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Bioequivalence Evaluation of Two Clopidogrel Immediate Release Tablet Formulations in Healthy Thai Volunteers Under Fasting Conditions

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Abstract

Clopidogrel is used for acute coronary syndrome and prevention of atherothrombotic events. To improve clinical outcomes, patient adherence to treatment is necessary. However, continuous use of branded product may cause economic burden to patients and healthcare system. The Government Pharmaceutical Organization (GPO), Thailand had developed a generic product of clopidogrel to reduce cost of treatment and improve accessibility to medicines for Thai people. Bioequivalence study was conducted for two purposes: to compare pharmacokinetic parameters describing the rate and extent of absorption of the test and reference formulations, and to evaluate the tolerability of the formulations in healthy Thai subjects. Comparative *in vitro* dissolution tests were performed to support the decision on the conduct of *in vivo* bioequivalence study. The present study was a comparative randomized, single dose, two-way crossover, open-label study which included 110 healthy male and female subjects under fasting conditions. A single dose of either the test or reference formulation was administered in each period, separated by 7-day washout period. Plasma samples were collected over a period of 24 hours and analyzed using a validated liquid chromatography-mass spectrometry method. Pharmacokinetic parameters describing the rate and extent of absorption were determined from plasma concentration-time profiles and statistically compared. The analysis of variance did not show any significant difference between the two formulations. The 90% confidence interval of geometric least square mean ratios (test/reference) for log-transformed $AUC_{0-tlast}$, $AUC_{0-\infty}$ and C_{max} were within 80.00-125.00% of bioequivalence criteria (82.79–102.70% for AUC_{0-24h}, 83.38–103.45% for $AUC_{0-\infty}$, and 85.84–106.89% for C_{max}). Both treatments were well tolerated, and no serious adverse events were reported. It was concluded that two clopidogrel 75-mg formulations were bioequivalent and could be used interchangeably.

Keywords: Clopidogrel; Bioequivalence; Pharmacokinetic; LC-MS/MS

Introduction

Clopidogrel is a thienopyridine prodrug that must be converted into its active metabolite to exert antiplatelet activity. The active metabolite specifically and irreversibly binds to P2Y12, a subtype of the adenosine diphosphate (ADP) receptor, on the surface of platelets. In absence of ADP binding, glycoprotein IIb/IIIa complex is not activated, thereby inhibiting platelet aggregation for the lifespan of the platelet [1,2]. Clopidogrel is used for acute coronary syndrome (unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI)), recent myocardial infarction (MI), stroke and peripheral artery disease. The recommended dose for acute coronary syndrome is 300 mg loading dose followed by 75 mg maintenance dose per day. Clopidogrel 75 mg is typically used in combination with 75-325 mg of aspirin to prevent atherothrombotic events in patients [1,3-5].

Approximate 50% of oral clopidogrel dose is absorbed in gastrointestinal tract. Maximum concentration occurs approximately within 1 hour after dosing. Clopidogrel absorption is not affected by food, but probably limited by P-glycoprotein uptake [2,4]. The metabolism of clopidogrel is mediated by esterase and cytochrome P450 (CYP) enzymes. Around 85-90% of clopidogrel is hydrolyzed into inactive carboxylic acid metabolite via hepatic first-pass metabolism. On the other hand, active metabolite of clopidogrel is primarily formed through CYP2C19 (about 50% of formed active metabolite), and partially formed through another subtype of CYP450 [2]. According to the metabolic pathway, CYP2C19 polymorphisms and concomitant used of CYP2C19 inducers or inhibitors could clinically alter platelet aggregation effect [4,6]. The elimination half-life determined by major circulating metabolite is 7.2-7.6 hours. The linearity of pharmacokinetics was demonstrated over the dose range between 50 and 150 mg [7].

