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# Pharmacokinetic Properties of Ondansetron in Combination with Ijintang-gamibang, Polyherbal Complex in Rats

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ABSTRACT
Ondansetron is used mainly as an antiemetic in emetogenic cancer chemotherapy and radiotherapy and post-operative nausea and vomiting (NV). However, recent study recommend reducing ondansetron dose because of possible life-threaten cardiotoxicity problems. Ijintang-gamibang (IJTGMB) is a polyherb complex, a famous traditional digestive drug in Korean medicine, which has shown the protective and functional benefits in gastrointestinal impairments. Therefore, the influences of IJTGMB on ondansetron pharmacokinetics were examined for the combination therapy. One batch of rats received single dosing of ondansetron with IJTGMB (combination) or ondansetron with distilled water (control). The IJTGMB or distilled water was co-administered orally within 5 min after ondansetron. Another batch of rats received repeated dosing of the combination for 8 days after pretreatments with IJTGMB for 6 days or the control for 8 days after pretreatments with distilled water for 6 days. The plasma samples were analyzed by various pharmacokinetic parameters including $T_{max}$, $C_{max}$, AUC, $t_{1/2}$ and $MRT_{inf}$. In the single dosing, plasma concentration of ondansetron was not different between the combination and control and the pharmacokinetic parameters were not different between the both treatments. In the initial treatment of the repeated dosing after the pretreatments, the kinetics of ondansetron concentration and the pharmacokinetic parameters showed no differences between the both treatments. It suggests little influences of IJTGMB on ondansetron pharmacokinetics in single dosing with or without pretreatments with IJTGMB. However, after repeated dosing for 8 days, ondansetron in plasma was detected lower and longer in the combination than control. In addition, among the parameters assessed here, AUC of ondansetron was significantly reduced in combination compared to control, meaning reduced bioavailability of ondansetron by repeated co-administration with IJTGMB for 8 days. These may provide useful information for proper dosing regimen of the novel combination therapy.

**Key words:** Ondansetron, ijintang-gamibang, polyherb, combination, pharmacokinetics

## INTRODUCTION

Nausea and Vomiting (NV) are symptoms of protective physiological mechanisms to eliminate causes of gastric irritation or underlying illness in body parts such as the brain, liver or bowel (Donnerer, 2003). NV is also occurred in patients with chronic diseases, especially cancer, followed by medical treatments. Numerous antiemetic agents have been

Table 1: Eight types of herb consisting of Ijintang-gamibang aqueous extracts

| Herbs | Names | Amounts (g) |
|---|---|---|
| Pinella rhizoma | *Pinellia ternate* (THUNB) BREIT | 16 |
| Citri pericarpium | *Citrus unshiu* MARKOVICH | 8 |
| Holelen | *Poria cocos* WOLF | 8 |
| Atractylodis rhizoma | *Atractylodes japonica* KOIDZ | 8 |
| Massa medicata fermentata | - | 8 |
| Hordei fructus germiniatus | *Hordeum vulgare* LINNE var. *hexastichon* ASCHERS | 8 |
| Coptidis rhizoma | *Coptis japonica* (THUNB), MAKINO | 8 |
| Glycyrrhizae radix | *Glycyrrhiza uralensis* FISCH | 4 |
| Total | 8 types | 68 |

Individual herbs were purchased from Omni Herb (Youngcheon, Korea) and used for Ijintang-gamibang aqueous extracts at indicated amounts

developed for reducing the unpleasant symptoms resulting in dehydration and imbalanced electrolytes and minerals in the body. The antiemetic drugs can be categorized into competitive antagonist for dopaminergic or serotonergic receptors (5-hydroxytryptamine; 5-$HT_3$ receptors), prokinetics, antihistamines, anticholinergics and neuroleptics (Donnerer, 2003). The various drugs are frequently used in combination with different drugs for enhancing the antiemetic effects rather than monotherapy by a single drug (Jordan *et al*., 2014).

