Effect of chongmyungtang, a traditional Korean polyherbal formula, on the Pharmacokinetic profiles of donepezil in rats

Kyung-Min Baek[1], Oh-Dae Kwon[2], Soo-Jin Park[3], Chang-Hyun Song[3*] and Sae-Kwang Ku[3*]
[1]Department of Internal Medicine, College of Korean Medicine, Daegu Haany University, Gyeongsan, Republic of Korea
[2]Department of Neurology, Catholic University of Daegu School of Medicine, Daegu, Republic of Korea
[3]Department of Anatomy and Histology, College of Korean Medicine, Daegu Haany University, Gyeongsan, Republic of Korea

Abstract: Chongmyungtang (CMT) is a famous Korean herbal medicine for improving learning and memory, which has been reported to have anti-cholinergic and neuroprotective effects. Therefore, drug-drug interactions were examined between CMT and donepezil as a first screening of combination therapy for cognitive deficits. Rats received oral co-administration of donepezil with distilled water as a control or donepezil with CMT as a combination. The distilled water or CMT was co-administered at intervals within 5min after donepezil or 1.5h intervals. The plasma samples were analyzed for donepezil concentration and its pharmacokinetic parameters of T_{max}, C_{max}, AUC, $t_{1/2}$ and MRT_{inf}. In the single co-administration at intervals within 5min, donepezil was detected lower in the combination than control at 0.5h and 2h post-treatment ($P<0.05$). In addition, the combination showed significant increases in MRT_{inf} compared to the control ($P<0.05$). This suggests drug-drug interactions between donepezil and CMT in the co-administration within 5 min. However, no meaningful differences were found in the pharmacokinetic profiles of donepezil by single dosing with CMT at 1.5h intervals and even by the repeated dosing for a week at 1.5h intervals potential combination therapy of donepezil with CMT.

Keywords: Donepezil, Chongmyungtang, pharmacokinetics, herbal products and rat.

INTRODUCTION

Donepezil (Aricept^{TM}) is a reversible acetyl cholinesterase (AChE) inhibitor, which prevents the hydrolysis of acetylcholine. It is not used mainly for the palliative treatment of mild to moderate Alzheimer's disease (AD) related to the functional loss of cholinergic pathway (Birks and Harvey, 2006), but also for the treatment of other cognitive disorders including Lewy body dementia (Rogers, 1998) and vascular dementia (Malouf and Birks, 2004). In addition, donepezil is reported to ameliorate sleep apnea in AD (Moraes *et al.*, 2008) and speech deficits in autism (Handen *et al.*, 2011). Although donepezil is a well-tolerated drug, preclinical studies have shown relatively severe toxicity at 50% of lethal dose in experimental animal models (Pfizer Canada Inc., 2013). There have been reported potential side effects in the gastrointestinal system through the cholinergic stimulation by the initial treatment of donepezil or its increased doses, such as nausea and vomiting and abdominal pains (Dunn *et al.*, 2000; Shintani and Uchida, 1997). It has also been reported to have bradycardia, anorexia, vivid dreams and mania (Benazzi, 1999; Lockhart *et al.*, 2009; Umegaki *et al.*, 2008). Therefore, the clinical use of donepezil should be cautious in patient with cardiac disease, chronic obstructive pulmonary disease, gastrointestinal disorders or seizures.

To reduce the side effects and enhance the efficacy of donepezil, the combination therapies of donepezil have been interested especially in the manifestation of AD or elderly patients with decreased cholinergic pathway. As results of trials for the combination therapies, various drug-drug interactions have been evaluated. The pharmacokinetic studies have shown no interactions with cimetidine (Tiseo *et al.*, 1998c), theophylline (Tiseo *et al.*, 1998a), warfarin (Tiseo *et al.*, 1998b) or digoxin (Shintani and Uchida, 1997; Tiseo *et al.*, 1998d), suggesting possibilities to co-administer donepezil with them as a combination therapy. However, there are significant interactions with ketoconazole and quinidine (Shintani and Uchida, 1997; Tiseo *et al.*, 1998e).