Nowadays, third-generation oral antiplatelet therapies e.g. prasugrel and ticagrelor have been demonstrated to be more effective than clopidogrel [5]. However, clopidogrel has been preferably used by physicians due to safety concerns of new agents. In addition, the lower cost of generic clopidogrel compared to third-generation oral antiplatelet therapies has contributed to treatment decision of the physicians [8]. Above all, patient adherence to treatment is necessary to improve clinical outcomes. However, continuous use of branded product may cause economic burden to patients and healthcare system. The Government Pharmaceutical Organization (GPO), Thailand had developed a generic product of clopidogrel to reduce cost of treatment and improve accessibility to medicines for Thai people. To ensure that the generic product (Clopidogrel GPO®) maintains the same pharmacokinetics and tolerability as the reference product (Plavix®), bioequivalence study was conducted. The present study was a comparative randomized, single dose, two-way crossover study conducted in 110 healthy Thai volunteers under fasting state with the purpose of comparing pharmacokinetic parameters describing the rate and extent of absorption of the test and reference formulations, and evaluating the tolerability of the formulations in healthy Thai subjects.

Materials and Methods

Study Products

Clopidogrel GPO®, clopidogrel bisulfate 75 mg tablets (Lot No. S580075) manufactured by GPO, Thailand were used as the test product and Plavix®, 75 mg tablets (Lot No. 5A437) manufactured by Sanofi Winthrop Industrie, France were used as the reference product.

Chemicals and Reagents

Clopidogrel bisulfate bearing Lot No. R018J10, 99.6% purity was obtained from USP (Rockville, MD). Clopidogrel-d4, internal standard bearing Lot No. 1117-063A2, 98.5% purity was procured from TLC Pharmachem Inc. (Ontario, Canada). All solvents used for sample analysis were HPLC grade. Only ultrapure water (in-house) was used in all experiments. The reagents used for *in vitro* dissolution test and sample preparation were analytical grade.

In vitro Dissolution

Comparative *in vitro* dissolution tests were performed for 12 tablets of each Clopidogrel GPO® and Plavix®. The dissolution was tested in 1000 mL of 4 different dissolution media: KCl/HCl buffer pH 2.0, 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 maintained at 37.0 ± 0.5 ºC. USP type II apparatus with agitation speed 50 rpm was used. The contents of active ingredient in 10-mL samples withdrawn at 10, 15, 20, 30, 45 and 60 minutes were analyzed by ultraviolet–visible spectrophotometer (Lambda 35, PerkinElmer®, UK) at 220-nm wavelength. The results of *in vitro* dissolution were reported as similarity factor (f_2).

Subjects

The number of subjects was calculated by considering the estimated intra-subject variability, T/R ratio 95%, significant level 5%, power ≥ 80% and bioequivalence limits of 80.00-125.00% [9]. One hundred and ten healthy Thai subjects were enrolled in the study assuming 20% dropout and withdrawal rate. The volunteers were healthy males and females at the age between 18 and 55 years with a body mass index (BMI) between 18 and 25 kg/m^2. They had no evidence of underlying disease or clinically significant abnormal finding during screening, medical history examination, physical examination, or laboratory examination. Female subjects were not pregnant or breastfeeding at all time of the study. Females with childbearing potential were instructed to use acceptable methods of birth control e.g. non-hormonal methods throughout the study.

The subjects were thoroughly examined for known history of hypersensitivity to clopidogrel or any excipients, allergic reactions after taking any medications, peptic ulcer disease, bleeding disorders, past surgery, alcohol dependence, drug abuse, recent blood donation, and recent participation in clinical drug research. They were instructed to abstain from consumption of any grapefruit, pomelo or orange-based products, xanthine containing products, and tobacco containing products. In addition, smoking and use of other medications including over-the-counter products and herbal remedies were restricted prior to dosing and during the study. All subjects were well informed and provided the written informed consent before study participation at International Bio Service Co., Ltd., Golden Jubilee Medical Center, Mahidol University, Thailand.

