	**84.59**	4.68	5.53	
	in plasma	596.488	592.570	575.157	608.472	615.173	597.57	15.47	2.59	99.60
Medium	in mobile phase	552.418	555.066	546.387	555.190	570.560	555.92	8.93	1.61	92.65
(600)	% recovery	107.98	106.76	105.27	109.60	107.82	**107.48**	1.60	1.49	
	in plasma	1,155.562	1,213.728	1,342.418	1,348.287	1,270.971	1,266.19	83.01	6.56	105.52
High	in mobile phase	1,276.920	1,252.553	1,232.736	1,255.234	1,247.998	1,253.09	15.91	1.27	104.42
(1,200)	% recovery	90.50	96.90	108.90	107.41	101.84	**101.11**	7.60	7.52	
	in plasma	149.009	159.307	124.608	80.442	67.829	116.239	40.69	35.01	116.24
IS										
	in mobile phase	106.635	94.732	91.355	88.227	86.220	93.433	8.05	8.62	93.43
(100)	% recovery	139.74	168.17	136.40	91.18	78.67	**122.83**	37.00	30.13	

6. Stability

6.1 Freeze thaw stability

The stability of quetiapine at the concentrations of low (4 ng/mL) and high (1,200 ng/mL) kept frozen at -70 °C before and after freeze and thaw stability test was shown in Table 12. After three cycles of freezing and thawing, the percentage of quetiapine change at concentrations of 4 and 1,200 ng/mL were 0.09 and 6.52%, respectively. The CV of all measured concentrations was less than 15%. The results indicated that no significant degradation after three freeze-thaw cycles was observed.

6.2 Short term stability

The short term stability was investigated to ensure that quetiapine was not degraded in plasma samples at room temperature for a time period to cover the sample preparation. QC sample at concentrations of low (4 ng/mL) and high (1,200 ng/mL) were left at room temperature for 2 and 6 hr. The samples were then processed and analyzed. The results, shown in Table 13, indicated that quetiapine was stable during the exposure period. The percentages of quetiapine change at the concentrations of 4 and 1,200 ng/mL on standing at room temperature for 2 and 6 hr were 8.64, 0.23, 2.75 and 7.56%, respectively.

6.3 Long term stability

The stability of quetiapine was evaluated by analyzing QC samples which were kept at -70 °C for 14 and 60 days. Quetiapine was stable for 60 days with % change of 9.45 and 11.76 at the concentrations of low (4 ng/mL) and high (1,200 ng/mL), respectively, as shown in Table 14.

6.4 Post preparative stability

As delay injection may occasionally occur, therefore stability of quetiapine was evaluated by leaving the samples in the autosampler for 8 hr before injection. The quantitative results indicated that quetiapine was stable in the autosampler up to at least 8 hr with % change of 2.37 and 2.78 % at the concentrations of 4 and 1,200 ng/mL, respectively. The results were shown in Table 15.

6.5 Stock solution stability

Quetiapine and clozapine (IS) prepared by dissolving suitable amount of each pure substance in methanol and kept at -20 °C and -70 °C for 14 days. Stock solutions of quetiapine

(10 µg/mL) and IS (1 µg/mL) in methanol was investigated. The results presented in Table 16 indicated that the stock solution of quetiapine was stable in methanol at -20°C and -70 °C for 14 days. Clozapine was stable in methanol at -70 °C for 14 days. There was no evidence of degradation of quetiapine and clazapine under these conditions.

Study Phase Validation The results presented in Table 17

Table 12. Freeze thaw stability of quetiapine in plasma.

	Low QC conc.(4 ng/mL)		**High QC conc.(1,200 ng/mL)**	
Sample No.	0 Hour	72 Hour (3 cycle)	0 Hour	72 Hour (3 cycle)
1	4.22	3.95	1,131.77	1,259.37
2	3.99	3.89	1,213.96	1,215.85
3	3.66	4.03	1,124.67	1,221.37
Mean	3.96	3.96	1,156.80	1,232.20
SD	0.28	0.07	49.63	23.70
%CV	7.11	1.84	4.29	1.92
%Accuracy	98.97	98.88	96.40	102.68
% change	**-**	**0.09**	**-**	**6.52**

Table 13. Short-term stability at room temperature of quetiapine in plasma.

	Low QC conc.(4 ng/mL)			**High QC conc.(1,200 ng/mL)**		
Sample No.	0 Hour	2 Hour	6 Hour	0 Hour	2 Hour	6 Hour
1	3.93	3.92	3.83	1,294.45	1,237.56	1,086.45
2	3.81	4.35	3.81	1,210.75	1,174.62	1,151.51
3	3.49	3.93	3.61	1,222.84	1,213.42	1,208.40
Mean	3.74	4.07	3.75	1,242.68	1,208.53	1,148.79
SD	0.23	0.25	0.12	45.24	31.75	61.02
%CV	6.09	6.10	3.20	3.64	2.63	5.31
%Accuracy	93.56	101.64	93.78	103.56	100.71	95.73
% change	**-**	**8.64**	**0.23**	**-**	**2.75**	**7.56**

Table 14. Long-term stability at -70 °C of quetiapine in plasma.

	Low QC conc. (4 ng/mL)			**High QC conc. (1,200 ng/mL)**		
Sample No.	0 Day	14 Day	60 Day	0 Day	14 Day	60 Day
1	3.77	3.55	3.60	1,231.29	1,116.17	1061.18
2	4.31	3.54	3.59	1,258.88	1,120.61	1117.13
3	3.95	3.59	3.69	1,271.94	1,119.44	1141.55
Mean	4.01	3.56	3.63	1,254.04	1,118.74	1106.62
SD	0.28	0.03	0.06	20.76	2.30	41.20
%CV	6.90	0.73	1.57	1.66	0.21	3.72
%Accuracy	100.19	89.07	90.73	104.50	93.23	92.22
% change	-	**11.10**	**9.45**	-	**10.79**	**11.76**

Table 15. Post preparative (autosampler) stability at room temperature of quetiapine in plasma.

	Low QC conc. (4 ng/mL)		**High QC conc. (1,200 ng/mL)**	
Sample No.	0 Hour	8 Hour	0 Hour	8 Hour
1	3.89	4.01	1,044.51	1,102.19
2	3.97	4.06	1,080.32	1,139.20
3	3.82	3.89	1,203.03	1,179.12
Mean	3.89	3.99	1,109.29	1,140.17
SD	0.08	0.09	83.13	38.47
%CV	1.96	2.20	7.49	3.37
%Accuracy	97.33	99.64	92.44	95.01
% change	-	**2.37**	-	**2.78**

Table 16. Stock solution stability at -20°C and -70°C for 14 days of quetiapine and IS

	Quetiapine **10 µg/mL**			**IS** **1 µg/mL**		
Sample No.	0 h (room temp)	14 day (at -20°C)	14day (at -70°C)	0 h (room temp)	14 day (at -20°C)	14 day (at -70°C)
1	10.19	10.29	10.40	0.97	0.96	0.99
2	10.27	10.00	10.50	0.98	0.94	0.99
3	10.33	10.39	10.23	1.00	0.97	0.97
Mean	10.26	10.23	10.38	0.98	0.95	0.98
SD	0.07	0.20	0.14	0.01	0.02	0.01
%CV	0.72	1.98	1.33	1.49	1.79	0.87
%Accuracy	102.64	102.27	103.77	98.03	95.40	98.40
% change	**-**	**- 0.36**	**1.10**	**-**	**- 2.69**	**0.37**

Table 17. Detail of standard curve and QC analysis

Assay date	Subject number	Standard curve equation	R^2	Number of sample per batch	Number of QC per batch
28 Oct 2009	S7P1, S9P1	y = 2.82857X-1.0421	0.9966	36	6 (all pass)
29 Oct 2009	S18P1, S20P1	y = 2.94175X-0.9967	0.9959	36	6 (all pass)
29 Oct 2009	S8P1, S1P1,	y = 2.66834X-0.8808	0.9974	36	6 (all pass)
30 Oct 2009	S3P1, S10 P1	y = 2.67032X-0.5868	0.9952	36	6 (all pass)
3 Nov 2009	S5P1, S16P1	y = 2.78078X-0.5555	0.9972	36	6 (all pass)
4 Nov 2009	S11P1, S12P1	y = 2.7355X-0.7878	0.9934	36	6 (all pass)
5 Nov 2009	S2P1, S14 P1	y = 1.8860X-0.6969	0.9973	36	6 (all pass)
9 Nov 2009	S4P1, S21P1	y = 1.8375X-0.9344	0.9985	36	6 (all pass)
10 Nov 2009	S6P1, S17P1	y = 2.69613X-0.1289	0.9971	36	6 (all pass)
11 Nov 2009	S1P2, S3P2	y = 2.80501X-0.1489	0.9923	36	6 (all pass)
12 Nov 2009	S19P1, S22P1	y = 2.07385X-0.6066	0.9953	36	6 (all pass)
12 Nov 2009	S8P2, S10P2	y = 1.93269X-0.5381	0.9971	36	6 (all pass)
13 Nov 2009	S23P1, S24P1	y = 2.28479X-1.2315	0.9974	36	6 (all pass)
16 Nov 2009	S7P2, S9P2	y = 1.84934X-0.3715	0.9921	36	6 (all pass)
16 Nov 2009	S18P2, S20P2	y = 1.9177X-0.6183	0.9938	36	6 (all pass)
17 Nov 2009	S5P2, S11P2	y = 2.31767X-0.6486	0.9955	36	6 (all pass)
17 Nov 2009	S12P2, S16P2	y = 2.51029X-1.2025	0.9956	36	6 (all pass)
19 Nov 2009	S13P2, S14P2	y = 2.41888X-1.5404	0.9960	36	6 (all pass)
19 Nov 2009	S15P2, S21P2	y = 2.51062X-1.3697	0.9949	36	6 (all pass)
25 Nov 2009	S2P2, S4P2	y = 2.59772X-1.2329	0.9981	36	6 (all pass)
25 Nov 2009	S17P2	y = 2.35862X-1.4540	0.9969	18	6 (all pass)
27 Nov 2009	S22P2, S24P2	y = 2.26896X-0.9075	0.9965	36	6 (all pass)
27 Nov 2009	S19P2	y = 2.37636X-0.8360	0.9972	18	6 (all pass)
8 Dec 2009	S13P1, S15P1	y = 2.49455X-1.3236	0.9975	36	6 (all pass)
11 Dec 2009	S6P2	y = 2.40173X-1.0057	0.9996	18	6 (all pass)
17 Dec 2009	S23P2	y = 2.40173X-1.0057	0.9996	18	6 (all pass)

Subjects

The demographic characteristics of the 24 subjects were illustrated in Table 18. The mean ± S.D. of age, weight, height and BMI of the subjects were 23.92 ± 5.50 years, 60.54 ± 7.01 kg, 170.94 ± 6.00 cm and 20.69 ± 1.79 kg/m^2, respectively. All subjects were healthy on the basis of medical history, physical examination, hematological and blood chemistry investigations (Table 19). All subjects could participate in both phases of the study without any serious side effect was shown in Table 20.

Table 18. Demographic data of the 24 healthy male volunteers enrolled in the study.

Subject No.	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m^2)
1	29	74	177	23.62
2	22	57	174	18.82
3	21	62.5	175	20.41
4	22	50	162	19.05
5	21	75	179	23.41
6	22	55	173	18.37
7	21	64	172	21.63
8	21	55	164	20.45
9	21	50.5	166	18.33
10	21	54	163	20.32
11	31	55	162	20.95
12	22	69	183	20.60
13	20	55	170	19.03
14	20	61	173	20.38
15	20	65	174	21.47
16	28	72	171	24.62
17	21	61	173	20.38
18	20	62	173.5	20.72
19	25	65	164	24.14
20	20	62	177	19.79
21	21	61	179	19.04
22	42	58	167	20.80
23	31	52	167	18.65
24	32	58	164	21.56
Mean	23.92	60.54	170.94	20.69
SD	5.50	7.01	6.00	1.79

Table 19. Blood chemistry and complete blood count of the 24 healthy volunteers enrolled in the study.

Subject No.	FBS	BUN	Cr	CHOL	TRIG	HDL	LDL	VLDL	DBI	TBL	SGOT	SGPT	ALP	TP	ALB	Uric acid	WBC	Hct	HB	PMN	EOS	LYMPH	MONO
1	103	14.1	1.17	185	44	40	136	9	0.2	1.0	19	37	56	7.8	4.2	5.8	4,200	40	13.3	43	3	54	-
2	81	9.6	1.28	155	78	67	72	16	0.6	1.3	14	15	56	8.6	5.2	5.5	7,600	42	14.4	77	1	21	1-
3	84	13.5	1.18	210	77	53	142	15	0.1	0.75	17	14	71	7.9	4.6	6.2	9,000	41	13.5	78	3	19	-
4	88	12.8	1.09	237	99	67	150	20	0.12	0.49	18	19	70	8.3	4.1	6.5	6,500	46	15.4	61	5	34	-
5	83	8.9	1.17	181	79	63	102	16	0.2	0.73	18	16	69	7.8	4.3	6.8	6,800	45	15	49	-	51	-
6	83	6.2	1.03	150	69	56	84	14	0.1	0.63	13	10	49	8.3	5.2	5.1	6,100	42	14.5	36	-	62	2
7	82	8.8	1.17	184	67	53	118	13	0.38	1.09	15	18	74	8.3	4.6	6.6	4,300	45	15	55	-	45	-
8	88	12.3	1.28	241	74	60	166	15	0.2	1.0	21	20	51	8.3	4.3	5.4	8,400	43	14.8	75	-	25	-
9	77	10.2	0.86	162	65	63	86	13	0.21	0.66	19	20	59	8.9	5.0	6.2	6,600	48	16	62	1	36	1
10	90	11.1	1.2	241	70	56	171	14	0.2	1.0	15	12	80	8.2	4.7	6.0	6,600	42	14.6	50	2	47	1
11	88	9.6	1.07	258	142	53	177	28	0.2	0.83	23	18	65	7.8	4.7	6.1	6,000	44	14	41	3	54	2
12	78	12.1	1.33	201	75	49	137	15	0.08	0.5	24	25	45	7.4	4.2	6.8	5,300	42	14	74	-	24	2
13	90	9	1.1	128	71	63	51	14	0.04	0.2	19	15	74	7.8	4.7	4.5	8,400	41	13.5	67	-	29	4
14	81	9.1	1.3	168	78	63	89	16	0.02	0.47	20	13	61	8.2	4.5	5.7	6,100	42	13.8	61	-	35	4
15	84	17.6	1.36	186	106	49	116	21	0.2	0.75	25	31	89	8.3	4.6	5.3	6,200	46	15	29	3	65	3
16	82	10.7	1.03	241	359	49	120	72	0.14	0.59	23	28	55	7.9	4.9	5.0	5,400	40	13.3	58	-	41	1
17	101	13.0	1.16	209	60	63	134	12	0.16	0.48	19	19	55	7.6	4.2	6.7	5,700	42	14	56	2	42	-
18	80	12.9	1.2	205	172	56	115	34	0.2	0.67	25	34	59	7.8	4.8	6.2	4,800	45	14.4	63	-	34	3
19	99	11.4	1.27	204	95	46	139	19	0.5	1.34	23	17	21	8.1	3.9	5.6	7,200	39	12.8	55	3	40	2
20	76	10	1.1	173	89	46	109	18	0.2	1.0	12	9	129	8.2	4.2	5.8	6,100	44	14.1	69	-	27	4
21	80	7.9	1.29	142	154	49	62	31	0.08	0.22	31	26	78	7.9	3.2	6.2	6,400	45	14.8	46	-	49	5
22	89	17.5	1.19	303	89	91	194	18	0.15	0.50	19	13	48	7.2	4.1	4.6	4,100	43	14.2	43	5	52	-
23	81	9.3	1.1	211	40	56	147	8	0.2	0.64	15	11	98	7	4.4	6.0	4,700	45	12.3	55	-	41	4
24	81	9.4	1.35	236	156	40	165	31	0.2	0.5	19	20	58	8.3	5.0	5.4	4,400	39	13	51	5	43	1
Mean	85.38	11.13	1.18	200.46	100.33	56.29	124.25	20.08	0.2	0.72	19.42	19.17	65.41	8.00	4.48	5.83	6,120.83	42.96	14.15	56	2	40	2
SD	7.23	2.76	0.12	41.35	64.93	10.76	37.64	12.98	0.13	0.3	4.44	7.51	20.82	0.43	0.45	0.65	1357.42	2.37	0.87	13	2	12	2

Table 20. Adverse effects of Seroquel® and Ketipinor® in the 24 subjects.

Side effect	Seroquel®		Ketipinor®	
	Number	%	Number	%
Somnolence	24	100	24	100
Orthostatic hypotension	2	8.34	2	8.34
Nasal congestion	2	8.34	2	8.34
Myalgia	1	4.17	-	-

All volunteers could tolerate the side effects of both drugs. No serious side effect was observed and no subject withdrew from the study. Adverse effects of Seroquel® and Ketipinor® were somnolence (100% in both products), orthostatic hypotension (8.34% in both products), nasal congestion (8.34% in both products) and myalgia (4.17% in Seroquel®), respectively

Pharmacokinetic analyses and bioequivalence assessment

The plasma concentration-time profile of Seroquel® and Ketipinor® after a single oral dose of 200 mg in the 24 subjects were shown in Figures 11-34. The average plasma concentration-time curve of Seroquel® and Ketipinor® after a single oral administration of 200-mg in the 24 subjects were shown in Figures 35. The individual and mean±SD of plasma quetiapine concentrations at various sampling times after a single oral dose of 200 mg of Seroquel® and Ketipinor® to 24 subjects were presented in Table 21 and 22, respectively. Quetiapine pharmacokinetic parameters of individual subject following a single oral dose of 200-mg of Seroquel® and Ketipinor® were shown in Table 23 and Table 24.

