

# Bioequivalence Study of 50 mg Sertraline Tablets in Healthy Thai Volunteers

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**Objective:** To determine the bioavailability of 50 mg sertraline tablets between the test product (Zotaline<sup>®</sup>, M&H Manufacturing Co., Ltd., Thailand) and the reference product (Zoloft<sup>®</sup>, Pfizer Australia Pty Ltd., Australia).

**Material and Method:** An open-labeled, single dose, 2-treatment, 2-period, 2-sequence, randomized crossover study under fasting conditions with 14 days washout period was conducted in 24 healthy Thai volunteers. Blood samples were collected before dosing and at frequent intervals for up to 96 h post dose. Analysis of sertraline concentrations was performed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.

**Results:** Twenty-four volunteers completed both treatment periods. Pharmacokinetic parameters were determined using the non-compartment model. The 90 percent confidence intervals of the geometric mean ratios (test/reference) of  $C_{max}$  104.47% (96.64%-112.93%),  $AUC_{0-96}$  108.06% (100.71%-115.94%) and  $AUC_{0-\infty}$  108.39% (100.93%-116.40%) fell within the equivalence range (80%-125%). There was no significant difference of the  $T_{max}$  parameter between the two formulations ( $p > 0.05$ ). No serious adverse events related to the study drugs were found.

**Conclusion:** The two formulations of sertraline tablets were bio-equivalent in Thai healthy volunteers.

**Keywords:** Bioequivalence, Sertraline, Therapeutic equivalency

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Sertraline is a Selective Serotonin Reuptake Inhibitors (SSRIs) used as a major therapeutic advance in psychiatry and drugs of choice for treatment of major depressive disorder. The sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT) into human platelets. It has only very weak effects on norepinephrine and dopamine neuronal reuptake, and no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic

drugs<sup>(1-3)</sup>. Sertraline does not inhibit monoamine oxidase<sup>(2,3)</sup>.

Plasma concentrations of sertraline and desmethyl sertraline (major metabolite)<sup>(4,5)</sup> slowly appeared in plasma with peak concentrations ( $C_{max}$ ) occurring 4-8 h after ingestion ( $T_{max}$ ). Co-administration with food increased  $C_{max}$  by approximately 25%, while  $T_{max}$  decreased from 8 h post-dosing to 5.5 h. Sertraline is highly bound to plasma proteins<sup>(6,7)</sup>. Sertraline undergoes extensive first pass metabolism, multiple cytochrome P450 (CYP) isoforms appear to be responsible for the metabolism of sertraline<sup>(8,9)</sup>. Linear pharmacokinetics is suggested for sertraline titration (50-200mg, o.d.). The plasma elimination half-life ( $t_{1/2}$ ) in healthy volunteers is approximately 26 hours<sup>(10)</sup>. The elimination rate constant is higher in young males than in females or subjects > 65 years (0.031/hr vs. 0.022/hr for young females vs. 0.019/hr in the elderly)<sup>(6,7)</sup>.

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The availability of generic formulation of sertraline will increase the choices for drug prescriptions in treatment of depression. The bioequivalence study is designed to evaluate the quality of the generic formulation for assuring clinicians to prescribe generic formulation interchangeably with the original formulation with similar toxicity and efficacy. Considerably, this *in vivo* bioequivalence study is necessary for market application of the generic formulation.

## Material and Method

### Study preparations

Sertraline 50 mg tablets were used in the test preparation: Zotaline<sup>®</sup> manufactured by M&H Manufacturing Co., Ltd., Thailand (Lot no. ZOT 006, expiry April 10, 2009) and reference preparation: Zoloft<sup>®</sup> by Pfizer Australia Pty Ltd., Australia (Lot no. 714720026, expiry Feb, 2012).

### Study population

The present study was carried out at the Siriraj Clinical Research Center, Siriraj Hospital, Bangkok, Thailand. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand (No. Si 294/2008 on June 13, 2008) and Thai Food and Drug Administration, Ministry of Public Health, Thailand<sup>(11)</sup>. In addition, the protocol was performed in accordance with the Declaration of Helsinki Principles as outlined in Guidelines for Good Clinical Practice (GCP)<sup>(11,12)</sup>. All subjects were given a detailed description of the study and written informed consent was obtained prior to the enrollment.

