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Bioequivalence Study of Donepezil 10 mg Orally Disintegrating Tablets in Healthy Thai Volunteers Under Fasting Conditions

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Abstract

Donepezil is a potent, selective, noncompetitive and reversible inhibitor of acetylcholinesterase, commonly used for the treatment of Alzheimer's disease. The form of orally disintegrating tablets (ODTs) is a good alternative dosage form for patients who have a difficulty in swallowing conventional tablets or capsules. The Government Pharmaceutical Organization (GPO), Thailand had developed a generic product of donepezil ODTs with a lower price that would be beneficial for long-term treatment. The purpose of this study was to evaluate the bioequivalence between the generic formulation, Doracept 10 mg ODTs (GPO) and the originator, Aricept Evess 10 mg ODTs (Eisai Co., Ltd.). A randomized, single-dose, two-way crossover, open-label bioequivalence study was conducted in 30 healthy Thai volunteers under fasting conditions. The plasma samples were analyzed for donepezil concentration using a validated liquid chromatography tandem mass spectrometry method. Non-compartmental model was used for pharmacokinetic analysis. The mean values (±SD) of pharmacokinetic parameters (test vs. reference) were 638.663 ± 110.985 vs. 607.588 ± 80.986 ng.hr/mL for $AUC_{0\text{-}72h}$, and 26.293 ± 6.097 vs. 25.171 ± 5.460 ng/mL for C_{max}. The 90% confidence intervals of geometric least squares mean ratio (test/reference) of log-transformed $AUC_{0\text{-}72h}$ and C_{max} were 101.29-107.83% and 94.99-114.65%, respectively which were within the acceptance range of 80.00-125.00%. Both products were generally well tolerated by the healthy Thai subjects. The results of this study indicated that both formulations were bioequivalent in terms of the rate and extent of drug absorption.

Keywords: Donepezil; Pharmacokinetics; Bioequivalence; ODT

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder which is the most common cause of dementia in the elderly population. In Alzheimer's disease patients, cholinergic neurotransmission is gradually declined correlated with reduced cognitive function and disease progression [1]. Acetylcholinesterase inhibitors can prevent the hydrolysis of acetylcholine, thereby increasing acetylcholine levels in the neural synapse [2]. Targeting the cholinergic system represents a promising treatment for Alzheimer's disease patients in slowing the development of the disease, improving behavioral symptoms and maintaining mental function.

Donepezil hydrochloride, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride is a potent, selective, noncompetitive and reversible inhibitor of acetylcholinesterase, most commonly used for the treatment of Alzheimer's disease [1–3]. Its molecular formula is $C_{24}H_{30}ClNO_3$ and the chemical structure is shown in Figure 1. Donepezil has relatively oral bioavailability of 100% after oral administration [4]. The peak concentrations of drug are achieved in approximately 2 to 5 hours [5]. Following once daily dosing, the steady-state plasma concentrations are reached in 14 to 21 days [6]. The pharmacokinetics of donepezil are relatively linear over a dose range of 1 to 10 mg, with the average apparent clearance of 0.13 to 0.19 L/h/kg [4,7]. The drug has elimination half-life of approximately 72 to 81 hours allowing once-daily administration [5,6,8]. Donepezil is excreted as unchanged form in urine and feces accounted for 57% and 15% of the dose, respectively [9]. The daily dose of donepezil should start at 5 mg for at least a month, and it can be increased to 10 mg if it is tolerated. Dose adjustment is not required in patients with renal or hepatic impairment [10].