Study Design

The bioequivalence study of clopidogrel was designed as a comparative randomized, single dose, two-way crossover trial. All enrolled subjects were checked in to the clinical facility prior to drug administration. After at least 10-hour fasting, one tablet of the test or reference product was given as per the randomization schedule with 240-mL water. The study drugs were administered to the subjects in sitting posture and they were remained in this posture for the first 2 hours after administration. Thereafter, the subjects could engage only in normal activities while avoiding heavy physical exertion. Food and water intake were restricted for 4 hours and 1 hour after dosing, respectively. Washout period between the administrations of two formulations was 7 days to ensure complete drug elimination given that half-life of clopidogrel is around 7.2-7.6 hours [7]. Subjects were monitored and asked about any adverse events throughout the study. Clinical and laboratory examinations were performed periodically to evaluate tolerability

and to ensure welfare of study subjects. The clinical study protocol was approved by the Institute for the Development of Human Research Protection (IHRP), Department of Medical Sciences, Ministry of Public Health, Thailand on 23 December 2015 (letter no. 1483/2558). The study was conducted as per the protocol, ICH 'Guidance on Good Clinical Practice', Declaration of Helsinki, and the standard operation procedures (SOPs) of International Bio Service Co., Ltd., Golden Jubilee Medical Center, Mahidol University, Thailand.

Blood Sampling

Total of 22 blood samples, each of around 6 mL (around 7 mL in case of pre-dose sample) were collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (0 hour) and at 0.17, 0.25, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 hours following drug administration. The time points were designed to capture the anticipated C_{max} around 1 hour and the elimination phase following pharmacokinetics profile of clopidogrel. Blood samples were collected using syringe through an indwelling intravenous cannula placed in the forearm vein of the subjects. Then the samples were transferred into pre-labeled vacutainers containing dipotassium ethylenediaminetetraacetate (K_2EDTA) as anticoagulant. The vacutainers were inverted gently to ensure the mixing of tube contents, and subsequently placed upright in wet ice water bath until centrifugation at 3,000±100 relative centrifugal force (rcf) for 5 minutes at below 10 °C to separate plasma. After centrifugation, the separated plasma was transferred to pre-labeled polypropylene tubes in two separate aliquots and stored upright in a freezer maintained at -55 °C or colder until analysis.

Sample Preparation

The plasma samples were analyzed at GPO, Thailand as per in-house SOPs complying with Guideline on Bioanalytical Method Validation of European Medicines Agency (EMA) [10] and the U.S. FDA Guidance for Industry: Bioanalytical Method Validation [11]. The subject samples were analyzed along with 8 calibration standards (20.22 - 8022.43 pg/mL) and 4 sets of quality control samples at 4 different levels: 6059.20, 4059.66, 811.93 and 60.08 pg/mL. First, 250 µL of each sample was aliquoted into pre-labeled tube. Then 50 µL of ISTD solution containing 4000 pg/mL of Clopidogrel-d4 and 250 µL of 0.5 mM ammonium acetate buffer (pH 6.0) were added into each sample. After that, 2 mL of methyl-tert-butyl ether was added to each tube, followed by vortexing for 3 minutes. The samples were centrifuged at 3400±100 rcf for 5 minutes at 10 °C. The plasma layer was flash frozen, and the organic layer was transferred into another set of pre-labeled tubes. The transferred samples were evaporated to dryness at 30 °C. Finally, the dried samples were reconstituted with 150 µL of mobile phase (mixture of 0.5 mM Ammonium acetate buffer (pH 6.0) and acetonitrile at a ratio of 10:90 v/v).