The twenty-four healthy male and female volunteers between the ages of 18-45 years with a body mass index between 18-24 kg/m<sup>2</sup> were assessed to be in good physical condition and normal laboratory result for hematologic and blood biochemistry parameters. Female volunteers who were pregnant or lactating were not eligible for participation. Subjects with a history of hypersensitivity to any ingredients in the sertraline products and/or related drugs or its constituents were excluded from the study<sup>(11-13)</sup>.

### Study design

The present study was an open-labeled, single dose, 2-treatment, 2-period, 2-sequence, randomized crossover study under fasting condition with 14 days washout period<sup>(14,15)</sup>. Subjects were randomly allocated to two groups by the sequence of

product administered [Test-Reference (TR) and Reference-Test (RT) group]. In each period, single dose of 50 mg sertraline tablet of the test or reference product was administered along with 220 ml of drinking water after an overnight fasting of at least 10 hours and volunteers were hospitalized for the first 24 hours in the Siriraj Clinical Research Center, Siriraj Hospital. Physical examination was performed and adverse events were close-monitored and assessed throughout the participation period. Further blood samplings were collected at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hours after drug administration (test or reference). Subjects were released from the ward after 24 hour sampling and were scheduled for 48, 72 and 96 h blood sampling. Serum was separated by centrifugation and then stored at -70°C until analysis.

### Sertraline analysis by LC-MS/MS

Briefly, desipramine hydrochloride as an internal standard (IS) solution. After the plasma was separated into two aliquots, they were injected into the LC-MS/MS system<sup>(9,16)</sup>. Chromatographic separation was carried out on LC-MS/MS with C18 column (3 µm, 150 mm x 2.0 mm i.d.). Mass spectra were obtained using a Quattro Micro mass spectrometer (Micromass, UK) equipped with electrospray ionization (ESI) source. The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode. The data acquisition was ascertained by Masslynx 4.0 software. For quantification the peak area ratios of the target ions of the drugs to those of the internal standard were compared with weighted (1/x) calibration curves in which the peak area ratios of the calibration standards were plotted versus their concentrations<sup>(13)</sup>. Validation of this method was performed as recommended by USFDA<sup>(13)</sup>.

### Pharmacokinetic and Statistical analysis

The individual plasma drug concentration-time curve was plotted and the pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin<sup>®</sup> software version 3.1 (Scientific Consulting Inc., Apex, North Carolina). For the purpose of bioequivalence analysis AUC<sub>0-96</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> were considered as the primary variables. Two-way analysis of variance (ANOVA) for crossover design was performed for log-transformed data and used to assess the effect of formulations, periods, sequences and subjects nested in sequence on these parameters. The difference between two related parameters was considered statistically

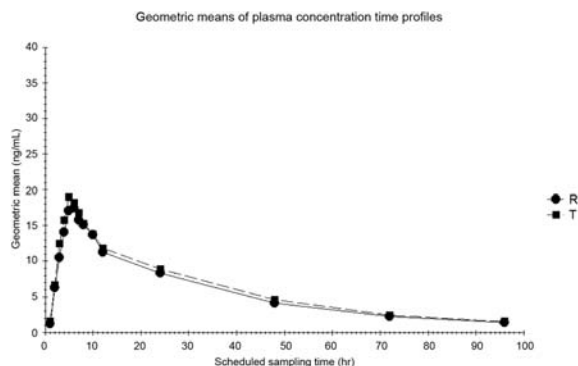
significant for p-value equal to or less than 0.05. 90% confidence interval (CI) for the ratios of geometric mean Test/Reference (T/R) for  $AUC_{0-96}$ ,  $AUC_{0-\infty(obs)}$  and  $C_{max}$  was calculated based on least squares means from the ANOVA of log-transformed data. The 90% confidence intervals for the ratio of  $AUC_{0-96}$ ,  $AUC_{0-\infty(obs)}$  as well as  $C_{max}$  values of the test preparation over those of the reference product were estimated. A non-parametric statistical analysis, Friedman's test using Kinetics 2000 software was performed on  $T_{max}$  and considered significant difference between test and reference formulations when  $p < 0.05$ . The 90% geometric confidence intervals of the ratio (T/R) of least-squares means from the ANOVA of the log-transformed  $AUC_{0-96}$ ,  $AUC_{0-\infty(obs)}$  and  $C_{max}$  should be within 80.00% to 125.00%.