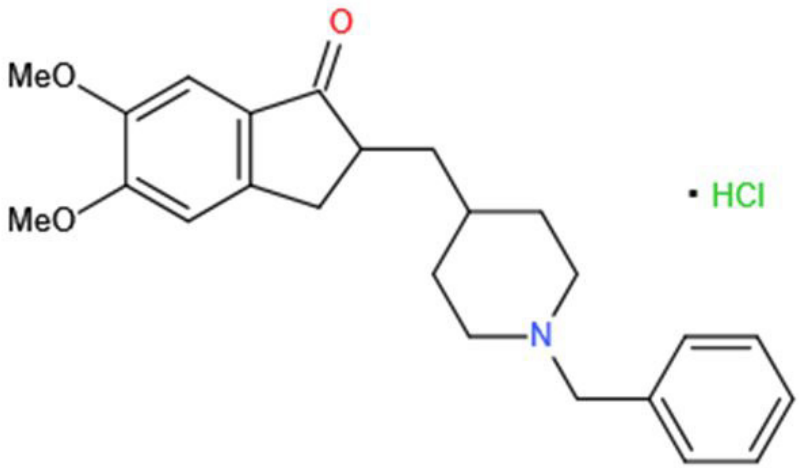

Figure 1: Chemical structure of donepezil hydrochloride

The form of orally disintegrating tablets (ODTs) is a good alternative dosage form for patients who have a difficulty in swallowing conventional tablets or capsules. The ODT dosage form helps improve patients compliance [11], as well as caregivers' satisfaction compared with film-coated tablets [12]. In addition, pharmacokinetic equivalence has been demonstrated between conventional donepezil tablets and donepezil ODTs [10,13]. The Government Pharmaceutical Organization (GPO) had developed the generic product of donepezil with a lower cost that would be beneficial for patients who require long-term use of medication. Therefore, the bioequivalence study was conducted to compare the rate and extent of absorption between the two formulations of donepezil and evaluate the safety of the formulations in healthy Thai volunteers. To our best knowledge, this is the first report characterizing pharmacokinetics of donepezil and supporting the interchangeability use of the generic product in treatment of Alzheimer's disease in Thai population.

Material and Method

Study products

The test product was Doracept, donepezil hydrochloride 10 mg ODTs manufactured by The Government Pharmaceutical Organization (GPO), Thailand (Batch no. S570051). The reference product was Aricept Evess, donepezil hydrochloride 10 mg ODTs manufactured by Eisai Co., Ltd., Tokyo, Japan (Batch no. 3YA25M).

Comparative dissolution study

Prior to bioequivalence study, the pharmaceutical equivalence between the test and reference products was evaluated by using *in vitro* dissolution testing in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 medium. The dissolution study was carried out on 12 units each of the test and reference products using the Apparatus II (paddle). The dissolution profiles were to be accepted as similar according to the regulatory guidelines for conducting bioequivalence studies [14].

Study design

A comparative randomized, single dose, two-way crossover, open label bioequivalence study of two donepezil 10 mg ODT formulations was conducted in healthy Thai male and female adult subjects, under fasting conditions allowing washout period of 28 days between treatments. The subjects either received the test or reference product in period I, and switched to the other product in period II as per the randomization schedule generated using the SAS® version 9.3 (SAS Institute Inc., USA). The study protocol was reviewed and approved by the Institute for the Development of Human Research Protections (IHRP), Department of Medical Sciences, Ministry of Public Health, Thailand (Letter No. 312/2558). The study was conducted at Clinical Research Center, Department of Medical Sciences, Ministry of Public Health, Nontaburi, Thailand.

Study subject

The sample size of subjects was determined by considering 20% of intra-subject variability (in-house), T/R ratio at 95%, significant level at 5%, power ≥ 90% and bioequivalence limits of 80.00-125.00% which yielded a sample size of 24 subjects [15]. However, thirty healthy Thai male and female subjects were enrolled in the study to compensate estimated 20% dropouts. Subject inclusion criteria included the age between 18-55 years, having a body mass index (BMI) between 18.0-25.0 kg/m^2. A negative pregnancy test and non-breastfeeding were additionally required for female subjects. All subjects were determined healthy based on the medical history, physical examination and laboratory examinations including complete blood count, hematocrit, hemoglobin, fasting blood sugar, blood urea nitrogen, serum creatinine, alkaline phosphatase, alanine aminotransferase, aspartate transaminase, total bilirubin, total protein, albumin, hepatitis B test, urine analysis, and 12-Lead ECG.

