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Pharmacokinetic Profiles of Donepezil in Combination with Gwibi-Chongmyungtang in Rats

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ABSTRACT

Donepezil, an acetylcholinesterase inhibitor, is mainly used for treatment of dementia. Recently, the combination therapy with donepezil has been interested to enhance the efficacy and reduce the potential side effects. Gwibi-Chongmyungtang (GCMT) is one of the most famous Korean medicines used for improving learning and memory. Therefore, pharmacokinetic interactions between donepezil and GCMT were examined for the combination therapy. Rats received oral coadministration of donepezil with GCMT (combination) or donepezil with distilled water (control). The distilled water or GCMT was coadministered by single dosing within 5 min after donepezil or by repeated dosing for a week at 1.5 h intervals. The plasma samples were analyzed for the donepezil concentration and the pharmacokinetic parameters (T_{max} , C_{max} , AUC, $t_{1/2}$ and MRT_{inf}). In the single oral coadministration with GCMT within 5 min after donepezil, the combination resulted in reduced plasma concentration of donepezil compared to control, suggesting pharmacokinetic interactions between donepezil and GCMT. There were no differences in the plasma concentration between the combination and control, when GCMT was coadministered at 1.5 h intervals. However, the repeated dosing of combination for a week at 1.5 h intervals decreased plasma concentration of donepezil compared to control. Pharmacokinetic analyses showed reduced AUC_{0-4} and AUC_{0-inf} in the single dosing of combination within 5 min and repeated dosing of combination for a week at 1.5 h intervals, suggesting that GCMT can reduce the bioavailability of donepezil. The current results showed that GCMT is hard to use in combination with donepezil by coadministration within short interval, 5 min or a week repeated dosing despite at 1.5 h intervals.

Key words: Donepezil, Gwibi-Chongmyungtang, pharmacokinetics, herbal products, rat

INTRODUCTION

With an increase of the aging population, one of the major concerns may be dementia leading to learning deficit, memory loss and other cognitive impairments (Kalaria, 2010). The

most common cause of dementia is involved in Alzheimer's Disease (AD) and other causes are various cerebrovascular, metabolic or neurodegenerative disorders which affect parts of the brain. There are consistent evidences showing that acetylcholinesterase (AChE) inhibitors (e.g., donepezil and

rivastigmine) and N-methyl-D-aspartate receptor antagonist (NMDA) receptor antagonists (e.g., memantine) have beneficial effect in the treatment of AD (Herrmann *et al.*, 2011). Among them, donepezil has not been reported to be effective in the mild to moderate AD (Birks and Harvey, 2006) but also in the Lewy body dementia (Rogers, 1998) and vascular dementia (Malouf and Birks, 2004). In addition, donepezil ameliorate sleep apnea in AD (Moraes *et al.*, 2008) and speech deficits in autism (Handen *et al.*, 2011).

Although the donepezil is a well-tolerated drug, the clinical applications are very limited with potential side effects in the cholinergic-stimulated gastrointestinal system, especially in the initial treatment of donepezil or its increased doses (Shintani and Uchida, 1997; Dunn *et al.*, 2000). The other side effects include bradycardia, anorexia, vivid dreams and mania (Benazzi, 1999; Umegaki *et al.*, 2008; Lockhart *et al.*, 2009). Furthermore, considering that the AChE inhibitors act mainly on the cerebral cortex and basal forebrain and the pathogenesis of the dementia has not been fully elucidated, the therapeutic benefits of donepezil may represent a less component of the disease process (McGleenon *et al.*, 1999). Therefore, the combination therapies with donepezil have been interested especially in the manifestation of AD and elderly patients with dementia for enhancing the efficacy with reduced side effects. There have been reported to use a donepezil in combination with memantine (McKeage, 2009; Atri *et al.*, 2013), cerebrolysin (Alvarez *et al.*, 2011), gabapentin (Boyle *et al.*, 2014), selegiline (Takahata *et al.*, 2005), rimonabant (Wise *et al.*, 2007) or vitamin E (Klatte *et al.*, 2003) which has shown therapeutic potentials in AD more than donepezil alone.