Chongmyungtang (CMT) is one of the traditional Korean herbal medicines which ~~have~~ has been widely used for improvement of learning and memory (Huh, 2005). It is composed of 3 kinds of herbs containing *Polygala tenuifolia* Willd, *Acorus gramineus* Soland and *Poria cocos* Wolf (table 1). Preclinical studies have revealed the therapeutic potentials of CMT for treatment of amnesia (Lee *et al.*, 2010; Lee *et al.*, 2006). The exact mechanisms are unclear, but CMT has been reported to ameliorate the cognitive deficits by inhibition of cholinergic activity and promotion of antioxidant activity (Lee *et al.*, 2011; Lee *et al.*, 2010). Furthermore, CMT has shown neuroprotective effects against neurotoxicity induced by kainic acid (Jang *et al.*, 1997) and anti-inflammatory effects via inhibiting production of tumor necrosis factor-alpha (Kim *et al.*,

**Corresponding authors* e-mails: dvmsong@hotmail.com, gucci200@hanmail.net.
Kyung-Min Baek and Oh-Dae Kwon contributed equally to this.

1999). The therapeutic potentials suggest that CMT may achieve synergic pharmacodynamics with donepezil and further induce functional improvement in the cognitive deficits. Therefore, for the possibilities to use CMT as a combination therapy with donepezil, the pharmacokinetic interaction was investigated in rat preliminarily.

MATERIALS AND METHODS

Drugs

Three kinds of herbs composing CMT were purchased 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 (Daegu, Korea). Briefly, the herbs were boiled in 2 L of distilled water (DW) for 3 h at 80ºC 3 times and then filtrated. The filtrate was decompressed using a rotary vacuum evaporator (Rotavapor R-144, Buchi Labortechnik AG, Switzerland) and lyophilized in a programmable freeze dryer (Labconco Freezone 1, Labconco Corp., MO, USA). Total acquired extracts of CMT were yield 9.10%. Donepezil (Jeil Pharm., Co., Ltd, Youngin, Korea) was used as a control drug. The powders of CMT and donepezil were well dissolved in DW up to 20 mg/ml and 10 mg/ml, respectively. The drugs were stored at 4ºC in dark until use.

Animals

All procedures for animal experiments were carried out with approval of the Institutional Animal Care and Use Committee at Daegu Haany University. Six week old male Sprague-Dawley rats were purchased from SLC Inc. (Shizuoka, Japan). A total of 18 rats were housed in polycarbonate cage with 4 or 5 rats per cage, and maintained in a room controlled at a temperature of 20-25 ºC and humidity of 40-45% with dark and light cycle of 12/12 h. Feed and water were supplied free to access.

Treatments

After rats were acclimatized for 2 weeks, one batch of 8 rats received single oral co-administration of donepezil with DW as a control or donepezil with CMT as a combination. The DW or CMT was co-administered within 5 min after donepezil. Another batch of 10 rats received repeated oral co-administration of the control or combination once a day for a week. The repeated co-administration was performed at 1.5h intervals after donepezil. Donepezil and CMT were used at 10mg/kg and 100mg/kg, respectively, based on donepezil toxicity (Pfizer, 2013) and pharmacodynamics of CMT (Jang *et al.*, 1997; Lee *et al.*, 2011; Lee *et al.*, 2006). The body weight was measured a day before the treatment and after every treatment, using an automatic electronic balance (Precisa Instrument, Switzerland).