Instrumentation

Each sample was injected at 10 µL through Chromolith® HighResolution RP-18e 100 × 4.6 mm column. The autosampler and column oven temperatures were set at 4 °C and 40 °C, respectively. The mobile phase was eluted in isocratic mode at a flow rate of 0.8 mL/min. Tandem mass spectrometry (MS/MS) with an electrospray ion source was used for detection in the positive multiple reaction monitoring (MRM) transitions m/z 321.96 to 211.83 for clopidogrel and m/z 327.99 to 217.85 for clopidogrel-d4. The mass parameters were set at 4000 volts for spray voltage, 350 °C for vaporizer temperature, 300 °C for capillary temperature, 40 psi for sheath gas pressure, and 10 psi auxiliary gas pressure. Liquid chromatography tandem mass spectrometry (LC-MS/MS) system used in this study was Nexera™ (Shimadzu Corporation, Japan) couple with TSQ Quantum Ultra (Thermo Fisher Scientific, USA). Data acquisition and evaluation of chromatographic data were performed using Xcalibur™ version 3.0.63.3 and LCquan™ version 2.9.0.34.

Pharmacokinetic and Statistical Analysis

Estimation of pharmacokinetic parameters was carried out by non-compartmental analysis, Phoenix WinNonlin Software version 6.3 (Pharsight Corporation, USA). The area under the plasma concentration versus time curve from time zero to the last measurable concentration (AUC_{0-24h}) was calculated using linear trapezoidal method. The area under the plasma concentration versus time curve from time zero to time infinity ($AUC_{0-\infty}$) was estimated using last measurable concentration (C_t) and terminal elimination rate constant (λ_z). The maximum concentration (C_{max}) and time at maximum plasma concentration (t_{max}) were directly obtained from the concentration-time data. The AUC_{0-24h}, $AUC_{0-\infty}$ and C_{max} were primary pharmacokinetic parameters used for bioequivalence evaluation. However, t_{max}, λ_z and half-life ($t_{1/2}$) were reported as secondary parameters.

The statistical analysis was carried out using SAS® version 9.3 (SAS Institute Inc., USA). Analysis of variance (ANOVA) were performed for log-transformed of primary parameters (AUC_{0-24h}, $AUC_{0-\infty}$, and C_{max}) using PROC GLM of SAS®. The ANOVA model included sequence, formulation, and period as fixed effects. Subject nested within sequence were included as a random effect, as well as an error term for sequence effect testing. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% ($\alpha = 0.05$). The 90% confidence interval (CI) for geometric least square mean ratio (test/reference) for log-transformed primary pharmacokinetic parameters should be within 80.00-125.00% of bioequivalence criteria. Wilcoxon signed-rank test was performed to compare t_{max} of the test and reference product at p-value = 0.05.

Results

In vitro Dissolution Study

The comparative dissolution profiles of the Clopidogrel GPO® and Plavix® in different dissolution media are showed in Figure 1 to 4. In KCl/HCl buffer pH 2.0, the f_2 could not be calculated as %CV of any product was more than 10% from second to last selected time point. However, the f_2 values for the dissolution test in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 were 69, 76 and 75, respectively which were within acceptance criteria of 50-100. Therefore, the comparative dissolution profiles of clopidogrel in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 were accepted as similar.

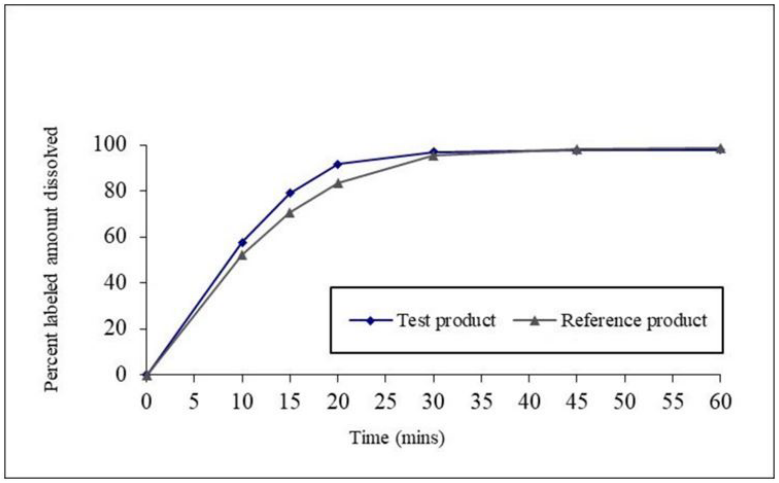

Figure 1: Dissolution profiles of the test and reference products in KCl/HCl buffer pH 2.0