Treatment with 5-$HT_3$ receptor antagonists in combination with corticosteroids is the most common intervention for NV (Roila *et al*., 1998; Gralla *et al*., 1999). Ondansetron is a 5-$HT_3$ receptor antagonist commonly used as an antiemetic for emetogenic cancer chemotherapy (Milne and Heel, 1991; Beck *et al*., 1993) and radiotherapy (Henriksson *et al*., 1992; Martin *et al*., 1998) and postoperative NV (Dershwitz *et al*., 1992b; Scuderi *et al*., 1993). Ondansetron is a well-tolerated drug with a few adverse effects (Markham and Sorkin, 1993) but the clinical use is relatively restrict with a low 50% Lethal Dose ($LD_{50}$) in preclinical studies; $LD_{50}$ in rats are 95 and 20.1 mg $kg^{-1}$ via single oral and intravenous route, respectively (Hospira Inc., 2009). Furthermore, recent reports issue a warning for a use of ondansetron because of QT interval prolongation involved in the potentially fatal arrhythmia torsade de pointes (Charbit *et al*., 2008; McKechnie and Froese, 2010; Hafermann *et al*., 2011). It suggests that ondansetron should be carefully used for patients especially with hypokalemia, hypomagnesemia, congestive heart failure or bradyarrhythmia. U.S. Food and Drug Administration recommends reducing ondansetron dose via regimen of 0.15 mg $kg^{-1}$ 3 times in a day rather than previous single dosing of 32 mg (Doggrell and Hancox, 2013).

Natural herbs have been receiving increasing attention to develop novel drugs and refer the effective pure chemicals (Ji *et al*., 2009). Ijintang (Nichin-to in Japanese and Er chen tang in Chinese), a herbal formula, is one of the most famous digestive drugs in traditional Korean medicines consisted of 4 types of Pinella Rhizoma, Citri Pericarpium, Holelen Red and Glycyrrhizae Radix. It is mainly used for treatment of NV and inflammatory responses in patients with gastritis, chronic tracheitis or bronchitis (Scheid, 2009). Ijintang-gamibang (IJTGMB) is based on the ingredients of Ijintang and added with 4 more types of herb, Atractylodis Rhizoma, Massa Medicata Fermentata, Hordei Fructus Germiniatus and Coptidis Rhizoma (Table 1). The individual ingredients have additional anti-inflammatory effects (Cho *et al*., 1998; Kanauchi *et al*., 2001; Li *et al*., 2007) and functional benefits to ameliorate the gastrointestinal impairments (Resch *et al*., 1998; Satoh *et al*., 2000; Lee *et al*., 2003; Yoshizawa *et al*., 2004). The therapeutic effects of IJTGMB on the gastrointestinal disorder have been reported in animal experiments (Ok *et al*., 2002; Choi, 2010) and clinics (Oh *et al*., 2005). It suggests a possibility to use IJTGMB in combination with ondansetron at a low dose. Therefore, to determine the bioequivalence of ondansetron with IJTGMB, the influences of IJTGMB on ondansetron, pharmacokinetics were examined via comprehensive pharmacokinetic analyses.

## MATERIALS AND METHODS

**Materials:** Ondansetron hydrochloride dehydrate was purchased from Qufu Hongly Chemical Ind. Co., Ltd. (Shandong, China). For IJTGMB, 8 types of herb with complete morphology were purchased from Omni Herb (Youngcheon, Korea) (Table 1). The herbs were boiled in distilled water for 3 h at 60°C 3 times and the filtrate was decompressed by a rotary vacuum evaporator (Rotavapor R-144, Buchi, Flawil, Switzerland) and lyophilized in a freeze dryer (FreeZone lL Benchtop, Labconco Corp., Kansas City, MO, USA). The powders of ondansetron and IJTGMB were stored at 4°C in dark until use.