The comparison of quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200 mg of Ketipinor® and Seroquel® were shown in Table 25. The mean±SD of C_{max} for the test and reference formulations were 632.27±304.43 and 638.83±214.49 ng/mL, respectively. The AUC_{0-48} and $AUC_{0-\infty}$ values, were 2,625.21±972.14 and 2,640.25±979.10 ng.h/mL, respectively after the administration of the test formulation, and 2,511.82±704.21 and 2,526.45±704.37 ng.h/mL, respectively, after the administration of the reference formulation. T_{max} values for the test and reference formulations were 1.34±1.11 and 1.01±0.63 hr, respectively. $T_{1/2}$ for the test and reference formulations were 5.15±1.17 and 4.86±1.35 hr, respectively. The volume of distribution adjusted for bioavailability (V_d/F) for the test and reference formulations were 0.70 ± 0.52 and 0.60 ± 0.25 L, respectively. The total drug clearance adjusted for bioavailability (CL/F) for the test and reference formulations were 0.09 ± 0.04 and 0.09 ± 0.03 L/hr, respectively. The mean extrapolate portion of the plasma concentration-time curves of Ketipinor® and Seroquel® were 0.56 and 0.61%, respectively, which were less than the acceptable value of 20%.

Statistical analysis of BE

The results of two-way ANOVA test of the log-transformed values of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ of Ketipinor® and Seroquel® were shown in Table 26. The ANOVA study has shown that formulation and period had no significant effect on C_{max}, AUC_{0-48} or $AUC_{0-\infty}$ at the significant level of 0.05. Although the sequence had significant effect on AUC_{0-48} and $AUC_{0-\infty}$ but

the results have shown that all the pharmacokinetic parameters of both products were not significant different.

The pharmacokinetic parameters of C_{max}, AUC_{0-48}, $AUC_{0-\infty}$, AUC extrapolated (%), T_{max}, $T_{1/2,}$ Vd/F, CL/F, and K_e of Ketipinor® and Seroquel® were calculated for quetiapine as presented in Table 27. Table 28 demonstrated the 90% CI, geometric mean ± SD, and power of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ for Ketipinor® and Seroquel®. The 90% CI of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ for Ketipinor®/Seroquel® were 80.75-102.60, 91.32-108.42 and 88.47-106.77%, respectively. These values were within the acceptable range of the Thai FDA criteria, 80.00-125.00%. The power of tests obtained from this study for pharmacokinetic parameters C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ were found to be 92.16, 96.34 and 95.96%, respectively which were greater than 80%.

The results from the ANOVA test confirmed the bioequivalence of Ketipinor® (test product) with the Seroquel® (reference products) in term of the rate and extent of absorption.

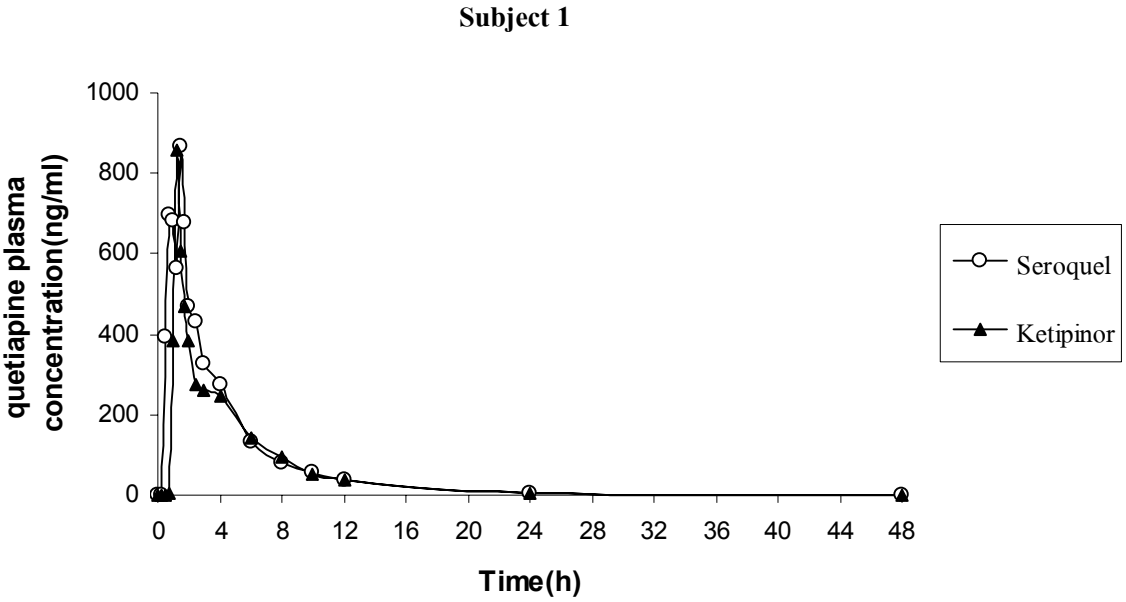


Figure 11. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 1.

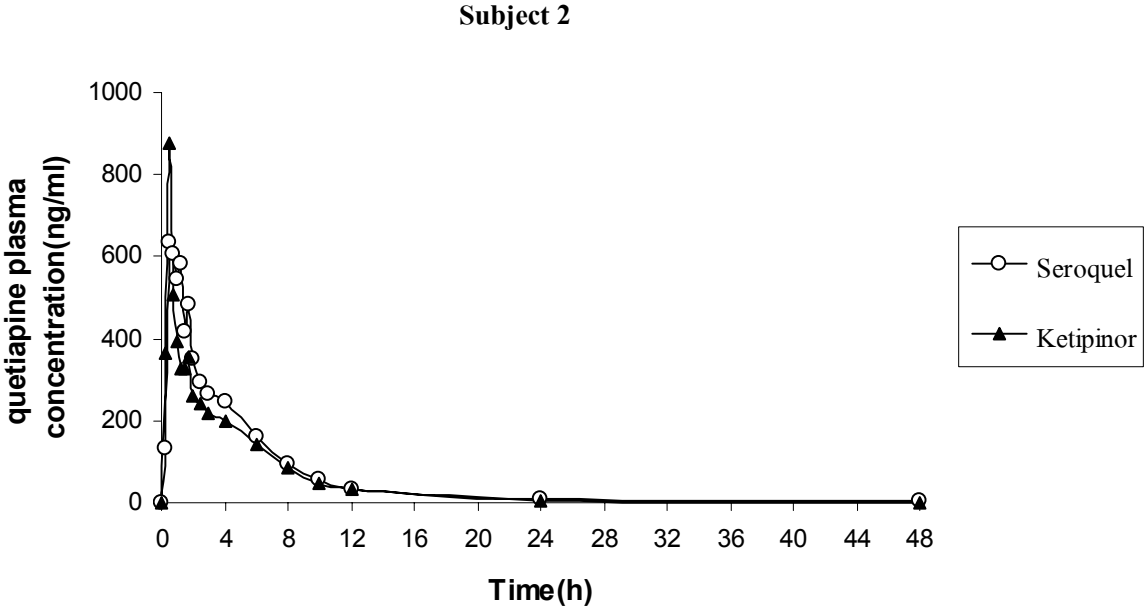


Figure 12. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 2

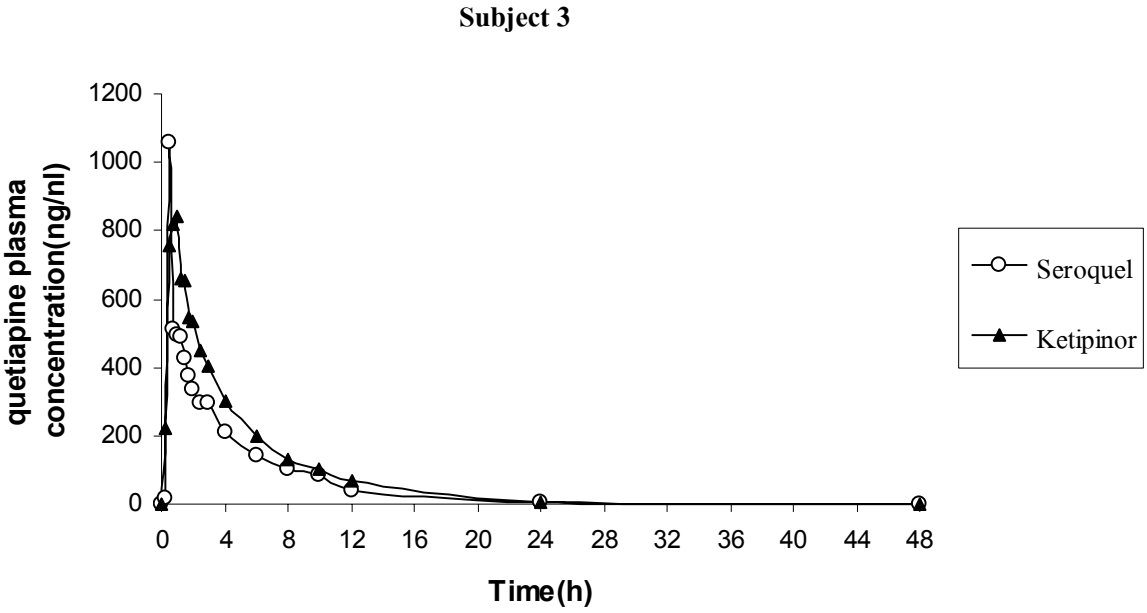


Figure 13. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 3.

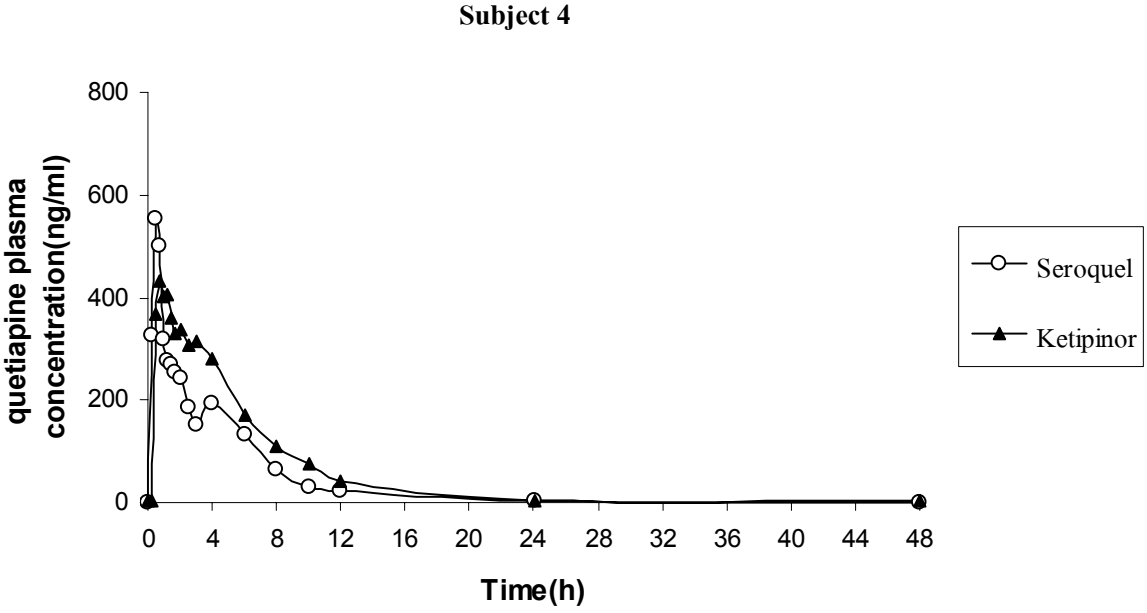


Figure 14. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 4**.**

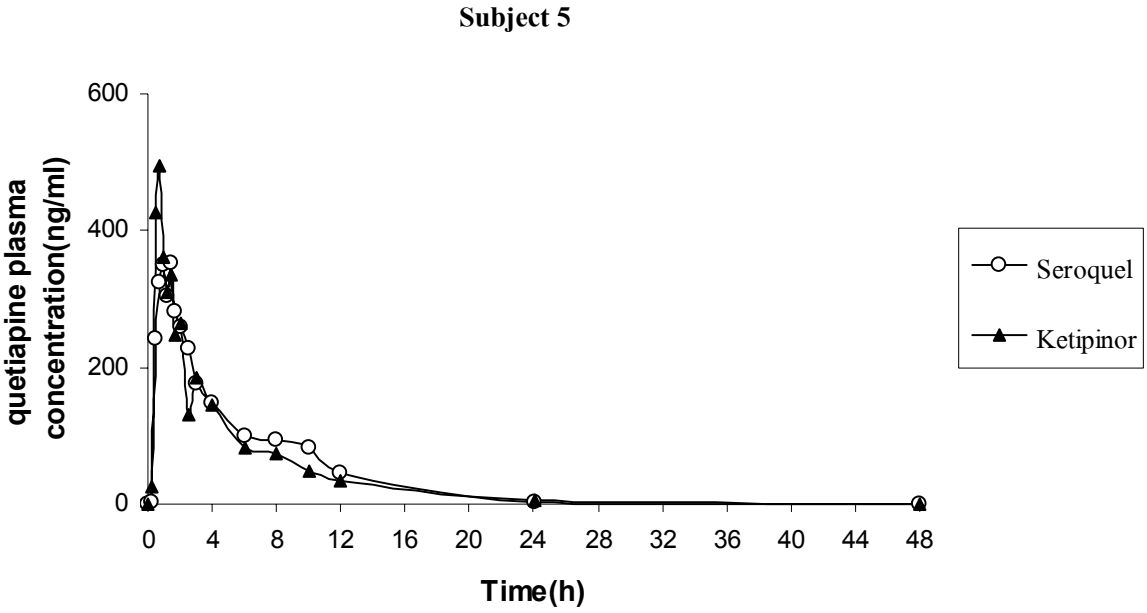


Figure 15. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 5.

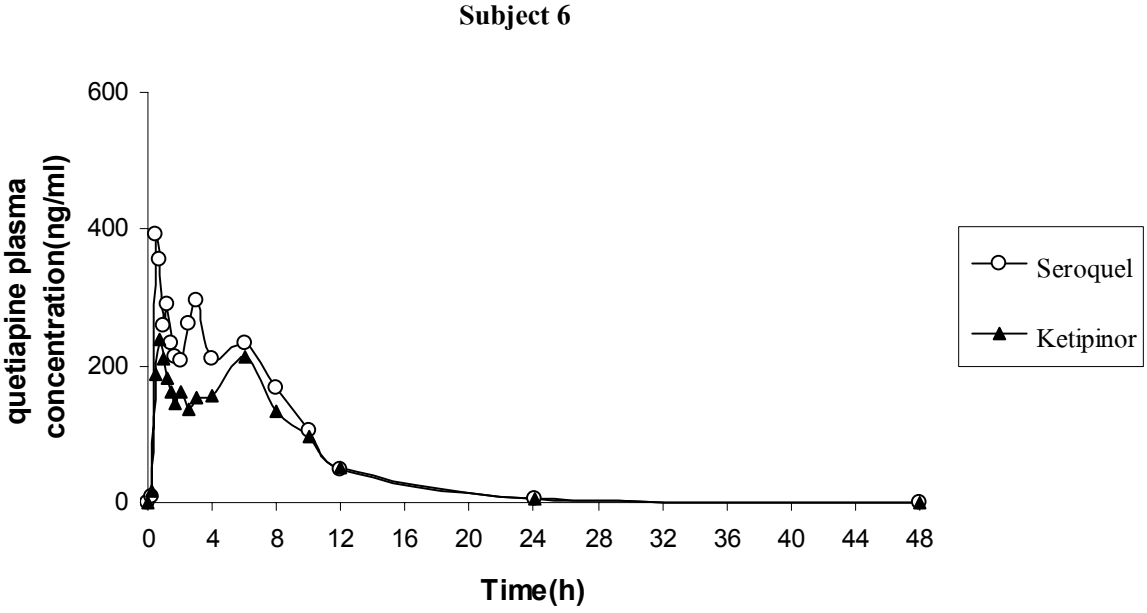


Figure 16. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 6.

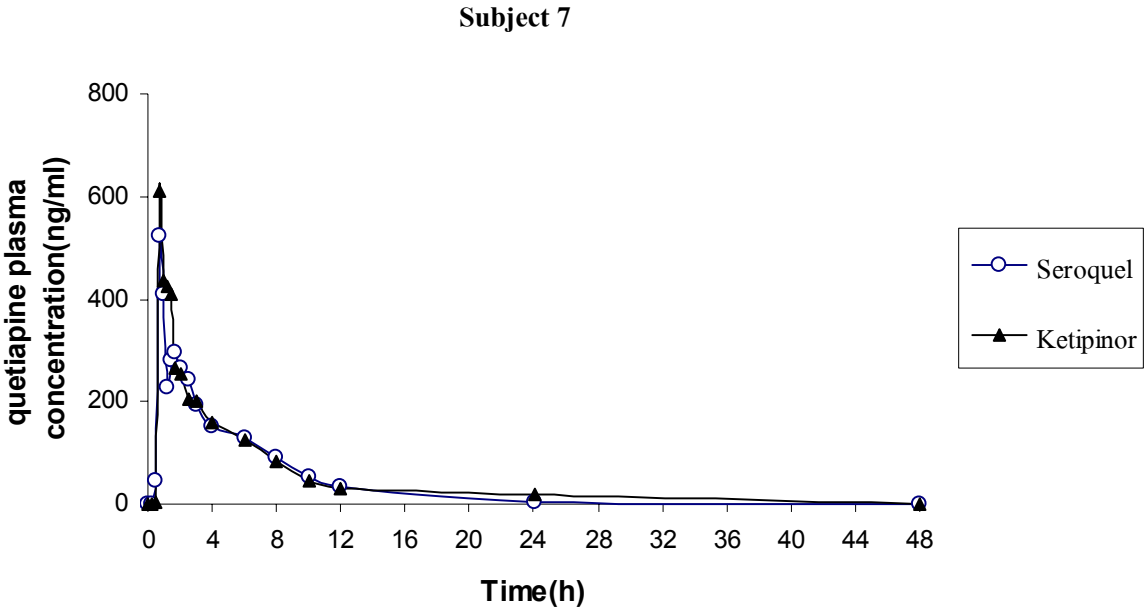


Figure 17. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 7.