The participants who were contraindicated or hypersensitive to donepezil or any excipient in the formulations were excluded. Those with underlying diseases, cigarette smoking, alcohol dependence, recent blood donation or participation in any clinical trial were not enrolled. All subjects were restricted from any xanthine containing food or beverages (e.g., tea, coffee, chocolates or cola drinks), tobacco, tobacco containing products, grapefruit, pomelo, orange, or any products containing these fruits, alcohol or alcoholic products prior to study initiation and for entire duration of the study. The subjects were informed about risks and benefits of the study and signed informed consent before participating in the study. The adverse events were monitored throughout the study period and recorded in case record forms.

Dosing and blood sampling

Subjects were admitted at the clinical facility one night before study drug administration. After an overnight fasting for at least 10 hours, 20 mL of water was given before directly applying an ODT tablet on the tongue in sitting posture. Once the tablet was completely disintegrated, the subjects were asked to swallow drug-dispersed saliva. No water, except the 20 mL given before drug administration was allowed for an hour before and after drug administration. Food was restricted for 4 hours after dosing.

Blood samples were collected into vacutainers containing dipotassium ethylenediaminetetraacetate (K_2EDTA) by the indwelling venous cannula at total 23 sampling time points (pre-dose (0), 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 48 and 72 hours after administration) from each subject in each period. After collection, the blood samples were centrifuged at 3000 relative centrifugal force (rcf), below 10 °C for 5 minutes to separate plasma. Plasma samples were divided into two aliquots as per the study protocol (back-up lot was used in case of reanalysis) and stored at -65 ± 10 °C until completion of analysis.

Bioanalytical method validation

The plasma concentrations of donepezil in study samples were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method using donepezil-d5 as an internal standard. The US FDA guidance for industry on bioanalytical method validation [16] and the European Medicines Agency guideline on bioanalytical method validation [17] were followed.

Sample analysis

All plasma samples were analyzed at GPO within the timeframe supported by the data of long-term stability of analyte in matrix. The analyte and internal standard were extracted from plasma using liquid-liquid extraction method. Hexane and ethyl acetate mixture (80:20 v/v) was used as an extraction solvent. The samples were vortexed and centrifuged at 3400 ± 100 rcf, 10 °C for 5 minutes. Then the plasma layer was flash frozen and the organic layer was transferred into pre-labeled tube. The organic layer was evaporated at 40 °C to dryness using centrifugal vacuum evaporator and subsequently reconstituted with 200 µL of mobile phase. The contents were transferred into appropriate vials for analysis. The plasma concentrations of donepezil in study samples were determined by a liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The analyte and internal standard were monitored in the positive ion mode at MRM transitions of *m/z* 380.210→91.020 and *m/z* 385.200→96.020 for analyte and internal standard, respectively. The chromatographic system consisted of ACE 3 C18 100×4.6 mm column as a stationary phase. A mixture of 10 mM ammonium formate buffer (pH 5.0) and methanol (20:80 v/v) was used as the mobile phase pumped at a flow rate of 0.5 mL/minute. The samples were injected at 2 µL. 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 2.2.0.48 and LCquan™ version 2.8.0.51.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters including the area under the plasma concentration curve from administration to 72 hours after dosing (truncated AUC at 72 hours: $AUC_{0\text{-}72h}$), maximum plasma concentration (C_{max}) and time at maximum plasma concentration (t_{max}) were determined by non-compartmental model using Phoenix WinNonlin Software Version 6.3 (Pharsight Corporation, USA). $AUC_{0\text{-}72h}$ and C_{max} were primary pharmacokinetic parameters used for bioequivalence evaluation. However, t_{max} was reported as a secondary pharmacokinetic parameter.

