INTRODUCTION

Bioequivalence is defined as “the absence of significant differences 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 appropriate designed study” (1, 2). Bioequivalence studies compare both the rate and extent of drug absorption, on the basis that if two formulations exhibit similar drug concentration-time profiles in the blood or plasma, they should exhibit similar therapeutic effects (1, 2). The method of bioequivalence studies include pharmacokinetic, pharmacodynamic, clinical trial and *in vitro* studies (1, 2). Product quality bioequivalence study frequently relies on pharmacokinetic measurements such as maximal concentration (C_{max}) and area under the plasma concentration-time curve (AUC) that are reflective of the rate and extent of drug absorption (1, 2). A typical study recommended by the US FDA is conducted as a crossover study with the two phases of treatment separated by an adequate washout period (1, 2). In this type of study, clearance (CL), volume of distribution (V_d), and absorption, as determined by physiological variables are assumed to have less intra-subject variability since each subject serves as his or her own control when compared to the variability a rising from drug formulation (1, 2). Therefore, differences between the two products due to formulation factors can be determined (1, 2). A single-dose pharmacokinetic study is also recommended, since they are generally more sensitive in assessing release of the drug substance from the drug product into the systemic circulation (3). The study population should be healthy volunteers (18-55 y old) and capable of giving informed consent (3). To compare the pharmacokinetic parameters in a typical study, data should be analyzed using an average bioequivalence criterion and parametric methods are recommended for the analysis of log-transformed pharmacokinetic parameters (1, 2). The general approach is to constructed a 90% confidence interval (90% CI) for the quantity $\mu_T - \mu_R$ and to reach a conclusion of bioequivalence if this CI is

contained in the interval of 0.8-1.25 (1, 2). The 90% CI for the difference in the mean of the log-transformed data should be calculated using ANOVA (1, 2). The anti-logs of the confidence limits obtained constitute calculated using analysis of variance (1, 2). The antilogs of the confidence limits obtained constitute the 90% CI for the ratio of the geometric means between the test and reference products (1, 2).

Alzheimer's disease (AD) is a chronic, progressive, neurodegenerative disorder of the brain characterized clinically by deterioration in the key symptoms of activities of daily living, behavior and cognition (4). Approximately 2 to 3% of individual between 65 to 84 years of age and 25 to 50% of individuals over 85 suffer from this disease (5). In the United states, the disease accounts for about $100 billion per year in medical and custodial expenses, with the average patient requiring an expenditure of about $27,000 per year for medical and nursing care (6, 7). In addition, 80% of caregivers report stress, and about 50% report depression (6, 7).

The cholinergic hypothesis states that the decline in AD is secondary to deficits in central cholinergic neurotransmission resulting from a loss of acetylcholine (ACh) (4). Cholinesterase (ChE) inhibitors enhance central cholinergic function by inhibiting the enzyme that degrades ACh, thereby increasing the availability of ACh to stimulate nicotinic and muscarinic receptors within the brain (4). ChE inhibitors have been and remain the standard approach to the symptomatic treatment of AD (8, 9). Three ChE inhibitors are commonly prescribed for the symptomatic treatment of AD, the acetylcholinesterase (AChE)-selective inhibitors, donepezil and galantamine, and the dual AChE and butyrylcholinesterase (BuChE) inhibitor, rivastigmine (8, 9). A fourth agent, tacrine, is no longer routinely prescribed due to a high incidence of hepatotoxicity at therapeutic dose (8, 9).

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase approved for the symptomatic treatment of AD (10, 11). Since current theories on the pathogenesis of AD attribute some of them to a deficiency of cholinergic neurotransmission, AChE inhibitors, which prevent the hydrolysis of ACh, will exert its therapeutic effect by enhancing cholinergic function (10). Donepezil is potent and more selective AChE inhibitor in the central nervous system with little effect on AChE in peripheral tissue, therefore has a lower incidence of GI adverse events (10). There are no differences in cardiovascular adverse effects between placebo and

donepezil groups in the clinical trials (12). Donepezil produces modest improvements in cognitive scores in AD patients and has a long half-life allowing once-daily dosing (12). Data from single and multiple-dose studies of donepezil in patients with moderately to severely impaired renal function indicate that donepezil is safe and well tolerated in these groups (13). Both in vitro and clinical studies have shown that donepezil is not associated with drug-drug interaction (10). Although insomnia and other sleep disorders have been reported following administration of donepezil, lengthening the time period before increasing the dose of donepezil from 5 to 10 mg per day or switching to morning dosing can reduce these events to the levels of placebo-treated patients (10).

A generic preparation of donepezil has been developed for clinical use with a lower cost. Although a generic and the innovator preparations contain the same active ingredient, they may differ from each other in term of manufacturing processes as well as content of excipients, which may result in differences in pharmacokinetics, especially in term of absorption. Therefore, this study investigated the influence of the formulations on the pharmacokinetics of the two products in healthy Thai male volunteers. Since the elderly population is on sharp rise in Thailand, the information obtained from this study in Thai volunteers can be more relevant for Thai patients with AD and can also be used as guidelines for selection of appropriate donepezil products and dosage regimen suitable for individual patients, and can better improve the outcome and quality of life of AD patients. The use of an alternative generic donepezil would also prove to be more cost-effective for this chronic degenerative disease.