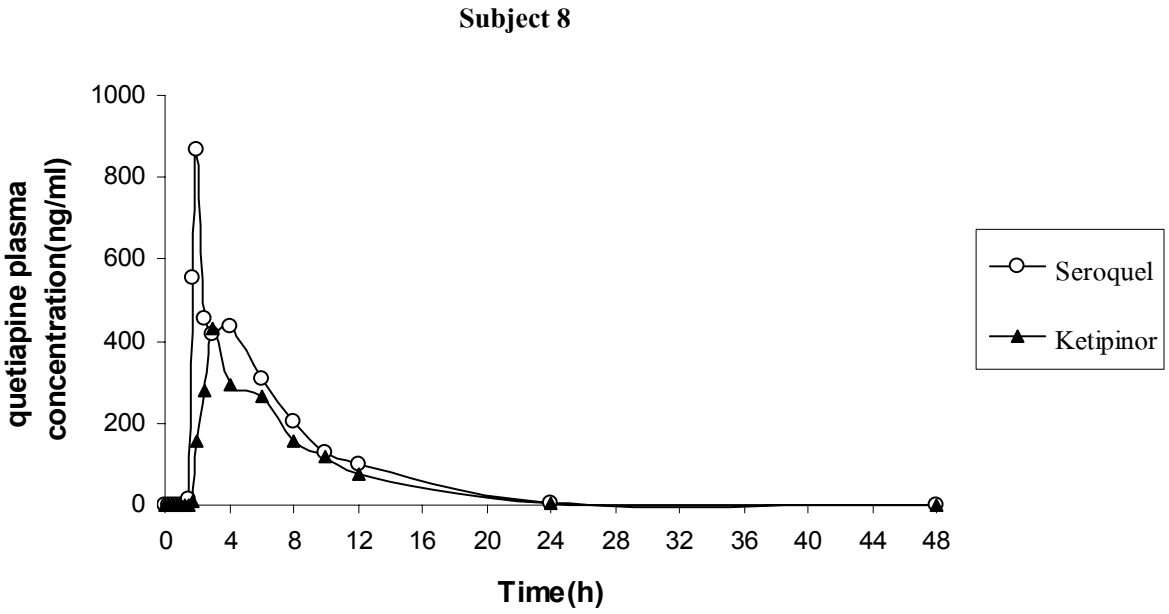


Figure 18. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 8.

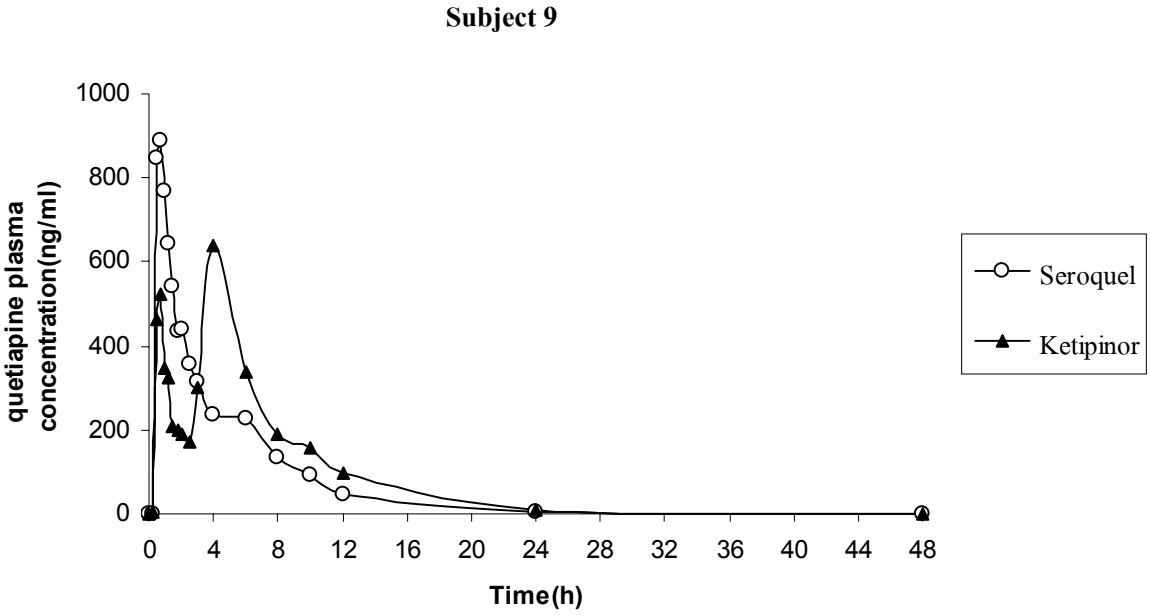


Figure 19. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 9.

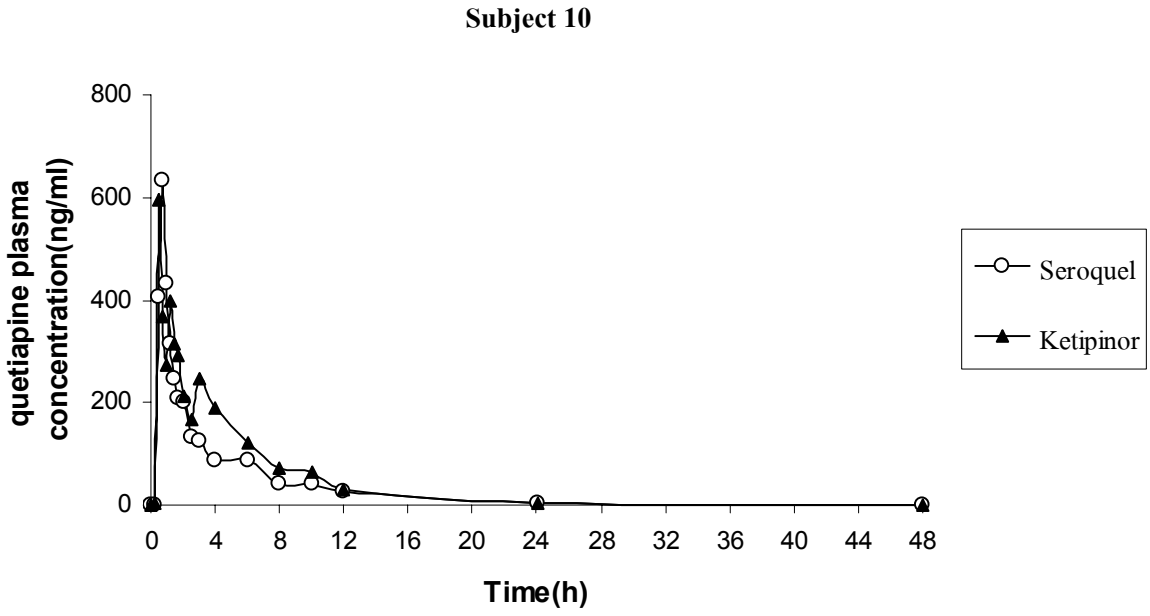


Figure 20. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 10.

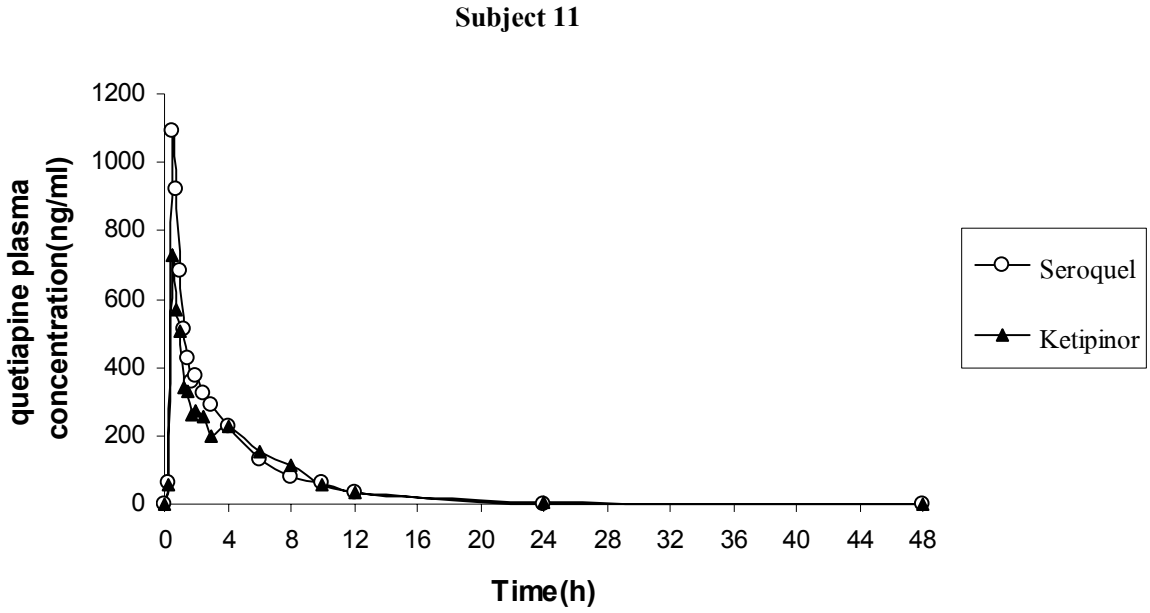


Figure 21. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 11.

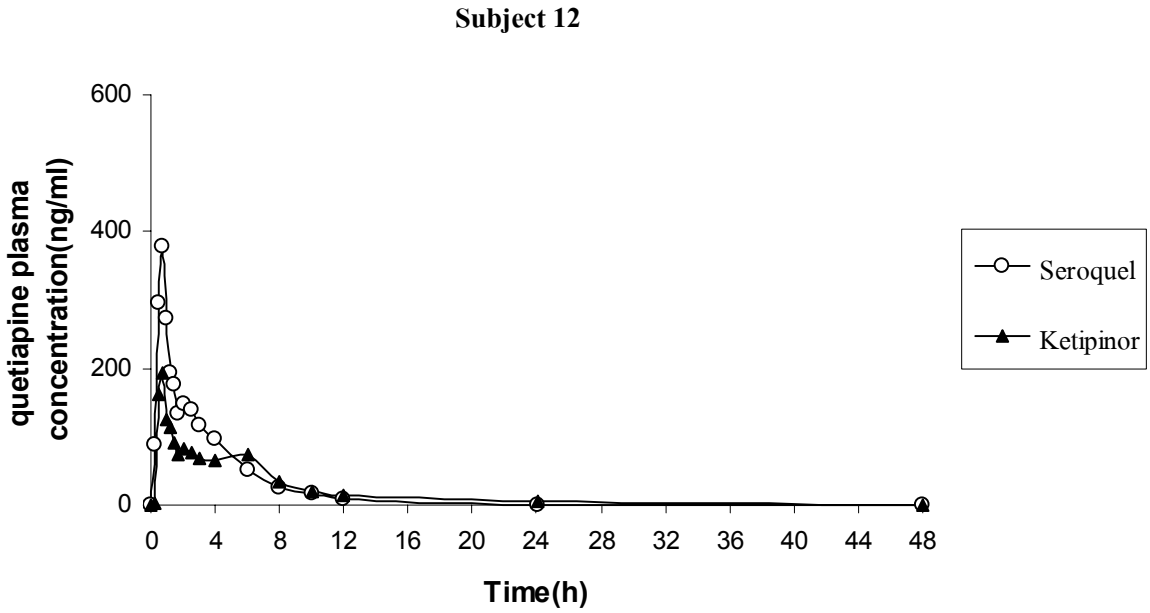


Figure 22. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 12.

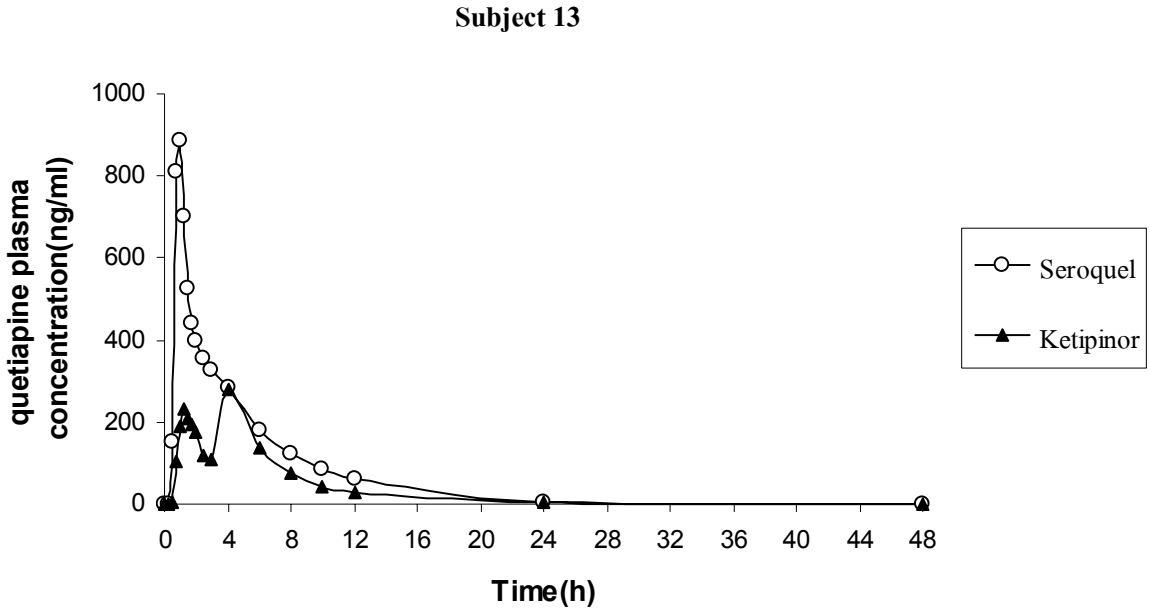


Figure 23. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 13.

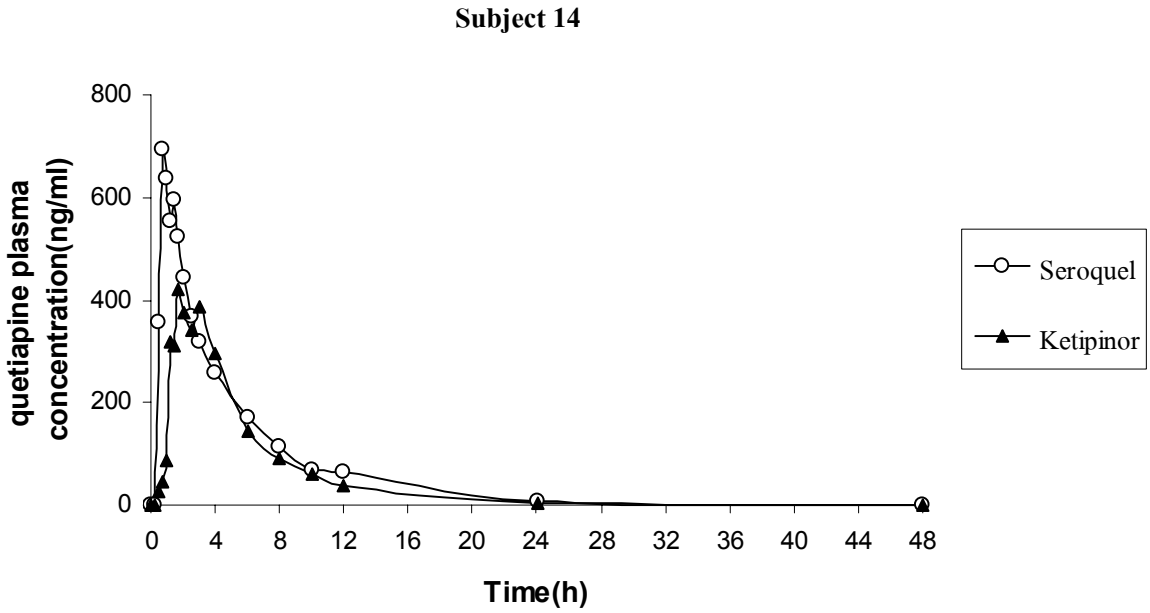


Figure 24. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 14.

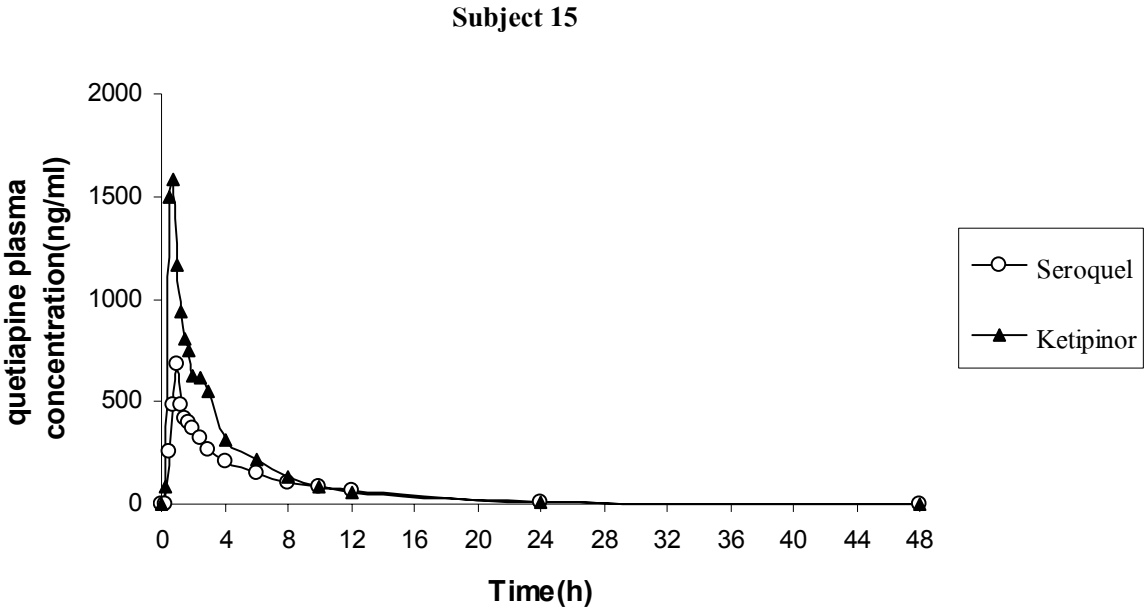


Figure 25. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 15.