The statistical comparison of the primary pharmacokinetic parameters ($AUC_{0\text{-}72h}$ and C_{max}) between the two formulations was carried out by using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA). The $AUC_{0\text{-}72h}$ and C_{max} were transformed to log scale before carrying out the statistical analysis. ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence, subject (sequence) as a random effect. Sequence effect was tested using subject (sequence) as an error term. F-test

was performed to determine the statistical significance of the effects involved in the model. The bioequivalence between the test and reference products was to be concluded when the 90% confidence intervals (CIs) of ratio of geometric least squares mean for log-transformed AUC_{0-72h} and C_{max} of donepezil fell within the acceptance range of 80.00-125.00% [14,18]. The t_{max} was compared using the Wilcoxon sign-rank test. All statistical calculations were performed at a significance level of 5% (α=0.05).

Results

Comparative dissolution study

The comparative dissolution profiles of two formulations of donepezil, Doracept and Aricept Evess were accepted as similar without f_2 calculation since the results showed that donepezil in both formulations were dissolved more than 85% of the labeled amount within 15 minutes in 0.1 N HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8 medium.

Demographic characteristics of subjects

For 30 enrolled subjects, there were 17 males and 13 females. A mean ± SD of age was 32.77 ± 9.45 years (ranging from 18 to 51 years) and a mean ± SD of BMI was 21.49 ± 2.09 kg/m^2 (ranging from 18.67 to 24.98 kg/m^2). A total of 19 subjects (15 male subjects and 4 female subjects) received both test and reference products and completed the study as per the approved protocol. Out of 11 subjects who did not complete the study, 9 subjects were withdrawn during period I due to vomiting within 6 hours after dosing (two times of the median t_{max}). Two subjects dropped out before check-in of period II due to personal reasons.

Bioanalytical method validation

The validated calibration curve ranged from 0.508 to 74.981 ng/mL. The lower limit of quantification of this method was 0.508 ng/mL. The between-run accuracy was between 102.8 and 104.8% while the precision calculated as %CV was less than 5%. The mean extraction recovery of donepezil was 88.4% while that of donepezil-d5 was 91.3%. Short-term stability showed that donepezil was stable in plasma at least 18 hours at room temperature. Long-term stability showed that donepezil was stable in plasma for at least 104 days when stored at -65 ± 10 °C.

Sample analysis

A total of 976 samples collected in the study were successfully analyzed in 12 analytical runs. All samples from the subjects who were withdrawn and dropped out were analyzed, but the data from these subjects were not included for pharmacokinetic and statistical analysis. The between-run precision (CV, %) of the calibration curve standards and quality control samples ranged from 1.1 to 3.3% and 4.3 to 6.9%, respectively. The between-run accuracy was within ±15% of the nominal concentrations for both calibration curve standards and quality control samples.

After all plasma samples were analyzed, abnormal drug concentrations were observed in a subject after receiving the reference product in period II as shown in Figure 2. Reanalysis of the samples reproduced the original results. The concentrations were around 1-3 ng/ml at all time points. All activities were thoroughly investigated and found that they were performed in accordance with the protocol. From retrospective investigation, however, the subject reported the spitting of saliva at 5 minutes post-dose during the urination. As the pill of the study product was not found due to the characteristic of the ODT, the subject did not notify the clinical investigator and was not withdrawn from the study instantly. Considering that the situation occurred before 2 times median t_{max} in the period when the reference product was administered, it was highly possible that some amounts of drug disintegrated in the saliva was not absorbed [14,18]. It was justifiable to exclude this subject data from the pharmacokinetic and statistical analysis since the concentration data of this study subject was unreliable. Consequently, the plasma concentration data of total 18 subjects were used for pharmacokinetic and statistical analysis.