In traditional Korean medicine, the strategies for the cognitive impairments have focused on functional improvement of the heart, spleen and liver and treatments of mental and physical exhaustion (Heo, 2009). The accumulated clinical records have shown the therapeutic potentials in the amnesia, by treatments with Gwibitang (GBT) for damages of heart and spleen caused by anxiety and thoughts and Chongmyungtang (CMT) for improving learning and memory. The GBT and CMT are composed of 10 and 3 kinds of herbs, respectively (Table 1). The therapeutic effects of GBT have

been revealed by enhancement of memory via increased cell proliferation in the rat hippocampus (Oh *et al.*, 2005) and amelioration of the chronic fatigue syndrome in patients via regulation of immune response. In addition, there are many evidences for the therapeutic potentials of CMT on the amnesia (Lee *et al.*, 2010), AD (Park *et al.*, 2006; Lim *et al.*, 2010; Lee *et al.*, 2011) and dementia (Oh and Kim, 2006). For the synergic effects, there have been several clinical combination drugs with small changes in the amounts and kinds of the polyherb, GBT (Dharmananda, 1998). The Gwibi-Chongmyungtang (GCMT) is a combination drug composed of 13 kinds of herbs for the GBT and CMT (Table 1) (Lin and Zuo, 2002). The GCMT also has been used clinically for improving and memory in Korean traditional medicine and it has shown neuroprotective effects in AD rat model (Lee *et al.*, 2007). It suggests that GCMT may enhance the therapeutic effects of donepezil and further induce functional improvement in the cognitive deficits. Therefore, the effects of GCMT on donepezil pharmacokinetics were examined firstly for the combination therapy.

MATERIALS AND METHODS

Animals: A total of 18 male Sprague-Dawley rats were obtained from the Japan SLC Inc. (Shizuoka, Japan) at an age of 6 weeks. Rats were allocated to polycarbonate cage with 4 or 5 rats per cage and maintained in a room controlled at a temperature of 20-25°C and humidity of 40-45% with diurnal lighting on 12:12-h light:dark cycle. Feed and water were supplied free to access. The animal studies were performed with approval of the Institutional Animal Care and Use Committee at Daegu Haany University (Gyeongsan, Korea) (Approval No. DHU2011-017).

Drugs: For GCMT, 13 kinds of herbs were obtained from Jecheon Hanbang Yakcho (Jecheon, Korea) after confirming the morphology under microscopy (Table 1). The aqueous extracts from the herbs were prepared at Department of Herbalogy, College of Korean Medicine, Daegu Haany University (Gyeongsan, Korea). Briefly, the herbs were boiled in 2 L of distilled water for 3 h at 80°C 3 times and then

Table 1: Composition of herbs for aqueous extracts of Gwibi-Chongmyungtang

Herbs	Scientific names	Amounts (g)
Polygalae Radix	<i>Polygala tenuifolia</i> Willd.	12
Acori Gramineri Rhizoma	<i>Acorus gramineus</i> Soland.	12
Hoelen cum radix	<i>Poria cocos</i> Wolf	12
Angelicae Gigantis Radix	<i>Angelica gigas</i> N.	4
Longan Arillus	<i>Dimocarpus longan</i> Lour	4
Zizyphi Semen	<i>Zizyphus jujuba</i> Miller	4
Ginseng Radix Alba	<i>Panax ginseng</i> C.A.Meyer.	4
Astragali Radix	<i>Astragalus membranaceus</i> Bunge	4
Atractylodis Rhizoma Alba	<i>Atractylodes ovata</i> (Thunb.) DC.	4
Aucklandiae Radix	<i>Aucklandia lappa</i> Decne.	2
Glycyrrhizae Radix et Rhizoma	<i>Glycyrrhiza uralensis</i> Fisch	1.2
Zingiberis Rhizoma Crudus	<i>Zingiber officinale</i> Roscoe	6
Zizyphi Fructus	<i>Zizyphus jujuba</i> var. <i>Inermis</i> (Bunge) Rehder	4