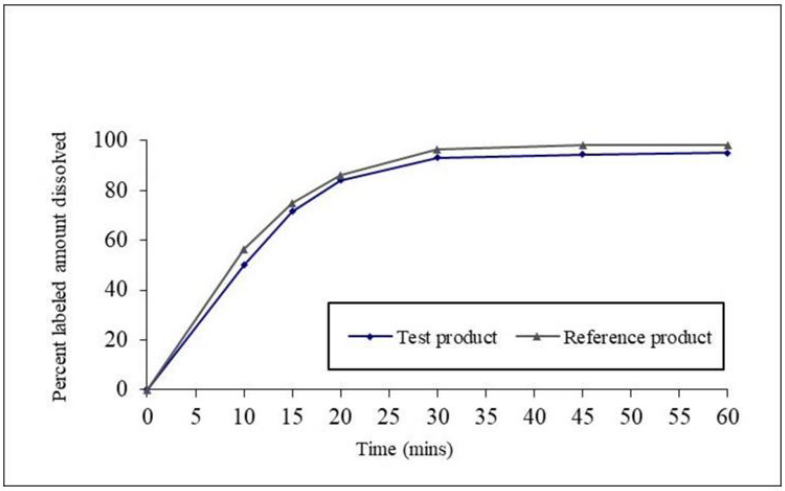

Figure 2: Dissolution profiles of the test and reference products in 0.1 N HCl

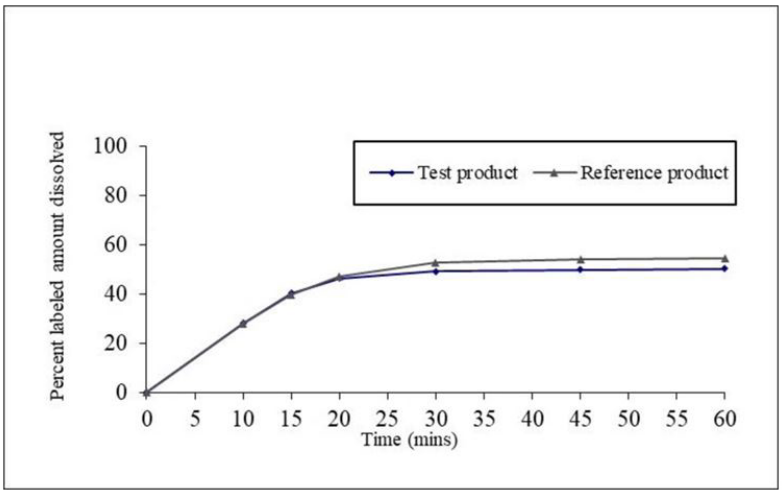

Figure 3: Dissolution profiles of the test and reference products in acetate buffer pH 4.5