**Animals and treatments:** All experiments were carried out with approval of the Institutional Animal Care and Use Committee at Daegu Haany University (Gyeongsan, Korea) (Approval No. DHU2011-018). Six week old male Sprague-Dawley rats were purchased from Japan SLC Inc. (Shizuoka, Japan). Rats were housed in a room controlled at 20-25°C and 40-45% humidity and maintained on 12 h light/dark cycle with food and water *ad libitum*. After 2 weeks acclimation, one batch of 10 rats received single dosing of combination treatment of ondansetron with IJTGMB or control of ondansetron with distilled water (Fig. 1). The treatment was performed via oral co-administration within 5 min between ondansetron and IJTGMB or distilled water. Another batch of 10 rats received repeated dosing of the combination treatment for 8 days after pretreatments with IJTGMB for 6 days or control for 8 days after pretreatments with distilled water for 6 days. Ondansetron was used at a dose of 10 mg $kg^{-1}$

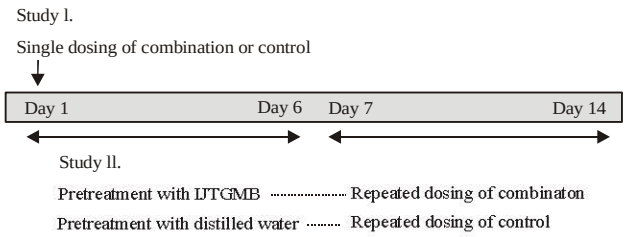


Fig. 1: Experimental design for co-administration of ondansetron with Ijintang-gamibang. For study I: One batch of 10 rats received single dosing of ondansetron with Ijingtang-gamibang (IJTGMB) (combination) or ondansetron with distilled water (control). For study II: Another batch of 10 rats received repeated dosing of the combination for 8 days after pretreatments with IJTGMB for 6 days or control for 8 days after pretreatments with distilled water for 6 days. The combination or control was co-administered orally within 5 min between ondansetron and IJTGMB or distilled water

according to safety datasheet from Hospira Inc (2009) and IJTGMB was used at 100 mg $kg^{-1}$ based on clinical practice. The body weight was measured at every treatment.

**Plasma sample collection:** Rats were fasted overnight before the treatment to avoid diet effects on pharmacokinetic analyses. Blood samples from the retro-orbital plexus was collected in 50 IU heparinized tubes at 0.5 h prior to the treatment and 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-treatment. The samples were immediately centrifuged at 11,400×g for 10 min and the supernatant was carefully separated from the blood cells. The small aliquot of plasma was stored at -70°C until pharmacokinetic analyses.

**Sample preparation and calibrations:** For calibration, 1.0 ng $mL^{-1}$ ondansetron (Sigma, MO, USA) in 50% acetonitrile was used as a primary stock solution and 500 ng $mL^{-1}$ carbamazepine (Sigma) in acetonitrile was used as an IS solution. Working standard solutions were prepared by dilution of primary stock solution with acetonitrile and stored at -20°C in dark until use. The working standard solutions and sample plasma were mixed with internal standard solutions in acetonitrile and centrifuged at 9,700×g for 10 min at 4°C. The resultant supernatant was transferred to injection vials for Liquid Chromatography Mass-/Mass-Spectrometry (LC MS/MS).

**LC MS/MS conditions:** Chromatographic analysis was performed using an Agilent 1100 Series HPLC (Agilent Technologies, Santa Clara, CA, USA) equipped with on-line degasser, binary pump, auto-sampler and column compartment. Separation of the analyte from the material was achieved at ambient temperature 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 for chromatographic separation was composed of 5-95% acetonitrile including 0.1% formic acid in distilled water and it was delivered isocratically at a flow rate of 0.3 mL $min^{-1}$. The column effluent was monitored using an API 2000 triple-quadruple mass-spectrometric detector (Applied Biosystems, Foster City, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode and controlled by the Analyst version 1.4.2 software (Applied Biosystems). Samples were introduced to the interface through a Turboion Spray 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 multiple reaction monitoring detection method was employed for ondansetron; the transitions monitored were IS: m/z 237>194 (retention time: 2.7 min); ondansetron: 294>170 (retention time: 2.5 min). Calibration curves of ondansetron were linear over the ranges studied with $R^2$>0.999. The lower limit of ondansetron quantification was 0.1 ng $mL^{-1}$.