Thirteen kinds of herbs were used for aqueous extracts of Gwibi-chongmyungtang as a combination drug of Gwibitang (GBT) and Chongmyungtang (CMT) at indicated amounts. The first 3 herbs are for CMT and the other herbs are for GBT

filtrated. The filtrate was decompressed using a rotary vacuum evaporator (Rotavapor R144, Buchi Labortechnik AG, Switzerland) and lyophilized in a programmable freeze dryer (Labconco Freezone 1, Labconco Corp., MO, USA). Total acquired extract was 9.0 g (yield 12.30%). Donepezil was obtained from Jeil Pharm., Co., Ltd (Youngin, Korea). Donepezil was used at 10 mg kg⁻¹, based on safety dosage from donepezil toxicity (Pfizer Canada Inc., 2013) and GCMT was used at 100 mg kg⁻¹, based on pharmacodynamics of GCMT in a clinical use. The powders of GCMT and donepezil were stored at 4°C in dark until use.

Groups and treatments: After 2-week acclimation, one batch of 10 rats received single oral dosing of donepezil with distilled water (control group) or donepezil with GCMT (combination group). All drugs were administered orally using oral gavage and the distilled water or GCMT was coadministered within 5 min after donepezil. Another batch of 8 rats received repeated oral dosing of the control or combination once a day for a week. The coadministration of repeated dosing was performed at 1.5 h intervals between donepezil and distilled water or GCMT. The body weight was measured on day at every treatments.

Plasma sampling: After slight anesthesia under ethyl ether (Duksan Pure Chemical, Seoul, Korea), the plasma samples were collected from the retro-orbital plexus into 50 IU heparinized tubes at 0.5 h prior to the coadministration and 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-coadministration. The samples were immediately centrifuged at 11,400×g for 10 min and the supernatants were stored as 200 µL aliquots at -70°C until high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) analysis.

Sample preparation and calibrations: Donepezil (Sigma, MO, USA) was prepared at 1.0 mg mL⁻¹ in acetonitrile for primary stock solution and further diluted in acetonitrile for dose-dependent working standard solutions. Carbamazepine (Sigma, MO, USA) was prepared at 500 ng mL⁻¹ in acetonitrile for Internal Standard (IS) working solution. The working standard solutions were mixed with blank plasma and IS working solution in acetonitrile for the calibration of donepezil and plasma samples were mixed with IS working solution in acetonitrile for the plasma analyses.

The mixtures were centrifuged at 9,700×g for 10 min at 4°C and the supernatants were injected into the LC-MS/MS system.

LC-MS/MS conditions: The concentration of donepezil was measured by LC-MS/MS using an API 2000 system (Applied Biosystems, Foster City, CA, USA) with an Agilent 1100 Series HPLC (Agilent Technologies, Santa Clara, CA, USA). Analyte was separated using Waters Xterra MS C₁₈ columns (2.1×50 mm, 3.5 µm) (Waters Corp., Milford, MA, USA) at column oven of 30°C. The mobile phase was composed of 2-98% acetonitrile in distilled water containing 0.1% formic

acid and it was gradiently delivered at 0.35 mL min⁻¹. The Turboion Spray was introduced in the positive ion mode at 400°C and 5.0 kV. Nitrogen was used as nebulizer, curtain and collision-gas with set of 12, 6 and 8 psi, respectively. The mass transitions used to quantify donepezil and IS were m/z 380→170 (retention time: 2.3 min) and 237→194 (retention time: 2.4 min), respectively. Calibration curves of donepezil were linear over the ranges studied with R²>0.999 and the lower limit of quantification was 1.0 ng mL⁻¹. The analytical data were processed by the Analyst version 1.4.2 software (Applied Biosystems).