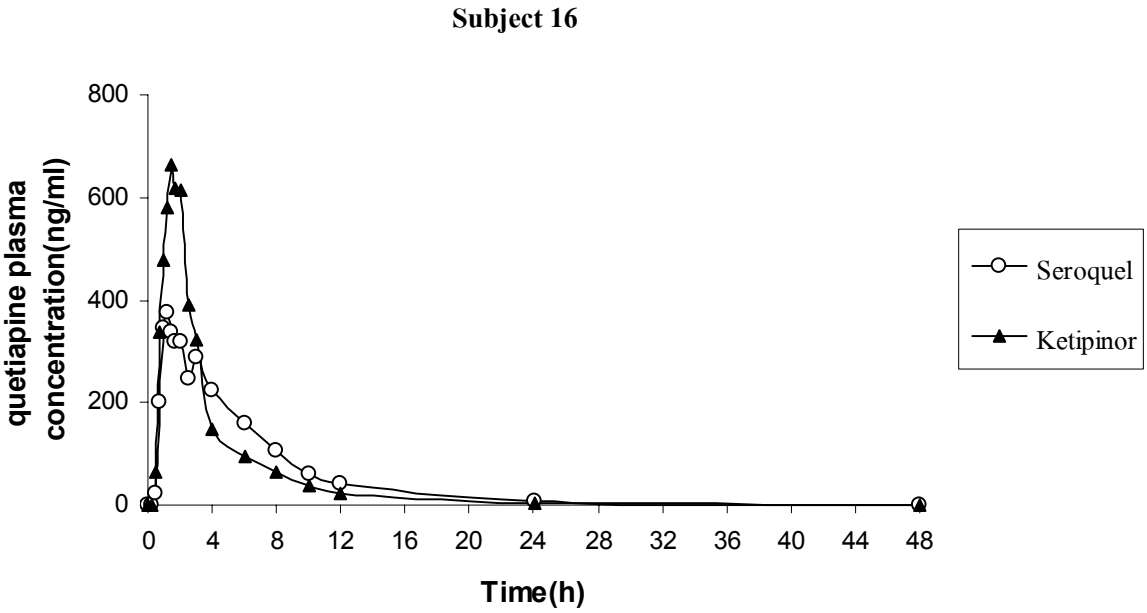


Figure 26. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 16.

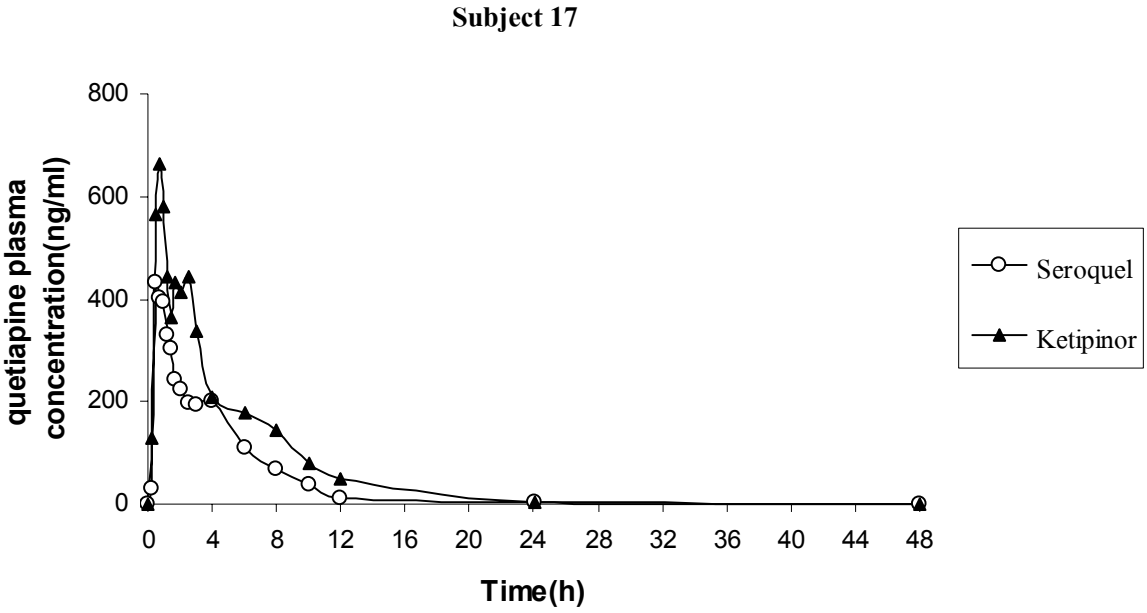


Figure 27. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 17.

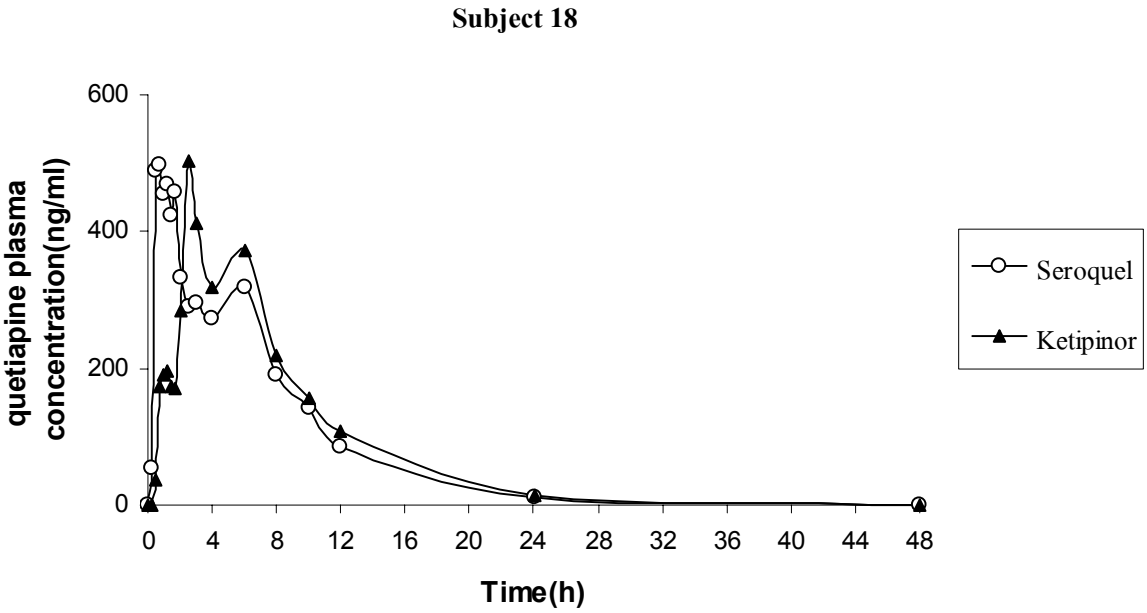


Figure 28. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 18.

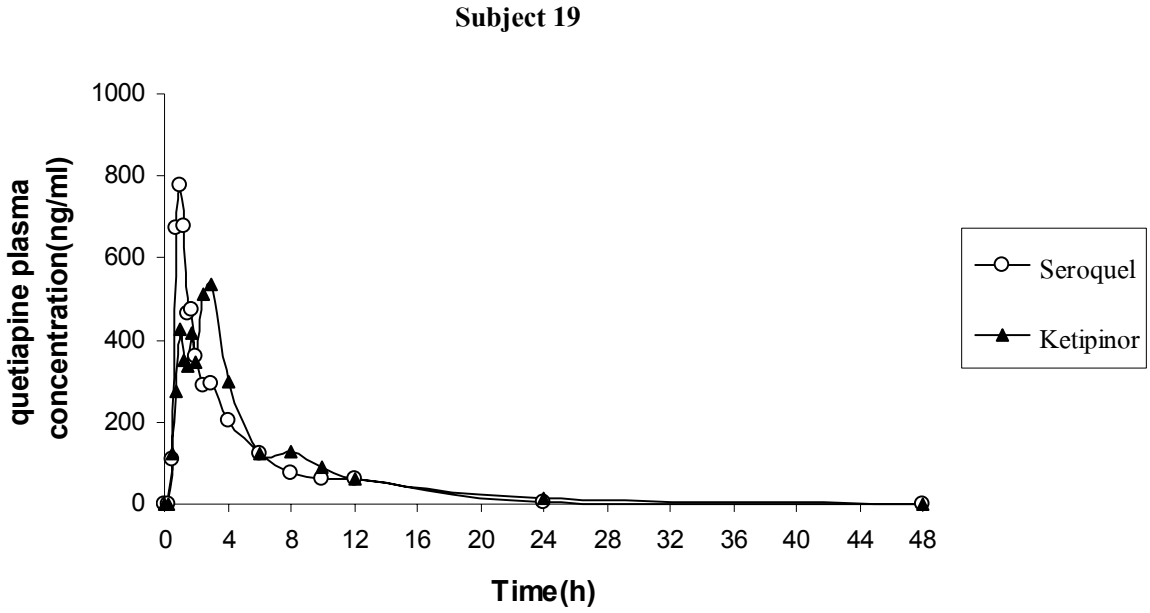


Figure 29. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 19.

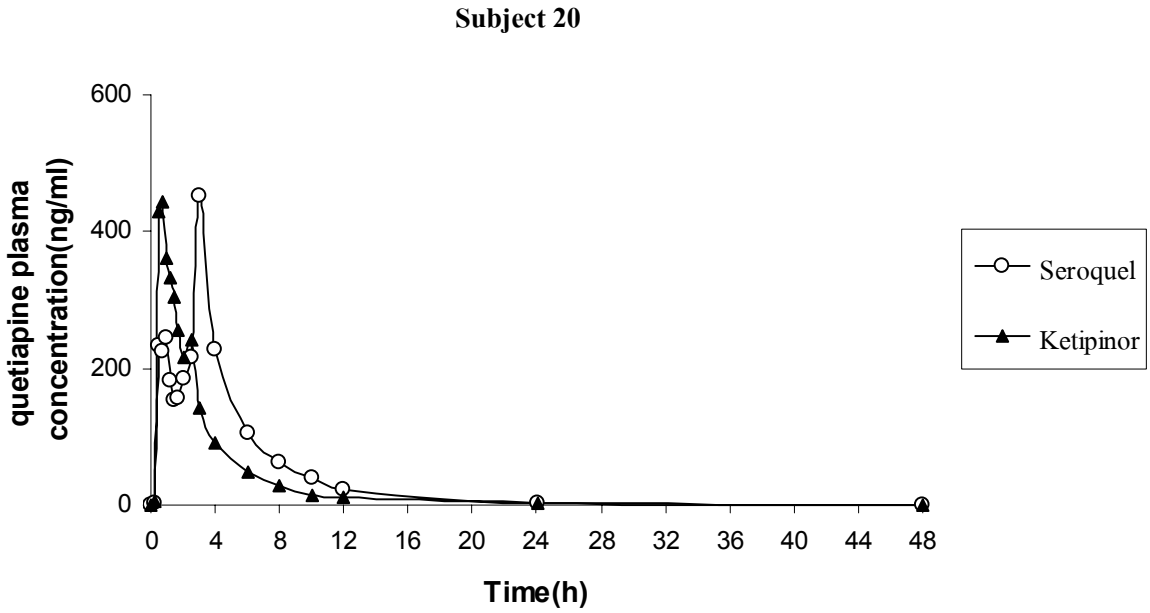


Figure 30. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 20.

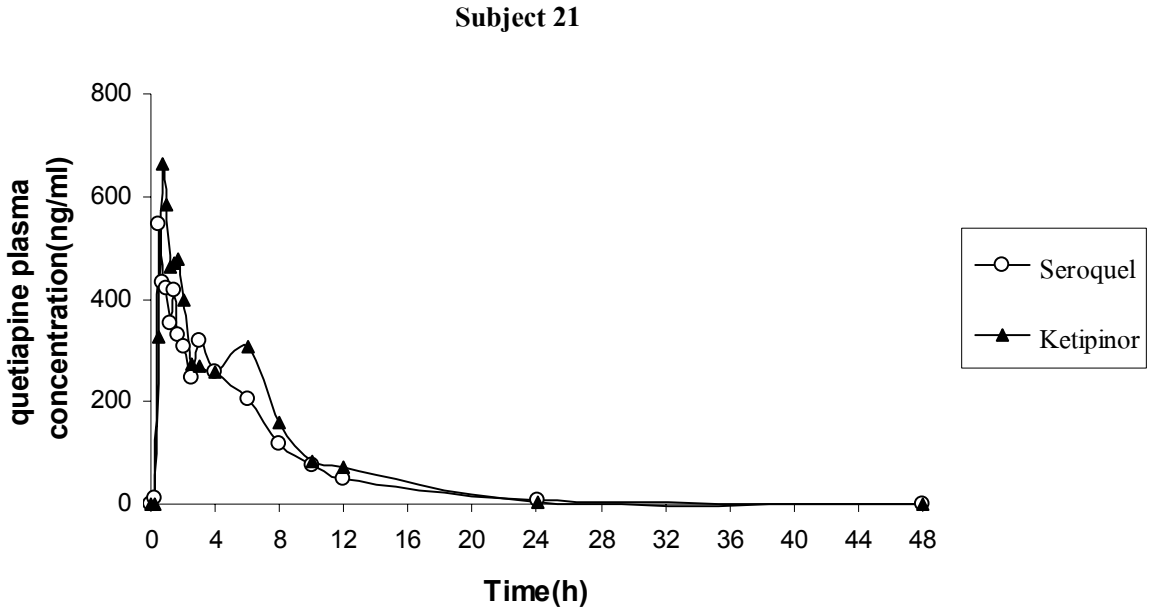


Figure 31. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 21.

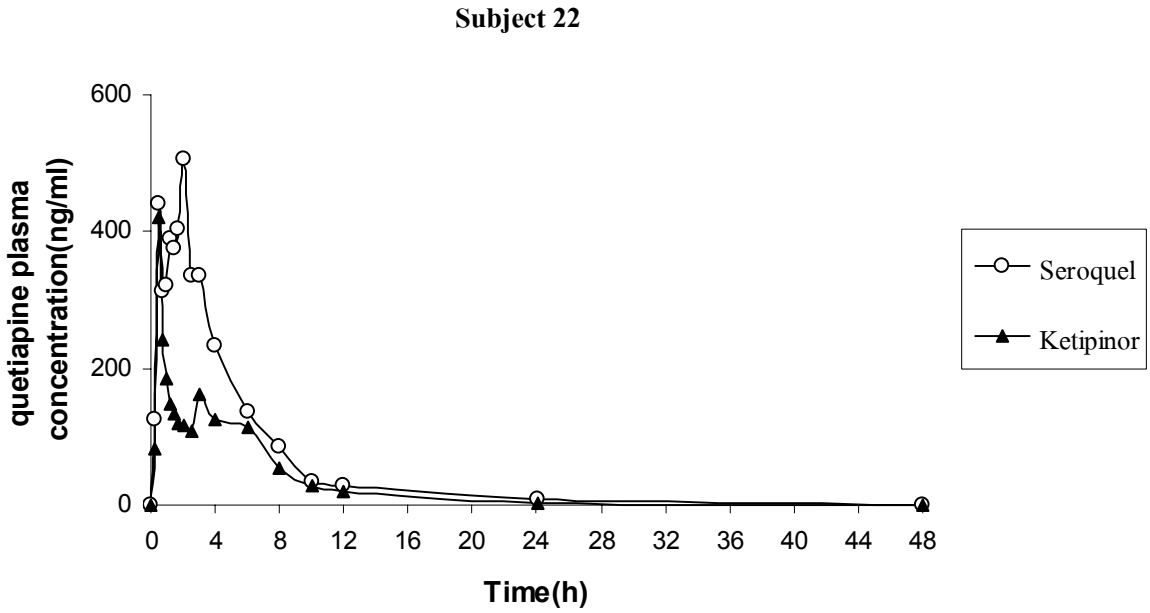


Figure 32. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 22.