Plasma collection

All animals were fasted overnight before the treatment, and further for 3 h after the treatment. For blood samples, animals were slightly anesthetized under ethyl ether (Duksan Pure Chemical, Seoul, Korea), and the samples of 0.5ml were collected from the retro-orbital plexus into 50 IU heparinized tubes at 0.5h before the treatment and 0.5, 1, 2, 3, 4, 6, 8 and 24h after the treatment. Then, the samples were immediately centrifuged at 11,400xg for 10 min for the plasma samples, and the aliquots were stored at -70ºC 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 in acetonitrile for primary stock solution, and further diluted in acetonitrile for working standard solutions. Carbamazepine (Sigma, MO, USA) was prepared at 500ng/ml in acetonitrile for internal standard (IS) working solution. The standard solutions were stored at -20 ºC in dark until use. For the calibration of donepezil, each 100µl of blank plasma, working standard solution and IS working solution were mixed with 100µl of acetonitrile. The mixtures were centrifuged at 9,700x g for 10 min at 4ºC. The clear supernatants were transferred to injection vials, and injected into the LC-MS/MS system. For the plasma samples, each 100µl of the plasma sample and the IS working solution were mixed with 200µl of acetonitrile. The mixtures were centrifuged at 9,700 x g for 10 min at 4ºC, and the supernatants were used for injection into the LC-MS/MS system.

LC-MS/MS conditions

Chromatographic analysis was performed using high-performance liquid chromatography (Agilent 1100, Agilent Technologies, CA, USA) equipped with on-line degasser, binary pump, autosampler and column compartment. Separation of the analyte from potentially interfering material was achieved at ambient temperature using columns (Xterra MS C18, 2.1×50 mm, 3.5µm, Waters Corp., MA, USA) at a column oven of 30ºC. The mobile phase for the chromatographic separation was composed of 2% to 98% acetonitrile in distilled water including 0.1% formic acid, and it was delivered isocratically at a flow rate of 0.35ml/min. The column effluent was monitored using a triple-quadruple mass-spectometric detector (API 2000, Applied Biosystems, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode, and controlled by analyses software (Analyst version 1.4.2, Applied Biosystems, CA, USA). Samples were introduced to the interface through a turbo ionspray (API 2000, Applied Biosy stems, CA, USA) with a temperature set at 400 °C and a high positive voltage of 5.0 kV. Nitrogen was used as a nebulizer gas, curtain gas, and collision gas with a set of 12, 6 and 8 psi, respectively. The multiple reaction monitoring detection method was employed for the

detection of donepezil; the transitions monitored were carbamazepine (IS): m/z 237>194 (retention time: 2.4 min), donepezil: 380>91 (retention time: 2.3 min). Calibration curve of donepezil was linear over the ranges studied with r^2>0.999 and the lower limit of quantification was 1ng/ml.

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) (Bailer, 1988; Gibaldi and Perrier, 1982). 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 are represented as means ± standard deviation (SD). Variance homogeneity was examined using the Levene test. ~~If~~ When the Levene test indicated no significances, data was analyzed by independent t-test, otherwise, the data was analyzed by a non-parametric comparison test, Mann-Whitney U (MW) test. The statistical significance was considered at P-value < 0.05.

RESULTS

Body weight changes

No meaningful changes on body weights and gains were detected between the combination and control in the single oral co-administration within 5 min (data not shown). There were also no significant differences in the body weights between the both groups in the repeated co-administration for a week at 1.5 h intervals (table 2).

Pharmacokinetic profiles of donepezil in single co-administration with CMT at intervals within 5 min

Plasma concentration. Donepezil was detected at 0.5 h to 8h after the single co-administration of control or combination (fig. 1). However, comparing to the control, the combination group showed significantly inhibited absorption of donepezil at 0.5h and 2h after the co-administration (p<0.05). The ratios of concentration in the combination to control were 55.4, 69.7, 73.8, 81.9, 64.5, 88.4 and 90.4% at 0.5, 1, 2, 3, 4, 6 and 8h after the co-administration, respectively.

Pharmacokinetic parameters

Comparing to the control, MRT_{inf} of donepezil was significantly increased by 109.7% in the combination despite a small change (p<0.05). However, other pharmacokinetic profiles of donepezil showed non-significant differences in the present study. The ratios in the combination to control were 67.8% in C_{max}, 166.7% in T_{max}, 71.4% in AUC_{0-t}, 72.6% in AUC_{0-inf} and 108.5% in $t_{1/2}$ (table 3).