## Results

Twenty four healthy Thai adults (12 male and 12 female) were randomly equally divided into 2 groups [Test-Reference (TR) and Reference-Test (RT)] according to the sequence of drug administration. Thus, the present study was balanced in each sequence. The demographic characteristics were not statistically different between groups.

### Bio-analysis and pharmacokinetics

Plasma sertraline was measured by LC-MS/MS method. The calibration curves were found to be linear over the concentration range of 0.5-50.0 ng/mL for sertraline. The coefficient of determination ( $r^2$ ) was 0.999076. The percentage of coefficients of variation (% CV) of within-run precision and between-run precision in this analytical study were 2.25%-10.41% and 6.21%-7.43%, respectively. All of values were



**Fig. 1** Average  $\pm$  SD of plasma concentration-time profile of sertraline (n = 24); normal plot

within 15% of the actual values, which was in an acceptable range. The average values of recovery percentages of within-run accuracy and between-run accuracy in this analytical study were 93.28%-111.55% and 101.83%-102.01%, respectively (80%-120%).

No significant difference was observed in any of the analyzed pharmacokinetic parameters (Table 1). The geometric means  $C_{max}$  for the reference and test formulations were 19.8 ng/mL and 20.7 ng/mL, respectively. The median (range) of  $T_{max}$  was 5.00 (2-7) h for the reference formulation and 5.00 (2-10) h for the test formulation (Fig.1).

### Bioequivalence analysis

The statistical analysis obtained from the present study showed that the point estimate 90% CI of the geometric mean ratio (test/reference) of  $C_{max}$ ,  $AUC_{0-96}$  and  $AUC_{0-\infty(obs)}$  were entirely within the equivalence criteria (80.00-125.00%) which were

**Table 1.** Pharmacokinetic parameters of Test (Zotaline®) and Reference (Zoloft®) with 90% confidence interval of the geometric mean ratios (Test/Reference)

Pharmacokinetic parameters	Product (mean $\pm$ SD)		90% CI of the geometric mean	Power
	Test (Zotaline®)	Reference (Zoloft®)		
$T_{max}$ (hr)	4.75	5.25	-	
$T_{1/2}$ (hr)	29.30	29.30	-	
$C_{max}$ (ng/mL)	21.80 $\pm$ 6.95	20.60 $\pm$ 6.01	96.64-112.93	0.9980
$AUC_{0-96}$ (ng.h/mL)	617.00 $\pm$ 273.00	580.00 $\pm$ 270.00	100.71-115.94	0.9994
$AUC_{0-\infty(obs)}$ (ng.h/mL)	730.00 $\pm$ 462.00	675.00 $\pm$ 408.00	100.93-116.40	0.9993

$T_{max}$  = time for the maximal plasma concentration,  $T_{1/2}$  = half-life, AUC = area under concentration-time curve,  $C_{max}$  = maximum plasma concentration, CI = confidence interval

**Table 2.** Incidence of adverse events

Adverse events	Reported incidence		Total
	Test (Zotaline®)	Reference (Zoloft®)	
Drowsiness	11	9	20
Loose stool	6	11	17
Nausea	3	3	6
Abdominal cramp	-	4	4
Dizziness	2	2	4
Fever	-	2	2
Vomiting	1	-	1
Diarrhea	1	-	1
Dermatitis	1	-	1
Total	25	31	56

104.47%, 108.06% and  $AUC_{0-\infty(obs)}$  108.39%, respectively (Table 1). Accordingly, the present study confirms that the sample size was adequate when the power of all parameters were above 80%.

#### Adverse events

Sertraline was well tolerated. There were only mild adverse events from both sertraline formulations. Most common adverse events were drowsiness, loose stool and nausea (Table 2).