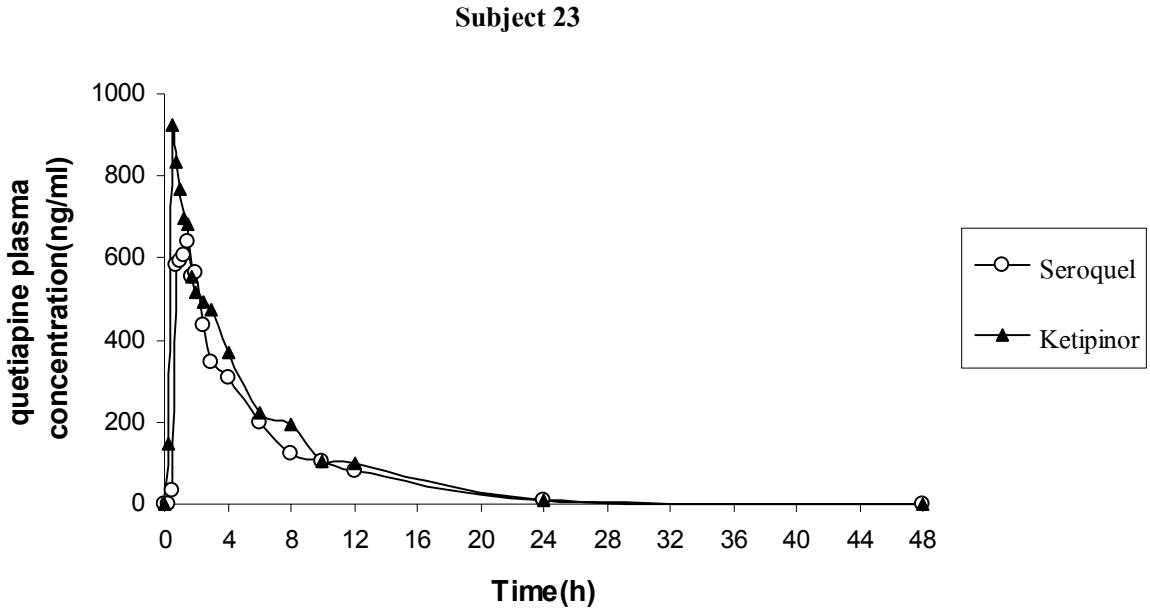


Figure 33. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 23.

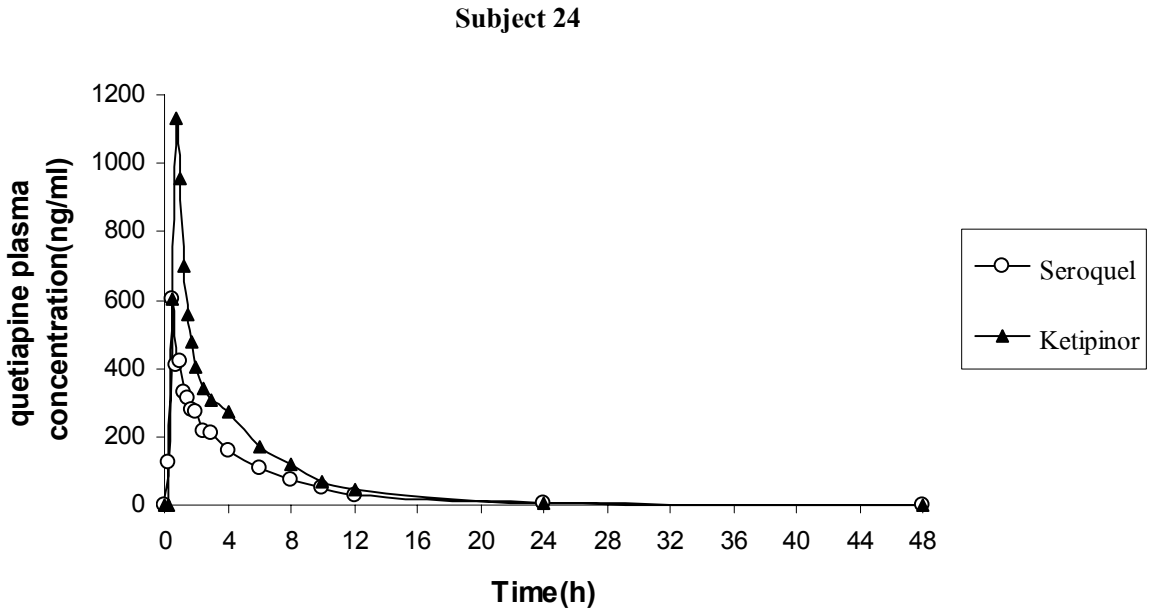


Figure 34. Plasma concentration-time profiles after a single oral administration of 200-mg Seroquel® and Ketipinor® in subject No. 24.

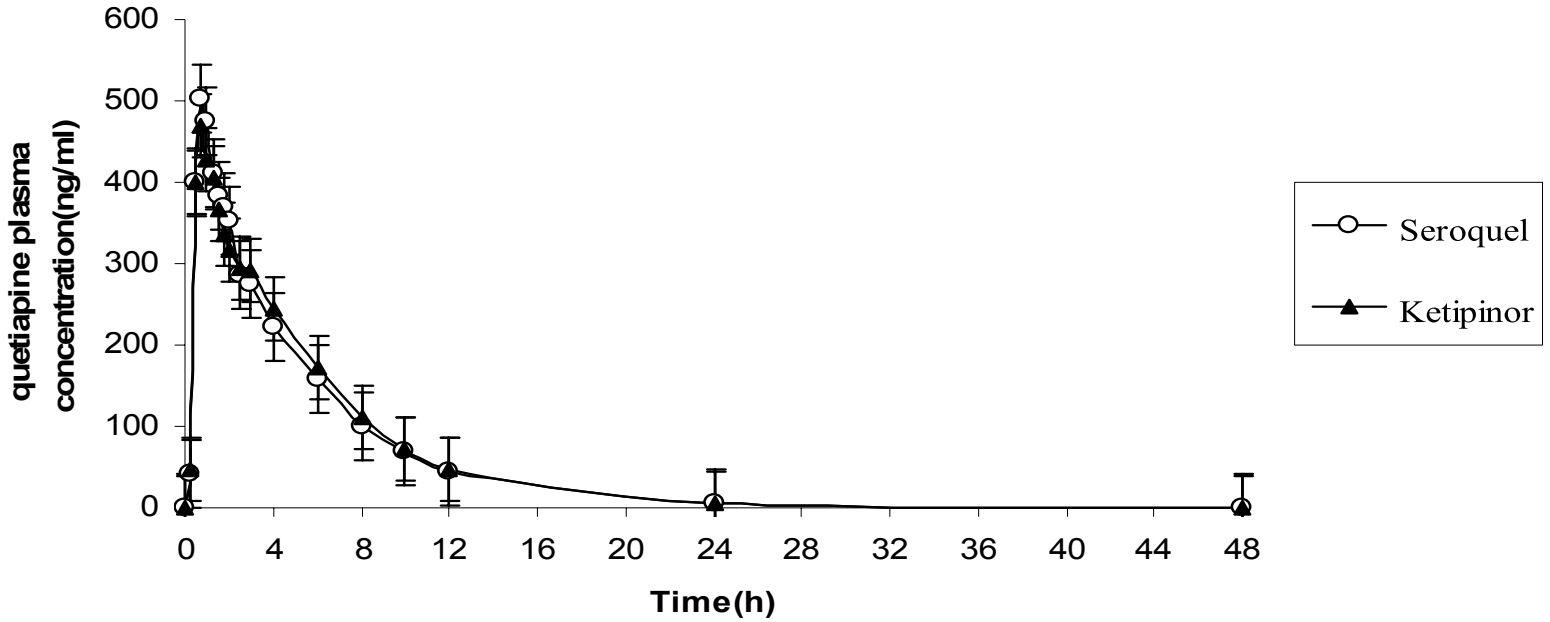


Figure 35. The average plasma concentration-time curve of Seroquel® and Ketipinor® after a single oral administration of 200-mg in the 24 subjects

Table 21. The plasma concentration-time profile of quetiapine after a single oral dose of 200 mg of Seroquel® to 24 subjects.

Subject No.	P1	P2	Plasma concentration of quetiapine (ng/mL)																	
			T_1 0	T_2 0.25 h	T_3 0.5 h	T_4 0.75 h	T_5 1 h	T_6 1.25 h	T_7 1.5 h	T_8 1.75 h	T_9 2 h	T_{10} 2.5 h	T_{11} 3 h	T_{12} 4 h	T_{13} 6 h	T_{14} 8 h	T_{15} 10 h	T_{16} 12 h	T_{17} 24 h	T_{18} 48 h
1		/	0	1.67	392.6	696.2	682.9	563.3	868.4	676.2	471.3	430.5	325.7	275.9	131.6	80.74	59.13	37.52	5.871	<LLOQ
2	/		0	134.7	632.9	605.9	544.8	583	415.4	482.8	351.3	291.6	265.1	244.1	161.1	95.41	58.93	33.45	8.227	2.775
3	/		0	19.77	1060	511.9	496.9	487.6	427.2	374.4	337.4	298.5	293.9	211.2	142	101.8	86.94	41.46	3.831	<LLOQ
4		/	0	324.60	554.5	500.5	318.4	277.3	270.3	254.8	243.7	185.1	150.9	194.4	133.6	64.4	29.06	22.26	2.059	<LLOQ
5	/		0	2.008	240.40	323.8	350.3	303.4	351.6	282.9	257.4	226.9	176.4	148.6	98.54	94.9	82.29	44.15	3.349	1.135
6	/		0	7.455	393.3	354.5	257.6	291.4	232.7	214.4	207.5	262.4	296	211.7	233.4	167.2	105.5	47.87	4.493	<LLOQ
7		/	0	<LLOQ	46.24	523.6	409.3	228.9	281	296	266.4	243	194	151.4	128.6	90.08	51.39	33.59	3.668	<LLOQ
8	/		0	<LLOQ	<LLOQ	<LLOQ	0.729	0.758	14.85	554.6	868.3	455	418.2	435.5	307.5	203.3	129.6	99.85	4.427	<LLOQ
9	/		0	1.685	848.1	887.3	769.9	643.3	540.7	435.8	441.5	358.3	316.7	238.3	225	132.7	92.19	44.43	3.552	<LLOQ
10		/	0	<LLOQ	406.3	631.5	432.6	315.2	247.6	208.6	201.4	133.2	125	87.46	86.6	40.28	41.22	25.3	2.678	0.953
11		/	0	65.06	1090	924	680.3	510.4	424	358.7	376.3	327	287.4	225.9	130.9	78.15	62.91	33.47	1.409	<LLOQ
12	/		0	89.51	295.6	379.6	273.1	194.5	175	134.2	147.4	140.6	115.3	95.72	50.51	24.88	17.82	8.489	0.962	<LLOQ
13	/		0	0.928	151.8	808.8	885.6	700.6	524.8	440.1	398.4	354.4	326	286.2	178	122.3	83.49	59.63	5.444	0.976
14		/	0	1.511	355.3	694.5	636.6	553.6	595	522.1	442.5	369.4	317.4	258.4	171.3	113.9	69.07	63.62	6.81	0.963
15	/		0	0.755	253	481.4	683.8	482.4	416.5	400	371.1	325	267.4	205	150	102.3	86.58	65.98	6.944	1.059
16		/	0	0.872	24.11	200.4	343.6	376	336.6	371.2	318.7	248.1	288.1	223.4	157.6	105.7	60.93	41.14	9.106	1.772
17		/	0	30.08	431.8	401.7	393.1	329.3	304.7	240.8	223.9	196	194.1	201.3	110.8	66.85	39.22	13.17	2.484	0.764
18	/		0	53.85	487.8	498.5	455.4	468.6	424	458.1	333.8	289.1	294.4	273.3	319.6	189.6	143.2	86.34	9.974	1.026
19	/		0	<LLOQ	107.7	674.3	776.8	678.7	464.7	475.3	358	287.7	293.1	205.9	125	78.16	63.87	61.64	5.331	0.907
20		/	0	2.435	233.2	224	243.7	181.9	153.9	156.9	185.2	215.8	451.2	228.6	105.8	63.21	38.64	22.97	3.684	<LLOQ
21		/	0	12.86	544.4	433.2	420.5	351.2	415.6	331.6	306.4	247.3	317.7	259.3	204	117.2	77.2	50.48	5.973	1.069
22		/	0	125.9	441.9	313.2	320.8	388.7	375.3	404.8	505.6	334.7	334.8	233.9	137.6	85.5	34.92	27.02	7.362	<LLOQ
23	/		0	<LLOQ	31.64	581.5	590.3	608.7	637.9	554.1	562.6	436.2	345.6	306.1	200.5	123	102.9	81.98	7.424	1.058
24		/	0	123.4	605	409.9	418.8	331.9	311.6	280.7	272.1	215.6	210.3	160.7	108.3	74.98	50	25.97	5.773	0.831
Mean			0	41.63	401.15	502.51	474.41	410.44	383.72	371.21	352.01	286.31	275.20	223.43	158.24	100.69	69.46	44.66	5.03	0.64
S.D.			0	75.09	299.35	219.45	207.18	176.66	176.37	136.99	152.64	87.51	84.20	71.04	64.43	42.25	31.09	23.13	2.40	0.71

P1 : Phase 1 ; P2 : Phase 2; LLOQ = 0.7 ng/mL

Table 22. The plasma concentration-time profile of quetiapine after a single oral dose of 200 mg of Ketipinor® to 24 subjects.

Subject No.	P1	P2	Plasma concentration of quetiapine (ng/mL)																	
			T_1 0	T_2 0.25 h	T_3 0.5 h	T_4 0.75 h	T_5 1 h	T_6 1.25 h	T_7 1.5 h	T_8 1.75 h	T_9 2 h	T_{10} 2.5 h	T_{11} 3 h	T_{12} 4 h	T_{13} 6 h	T_{14} 8 h	T_{15} 10 h	T_{16} 12 h	T_{17} 24 h	T_{18} 48 h
1	/		0	<LLOQ	<LLOQ	4.681	385.3	856.9	605.2	470.4	383.5	273.7	260.8	245.5	141.2	93.41	50.36	37.83	4.838	0.72
2		/	0	365	875.4	507.1	393	325.6	325.6	353.6	260.6	240.4	217.2	197.9	142.9	85.3	47.97	33.2	2.864	<LLOQ
3		/	0	221.2	757.3	818.9	840.1	658	652	544.3	532.7	448.6	406	303.6	201.6	133.6	101.4	68.85	5.701	<LLOQ
4	/		5.584	2.648	367.1	432.7	400.3	406.7	360.5	330.7	337.9	307.3	316.1	279.9	171.1	109.5	75.03	40.71	5.569	1.902
5		/	0	25.9	425.3	494.3	362.1	308.8	334.3	248.1	265.4	131.5	185.5	144.3	82.67	74.62	47.58	34.63	5.023	0.73
6		/	0	15.73	187.3	238.6	211	182	162.3	145.2	163.3	135.8	153.7	155.3	213.6	132.3	96.49	51.55	4.479	0.711
7	/		0	0.781	2.26	610.9	434.2	425.5	410.4	265.1	255.1	205.7	201.2	160.5	126.6	83.32	45.36	28.71	19.62	0.785
8		/	0	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	10.26	158.1	277.7	431.6	292.6	263.1	154.5	119.5	76.33	6.942	0.815
9		/	0	5.599	461.6	521.2	347.7	324.6	210.5	200.3	188.3	172.5	302.9	641.2	337.4	190.8	157.1	98.74	8.893	<LLOQ
10	/		0	4.495	595.4	367.5	272.7	397.4	312.9	290.7	213.5	168	246.9	191	120.7	72.91	65.5	31.21	2.597	<LLOQ
11	/		0	57.65	726.2	571.3	503.8	341.9	327.8	264.1	271.3	258.4	197.4	230.2	151.1	112.8	58.92	35.53	5.361	0.901
12		/	0	1.522	160.8	192.1	124.2	113.3	91.66	72.77	82.95	75.82	68.94	65.4	73.36	35.44	19.5	14.28	6.636	0.80
13		/	0	<LLOQ	2.823	106.2	190	233.3	206.3	192.9	177.7	118.9	107.8	278.3	137.9	75.03	44.39	30.41	3.926	0.867
14	/		0	1.207	24.69	45.73	87.87	320	310.5	422.4	377.2	341.9	386.1	294.6	143.6	90.9	59.78	37.21	3.615	0.745
15		/	0	83.92	1498	1585	1165	933.7	804.9	751.5	628.8	617.3	545.2	311.7	216.2	137	85.59	54.16	6.196	0.935
16	/		0	1.602	65.21	338.2	476.9	580.9	662.8	618.1	614.2	390.1	320.4	149.6	95.93	66	36.71	23.54	5.339	<LLOQ
17	/		0	129.3	563.1	664	580.5	444.9	362.2	431.8	415	445.1	337.2	207.6	176.8	144.8	78.41	47.78	4.958	<LLOQ
18		/	0	<LLOQ	35.61	172.7	190.2	196.6	173.2	170.7	285.7	504.6	412.9	318.2	372.8	218.7	155.9	107.6	15.63	<LLOQ
19		/	0	0.957	120.9	273.7	424.8	350.3	337.5	416.2	345.6	512.3	535.3	299.3	125	127.3	90.94	63.31	13.5	1.086
20	/		0.739	6.653	428.9	444.9	362.5	333.9	304.4	256.1	215.1	243.1	143.2	92.07	48.34	29.35	14.02	10.07	1.758	<LLOQ
21	/		0	0.853	324.6	663.9	584.8	461.3	472	479.1	397.1	274.6	268.9	258.1	306.4	161	85.09	72.63	5.657	0.979
22	/		0	82.32	422.1	242.8	186	149.1	133.4	118.7	116.5	109.3	162.3	125.1	113.2	53.7	29.73	21.01	2.709	<LLOQ
23		/	0	144.7	922.5	834.7	767.9	697.6	684.3	554.3	515.5	491.2	472.9	367.9	224.4	195	105.5	99.24	8.471	1.565
24	/		0	1.939	601	1133	955.5	699.4	555.1	479	405.7	338.4	304.4	272.9	171.7	116.7	69.85	43.81	6.339	0.9320
Mean			0.26	48.08	398.67	469.34	426.93	405.90	366.66	336.93	316.95	295.09	291.04	245.12	173.23	112.25	72.53	48.43	6.53	0.60
S.D.			1.14	89.08	376.39	369.28	280.98	231.70	206.03	183.83	150.12	148.30	131.07	115.62	82.01	49.50	37.60	26.85	4.23	0.54

P1 : Phase 1 ; P2 : Phase 2; LLOQ = 0.7 ng/mL

Table 23. Quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200-mg of Seroquel®.