**Pharmacokinetic analyses:** Ondansetron concentration was analyzed using a non-compartmental method on commercial pharmacokinetics data analyzer programs (PK solutions 2.0; Summit Research Services, Montrose, CO, USA) (DeVane, 1983; Bailer, 1988). The elimination rate constant ($K_{el}$) was calculated by log-linear regression of ondansetron concentration during elimination phase and the terminal half-life ($t_{1/2}$) was calculated by 0.693/$K_{el}$. The peak concentration ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$) were obtained by visual inspection in concentration-time curve. The area under the plasma concentration-time curve ($AUC_{0-t}$) from time zero to the time of the last measured concentration ($C_{last}$) was calculated using linear trapezoidal rule (Chiou, 1978). The AUC 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 to infinity ($MRT_{inf}$) was calculated by dividing the first moment of AUC ($AUMC_{0-inf}$) by $AUC_{0-inf}$.

**Statistical analyses:** All of the data is presented as Mean±Standard Deviation (SD) in 5 rats. Data for body weight and ondansetron concentration were firstly examined by test of homogeneity of variance (HOV) and followed by analysis of variance (ANOVA) with group of combination and control as a main effect. The day measuring body weights or time collecting plasma samples was treated as repeated measurements. If the data was passed at the test of HOV, they were compared by independent t-test for *post hoc* test, otherwise, they were compared by Mann-Whitney U test. Pharmacokinetic parameters were examined by Mann-Whitney U test as non-parametric comparisons because of small sample sizes with difficulties reaching to normal distribution. The statistical significance was defined as $p<0.05$.

## RESULTS

**Body weight changes:** In the single dosing, there were no evident differences in the body weight changes between the treatments of combination and control. In the on

Table 2: Body weight changes in rats received combination treatment of ondansetron with Ijintang-gamibang

| Parameters | Control after pretreatment with DW | Combination after pretreatment with IJTGMB |
|---|---|---|
| **Body weights** | | |
| Initial pretreatment [A] | 317.80±13.27 | 320.60±10.14 |
| Initial day of repeated dosing [B] | 335.80±15.83 | 337.80±11.54 |
| Last day of repeated dosing [C] | 342.40±19.07 | 343.80±14.74 |
| **Body weight gains during** | | |
| Pretreatment ([B]-[A]) | 18.00±3.54 | 17.20±3.70 |
| Repeated dosing ([C]-[B]) | 6.60±4.28 | 6.00±4.47 |
| All treat ([C]- [A]) | 24.60±7.77 | 23.20±5.22 |

A total of 10 rats received repeated dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination) for 8 days after pretreatments with IJTGMB for 6 days or repeated dosing of ondansetron with distilled water (DW) (control) for 8 days after pretreatments with DW for 6 days. The body weights were measured at the initial pretreatment and the initial and last day of repeated dosing. Values are expressed as Means±SD of body weights and body weigh changes in 5 rats

Table 3: Influences of Ijintang-gamibang on pharmacokinetic parameters of ondansetron in single dosing

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (ng mL$^{-1}$) | 179.00±85.07 | 152.08±94.53 |
| $T_{max}$ (h) | 0.50±0.00 | 0.50±0.00 |
| $AUC_{0-t}$ (ng h mL$^{-1}$) | 152.84±67.17 | 138.15±75.75 |
| $AUC_{0-inf}$ (ng h mL$^{-1}$) | 153.38±67.08 | 138.62±75.87 |
| $t_{1/2}$ (h) | 0.50±0.11 | 0.45±0.08 |
| $MRT_{inf}$ (h) | 0.87±0.04 | 0.90±0.03 |

A total of 10 rats received single dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination) or ondansetron with distilled water (control). The plasma samples used at Fig. 2 were analyzed for pharmacokinetic parameters including peak concentration ($C_{max}$), time to reach the $C_{max}$ ($T_{max}$), area under the ondansetron concentration-time curve ($AUC_{0-t}$), AUC zero to infinity ($AUC_{0-inf}$), terminal half-life ($t_{1/2}$) and mean residence time to infinity ($MRT_{inf}$). Values are expressed asMeans±SD in 5 rats