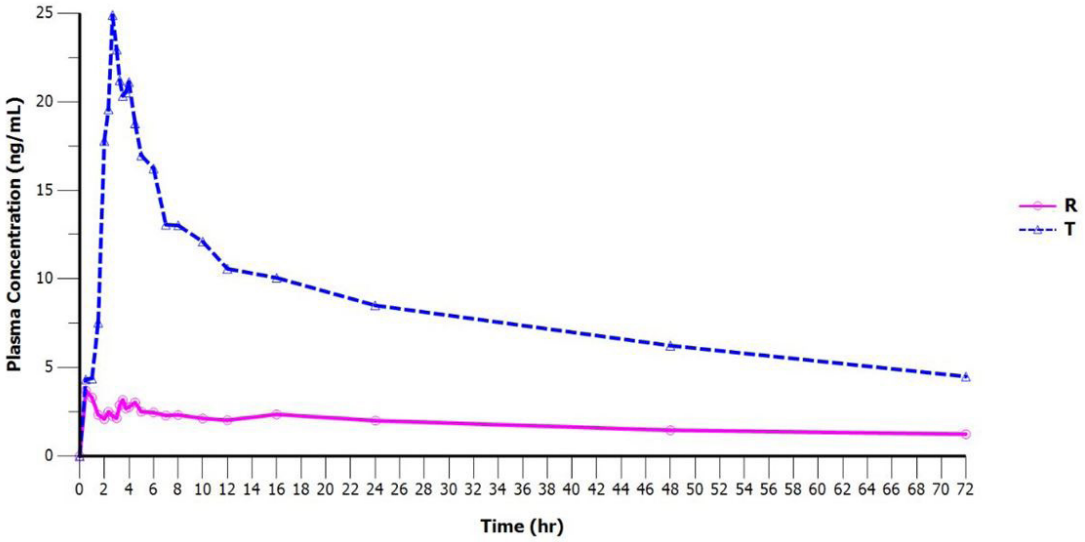

Figure 2: Donepezil plasma concentration-time profiles of subject having abnormal drug concentrations after the reference product (R) administration

Pharmacokinetics and statistical analysis

Product	Mean ± SD		Median t_{max} (hr) (Min,Max)
	AUC_{0-72h} (ng.hr/mL)	C_{max} (ng/mL)	
Test (N=18)	638.663 ± 110.985	26.293 ± 6.097	2.333 (1.000,3.000)
Reference (N=18)	607.588 ± 80.986	25.171 ± 5.460	2.333 (1.000,4.000)

Table 1: The pharmacokinetic parameters of the test and reference products of donepezil in 18 volunteers

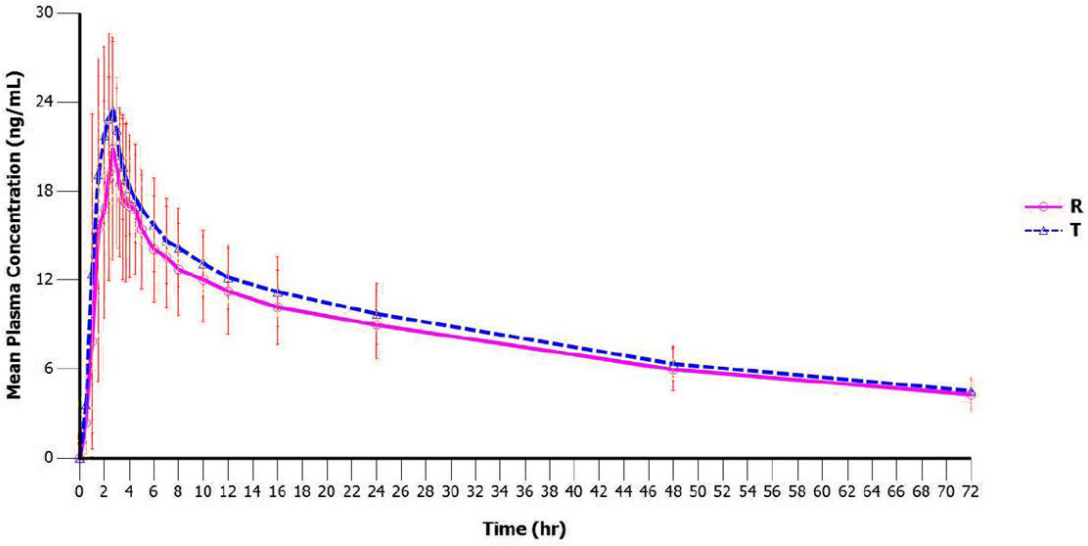

Figure 3: Mean plasma concentration-time profiles of donepezil after administration of the test (T, Doracept) and reference (R, Aricept Evess) formulations to healthy Thai subjects under fasting conditions