Subject No.	C_{max} (ng/mL)	AUC_{0-48} (ng.h/mL)	$AUC_{0-\alpha}$ (ng.h/mL)	AUC extrapolated (%)	T_{max} (hr)	$T_{1/2}$ (hr)	Vd/F (L)	CL/F (L/hr)	K_e (h^{-1})
1	868.43	2861.14	2897.14	1.24	1.50	4.25	0.42	0.07	0.16
2	632.91	2738.75	2764.23	0.92	0.50	6.36	0.66	0.07	0.11
3	1060.34	2632.1	2650.97	0.71	0.50	3.42	0.370	0.08	0.20
4	554.54	1836.02	1846.72	0.58	0.50	3.60	0.56	0.11	0.19
5	351.58	1963.21	1971.87	0.44	1.50	5.29	0.77	0.10	0.13
6	393.3	2619.09	2621.57	0.10	0.50	4.64	0.51	0.08	0.15
7	523.55	1837.56	1857.16	1.06	0.75	3.70	0.58	0.11	0.19
8	868.32	3668.95	3687.59	0.51	2.00	2.92	0.23	0.05	0.24
9	887.34	3203.52	3218.99	0.48	0.75	3.02	0.27	0.06	0.23
10	631.48	1500.43	1508.78	0.55	0.75	6.07	1.16	0.13	0.11
11	1089.57	2658.70	2663.95	0.20	0.50	2.58	0.28	0.08	0.27
12	379.57	992.64	997.39	0.48	0.75	3.42	0.99	0.20	0.20
13	885.57	3173.09	3180.13	0.22	1.00	5.01	0.45	0.06	0.14
14	694.46	3103.81	3111.21	0.24	0.75	5.33	0.49	0.06	0.13
15	683.78	2766.5	2774.98	0.31	1.00	5.55	0.58	0.07	0.13
16	376.02	2316.01	2335.52	0.84	1.25	7.63	0.94	0.09	0.09
17	431.85	1742.22	1747.47	0.30	0.50	4.76	0.79	0.11	0.15
18	498.45	3713.2	3720.78	0.20	0.75	5.12	0.40	0.05	0.14
19	776.81	2673.57	2680.94	0.27	1.00	5.63	0.61	0.07	0.12
20	451.17	1755.85	1778.51	1.27	3.00	4.27	0.69	0.11	0.16
21	544.4	2763.70	2771.59	0.28	0.50	5.12	0.53	0.07	0.14
22	505.62	2301.01	2367.81	2.82	2.00	6.29	0.77	0.08	0.11
23	637.89	3471.6	3479.47	0.23	1.50	5.16	0.43	0.06	0.13
24	605.01	1991.04	1999.92	0.44	0.50	7.41	1.07	0.10	0.09
Mean	**638.83**	**2511.82**	**2526.45**	**0.61**	**1.01**	**4.86**	**0.60**	**0.09**	**0.16**
S.D.	**214.49**	**704.21**	**704.37**	**0.58**	**0.63**	**1.35**	**0.25**	**0.03**	**0.05**

Table 24. Quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200-mg of Ketipinor®.

Subject No.	C_{max} (ng/mL)	AUC_{0-48} (ng.h/mL)	$AUC_{0-\alpha}$ (ng.h/mL)	AUC extrapolated (%)	T_{max} (hr)	$T_{1/2}$ (hr)	Vd/F (L)	CL/F (L/hr)	K_e (h^{-1})
1	856.94	2356.02	2362.49	0.27	1.25	6.22	0.76	0.08	0.11
2	875.39	2265.94	2280.10	0.62	0.50	3.43	0.43	0.09	0.20
3	840.11	3696.45	3724.08	0.74	1.00	3.36	0.26	0.05	0.21
4	432.69	2631.81	2646.80	0.57	0.75	5.47	0.60	0.08	0.13
5	494.32	1821.92	1827.88	0.33	0.75	5.66	0.89	0.11	0.12
6	238.63	2097.62	2103.26	0.27	0.75	5.50	0.75	0.10	0.13
7	610.9	2201.53	2207.99	0.29	0.75	5.70	0.75	0.09	0.12
8	431.64	2706.54	2712.34	0.21	3.00	4.93	0.53	0.07	0.14
9	641.20	3978.72	4022.41	1.09	4.00	3.41	0.24	0.05	0.20
10	595.4	1984.84	1987.69	0.14	0.50	4.57	0.66	0.10	0.15
11	726.20	2424.22	2430.96	0.28	0.50	5.19	0.62	0.08	0.13
12	192.13	893.50	903.24	1.08	0.75	8.43	2.69	0.22	0.08
13	278.33	1665.92	1672.78	0.41	4.00	5.49	0.95	0.12	0.13
14	422.38	2270.07	2275.18	0.22	1.75	4.75	0.60	0.09	0.15
15	1585.30	4506.01	4513.05	0.16	0.75	5.22	0.33	0.04	0.13
16	662.83	2170.06	2210.26	1.82	1.50	5.22	0.68	0.09	0.13
17	664.02	2963.26	2964.87	0.05	0.75	4.20	0.41	0.07	0.17
18	504.64	3722.96	3818.17	2.49	2.50	4.22	0.32	0.05	0.16
19	535.34	3103.09	3112.80	0.31	3.00	6.20	0.57	0.06	0.11
20	444.85	1272.01	1275.88	0.30	0.75	7.33	1.66	0.16	0.10
21	663.90	3348.58	3355.58	0.21	0.75	4.95	0.43	0.06	0.14
22	422.13	1297.86	1313.70	1.21	0.50	4.05	0.89	0.15	0.17
23	922.45	4412.69	4424.12	0.26	0.50	5.06	0.33	0.05	0.14
24	1132.80	3213.43	3220.30	0.21	0.75	5.11	0.46	0.06	0.14
Mean	**632.27**	**2625.21**	**2640.25**	**0.56**	**1.34**	**5.15**	**0.70**	**0.09**	**0.14**
S.D.	**304.43**	**972.14**	**979.10**	**0.59**	**1.11**	**1.17**	**0.52**	**0.04**	**0.03**

Table 25. Comparison of quetiapine pharmacokinetic parameters of individual subject after a single oral dose of 200 mg of Ketipinor® and Seroquel®

Subject No.	C_{max}		F_{rel} (T/R)	AUC_{0-48}		F_{rel} (T/R)	$AUC_{0-\alpha}$		F_{rel} (T/R)
	(T)	(R)		(T)	(R)		(T)	(R)	
1	856.94	868.43	0.99	2356.02	2861.14	0.82	2362.49	2897.14	0.82
2	875.39	632.91	1.38	2265.94	2738.75	0.83	2280.10	2764.23	0.82
3	840.11	1060.34	0.79	3696.45	2632.1	1.40	3724.08	2650.97	1.40
4	432.69	554.54	0.78	2631.81	1836.02	1.43	2646.80	1846.72	1.43
5	494.32	351.58	1.41	1821.92	1963.21	0.93	1827.88	1971.87	0.93
6	238.63	393.3	0.61	2097.62	2619.09	0.80	2103.26	2621.57	0.80
7	610.9	523.55	1.17	2201.53	1837.56	1.20	2207.99	1857.16	1.19
8	431.64	868.32	0.50	2706.54	3668.95	0.74	2712.34	3687.59	0.74
9	641.20	887.34	0.72	3978.72	3203.52	1.24	4022.41	3218.99	1.25
10	595.4	631.48	0.94	1984.84	1500.43	1.32	1987.69	1508.78	1.32
11	726.20	1089.57	0.67	2424.22	2658.70	0.91	2430.96	2663.95	0.91
12	192.13	379.57	0.51	893.50	992.64	0.90	903.24	997.39	0.91
13	278.33	885.57	0.31	1665.92	3173.09	0.53	1672.78	3180.13	0.53
14	422.38	694.46	0.61	2270.07	3103.81	0.73	2275.18	3111.21	0.73
15	1585.30	683.78	2.32	4506.01	2766.5	1.63	4513.05	2774.98	1.63
16	662.83	376.02	1.76	2170.06	2316.01	0.94	2210.26	2335.52	0.95
17	664.02	431.85	1.54	2963.26	1742.22	1.70	2964.87	1747.47	1.70
18	504.64	498.45	1.01	3722.96	3713.2	1.00	3818.17	3720.78	1.03
19	535.34	776.81	0.69	3103.09	2673.57	1.16	3112.80	2680.94	1.16
20	444.85	451.17	0.99	1272.01	1755.85	0.72	1275.88	1778.51	0.72
21	663.90	544.4	1.22	3348.58	2763.70	1.21	3355.58	2771.59	1.21
22	422.13	505.62	0.83	1297.86	2301.01	0.56	1313.70	2367.81	0.55
23	922.45	637.89	1.45	4412.69	3471.6	1.27	4424.12	3479.47	1.27
24	1132.80	605.01	1.87	3213.43	1991.04	1.61	3220.30	1999.92	1.61
Mean	**632.27**	**638.83**	**1.04**	**2625.21**	**2511.82**	**1.07**	**2640.25**	**2526.45**	**1.07**
S.D.	**304.43**	**214.49**	**0.49**	**972.14**	**704.21**	**0.34**	**979.10**	**704.37**	**0.34**

T (Test product): Ketipinor®; R (Reference product): Seroquel®

Table 26. Two-way ANOVA studies of natural ln-transformed data of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ of Ketipinor® and Seroquel®.

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
	Sequence	1	0.008	0.008	0.072	0.791
	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_{0-48}	Subject*Sequence	22	4.416	0.201	3.662	0.002
	Sequence	1	0.410	0.410	7.478	0.012
	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			
$AUC_{0-\infty}$	Subject*Sequence	22	4.674	0.212	3.215	0.004
	Sequence	1	0.310	0.310	4.694	0.041
	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 27. Pharmacokinetic parameters (mean ± SD) after a single oral dose of 200-mg of Ketipinor® and Seroquel® in the 24 healthy volunteers.

Pharmacokinetic parameters	**Ketipinor®**	**Seroquel®**
AUC_{0-48} (ng.hr/mL)	2,625.21 ± 972.14	2,511.82 ± 704.21
$AUC_{0-\infty}$(ng.hr/mL)	2,640.25 ± 979.10	2,526.45 ± 704.37
C_{max} (ng/mL)	632.27 ± 304.43	638.83 ± 214.49
T_{max} (hr)	1.34 ± 1.11	1.01 ± 0.63
$T_{1/2}$ (hr)	5.15 ± 1.17	4.86 ± 1.35
CL (L/hr)	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 28. The 90% CIs, geometric mean ± SD, and power of C_{max}, AUC_{0-48}, and $AUC_{0-\infty}$ for Ketipinor® and Seroquel®.

Pharmacokinetic parameters	**Geometric mean± SD**		**90% CI**	**Power of Test (%)**
	Ketipinor®	**Seroquel®**		
C_{max} (ng/mL)	566.79 ± 304.43	601.85 ± 214.49	80.75-102.60	92.16
AUC_{0-48} (ng.h/mL)	2,440.60 ± 972.14	2,416.32 ± 704.21	91.32-108.42	96.34
$AUC_{0-\infty}$ (ng.h/mL)	2,465.13 ± 979.10	2,422.55 ± 704.37	88.47-106.77	95.96

CHAPTER 5

DISCUSSION AND CONCLUSIONS

This study investigated the bioequivalence of two quetiapine formulations, between the test product, i.e. Ketipinor®, and the reference product, i.e. Seroquel®, in 24 healthy Thai male volunteers.

All the validated analytical method of quetiapine used in this study was accurate, precise and rugged. The validation results indicated that this method can be used for pharmacokinetic studies with desired precision and accuracy.

The sampling time in this study lasted for 48 h which was sufficient to cover more than 80% of the AUC, as the mean AUC-extrapolation (%) of Ketipinor® and Seroquel® were 0.56 and 0.61%, respectively which were less than 20%.

In this study, quetiapine was rapidly absorbed after a single oral administration and reached the C_{max} value at 1.34 and 1.01 hr for the test and reference formulations, respectively. The T_{max} was similar to the previous 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; Mahatthanatrakul *et al.,* 2008; Winter *et al.,* 2008). The C_{max} and AUC in a single dose after receiving 25 mg in healthy subjects were 53-79 ng/mL and 248-366 ng.hr/mL, respectively (Thyrum *et al*., 2000) and 45 ng/mL and 181 ng.hr/mL, respectively (Grimm *et al*., 2005). Previous studies in multiple doses of 150, 250 and 300 mg, the C_{max} were 437, 1,048 and 1,042 ng/mL, the AUC was 1,980, 3,642 and 4,650 ng.hr/mL, respectively (Davis *et al*., 1999; Wong *et al.,* 2001; Grimm *et al*., 2005). In this study, the mean ± SD of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ of Ketipinor® were 632.27 ± 304.43 ng/mL, 2,625.21 ± 972.14 ng.hr/mL, and 2,640.25 ± 979.10 ng.hr/mL, respectively. Those of Seroquel® were 638.83 ± 214.49 ng/mL, 2,511.82 ± 704.21 ng.hr/mL, and 2,526.45 ± 704.37 ng.hr/mL, respectively. In the present study, the minimum and maximum concentrations of quetiapine were 192.13 and 1,585.30 ng/mL, respectively and T_{max} was largely varied among individuals between 0.50 - 4 hr. T_{max} was largely varied among individuals, then C_{max} was also highly varied in individual subjects.

$T_{1/2}$ of both formulations were noticeably varied among individuals, i.e. between 2.58 - 8.43 hr. This variation in $T_{1/2}$ is similar to that of Thyrum *et al*. (2000), Li *et al.* (2004), Li *et al.* (2005), Grimm *et al*. (2005) and Winter *et al*. (2008). The longer $T_{1/2}$ and significantly deviates from the common range may result from the low activity of CYP3A4 and the shorter $T_{1/2}$ from the common range indicated high activity of CYP3A4. The CYP450 enzyme system is responsible for the metabolism of drug in human. Li *et al*. (2004) reported the individual variability of metabolism for quetiapine and its metabolites are due to genetic polymorphism of CYP3A4.

Inter-individual variation in pharmacokinetic parameters was always noted when the same dose was administered to different subjects. In this study, the inter-individual variation (%CV) of the observed C_{max} and AUC of quetiapine were similar to the previous report of 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. These results demonstrated that the high variation of pharmacokinetic parameters of individual is mainly due to difference in metabolism. The variability seen in the absorption of orally administered drugs is mainly due to different rates of gastric emptying, which are affected by various factors such as volume of liquid intake, volume of solid food intake and its fat content, physical activity of the subjects, emotion state (Tandom, 2002). Other physical and environmental factors, such as genetics, diseases, age, drugs given concomitantly, body weight, variations in diet and the like, can also contribute to inter- and intrasubject variability. Increased gastric emptying generally enhances bioavailability of orally administered drugs. Hence, to minimize variability, in this study we conducted under controlled conditions, such as activities of the healthy volunteers, body weight and age ranges limit and all subjects were under fasted conditions. Thus, the factors mentioned above were controlled. However, the plasma concentration-time profiles of both test and reference formulations in individual subjects were similar, therefore, it could be implied that the variation of the quetiapine profiles among different subjects mentioned above might be due to the different absorption characteristics of each individual subject. In the study, all subjects were in supine posture after taking the drug for 30 min. Renwick *et al.* (1992) suggested that posture may influence pharmacokinetics mainly through an effect on gastric emptying. Gastric emptying may be enhances when lying on the right side due to the stomach contents pooling over the pylorus, or

possibly due to effects on the skin pressure-vegetative reflex. Thus the effects of a single oral dose of quetiapine were delayed in supine compared with lied on the right side subjects. Generally, the double peak phenomenon is observed after the administration of a single dose to fasted patients. The rationale for the double peak phenomenon has been attributed to variability in drug absorption such as gastric emptying rate, variable gastrointestinal motility, and presence of food, enterohepatic recycling or disintegration failure of tablet dosage form (Shargel *et al*., 2005). There are other factors that may affect the absorption along the gastrointestinal tract, for example diseases, and demographics (age, gender, ethnicity, etc.). All subjects were treated with the same condition so double peak occurred might be due to difference in the enterohepatic circulation or redistribution. Granero and Amidon (2008) also suggested that enterohepatic circulation is a likely explanation for multiple peaks in ketoprofen plasma concentrations. In theory, drug or its metabolites which are excreted into bile which is usually glucoronide conjugated from the liver and excreted to duodenum of the small intestine, where it aids in digestion of drug or its metabolites. Subsequently they may be excreted into the feces or the drug may be reabsorbed to the liver (Godfrey *et al.,* 2010). The drug that undergo enterohepatic circulations shows as a possible for the double peak in the plasma drug-concentration curve following oral administration. Quetiapine is highly lipophilic, therefore it is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. This might be redistributed in the body which were the double peak in the plasma drug-concentration curve.

The results from the ANOVA study showed that formulation and period had no significant effect on C_{max}, AUC_{0-48} or $AUC_{0-\infty}$ at the significant level of 0.05, indicating that the crossover design performed as intended. Although the sequence had significant effect on AUC_{0-48} and $AUC_{0-\infty}$ but the results have shown that all the pharmacokinetic parameters of both products were not significant different. The 90% CI of C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ for Ketipinor®/Seroquel® were 80.75-102.60%, 91.32-108.42% and 88.47-106.77%, respectively. These values were within the acceptable range of the Thai FDA criteria, i.e. 80-125%.

The power of tests obtained from this study for pharmacokinetic parameters C_{max}, AUC_{0-48} and $AUC_{0-\infty}$ were found to be 92.16, 96.34 and 95.96%, respectively which were greater than 80%. This showed 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 enough in this study.