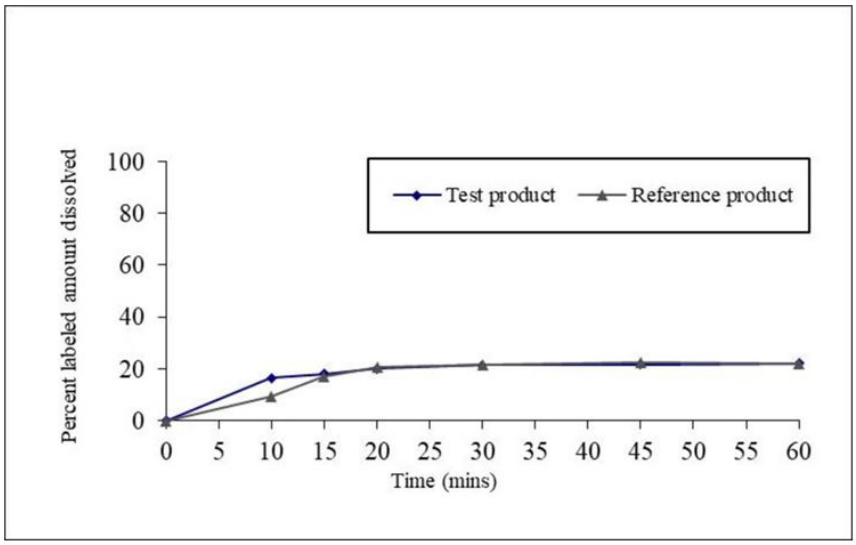

Figure 4: Dissolution profiles of the test and reference products in phosphate buffer pH 6.8

Demographic Characteristic of Subjects

One hundred and ten subjects were enrolled in the study and randomly divided into two groups, reference-test (RT) and test-reference (TR) consisting of 55 subjects each as per the randomization schedule. However, in period I, 4 subjects were withdrawn by the principal investigator as per predefined exclusion criteria. Additional 3 subjects dropped out before enrollment in period II due to personal reasons. Therefore, 103 subjects completed the study (49 male subjects and 54 female subjects). Their plasma concentration data were used for pharmacokinetic and statistical analysis. The mean ± SD of age, weight, height, and BMI of completed subjects were 31.55 ± 8.10 years, 58.86 ± 8.59 kg, 1.64 ± 0.08 m, and 21.87 ± 2.06 kg/m^2, respectively.

Sample Analysis

A total of 4598 samples were successfully analyzed in 56 analytical runs. The samples from the same subject were analyzed in the same analytical run. The between-run precision of the calibration curve standards ranged from 1.6 to 4.3% of the CV and the between-run accuracy ranged from 98.8 to 101.3% of the nominal concentrations. The correlation coefficient calculated from 8 calibration standards was more than 0.99 for all analytical runs. In addition, the range of percent CV and accuracy of quality control samples in each analytical run were 3.0-4.6% and 102.7-104.8%, respectively. The sample analysis was completed within 91 days as per validated long-term stability data.

Pharmacokinetic and Statistical Analysis

The mean plasma concentration of clopidogrel versus time curve after administration of the test and reference products are illustrated in semi-logarithmic scale (Figure 5). Pharmacokinetic parameters for the test and reference products from 103 subjects are summarized in Table 1. According to the results, clopidogrel was rapidly absorbed after oral administration attaining C_{max} around 2000 pg/mL at 50 minutes after administration. The elimination half-life of clopidogrel was about 3 hours for both formulations.

Parameter (Unit)	Un-transformed data (Mean ± SD, N=103)	
	Test	Reference
$AUC_{0\text{-}24h}$ (pg.hr/mL)	2634 ± 3124	2939 ±3640
$AUC_{0\text{-}\infty}$ (pg.hr/mL)	2785 ± 3248	3066 ± 3700
C_{max} (pg/mL)	1939 ± 2783	2087 ± 2941
t_{max} (hr)*	0.83 (0.50, 2.00)	0.83 (0.50, 2.50)
λ_z (1/hr)	0.50 ± 0.38	0.48 ± 0.38
$t_{1/2}$ (hr)	3.37 ± 6.46	3.05 ± 3.55
Extrapolated AUC (%)	6.19 ± 8.91	6.25 ± 6.18

*t_{max} were reported in Median (Min, Max)

Table 1: Pharmacokinetic parameters of test and reference formulations in healthy Thai volunteers

Statistical analysis was performed on the data obtained from the subjects who completed the study for both test and reference products (N=103). The results of ANOVA as shown in Table 2 suggested no statistically significant effect of sequence, period, and formulation on log-transformed $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, and C_{max}. The 90% CI of the geometric least squares mean ratio between the formulations was calculated for log-transformed $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$ and C_{max} as presented in Table 2. The results were within the

acceptance range of 80.00-125.00%. Wilcoxon signed-rank test indicated that there was insignificant difference in the median t_{max} between the test and reference products ($p > 0.05$).