#### Discussion

Sertraline, a selective serotonin reuptake inhibitor (SSRIs), was effectively used for treatment of depressive disorder that makes social and occupational impairment, suicidal ideation and at last suicidal behavior. An open label, single-dose, two-treatment, two-period, two-sequence randomized crossover in 24 healthy volunteers was considered appropriate and standard for bioequivalence evaluation of the generic and reference products. The 14 days washout period was long enough to prevent carryover from the first to second period since no baseline sertraline concentrations were detected at the beginning of the second period. The analytical of sertraline plasma concentration method (LC-MS/MS) and two-way analysis of variance (ANOVA) were used to assess two related parameters and demonstrated sufficient bioequivalence data.

In general, the pharmacokinetic parameters for both formulations were similar, as shown by previous published data<sup>(4,8,14-18)</sup>. The present study

demonstrated 90% geometric confidence intervals (90% CI) of the ratio (T/R) of log-transformed  $C_{max}$ ,  $AUC_{0-96}$  and  $AUC_{0-\infty(obs)}$  at 80%-125%. In addition, a non-parametric test, Friedman's test was performed on  $T_{max}$  and considered no statistic significant difference when  $p < 0.05$  as described before. Moreover, both formulations had no serious clinical adverse events and were well tolerated.

In conclusion, the generic (Zotaline®) and original (Zoloft®) products of Sertraline 50 mg are bioequivalent.

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## การศึกษาชีวสมมูลของยาเม็ดเซอร์ทาลีนขนาด 50 มิลลิกรัมในอาสาสมัครไทยสุขภาพแข็งแรง

สุวิมล นิยมในธรรม, สมฤดี ฉัตรสิริเจริญกุล, กอบธัม สติรกุล, ปิยภัทร พงศ์นรินทร์, สุพรชัย กองพัฒนากุล

**วัตถุประสงค์:** เพื่อศึกษาชีวสมมูลของยาเม็ดเซอร์ทาลีนขนาด 50 มิลลิกรัม ระหว่างผลิตภัณฑ์ยาสามัญ Zotaline<sup>®</sup> กับผลิตภัณฑ์ยาต้นแบบ Zolof<sup>®</sup>

**วัสดุและวิธีการ:** อาสาสมัครสุขภาพดีจำนวน 24 คน ได้รับการคัดเลือกให้เข้าร่วมการศึกษาที่ศูนย์วิจัยคลินิกศิริราช ตามรูปแบบการศึกษาคือ *open-labeled, single dose, 2-treatment, 2-period, 2-sequence, randomized crossover study under fasting condition* อาสาสมัครแต่ละคนได้รับประทานยาเม็ดเซอร์ทาลีนขนาด 50 มิลลิกรัม ทั้งสองตำรับหลังจากที่งดน้ำงดอาหารมา 10 ชั่วโมง โดยมีระยะเวลา *washout period* นาน 14 วัน มีการเก็บตัวอย่างเลือดในช่วงเวลา 96 ชั่วโมง ตัวอย่างเลือดจะได้รับการวิเคราะห์โดยวิธี *liquid chromatography with tandem mass spectrometry* ที่ได้รับการตรวจสอบความถูกต้องแล้ว

**ผลการศึกษา:** อาสาสมัครจำนวน 24 คนเข้าร่วมครบเวลาในการศึกษา ผลการศึกษาค่าทางเภสัชจลนศาสตร์ โดยใช้การวิเคราะห์แบบ *non-compartmental analysis* โดยมีค่า 90% ความเชื่อมั่นของค่า *log* ของค่าเฉลี่ยของยา Zotaline<sup>®</sup> กับ Zolof<sup>®</sup> ดังนี้  $C_{max}$  104.47% (96.64%-112.93%),  $AUC_{0-96}$  108.06% (100.71%-115.94%) and  $AUC_{0-\infty}$  108.39% (100.93%-116.40%) ซึ่งทุกค่าอยู่ในเกณฑ์ของการยอมรับความเท่าเทียมกันในการศึกษาชีวสมมูล (80-125%) ยาทั้งสองตำรับมีความปลอดภัยและพบเหตุการณ์ไม่พึงประสงค์ที่ไม่รุนแรงตลอดการศึกษา

**สรุป:** ยาเม็ดเซอร์ทาลีนทั้งสองตำรับมีชีวสมมูลซึ่งกันและกัน เมื่อศึกษาในอาสาสมัครไทยสุขภาพดี