Pharmacokinetic analyses: The plasma concentration of donepezil was analyzed using a non-compartmental method on commercial pharmacokinetics data analyzer programs (PK solutions 2.0; Summit, CO, USA) (Gibaldi and Perrier, 1982; Bailer, 1988). The elimination rate constant (K_{el}) was calculated by log-linear regression of donepezil concentration during elimination phase and terminal half-life (t_{1/2}) was calculated by 0.693/K_{el}. Peak concentration of donepezil (C_{max}) and time to reach the C_{max} (T_{max}) were obtained by visual inspection of the data in plasma concentration-time curve. Area under the concentration-time curve (AUC_{0-t}) from time zero to the time of the last measured concentration (C_{last}) was calculated using the linear trapezoidal rule (Chiou, 1978). The AUC from time zero to infinity (AUC_{0-inf}) was obtained by adding AUC_{0-t} and the extrapolated area was determined by C_{last}/K_{el}. The mean residence time zero to infinity (MRT_{inf}) was calculated by dividing the first moment of AUC by AUC_{0-inf}.

Statistical analyses: All data is represented as Means±Standard Deviation (SD). Variance of homogeneity was examined using the Levene test. If the Levene test indicated no significances, data was analyzed by independent t-test. If the Levene test indicated significances, data were analyzed by Mann-Whitney U test. The statistical significance was considered at p<0.05.

RESULTS

Body weight changes in coadministration of donepezil with GCMT: No meaningful changes on body weights were detected between the both groups of combination and control in the single oral coadministration within 5 min. There were also no differences in the body weights between the both groups in the repeated coadministration for a week at 1.5 h intervals (Table 2).

Changes on the pharmacokinetic profiles of donepezil in oral coadministration with GCMT within 5 min

Plasma concentration: Donepezil was detected at 0.5-8 h post-coadministration in the both groups of combination and control (Fig. 1). However, the plasma concentration of donepezil was lower in the combination group than control. There were border line of significances for the group (p = 0.07; F = 4.4) and interaction between group and time

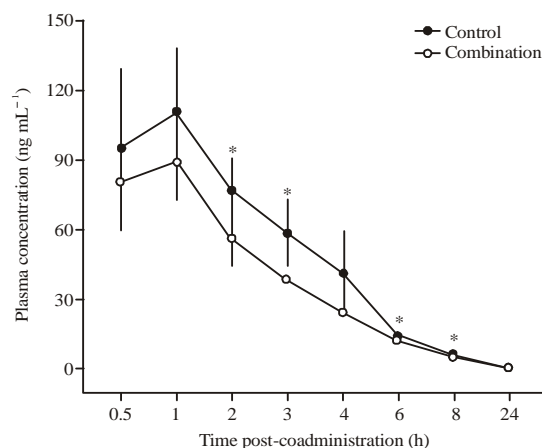


Fig. 1: Plasma concentration of donepezil in coadministration with Gwibi-Chongmyungtang within 5 min, rats received single coadministration of donepezil with distilled water (control, closed circles) or donepezil with Gwibi-Chongmyungtang (GCMT) (combination, open circles). The distilled water or GCMT were orally coadministered within 5 min after donepezil. The plasma concentration of donepezil was assessed at 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-coadministration and values were expressed as Means (ng mL⁻¹)±SD of 5 rats per group, *p<0.05

Table 2: Body weight changes in coadministration of donepezil with GCMT

Parameters	Control	Combination
Body weights at		
First treatment [A]	250.40±8.53	249.00±7.45
Last treatment [B]	264.80±9.36	260.20±8.44
Body weight gains		
[B]-[A]	14.40±2.30	11.20±2.28

Rats received repeated coadministration of donepezil with distilled water (control) or donepezil with GCMT (combination), once a day for a week at 1.5 h intervals. The body weights were measured at every coadministration and values are expressed as Mean±SD of 5 rats

(p = 0.08; F = 6.1). *Post-hoc* tests showed significances at 2, 3, 6 and 8 h post-treatment (p<0.05) and border line of significance at 6 h post-treatment (p=0.08). The ratios of concentration in the combination to control were 78.0, 82.5, 71.2, 64.4, 55.6, 67.7 and 66.8% at 0.5, 1, 2, 3, 4, 6 and 8 h post-coadministration, respectively.