In this study, the most common adverse event of quetiapine was somnolence for both formulations in all the 24 subjects. All subjects were sedated within 1 h after drug administration of both test and reference products which is similar to the report of Thyrum *et al*. (2000) and Grimm *et al.* (2005). Two subjects developed orthostatic hypotension and nasal congestion after administration of both formulations. Myalgia was found in one subject after administration of the reference product. These adverse events were mild to moderate and disappeared within 1 day without intervention. Blocking at histamine (H_1) and adrenergic α_1-receptor complained of sedation and orthostatic hypotension, respectively. All subjects participated in the study throughout both study periods without serious adverse events. No subject withdrew from the study due to intolerance to adverse effects.

In conclusion, the 90% CI of the ratios of C_{max} (80.75-102.60%), AUC_{0-48} (91.32-108.42%) and $AUC_{0-\infty}$ (88.47-106.77%) of the test and reference products were within 80-125%, which was within the acceptable range of bioequivalence in accordance to the Thai FDA guidelines. Therefore, it is concluded that the two quetiapine formulations, Ketipinor® and Seroquel®, used in this study, were bioequivalent in terms of both the rate and extent of absorption.

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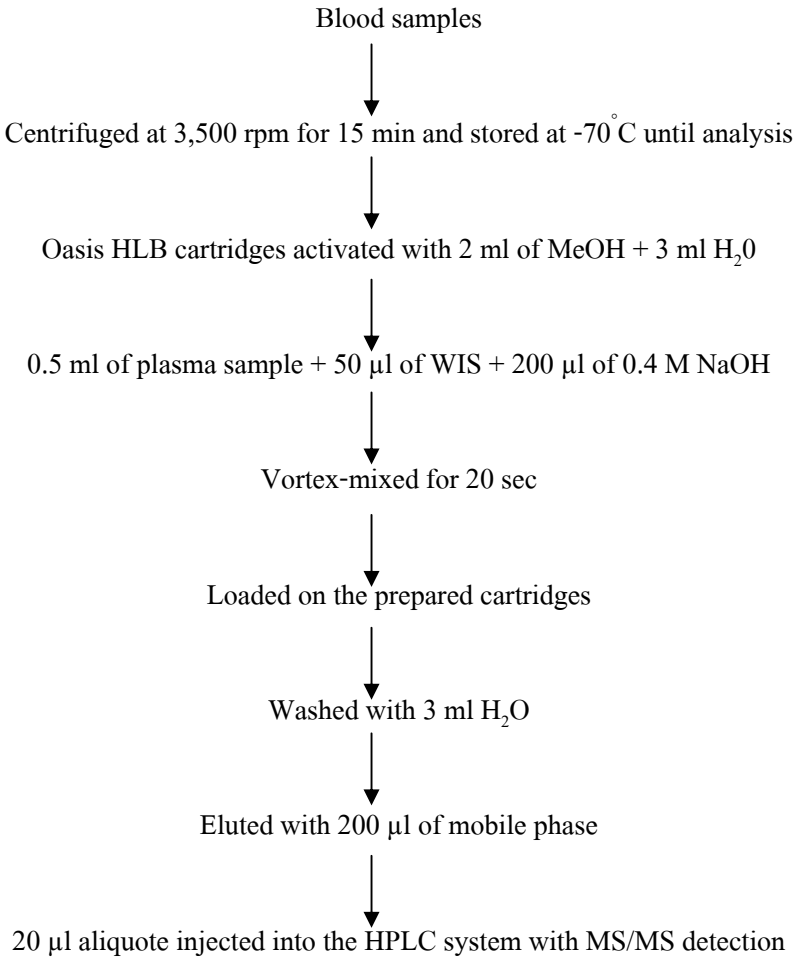
APPENDICES

APPENDIX A

Sample preparation (Barrett *et al.,* 2007)



APPENDIX B

หนังสืออนุมัติจากคณะกรรมการพิจารณาจริยธรรม

วท-จย/51/15-4

ที่ ศธ 0521.1.09/1042

คณะวิทยาศาสตร์
มหาวิทยาลัยสงขลานครินทร์
ตู้ ปณ 3 คอหงส์ 90112

หนังสือรับรองโครงการวิจัย

การศึกษาวิจัยที่ทำการทดลองในมนุษย์เรื่อง : การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบ เทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทย สุขภาพปกติ

หัวหน้าโครงการวิจัย : ผู้ช่วยศาสตราจารย์ นายแพทย์วีรวัฒน์ มหัทธนตระกูล
ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์

ได้ผ่านการพิจารณาและเห็นชอบจาก คณะกรรมการจริยธรรมการวิจัยที่ทดลองในมนุษย์ คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ แล้ว

ให้ไว้ ณ วันที่ 3 พฤศจิกายน 2551

(รองศาสตราจารย์ ดร.วิไลวรรณ โชติเกียรติ)
รองคณบดีฝ่ายวิจัยและบัณฑิตศึกษา ปฏิบัติราชการแทน
คณบดีคณะวิทยาศาสตร์

ที่ สธ 1003.7/ ๓๑๐๙

กองควบคุมยา
สำนักงานคณะกรรมการอาหารและยา
ถนนติวานนท์ จังหวัดนนทบุรี 11000

30 ก.ค. 2552

เรื่อง ผลพิจารณาการแก้ไขโครงร่างการศึกษาชีวสมมูลของผลิตภัณฑ์ยาสามัญ (NG)

เรียน ผศ. นพ. วีรวัฒน์ มหัทธนตระกูล (หัวหน้าภาควิชาเภสัชวิทยา)

อ้างถึง หนังสือ ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ เลขรับที่ 50/51(กข) ลงวันที่ 29 ธันวาคม 2551

ตามหนังสือที่อ้างถึง ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ ได้ยื่นแก้ไขโครงร่างการศึกษาชีวสมมูลของผลิตภัณฑ์ยาสามัญ (NG) ที่มีตัวยาสำคัญ คือ Quetiapine 200 mg / Tablet เสนอให้กองควบคุมยาพิจารณาดังความละเอียดตามที่แจ้งอยู่แล้วนั้น ขอเรียนว่ากองควบคุมยาโดยความเห็นร่วมกับผู้เชี่ยวชาญได้พิจารณาเอกสารโครงร่างการศึกษาชีวสมมูลดังกล่าวแล้ว

ผลการพิจารณา

☑ รับ

☐ ไม่รับ เนื่องจาก

จึงเรียนมาเพื่อทราบ

ขอแสดงความนับถือ

(นางสาวสุกัญญา เจียระพงษ์)
เภสัชกรชำนาญการพิเศษ
รักษาราชการแทน ผู้อำนวยการกองควบคุมยา

กลุ่มยาใหม่
โทร 0-2590-7192, 0-2590-7196
โทรสาร 0-2590-7204

ใบเชิญชวนให้อาสาสมัครเข้าร่วมโครงการวิจัย

เรื่อง

การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบเทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทยสุขภาพปกติ

เรียน ท่านผู้อ่านที่นับถือ

คณะผู้วิจัยขออธิบายและขอเชิญชวนท่านเข้าร่วมโครงการวิจัยดังนี้

เนื่องจากยา quetiapine ซึ่งเป็นยารักษาผู้ป่วยโรคทางจิตเวช โดยเฉพาะโรคจิตเภท นอกจากนี้ยังใช้ในการรักษาผู้ป่วยโรคจิตเภท-อารมณ์แปรปรวน เนื่องจากยาชนิดนี้มีโอกาสก่อให้เกิดผลข้างเคียงน้อยกว่ายารักษาโรคจิตเวชที่เคยใช้กันอยู่ ดังนั้นยาชนิดนี้จึงเป็นยาที่ได้รับความสนใจและถูกนำมาใช้ในการรักษาเพิ่มมากขึ้นเรื่อยๆ แต่เนื่องจากราคายาต้นแบบ คือยา Seroquel® มีราคาค่อนข้างสูง ดังนั้นหากมีการพัฒนาและผลิตยาชนิดนี้ขึ้นในประเทศก็น่าจะช่วยทำให้ราคายานี้ถูกลง ซึ่งเป็นการแบ่งเบาภาระค่าใช้จ่ายในการรักษาของผู้ป่วย และ เป็นการสงวนเงินตราไว้ในประเทศซึ่งจะช่วยลดการขาดดุลทางการค้าของประเทศได้ส่วนหนึ่งอีกด้วย

อย่างไรก็ตามแพทย์ผู้ใช้ยาอาจไม่แน่ใจถึงคุณภาพและประสิทธิภาพในการรักษาของยาสามัญที่ผลิตในประเทศรวมทั้งยาที่ผลิตจากต่างประเทศเมื่อเทียบกับยาต้นแบบที่ผลิตจากต่างประเทศ เนื่องจากไม่มีข้อมูลชีวสมมูล ของยาเหล่านี้ กองควบคุมยา สำนักงานคณะกรรมการอาหารและยา กระทรวงสาธารณสุขได้ตระหนักถึงปัญหาดังกล่าวจึงได้จัดระบบการขึ้นทะเบียนตำรับยาสามัญให้มีประสิทธิภาพยิ่งขึ้นโดยได้เพิ่มมาตรการให้มีการศึกษาชีวสมมูลของยาขึ้นโดยบริษัทผู้ผลิตยาสามัญต้องผลิตยาที่เมื่อทำการทดสอบในมนุษย์แล้วต้องมีค่าชีวประสิทธิผลไม่แตกต่างอย่างมีนัยสำคัญไปจากผลิตภัณฑ์ยาต้นแบบ เพื่อเป็นการแสดงให้เห็นว่ายาสามัญที่ผลิตขึ้นนี้ให้ผลในการรักษาเท่าเทียมกับยาต้นแบบจริงและมีความเหมาะสมที่จะอนุญาตให้จัดจำหน่ายได้ อย่างไรก็ดี เนื่องจากยังไม่เคยมีการศึกษาถึงชีวสมมูลของยา quetiapine ที่ผลิตในประเทศ คณะผู้วิจัยจึงสนใจที่จะทำการศึกษาเพื่อพัฒนาอุตสาหกรรมยาในประเทศไทย

ในการวิจัยนี้อาสาสมัครทุกคนจะได้รับการตรวจสุขภาพโดยแพทย์ และส่งตรวจตัวอย่างเลือดเพื่อประเมินสุขภาพก่อนเข้าร่วมโครงการโดยไม่เสียค่าใช้จ่ายใดๆ ในการเข้าร่วมโครงการนี้อาสาสมัครทุกคนต้องงดน้ำและอาหารหลังเที่ยงคืนจนถึงเช้าของวันทำการทดลองและจะให้รับประทานอาหารและดื่มน้ำได้หลังจากดำเนินการทดลองไปแล้วประมาณ 4 ชั่วโมง

การวิจัยนี้แบ่งเป็น 2 ตอน โดยมีช่วงห่างระหว่างตอน 2 สัปดาห์ แต่ละตอนมีรายละเอียดดังนี้

ตอนที่ 1 อาสาสมัครจะได้รับประทานยา Seroquel®หรือ ยาทดสอบ

อาสาสมัครทุกคนจะได้รับการเก็บตัวอย่างเลือดหลังรับประทานยา Seroquel® หรือ ยาทดสอบ ขนาด 200 มก. (เม็ดละ 200 มก. จำนวน 1 เม็ด) ครั้งเดียว โดยการสุ่มกลุ่มละ 12 คน ทำการเจาะเลือด ครั้งละประมาณ 5 มล. จากหลอดเลือดดำบริเวณด้านในของแขนโดยคาสายสวนไว้ (intravenous catheter) ที่เวลา 0 (ก่อนรับประทานยา) 15 , 30, 45 นาที, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, และ 48 ชั่วโมงหลังรับประทานยา ทำการปั่นแยกพลาสมาและเก็บไว้ที่อุณหภูมิ -70 องศาเซลเซียสเพื่อนำไปวิเคราะห์หาปริมาณยาต่อไป

ตอนที่ 2 อาสาสมัครจะได้รับประทานยา Seroquel® หรือ ยาทดสอบ ขนาด 200 มก. (เม็ดละ 200 มก. จำนวน 1 เม็ด) ครั้งเดียวโดยรับประทานพร้อมกับน้ำดื่ม 240 มล.โดยสลับชนิดของยากับในตอนที่1 และเก็บตัวอย่างเลือดเช่นเดียวกับในตอนที่ 1

หมายเหตุ : การคาสายสวนไว้ในหลอดเลือดดำเพื่อเก็บตัวอย่างเลือดจะคาไว้เพียง 12 ชั่วโมงเท่านั้น และการเจาะเลือดครั้งต่อๆไปจะเจาะเลือดจากหลอดเลือดดำบริเวณข้อพับของแขนเป็นครั้งๆไป

ในระหว่างการศึกษาวิจัยนี้อาสาสมัครทุกคนจะไม่ได้รับอนุญาตให้ดื่มสุราหรือสูบบุหรี่ และหากจำเป็นต้องได้รับยาอื่นใด โปรดแจ้งให้ผู้วิจัยทราบด้วย เนื่องจากยาบางชนิดอาจมีผลต่อระดับยาที่กำลังศึกษาได้

ผลข้างเคียงหรืออาการอันไม่พึงประสงค์จากยา

ยาในขนาดปกติที่ใช้ในการรักษาโรคทางจิตเวช คือ 300-600 มก./วัน โดยมักจะค่อยๆเพิ่มขนาดของยา คือ เริ่มจากขนาด 25 มก.วันละ 2 ครั้ง แล้วค่อยๆเพิ่มขึ้นครั้งละ 25-50 มก. วันละ 2 ครั้ง จนเป็นวันละ 300 มก. โดยให้วันละ 2 ครั้ง ซึ่งผู้ป่วยส่วนใหญ่มักจะทนต่อยาได้ดี แต่อย่างไรก็ดี ผู้ป่วยบางรายอาจเกิดผลข้างเคียงได้ ซึ่งผลอันไม่พึงประสงค์จากยานี้ที่พบบ่อยที่สุดคือ นอนไม่หลับ สั่น (agitation) อาการทางสมอง (extrapyramidal symptoms), วิตกกังวล และ ปวดศีรษะ

อาการที่รุนแรงที่สุด แต่พบได้น้อย คือ ไม่รู้สึกตัว(syncope), หัวใจเต้นผิดจังหวะ มีการขัดขวางการส่งสัญญาณไฟฟ้าจากหัวใจห้องบนไปหัวใจห้องล่าง (first degree AV-block) และอาการชัก

หากท่านเจ็บป่วยอันเนื่องมาจากการเข้าร่วมโครงการวิจัยนี้ ท่านจะได้รับการดูแลโดยแพทย์และให้การรักษาพยาบาลโดยท่านไม่ต้องเสียค่าใช้จ่ายใดๆ

อาสาสมัครจะได้รับค่าตอบแทนจากการเข้าร่วมงานวิจัย 4,000 บาท/คน (หากเข้าร่วมโครงการทั้ง 2 ตอน) แต่จะไม่ได้รับค่าตอบแทนหากเข้าร่วมโครงการไม่ครบทั้ง 2 ตอน ยกเว้น

จำเป็นต้องออกจากการทดลองเนื่องจากแพ้ยาหรือเกิดผลข้างเคียงจนไม่สามารถเข้าร่วมโครงการต่อไปได้ หรือมีเหตุสุดวิสัยที่เป็นเหตุให้จำเป็นต้องหยุดการเข้าร่วมโครงการก่อนสิ้นสุดโครงการ โดยจะได้รับค่า ตอบแทนตามสัดส่วนที่ได้ร่วมโครงการ

ไม่ว่าท่านจะเข้าร่วมโครงการวิจัยนี้หรือไม่ท่านจะยังคงได้รับการรักษาที่ได้มาตรฐานเช่นเดียวกับผู้ป่วยอื่นๆ หากมีความจำเป็นต้องเข้ารับการรักษาที่โรงพยาบาลสงขลานครินทร์ และหากท่านมีข้อสงสัยใดๆก่อนที่จะตัดสินใจเข้าร่วมโครงการนี้ คณะผู้วิจัยยินดีตอบข้อสงสัย หรือคำถามของท่านโดยท่านสามารถติดต่อคณะผู้วิจัยทุกท่านตามหมายเลขโทรศัพท์ที่ระบุไว้ด้านล่างนี้ (ในเวลาราชการ)

ผศ.นพ.วีรวัฒน์ มหัทธนตระกูล ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ ม.อ. โทร. 074-446678
รศ.น.พ.วิบูลย์ ฤทธิทิศ ภาควิชาเภสัชวิทยา คณะวิทยาศาสตร์ ม.อ. โทร. 074-446678

ขอขอบคุณอย่างสูง
คณะผู้วิจัย

เอกสารคำแนะนำสำหรับอาสาสมัคร (Subject Information Sheet)

หัวเรื่องที่ทำการศึกษา : "การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบเทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทยสุขภาพปกติ"

สถาบันที่ทำการศึกษา : ภาควิชา เภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์

สรุปโครงการศึกษาโดยย่อ :

การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบเทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก.โดยการรับประทาน ในอาสาสมัครชายไทยสุขภาพปกติ
การศึกษานี้แบ่งเป็น 2 ตอน โดยมีช่วงห่างระหว่างตอน 2 สัปดาห์ แต่ละตอนมีรายละเอียดดังนี้

ตอนที่ 1 อาสาสมัครจะได้รับประทานยา Seroquel®หรือ ยาทดสอบ

อาสาสมัครทุกคนจะได้รับการเก็บตัวอย่างเลือดหลังรับประทานยา Seroquel®หรือ ยาทดสอบ ขนาด 200 มก.(ขนาดเม็ดละ 200 มก. จำนวน 1 เม็ด) โดยรับประทานครั้งเดียวพร้อมกับน้ำดื่ม 240 มล. แบ่งกลุ่มอาสาสมัครเป็น 2 กลุ่มโดยการสุ่มกลุ่มละ 12 คน อาสาสมัครจะได้รับการเจาะเลือด ครั้งละประมาณ 5 มล. จากหลอดเลือดดำบริเวณด้านในของแขนโดยคาสายสวนไว้ (intravenous catheter) ที่เวลา 0 (ก่อนรับประทานยา) 15, 30, 45 นาที, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, และ 48 ชั่วโมงหลังรับประทานยา