Parameters	Geometric least squares mean ratio (90% CI)	Power	Intra subject CV (%)	ANOVA (p-value)		
				Sequence	Formulation	Period
ln (AUC_{0-24h})	92.2 (82.79-102.70)	96.1	49.2	0.2218	0.2143	0.2314
ln ($AUC_{0-\infty}$)	92.9 (83.38-103.45)	96.1	49.1	0.1852	0.2590	0.4195
ln (C_{max})	95.8 (85.84-106.89)	95.6	50.2	0.2045	0.5164	0.2182

Table 2: Statistical comparisons of pharmacokinetic parameters between test and reference formulations

Tolerability

The adverse events observed in this study are listed in Table 3. Both test and reference products were generally well tolerated by the study subjects. Six post-dose adverse events were reported in 6 subjects. Four adverse events (3.8%) reported in the subjects receiving the test formulation compared with 2 events (1.9%) reported in the subjects receiving the reference formulation. The most frequently reported adverse events were dizziness followed by headache and fever. All adverse events were possibly related to clopidogrel administration. The intensity of adverse events was mild and could recover without any medical treatment. All adverse events were reported to the ethics committee, Institute for Development of Human Research Protection (IHRP), Thailand.

Adverse event (AE)	Incidence by treatment groups			
	Test (N=106)		Reference (N=103)	
	N	%	N	%
Fever	1	0.9	0	0.0
Dizziness	2	1.9	1	1.0
Headache	1	0.9	1	1.0
Total AE	4	3.8	2	1.9

Table 3: List of adverse events

Discussion

The dissolution of the test and reference formulations were accepted as similar based on f_2 values calculated for 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. Although f_2 could not be calculated for KCl/HCl buffer pH 2.0, the dissolution profiles of both formulations were relatively superimposable (Figure 1). The comparative dissolution results were used to support the decision on the conduct of *in vivo* bioequivalence study.

The calculation suggested that 92 subjects were sufficient for the study. However, 110 subjects were enrolled by considering possible dropouts and withdrawals. High number of volunteers was also suggested by previous bioequivalence study in male Caucasians [12]. Rao TR, et al. demonstrated bioequivalence of clopidogrel with small number of subjects using pharmacodynamic approach [13]. However, pharmacokinetic approach is preferred as it is more accurate, sensitive and reproducible [14].

Around 6 mL of each blood sample was required to compensate approximately 50% loss during plasma separation. The remaining 3 mL of sample was required for analysis and possible repeat analysis. Higher volume was required for pre-dose sample as it was additionally used to evaluate the interference in bioanalysis caused by endogenous compounds in each subject. The samples were analyzed using the validated method. The precision and accuracy determined by calibration standards and quality control samples in the analytical runs also suggested that the analysis was reliable and reproducible.

Although clopidogrel is a prodrug, bioequivalence is recommended to be demonstrated using parent compound rather than its active metabolite. This is because the rate and extent of absorption derived from parent compound is more relevant to drug release from the formulation according to EMA guideline on the investigation of bioequivalence [15] and FDA published product-specific guidance for generic drug development [16]. The pharmacokinetic parameters of the test and reference formulations were comparable corresponding to similar plasma concentration-time profiles as presented in Figure 5. The extrapolated AUC beyond the last sampling time point was less than 10% suggesting that $AUC_{0-\infty}$ was reliably estimated. The pharmacokinetic parameters in this study were in agreement with previous study in the same population [17]. In addition, pharmacokinetic parameters in Thai population were comparable to Chinese [18]. However, the $AUC_{0-\infty}$ and $t_{1/2}$ reported for Mediterranean subjects were greater than observed in this study. (mean $AUC_{0-\infty}$ = 4868.249 pg·h/mL, median $t_{1/2}$ = 4 hours) [19]. In contrast, the C_{max} demonstrated in Argentinean population (913.49 pg/mL) were significantly lower than that observed in this study [20]. The pharmacokinetic of clopidogrel in Thai population resembled that in Caucasians receiving 150 mg clopidogrel [14]. The pharmacokinetics of clopidogrel might differ according to ethnicity [2,21]. Therefore, bioequivalence should be demonstrated in Thai population, in which the generic product is intended to be marketed.