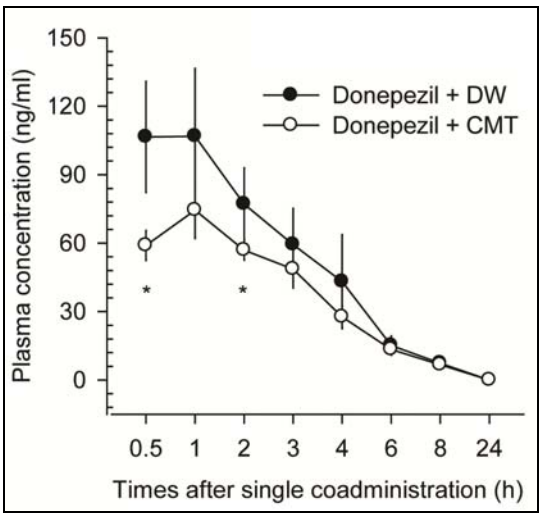

Fig. 1: Plasma concentration of donepezil after co-administration with distilled water (DW) or Chongmyungtang (CMT) within 5 min (Asterisks denote statistical significance at P<0.05).

Pharmacokinetic profiles of donepezil in repeated co-administration with CMT for a week at 1.5 h intervals

Since there were potential or significant drug interactions between donepezil and CMT by oral co-administration within 5 min, the effects of CMT on the pharmacokinetics of donepezil were examined after the single co-administration at 1.5h intervals and the repeated co-administration for a week at 1.5h intervals.

Plasma concentration

The plasma samples were collected after the initial and the last treatment of repeated co-administration of control or combination for a week at 1.5h intervals. Donepezil was detected at 0.5h to 8 h after the initial and the last treatment in the both groups (fig. 2). There were no significant differences in the donepezil concentration-time curve between the combination and control after the initial and the last treatment (p>0.10). After the initial co-administration, the ratios of concentration in the combination to control were 87.7, 94.4, 90.4, 105.2, 98.3, 85.3 and 89.9% at 0.5, 1, 2, 3, 4, 6 and 8 h post-treatment, respectively (fig. 2A). After the last co-administration, the ratios were 99.6, 82.0, 76.6, 90.9, 89.8 and 82.9% at 0.5, 1, 2, 3, 4, 6 and 8 h post-treatment, respectively (fig. 2B).

Table 1: Composition of herbs for aqueous extracts of Chongmyungtang

Herbs	Scientific Names	Amounts (g)
Polygalae Radix	Polygala tenuifolia Willd.	12
Acori Gramineri Rhizoma	Acorus gramineus Soland.	12
Hoelen cum radix	Poria cocos Wolf	12

Table 2: Body weight changes in co-administration of donepezil with distilled water (DW) or Chongmyungtang (CMT)

	Donepezil + DW	Donepezil + CMT
Body weights		
After the initial co-administration [A]	250.40±8.53	252.40±5.08
After the last co-administration [B]	264.80±9.36	265.20±5.45
Body weight gains: [B] – [A]	14.40±2.30	12.80±3.83

Table 3: Pharmacokinetic profiles of donepezil after co-administration with distilled water (DW) or Chongmyungtang (CMT) within 5 min (Asterisk denotes statistical significance at $P<0.05$)

Parameters	Donepezil + DW	Donepezil + CMT
C_{max} (ng/ml)	110.05±28.85	74.58±12.23
T_{max} (h)	0.75±0.29	1.25±0.50
AUC_{0-t} (h•ng/ml)	372.12±101.26	265.72±18.90
AUC_{0-inf} (h•ng/ml)	389.66±104.76	283.06±21.99
$t_{1/2}$ (h)	1.65±0.15	1.79±0.07
MRT_{inf} (h)	2.87±0.07	3.15±0.21*

Table 4: Pharmacokinetic profiles of donepezil after single oral co-administration with distilled water (DW) or Chongmyungtang (CMT) at 1.5 h intervals