ตอนที่ 2 อาสาสมัครจะได้รับประทานยา Seroquel® หรือยาทดสอบ ขนาด 200 มก. (เม็ดละ 200 มก. จำนวน 1 เม็ด) ครั้งเดียวโดยรับประทานพร้อมกับน้ำดื่ม 240 มล.โดยสลับชนิดของยากับในตอนที่1 และเก็บตัวอย่างเลือดเช่นเดียวกับในตอนที่ 1

หมายเหตุ : การคาสายสวนไว้ในหลอดเลือดดำเพื่อเก็บตัวอย่างเลือดจะคาไว้เพียง 12 ชั่วโมงเท่านั้น และการเจาะเลือดครั้งต่อๆไปจะเจาะเลือดจากหลอดเลือดดำบริเวณข้อพับของแขนเป็นครั้งๆไป

ผู้วิจัยจะนำตัวอย่างเลือดไปตรวจวิเคราะห์หาระดับยาและทำการวิเคราะห์ข้อมูลทางสถิติเพื่อสรุปผลการศึกษาต่อไป

วัตถุประสงค์ :

1.เพื่อศึกษาเปรียบเทียบอัตราและปริมาณการดูดซึมของยาทดสอบกับยาต้นแบบ (original drug) (ยา Seroquel®) ซึ่งผลิตโดยบริษัท AstraZeneca Pharmaceuticals ประเทศสหราชอาณาจักร

2.เพื่อให้ได้ข้อมูลเภสัชจลนศาสตร์ของยา quetiapine ในอาสาสมัครชายไทยสุขภาพปกติ

3.เพื่อให้ได้ยาที่มีคุณภาพตามมาตรฐานสากล สามารถขึ้นทะเบียนยาได้

ประโยชน์ที่คาดว่าจะได้รับ :

การศึกษาวิจัยนี้ถึงแม้จะไม่มีประโยชน์ต่ออาสาสมัครโดยตรง แต่ผลการศึกษาจะนำไปสู่การพัฒนาหรือนำเข้ายาที่มีราคาถูกลง ซึ่งจะเป็นประโยชน์ต่อผู้ป่วย และประเทศชาติอีกด้วย

ข้อปฏิบัติสำหรับอาสาสมัครก่อนและระหว่างเข้าร่วมการศึกษา :

- อาสาสมัครต้องงดอาหารก่อนการให้ยาอย่างน้อย 10 ชั่วโมง โดยสามารถดื่มน้ำได้ตามต้องการ ยกเว้น 1 ชั่วโมงก่อนและหลังการรับประทานยา
- หลังจากรับประทานยา 4 ชั่วโมง อาสาสมัครจึงรับประทานอาหารที่ผู้วิจัยจัดเตรียมไว้ให้ได้ โดยอาหารที่อาสาสมัครรับประทานในการศึกษาคาบที่ 1 และคาบที่ 2 เป็นอาหารมาตรฐานชนิดเดียวกัน และรับประทานให้แล้วเสร็จภายใน 15 นาที
- อาสาสมัครต้องไม่รับประทานอาหารหรือเครื่องดื่มที่มีส่วนผสมของแอลกอฮอล์ก่อนการศึกษาอย่างน้อย 2 สัปดาห์และจนกระทั่งเสร็จสิ้นการศึกษาทั้งสองคาบ
- อาสาสมัครต้องไม่รับประทานอาหารหรือเครื่องดื่มที่มีส่วนผสมของคาเฟอีน เช่น ชา กาแฟ ชอคโกแลต เป็นต้น ก่อนการศึกษาอย่างน้อย 48 ชั่วโมง และหลังการรับประทานยาจนกระทั่งเสร็จสิ้นการเก็บตัวอย่างเลือด
- อาสาสมัครต้องไม่รับประทานยาใดๆ ก่อนการศึกษาอย่างน้อย 14 วัน และจนกระทั่งสิ้นสุดการศึกษาทั้งสองคาบ
- อาสาสมัครต้องไม่ออกกำลังกายในระหว่างการทดลอง แต่สามารถปฏิบัติกิจกรรมเท่าที่จำเป็นได้

ความเสี่ยงที่อาจเกิดขึ้นระหว่างการศึกษา :

อาสาสมัครอาจเกิดการแพ้ยา เช่น นอนไม่หลับ สั่น (agitation) อาการทางสมอง (extrapyramidal symptoms) วิตกกังวล และ ปวดศีรษะ อาการที่รุนแรงที่สุด แต่พบได้น้อย คือ ไม่รู้สึกตัว (syncope) , หัวใจเต้นผิดจังหวะ มีการขัดขวางการส่งสัญญาณไฟฟ้าจากหัวใจห้องบนไปหัวใจห้องล่าง(first degree AV-block) และ อาการชัก

การดำเนินการเมื่อเกิดอันตรายจากการศึกษา :

ในระหว่างการศึกษา จะมีแพทย์คอยเฝ้าติดตามอาการของอาสาสมัครตลอดเวลา อย่างไรก็ดี ในกรณีที่เกิดอันตราย คณะผู้วิจัยได้จัดเตรียมยา สารน้ำและอุปกรณ์ช่วยชีวิตไว้แล้ว

หากท่านเจ็บป่วยอันเนื่องมาจากการเข้าร่วมโครงการวิจัยนี้ ท่านจะได้รับการดูแลโดยแพทย์และให้การรักษาพยาบาลโดยท่านไม่ต้องเสียค่าใช้จ่ายใดๆ

การตอบแทน ชดเชยแก่อาสาสมัคร :

อาสาสมัครจะได้รับค่าตอบแทนจากการเข้าร่วมงานวิจัย 4,000 บาท/คน (หากเข้าร่วมโครงการทั้ง 2 ตอน) แต่จะไม่ได้รับค่าตอบแทนหากเข้าร่วมโครงการไม่ครบทั้ง 2 ตอน ยกเว้นจำเป็นต้องออกจากการทดลองเนื่องจากแพ้ยาหรือเกิดผลข้างเคียงจนไม่สามารถเข้าร่วมโครงการต่อไปได้ หรือมีเหตุสุดวิสัยที่เป็นเหตุให้จำเป็นต้องหยุดการเข้าร่วมโครงการก่อนสิ้นสุดโครงการ โดยจะได้รับค่าตอบแทนตามสัดส่วนที่ได้ร่วมโครงการ

หากเกิดอันตรายใด ๆ จากการวิจัยดังกล่าว อาสาสมัครจะได้รับการรักษา พยาบาลโดยไม่คิดมูลค่า และจะได้รับการชดเชยรายได้ที่สูญเสียไประหว่างการรักษาพยาบาลดังกล่าว ตลอดจนเงินทดแทนความพิการที่อาจจะเกิดขึ้นโดยบริษัท.....ผู้ให้การสนับสนุนการวิจัยในครั้งนี้

สภาวะการณ์ และ/หรือเหตุผลที่อาจเพิกถอนอาสาสมัครออกจากการวิจัย :

1. อาสาสมัครไม่ปฏิบัติตามข้อปฏิบัติสำหรับอาสาสมัครก่อนและระหว่างเข้าร่วมการศึกษาดังกล่าวข้างต้น
2. อาสาสมัครเกิดอาการไม่พึงประสงค์ที่แพทย์เห็นควรให้ออกจากการศึกษา
3. อาสาสมัครต้องการถอนตัวออกจากการศึกษา

การเก็บรักษาความลับ :

ข้อมูลเกี่ยวกับการตรวจร่างกายและผลการทดลองของอาสาสมัครจะถูกเก็บเป็นความลับไม่แสดงชื่อและนามสกุลจริง โดยจะเปิดเผยเฉพาะในรูปของผลการวิจัยโดยรวมเท่านั้น

ชื่อและที่อยู่ของผู้รับผิดชอบการศึกษาและแพทย์ที่ดูแลอาสาสมัคร :

นพ. วีรวัฒน์ มหัทธนตระกูล ภาควิชา เภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โทร. 089-9869089

นพ. วิบูลย์ ฤทธิทิศ ภาควิชา เภสัชวิทยา คณะวิทยาศาสตร์ มหาวิทยาลัยสงขลานครินทร์ โทร. 074-446678

หนังสือแสดงความยินยอมเข้าร่วมโครงการวิจัย (Consent Form)

การวิจัยเรื่อง " การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบเทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก. โดยการรับประทานในอาสาสมัครชายไทยสุขภาพปกติ "

วันให้คำยินยอม วันที่…….เดือน…….พ.ศ……

ข้าพเจ้า(นาย/นาง/นางสาว)……นามสกุล……..……
อยู่บ้านเลขที่……..ถนน……..……..แขวง/ตำบล……เขต/อำเภอ……..จังหวัด…….....
รหัสไปรษณีย์……ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับเอกสารและอธิบายจากผู้วิจัยให้ทราบวัตถุประสงค์ของการวิจัย วิธีวิจัย อันตรายหรืออาการข้างเคียงที่อาจเกิดขึ้นจากการวิจัยหรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยได้ตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้นจนข้าพเจ้าพอใจ

ข้าพเจ้าเข้าร่วมโครงการนี้โดยสมัครใจ และมีสิทธิ์ที่จะบอกเลิกการเข้าร่วมโครงการวิจัยนี้เมื่อใดก็ได้ โดยการบอกเลิก จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะได้รับต่อไป

ข้าพเจ้าอนุญาตให้ผู้วิจัยเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าในหน่วยงานที่เกี่ยวข้องได้ตามที่ผู้วิจัยเห็นสมควร ผู้วิจัยรับรองว่า จะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับ และจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย

ในการวิจัยครั้งนี้จะมีการเจาะเลือดใน 3 ช่วงของการศึกษา คือ ช่วงที่ 1 การเจาะเลือดเพื่อคัดเลือกอาสาสมัครเป็นจำนวน…1…ครั้งๆละ…5….มิลลิลิตร ช่วงที่ 2 เจาะเลือดหลังจากการได้รับยาครั้งที่ 1 เป็นจำนวน……18…..ครั้งๆ ละ…5…..มิลลิลิตร และช่วงที่ 3 เจาะเลือดหลังจากการได้รับยาครั้งที่ 2 เป็นจำนวน…18….ครั้งๆ ละ…5……มิลลิลิตร รวมปริมาณเลือดที่ถูกเจาะในครั้งที่ 2 และ 3 ครั้งละ…90….มิลลิลิตร

ผู้วิจัยได้อธิบายให้ข้าพเจ้าทราบและเข้าใจแล้วว่า การเจาะเลือดเพียงเล็กน้อย โดยทั่วไปจะไม่เกิดอันตรายใด ๆ แก่ข้าพเจ้าเลย นอกจากอาจมีรอยช้ำบริเวณเจาะเล็กน้อย ซึ่งอาจหายได้เองภายใน 7 วัน

ผู้วิจัยรับรองว่า หากเกิดอันตรายใด ๆ จากการวิจัยดังกล่าว ข้าพเจ้าจะได้รับการรักษาพยาบาลโดยไม่คิดมูลค่า และจะได้รับการชดเชยรายได้ที่สูญเสียไประหว่างการรักษาพยาบาลดังกล่าว ตลอดจนเงินทดแทนความพิการที่อาจจะเกิดขึ้น และรายละเอียดเกี่ยวกับการรักษาพยาบาลหรือเงินชดเชยดังกล่าวข้าพเจ้าสามารถติดต่อได้ที่ ……..หัวหน้าโครงการวิจัย

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้วและมีความเข้าใจดีทุกประการ จึงได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม……..ผู้ยินยอม
ลงนาม……..ผู้รับผิดชอบการวิจัย
(ผศ.นพ. วีรวัฒน์ มหัทธนตระกูล)
ลงนาม……..พยาน
ลงนาม……..พยาน

ข้าพเจ้าไม่สามารถอ่านหนังสือได้ แต่ผู้วิจัยได้อ่านข้อความในใบยินยอมนี้ให้แก่ข้าพเจ้าฟังจนเข้าใจดีแล้ว ข้าพเจ้าจึงลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงนาม……..ผู้ยินยอม
ลงนาม……..ผู้รับผิดชอบการวิจัย
(ผศ.นพ. วีรวัฒน์ มหัทธนตระกูล)
ลงนาม……..พยาน
ลงนาม……..พยาน

แบบบันทึกข้อมูลอาสาสมัคร (Case Report Form)

การวิจัยเรื่อง

การศึกษาชีวสมมูลของยา quetiapine ระหว่างยาทดสอบเทียบกับยาต้นแบบ (Seroquel®) ขนาด 200 มก.โดยการรับประทาน ในอาสาสมัครชายไทยสุขภาพปกติ

1. การคัดกรองอาสาสมัคร (screening)

1.1 ข้อมูลส่วนตัว (Personal and Demographic data)

ชื่อ (Name) ……

ที่อยู่ (Address) ……

โทรศัพท์ (Tel. no.) ……วัน เดือน ปี เกิด (Date of birth) …….....……

อายุ (Years) ……..…ปี เพศ (Gender) □ ชาย (Male) □ หญิง (female)

ส่วนสูง (Height) ……ซม (cm) น้ำหนัก (Weight) ……...กก (kg)

Body Mass Index (BMI) …….kg / m^2 (18 – 25)

การสูบบุหรี่ (Smoking) □ ไม่เคย □ เคยแต่หยุดแล้ว □ สูบ ……มวน/วัน

การดื่มสุรา (Alcohol Drinking) □ ไม่เคย □ นานๆ ครั้ง □ บ่อย …..ครั้ง/สัปดาห์

ปริมาณชา/กาแฟที่ดื่ม/วัน …….ถ้วย

1.2 ประวัติการใช้ยา (Medical history)

โรคประจำตัว □ ไม่มี □ มี ……

การแพ้ยา □ ไม่มี □ มี ……

ยาที่ได้รับภายใน 1 เดือนก่อนนี้

□ ไม่มี □ มี ……

1.3 การตรวจร่างกาย (Physical examination)

Vital sign Blood pressure ……..(mmHg)
Pulse ……../min
Temperature…….. °C

1.4 การตรวจทางห้องปฏิบัติการ (Laboratory tests) วันที่ทำการตรวจ……/……../…….

Clinical Chemistry BUN …… (normal 5-23 mg%)
Creatinine …… (normal 0.8-1.4 mg%)
Total Bilirubin ……...(normal 0.2-1.0 mg%)
AST (SGOT) …….(normal <40 U/L)
ALT (SGPT) …….(normal <37 U/L)
Alk. Phosphatase……(normal 39-117..U/L)
Fasting blood sugar (FBS)…(normal 70-110 mg%)

Haematology WBC ……(normal 5,000-10,000)
Haemoglobin ……(normal 13.3-16.0 g%)
Haematocrit ……..(normal 40-48 %)
Platelets ….. …….(normal 400,000)

Virology Anti-HIV □ positive □ negative

1.5 เกณฑ์การคัดเลือกอาสาสมัครเข้าร่วมการศึกษา (Subject Inclusion Criteria)

	Yes	No
✓อาสาสมัครเพศชาย/หญิงอายุระหว่าง 20-45 ปี	□	□
✓ มีค่า Body Mass Index (BMI) 18 – 25 kg/m^2	□	□
✓ มีสุขภาพดี โดยผ่านการตรวจสอบประวัติการใช้ยา, การตรวจร่างกาย และ vital signs	□	□
✓ ผลการตรวจวินิจฉัยทางห้องปฏิบัติการคลินิกเป็นปกติ	□	□
✓ ยินยอมเข้าร่วมการศึกษาด้วยความเต็มใจและลงนามในหนังสือแสดงความยินยอมแล้ว	□	□

1.6 เกณฑ์การคัดเลือกอาสาสมัครออกจากการศึกษา (Subject Exclusion Criteria)

	Yes	No
× มีประวัติการแพ้ยาที่ใช้ในการศึกษาหรือยาอื่นในกลุ่มยาที่ใช้ในการศึกษา	□	□
× มีประวัติป่วยเป็นโรคระบบทางเดินอาหาร โรคตับ โรคไต โรคภูมิแพ้ หรือโรคอื่นๆ ที่อาจมีผลต่อ bioavailability ของยา	□	□
× มีประวัติดื่มสุราเป็นประจำ และมีการใช้สารเสพติด	□	□
× มีประวัติสูบบุหรี่เป็นประจำ (มากกว่า 10 มวนต่อวัน) หรือหากมีการสูบบุหรี่ปานกลาง (น้อยกว่า 10 มวนต่อวัน) และไม่สามารถอดการสูบบุหรี่ได้ก่อนเริ่มการศึกษาและระหว่างการศึกษา	□	□
× ได้รับการรักษาโรคด้วยยาอื่นภายใน 14 วันก่อนเริ่มการศึกษา โดยเฉพาะยาที่มีผล enzyme ในร่างกาย	□	□
× เคยเข้าร่วมการทดลองการศึกษาทางคลินิกอื่นๆ ภายใน 1 เดือนก่อนเริ่มการศึกษา	□	□

VITAE

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Education Attainment

Degree	Name of Institution	Year of Graduation
Bachelor of Science	Prince of Songkla University	2007

List of Publication and Proceeding

Charuwan Pradabsang, Werawath Mahatthanatrakul, Wibool Ridtitid and Somchai Sriwiriyajan. Bioequivalence Study of a Generic Quetiapine (Ketipinor®) and the Innovator Preparation (Seroquel®) 200 mg Given Orally in Healthy Thai Male Volunteers. *The 4th Sino-Thai conference on Traditional Medicine and Natural Products,* July 11st-13th, 2010, Khon Kaen, Thailand.