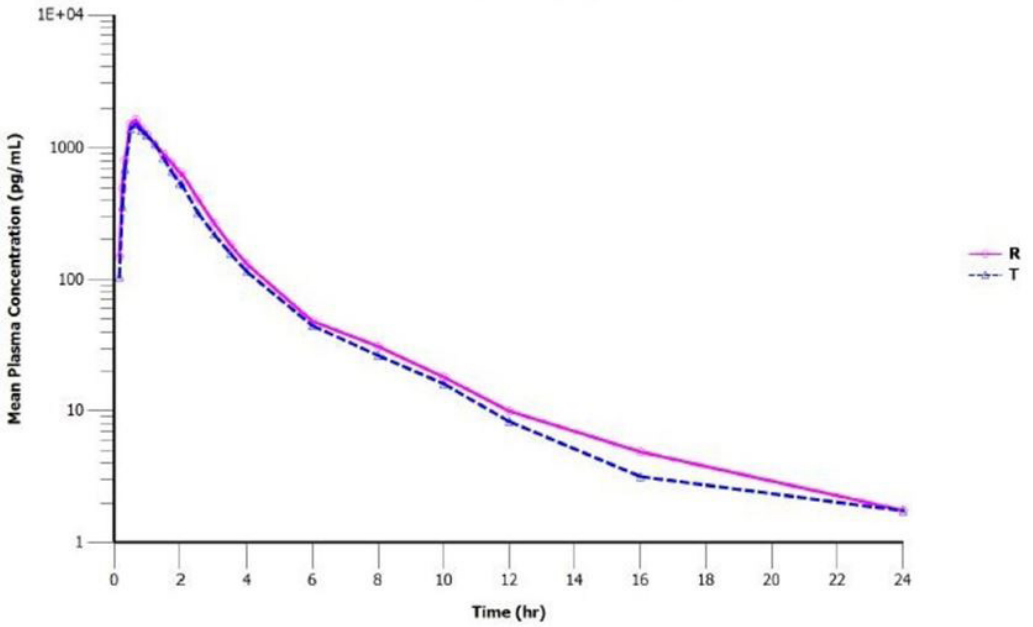

Figure 5: Semi-logarithmic plot of mean plasma concentration of clopidogrel versus time curves after administration of test product-T and reference product-R in healthy Thai volunteers under fasting conditions (N=103)

The similarity of pharmacokinetics describing the rate and extent of absorption between the test and reference formulations was confirmed based on statistical indices. The primary pharmacokinetic parameters: $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, and C_{max} were insignificantly different, as well as secondary parameter determined rate of absorption, t_{max}. Bioequivalence was concluded based on 90% CI of the geometric least squares mean ratio of log-transformed primary pharmacokinetic parameters. Only mild adverse events (dizziness, fever, and headache) were observed in this study. Both test and reference formulations were well tolerated. There were no subjects developed serious adverse events concerning to clopidogrel e.g. bleeding.

Conclusion

The bioequivalence study in healthy Thai volunteers demonstrated that pharmacokinetics describing rate and extent of absorption of Clopidogrel GPO® (test formulation) were statistically comparable to Plavix ® (reference formulation). Both treatments were well tolerated by the study subjects. It could be inferred that two formulations were bioequivalent and could be used interchangeably regarding the similarity on the pharmacokinetics and tolerability.

Acknowledgement

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