Eighteen subjects who provide evaluable data for both of the test and reference products were used for pharmacokinetic and statistical analysis. The primary pharmacokinetic parameters (AUC_{0-72h} and C_{max}) and secondary pharmacokinetic parameters (t_{max}) of the test and reference are presented in Table 1. The mean plasma concentration-time profiles of donepezil after administration of the test and reference products under fasting conditions are illustrated in Figure 3.

The results of ANOVA (Table 2) showed insignificant effect of sequence and period on log-transformed AUC_{0-72h} and C_{max}, but significant formulation effect was observed on AUC_{0-72h} ($p<0.05$). The 90% CIs calculated for the log-transformed primary pharmacokinetic parameters are presented in Table 2. The results demonstrated that the 90% CIs for the ratio of geometric least squares means of AUC_{0-72h} and C_{max} of donepezil were within the bioequivalence range of 80.00-125.00%. The powers of the tests were more than 90%, 100.0% for AUC_{0-72h} and 98.5% for $C_{max.}$ Wilcoxon sign-rank test was performed and indicated no significant difference in median t_{max} between the test and reference formulations ($p>0.05$).

Parameters	Geometric least squares mean ratio (90% CI)	Power (%)	Intra-subject CV (%)	ANOVA (p-value)		
				Sequence	Formulation	Period
ln AUC_{0-72h}	104.5 (101.29-107.83)	100.0	5.4	0.5509	0.0255	0.5528
ln C_{max}	104.4 (94.99-114.65)	98.5	16.3	0.1271	0.4400	0.8476

Table 2: Statistical comparison of the log-transformed primary pharmacokinetic parameters (N=18)

Safety

A total of 65 adverse events were reported in 19 subjects during the study periods (Table 3). There were 37 adverse events occurred in the period when the test products were administered while 28 adverse events were reported when the reference products were administered. The most commonly reported symptom was dizziness (35.4%), of which the incidence was comparable between subjects receiving the test and reference products. The other common adverse events were related to gastrointestinal system including nausea (15.4%), vomiting (13.8%), abdominal pain (10.8%), abdominal discomfort (6.2%), and diarrhea or loose stool (6.2%). Majority of the adverse events were mild to moderate in severity and showed relevance to the study drug. However, the symptoms of tendinitis and dysmenorrhea occurred before dosing and during menstrual cycle, respectively which were classified as irrelevant to the investigational medicinal products. Some adverse events could recover without any medications, while some could resolve with the prescribed medications which their use had been proven to not interfere in the determination of donepezil plasma concentration. All study subjects were re-evaluated for their safety at the end of the study and no abnormal findings were reported through physical and laboratory examinations.

Adverse events	Test product	Reference product
Dizziness	12	11
Fatigue	2	0
Increased sweat	1	1
Headache	1	0
Palpitation	1	0
Nausea	6	4
Vomiting	4	5
Diarrhea or Loose stool	2	2
Abdominal pain	6	1
Abdominal discomfort	1	3
Dysmenorrhea	0	1
Tendinitis	1	0
Total No. of adverse event	37	28