Pharmacokinetic parameters: There were no differences in C_{max}, T_{max}, t_{1/2} and MRT_{inf} between the both groups of combination and control (Table 3). However, AUC₀₋₄ and AUC_{0-inf} were significantly reduced by 27.9% and 27.8%, respectively, in the combination group compared with control (p<0.05).

Changes on the pharmacokinetic profiles of donepezil in oral coadministration with GCMT at 1.5 h intervals: Since drug-drug interactions were observed between donepezil and GCMT by single oral coadministration within 5 min

Table 3: Pharmacokinetic profiles of donepezil in single oral coadministration with Gwibi-Chongmyungtang within 5 min

Parameters	Control	Combination
C _{max} (ng mL ⁻¹)	113.24±25.99	90.66±17.36
T _{max} (h)	0.80±0.27	0.90±0.22
AUC ₀₋₄ (ng h mL ⁻¹)	362.99±90.04	261.66±37.14*
AUC _{0-inf} (ng h mL ⁻¹)	380.23±93.14	274.39±39.03*
t _{1/2} (h)	1.65±0.13	1.72±0.12
MRT _{inf} (h)	2.87±0.06	2.75±0.16

Rats received single coadministration of donepezil with distilled water (control) or donepezil with Gwibi-Chongmyungtang (GCMT) (combination). The GCMT or distilled water was coadministered within 5 min after donepezil. The plasma samples were analyzed for pharmacokinetic parameters above and values are expressed as Means±SD in 5 rats. *p<0.05

Table 4: Pharmacokinetic profiles of donepezil in single oral coadministration with Gwibi-Chongmyungtang at 1.5 h intervals

Parameters	Control	Combination
C _{max} (ng mL ⁻¹)	171.00±18.76	151.75±46.45
T _{max} (h)	0.75±0.29	1.13±0.63
AUC ₀₋₁ (ng h mL ⁻¹)	576.44±54.45	455.76±133.77
AUC _{0-inf} (ng h mL ⁻¹)	622.86±61.46	482.18±145.48
t _{1/2} (h)	2.07±0.16	1.86±0.20
MRT _{inf} (h)	3.26±0.33	2.96±0.25

Rats received single coadministration of donepezil with distilled water (control) or donepezil with Gwibi-Chongmyungtang (GCMT) (combination). The GCMT or distilled water was coadministered at 1.5 h after donepezil. The plasma samples were analyzed for pharmacokinetic parameters above and values are expressed as Means±SD in 4 rats

(Fig. 1 and Table 3), GCMT or distilled water was orally coadministered at 1.5 h intervals, approximate time of t_{1/2} in control, after donepezil.

Plasma concentration: Donepezil was detected at 0.5-8 h post-coadministration in the both groups of combination and control (Fig. 2a). There were no significant differences in the kinetics of donepezil concentration between the both groups.

Pharmacokinetic parameters: There were no differences in any pharmacokinetic parameters between the both groups of control and combination, although AUC₀₋₄ and AUC_{0-inf} were non-significantly reduced by 20.9 and 22.6%, respectively in the combination compared with control (Table 4).

Changes on the pharmacokinetic profiles of donepezil in repeated oral coadministration with GCMT for a week at 1.5 h intervals: To further determine the effects of GCMT on donepezil pharmacokinetics, coadministration of donepezil with GCMT or distilled water was repeated for a week.

Plasma concentration: Donepezil was detected at 0.5-8 h post-coadministration in the both groups of combination and control (Fig. 2b) but the kinetics showed lower concentration in the combination group compared with control. There were significant main effects for group (F = 9.3; p<0.05) and there were non-significant border line of interaction between group and time (F = 4.3; p = 0.06). *Post-hoc* tests showed significances at 0.5 h (p<0.01) and 2, 3, 6 and 8 h post-coadministration (p<0.05). The ratios of concentration in the combination to control were 57.8, 66.5, 68.2, 64.8, 62.6, 64.3 and 51.1% at 0.5, 1, 2, 3, 4, 6 and 8 h post-coadministration, respectively.