Parameters	Donepezil + DW	Donepezil + CMT
C_{max} (ng/ml)	178.40±23.19	159.94±56.32
T_{max} (h)	0.80±0.27	1.20±0.45
AUC_{0-t} (h•ng/ml)	590.58±56.78	554.01±128.25
AUC_{0-inf} (h•ng/ml)	639.62±65.10	596.58±143.45
$t_{1/2}$ (h)	2.12±0.18	2.03±0.30
MRT_{inf} (h)	3.26±0.29	3.22±0.28

Table 5: Pharmacokinetic profiles of donepezil after repeated oral co-administration with distilled water (DW) or Chongmyungtang (CMT) for a week at 1.5 h intervals

Parameters	Donepezil + DW	Donepezil + CMT
C_{max} (ng/ml)	345.80±81.96	284.80±87.80
T_{max} (h)	1.00±0.00	0.90±0.22
AUC_{0-t} (h•ng/ml)	1026.97±184.04	905.67±255.03
AUC_{0-inf} (h•ng/ml)	1105.33±206.44	966.37±277.89
$t_{1/2}$ (h)	2.11±0.24	1.96±0.19
MRT_{inf} (h)	3.05±0.28	3.02±0.37

Pharmacokinetic parameters

There were no significant differences in the pharmacokinetic parameters of donepezil between the combination and control after the initial co-administration of repeated treatment for a week at 1.5h intervals (table 4). The ratios in the combination to control were 89.7% in C_{max}, 150.0% in T_{max}, 93.8% in AUC_{0-t}, 93.3% in AUC_{0-inf}, 95.9% in $t_{1/2}$ and 98.7% in MRT_{inf}. Furthermore, there were also no differences in the parameters between the both groups after the last co-administration of the repeated treatment (table 5). The ratios in the combination to control were 82.4% in C_{max}, 90.0% in T_{max}, 88.2% in AUC_{0-t}, 87.4% in AUC_{0-inf}, 93.1% in $t_{1/2}$ and 99.3% in MRT_{inf}.

DISCUSSION

Till now, three AChE inhibitors, donepezil, galantamine and rivastigmine and non-competitive N-methyl-D-aspartate receptor antagonist, memantine are main medications for the cognitive manifestations of AD, approved by US Food and Drug Administration and the European Medicines Agency (Massoud and Gauthier, 2010). Recently, increasing interests have emerged in using a combination therapy for the treatment of AD. However, donepezil has shown to have drug interaction with memantine in rat (Hassan *et al.*, 2013). Besides, for the combination therapy with donepezil, various drug-drug interactions have been evaluated, however, there are a few studies on interactions between donepezil and herbal products. There have been reports showing little influences in the donepezil pharmacokinetics by combination with herbal products such as ginkgo biloba extracts (Yasui-Furukori *et al.*, 2004), digoxin (Tiseo *et al.*, 1998d), theophylline (Tiseo *et al.*, 1998a) or warfarin (Tiseo *et al.*, 1998b), which suggests potential combination therapy. The CMT is known as one of the most famous Korean medicines that improves the memory and functional cognition. Here, the pharmacokinetic profiles of donepezil showed significant drug-drug interaction with CMT after the oral co-administration within 5min, but no interactions after the single co-administration at 1.5h intervals and even after the repeated co-administration for a week at 1.5h intervals. These provide useful information for the combination therapy of donepezil with CMT.

In the single co-administration with CMT at intervals within 5 min, the plasma concentration of donepezil was significantly lower in the combination than control at early phase of 0.5 h and 2 h post-treatment (fig. 1). Donepezil is known to be well-absorbed in the intestinal tract with an oral bioavailability of 100% (Lu *et al.*, 2004; Rogers and Friedhoff, 1998). It has high bindings to the plasma protein; approximately 96% binding to albumins and α1-acid glycoprotein (Tiseo *et al.*, 1998g), but no influences in the absorption by food or time of donepezil administration donepezil (Mihara *et al.*, 1993). Here, comparing to the control, the co-administration with CMT within 5 min showed no significances in pharmacokinetic parameters of donepezil, C_{max} and AUC, implying drug absorption. However, the combination group showed significant increases in MRT_{inf} of donepezil compared with the control ($p<0.05$), suggesting that the co-administration with CMT within 5 min may inhibit the pathway of donepezil metabolism and excretion rather than the absorption. Donepezil is metabolized by cytochrome P450 isoenzymes, CYP2D6 and CYP3A4 (Tiseo *et al.*, 1998f; Tiseo *et al.*, 1998h). Previous study on donepezil combination with ketoconazole, an inhibitor of the CYT3A4, has shown repression of donepezil metabolism (Tiseo *et al.*, 1998e). These suggest that CMT may inhibit potentially, the donepezil metabolism or elimination by the co-administration within 5 min, even though the relevant mechanisms are unclear.