Table 3: Adverse events

Discussion

The study was designed to evaluate bioequivalence between the test and reference formulations under fasting conditions because no food effect was observed on the pharmacokinetics of donepezil, and this condition is the most sensitive to detect formulation difference [18,19]. The main purpose for development of the generic ODTs is to develop an alternative dosage form for patients with dysphagia. Therefore, the study was designed to administer the ODTs after mouth wetting and the subjects were asked to swallow drug-dispersed saliva. With this administration, the authentic ODT characteristics were evaluated as per the intended use of this dosage form. In addition, Aricept Evess can be administered with and without water and the bioequivalence when taken with water can be assumed if the bioequivalence is evaluated when taken without water [10,14]. Regarding long elimination half-life approximately 72 to 81 hours allowing once-daily administration [5,6,8], a washout period of 28 days used in this study was sufficient for complete elimination of the drug given in period I. In addition, the results of sample analysis showed no response of donepezil in pre-dose samples of all subjects in period II given that the limit of quantification (LLOQ) at 0.508 ng/mL was below 5% of the C_{max} supporting appropriate sensitivity of the assay [17].

From the sample size calculation, 24 subjects were required to establish bioequivalence between two donepezil formulations. Although only 18 subjects completed the study and their data were used for pharmacokinetic and statistical analysis, the data were sufficient for establishing bioequivalence with the power greater than 90%. The pharmacokinetic parameters of donepezil characterized in this study were in agreement with the results of the studies in Korean and Indonesian volunteers [4,20]. Although donepezil in different dosage forms were administered, the C_{max} and t_{max} observed in Korean volunteers receiving 10 mg conventional tablets were similar to those observed in Thai volunteers receiving 10 mg ODTs as supported by the pharmacokinetic equivalence between these formulations [10,13]. The mean C_{max} (±SD) of the reference tablet formulation was 26.35 (± 6.51) ng/mL in Korean volunteers [4], while that of the reference ODT formulation was 25.171 (± 5.460) ng/mL in Thai volunteers. The C_{max} of the reference products was attained at around 2 hours after administration in both populations. The mean AUC_{0-72h} and C_{max} observed after administration of reference 10 mg ODT tables in Indonesian volunteers were 697.33 ng.hr/mL and 23.78 ng/mL, respectively [20] which were comparable with the parameters observed in Thai volunteers (Table 1). The AUC of donepezil was truncated at 72 hours as it should cover the absorption phase of immediate release dosage form and could be used to assess bioequivalence of long half-life drug [14]. Moreover, the previous studies had demonstrated the use of truncated AUC for the assessment of bioequivalence of donepezil [20-22].

Considering the results of ANOVA testing for AUC_{0-72h} of donepezil, formulation effect was significant ($p<0.05$). It was ensured that the clinical and bioanalytical activities were standardized for all subjects and all study samples. The significant difference occurred as the variability of AUC_{0-72h} was lower than C_{max}. The mean square error for AUC_{0-72h} explaining the variation within the treatments was smaller than that of C_{max} whereas the variation between the treatment of both parameters were comparable resulting in larger test statistic value (F-value) for the AUC_{0-72h}. Additionally, the bioequivalence was concluded by 90% CIs for the ratio of geometric least squares means of AUC_{0-72h} and C_{max} of donepezil which were within the acceptance criteria of 80.00-125.00%. Therefore, a significant formulation effect did not interfere in the results of this study [23].

Although the adverse events were reported in 19 subjected accounted for 63.3% of the enrolled subjects, the intensity of the adverse events was mild to moderate. The safety and welfare of study subjects were thoroughly examined during the study, as well as confirmed at the end of study. No serious adverse events were reported, and all adverse events could resolve by the end of the study. Furthermore, 9 subjects who reported vomiting were withdrawn as per the pre-defined criteria in the study protocol and there were no dropouts due to drug intolerance. It is important to note that this study had limitation in evaluating tolerability after long-term use which should be further investigated.

Conclusions

According to the results of statistical analysis of the primary pharmacokinetic parameters in this study, it could be concluded that the test product (Doracept; GPO) and the reference product (Aricept Evess; Eisai Co., Ltd.) were bioequivalent with respect to the rate and extent of absorption. Both products were well tolerated by the study subjects without serious adverse events reported. The bioequivalence supported the registration of the donepezil hydrochloride 10 mg ODTs, manufactured by GPO, as well as the use as a generic substitute for the treatment of Alzheimer's disease.

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