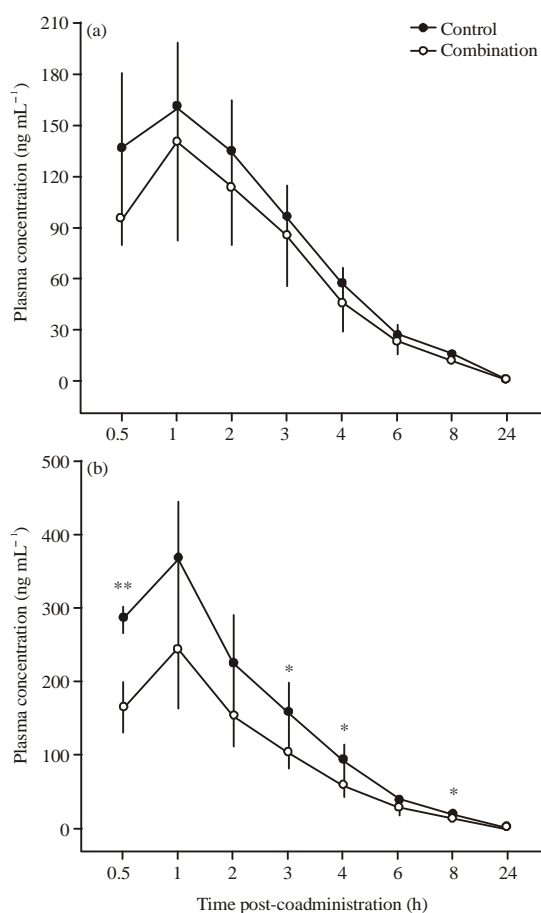


Fig. 2(a-b): Plasma concentration of donepezil in coadministration with Gwibi-Chongmyungtang for a week at 1.5 h intervals, Rats received oral coadministration of donepezil with distilled water (control, closed circles) or aqueous extracts of Gwibi-Chongmyungtang (GCMT) (combination, open circles). The coadministration with distilled water or CMT was performed once a day for a week at 1.5 h intervals after donepezil. The plasma concentration of donepezil was assessed at 0.5, 1, 2, 3, 4, 6, 8 and 24 h after the (a) Initial coadministration and (b) Last coadministration of the repeated dosing. Values were expressed as Mean (ng mL⁻¹)±SD of 5 rats per group. *p<0.05

Pharmacokinetic parameters: There were significant differences in AUC_{0-t} and AUC_{0-inf} between the both groups of combination and control (p<0.05) (Table 5). The AUC_{0-t} and AUC_{0-inf} were significantly reduced by 35.7 and 36.9%, respectively, in the combination group compared with control. C_{max} was also reduced by 33.5% in the combination group compared with control but the differences didn't reach to the significances (p = 0.07). Other parameters, T_{max}, t_{1/2} and MRT_{inf} were not different between the both groups.

Table 5: Pharmacokinetic profiles of donepezil in repeated oral coadministration with Gwibi-Chongmyungtang for a week at 1.5 h intervals

Parameters	Control	Combination
C _{max} (ng mL ⁻¹)	366.00±78.97	243.50±79.24
T _{max} (h)	1.00±0.00	1.00±0.00
AUC _{0-t} (ng h mL ⁻¹)	1051.88±202.54	676.82±180.35*
AUC _{0-inf} (ng h mL ⁻¹)	1132.62±227.72	714.18±202.36*
t _{1/2} (h)	2.09±0.27	1.85±0.26
MRT _{inf} (h)	3.03±0.32	2.82±0.21

Rats received repeated coadministration of donepezil with distilled water (control) or donepezil with Gwibi-Chongmyungtang (GCMT) (combination) for a week. The GCMT or distilled water was coadministered at 1.5 h intervals after donepezil. The plasma samples were analyzed for pharmacokinetic parameters above and values are expressed as Mean±SD in 4 rats. *p<0.05