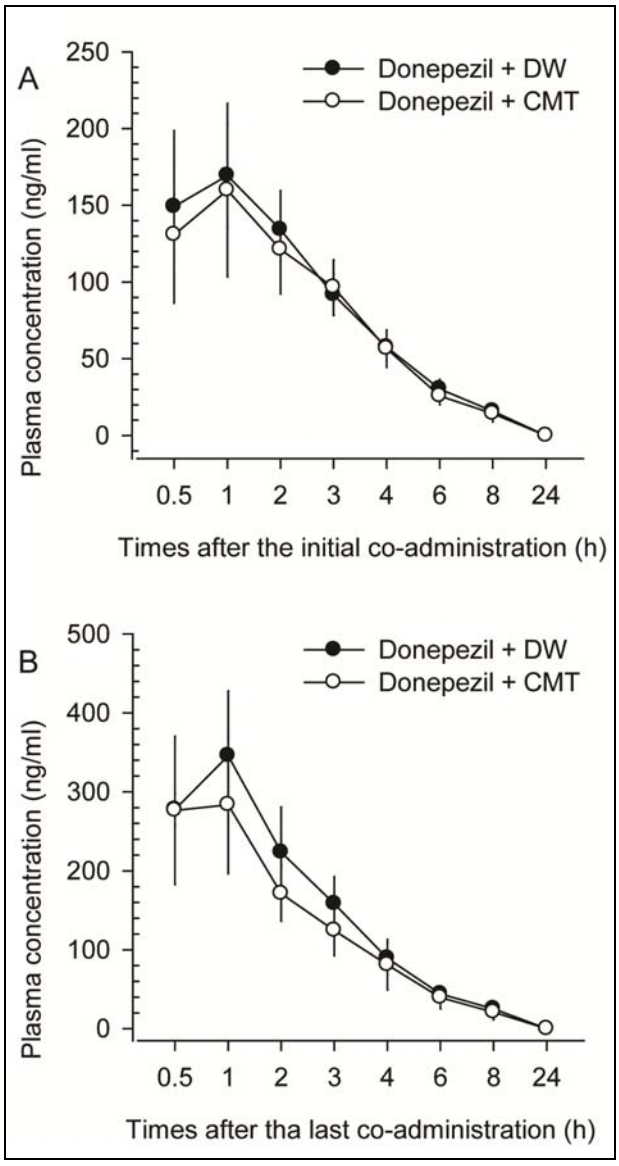

Fig. 2: Plasma concentration of donepezil after the initial (A) and the last (B) treatments in repeated co-administration with distilled water (DW) or Chongmyungtang (CMT) for a week at 1.5 h intervals.

In the repeated co-administration for a week at 1.5 h intervals, the combination group showed no meaningful changes in the pharmacokinetic profiles of donepezil as compared with control after single treatment (table 4 and fig. 2A) and even after a week repeated treatment (table 5 and fig. 2B). The results were considered as direct evidences that CMT has little influences in the donepezil absorption and elimination when CMT was co-administered at 1.5 h intervals after donepezil. It suggests important guidance for the proper dosing in the future pharmacodynamics studies on the combination therapy of

donepezil with CMT. However, considering that donepezil is usually prescribed in elderly patients with cognitive deficits, further studies need to modify the dosing regimen in ageing or various disease conditions.

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