DISCUSSION

The drug-drug interaction was examined between donepezil and GCMT as the first step of novel combination therapy for the dementia. The plasma concentration of donepezil was appeared to be reduced by the coadministration with GCMT within 5 min after donepezil (Fig. 1). No differences were observed in the donepezil concentration between the combination and control, when GCMT was coadministered at 1.5 h intervals after donepezil (Fig. 2a). However, the repeated dosing of the combination for a week at 1.5 h intervals influenced in the reduction of donepezil concentration (Fig. 2b). The results meant a drug-drug interaction in single dosing of the combination with GCMT within 5 min and repeated dosing at 1.5 h intervals despite no interactions in single dosing of the combination at 1.5 h intervals. The pharmacokinetic analyses showed detailed information; significant reduction of AUC in the single dosing of combination with GCMT within 5 min (Table 3) and the repeated dosing of combination for a week at 1.5 h intervals (Table 5). It suggests reduced bioavailability of donepezil by significant interactions between donepezil and GCMT.

Donepezil has an oral bioavailability of 100% via the intestinal tract (Rogers and Friedhoff, 1998; Lu *et al.*, 2004) and high bindings to the plasma protein (Tiseo *et al.*, 1998a). The absorption of donepezil is influenced little by food or time of donepezil administration (Mihara *et al.*, 1993). Here, the reduced plasma concentration of donepezil suggests that GCMT may inhibit the absorption of donepezil. Although the C_{max}, peak concentration of donepezil, was not different between the combination and control, it was slightly reduced in combination with GCMT (Table 3-5). In addition, considering that AUC is proportional measurements to the total amount of unchanged drug that reaches systemic circulation, the reduced AUC was regarded as reduced bioavailability of donepezil by the combination with GCMT. The donepezil is metabolized by cytochrome P450 isoenzymes, CYP2D6 and CYP3A4 (Tiseo *et al.*, 1998b; Tiseo *et al.*, 1998c). The other pharmacokinetic studies have shown that the coadministration of donepezil with CYP3A4 inhibitors including ketoconazole and quinidine, results in increased C_{max} and AUC₀₋₂₄ probably due to inhibition of donepezil metabolism (Shintani and Uchida, 1997; Tiseo *et al.*, 1998d). These suggest that GCMT may

increase the donepezil metabolism probably due to activation of cytochrome P450 isoenzymes but the relevant mechanisms are unclear.

To now, various drug-drug interactions have been evaluated for the combination therapy with donepezil. The pharmacokinetic studies have shown no interactions with cimetidine (Tiseo *et al.*, 1998e), theophylline (Tiseo *et al.*, 1998f), warfarin (Tiseo *et al.*, 1998g) or digoxin (Shintani and Uchida, 1997; Tiseo *et al.*, 1998h), suggesting possibilities to coadminister donepezil in combination with them. Although memantine, NMDA receptor antagonist, is also main medication for the cognitive manifestations of AD (Massoud and Gauthier, 2010), donepezil has interaction with memantine (Hassan *et al.*, 2013). In addition, there have been reported to have extrapyramidal side effects in patients with AD by combination of donepezil with risperidone, antipsychotics (Magnuson *et al.*, 1998; Liu *et al.*, 2002). Considering that the dementia can be enhanced in the cardiovascular disease, hypertension, diabetes and obesity (Kalaria, 2010), the GCMT with multi-targets for functional improvement in the heart, spleen and liver as well as ameliorating cognitive decline may have additional benefits in combination therapy for the dementia (Heo, 2009; Lee *et al.*, 2007). However, this study showed that GCMT is hard to use in combination with donepezil within 5 min or repeated dosing at 1.5 h intervals, because of the occurrence of significant pharmacokinetic interactions. It suggests that GCMT should be carefully used or contraindicated in patients having medication of donepezil. The further pharmacokinetic studies on GCMT combination with other cognitive medications may provide more information for increasing the clinical application of GCMT as an adjunctive medicine.

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