Table 4: Influences of Ijintang-gamibang on pharmacokinetic parameters of ondansetron after pretreatments with Ijintang-gamibang

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (ng mL$^{-1}$) | 336.20±62.27 | 257.40±62.05 |
| $T_{max}$ (h) | 0.50±0.00 | 0.50±0.00 |
| $AUC_{0-t}$ (ng h mL$^{-1}$) | 345.31±56.95 | 280.40±71.46 |
| $AUC_{0-inf}$ (ng h mL$^{-1}$) | 351.11±59.06 | 321.33±69.74 |
| $t_{1/2}$ (h) | 0.49±0.04 | 1.73±1.69 |
| $MRT_{inf}$ (h) | 0.99±0.10 | 1.81±1.24 |

A total of 10 rats received single dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination) after pretreatments with IJTGMB for 6 days or ondansetron with distilled water (control) after pretreatments with distilled water for 6 days. The plasma samples used at Fig. 3a were analyzed for pharmacokinetic parameters including peak concentration ($C_{max}$), time to reach the $C_{max}$ ($T_{max}$), area under the ondansetron concentration-time curve ($AUC_{0-t}$), AUC zero to infinity ($AUC_{0-inf}$), terminal half-life ($t_{1/2}$) and mean residence time to infinity ($MRT_{inf}$). Values are expressed as Means±SD in 5 rats

repeated dosing for 8 days after pretreatments with IJTGMB or distilled water for 6 days, the body weight changes also showed no differences between the both treatments (Table 2).

**Influences of IJTGMB on ondansetron pharmacokinetics in single dosing:** Ondansetron in plasma was detected up to 4 h post-treatment in the treatments of combination and control (Fig. 2). There were no differences in the kinetics of ondansetron concentration between the both treatments. There were no differences in any pharmacokinetic parameters between the both treatments (Table 3). It suggests little influences of IJTGMB on ondansetron pharmacokinetics when they were co-administered in the single dosing within 5 min.

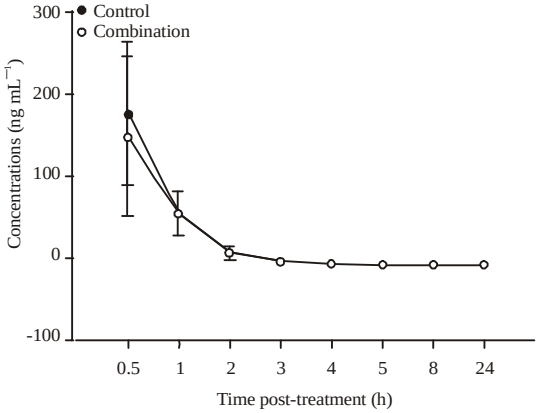


Fig. 2: Influences of Ijintang-gamibang on plasma concentration of ondansetron in single dosing. As indicated study I in Fig. 1, 10 rats received single dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination, open circles) or ondansetron with distilled water (control, closed circles). The plasma concentration of ondansetron was assessed at the indicated time and all values are expressed as Means±SD

**Influences of IJTGMB on ondansetron pharmacokinetics after pretreatment with IJTGMB:** In the initial treatment of repeated dosing after pretreatments for 6 days, ondansetron in plasma was detected up to 4 h post-treatment in the both treatments of combination and control (Fig. 3a). There were no differences in the kinetics of ondansetron concentration between the both treatments. There were no significant differences in any pharmacokinetic parameters between the both treatments (Table 4). It suggests little effect of IJTGMB on pharmacokinetics of ondansetron even after the pretreatments with IJTGMB for 6 days.

**Influences of IJTGMB on ondansetron pharmacokinetics in repeated dosing for 8 days:** In the repeated dosing of control for 8 days, ondansetron was detected up to 4 h after the last treatment, similarly with results in the single dosing or in the initial treatment after pretreatments for 6 days (Fig. 3b). However, in the repeated dosing of combination for 8 days, ondansetron was detected up to 8 h after the last treatment. The kinetic graph in the combination showed decreased

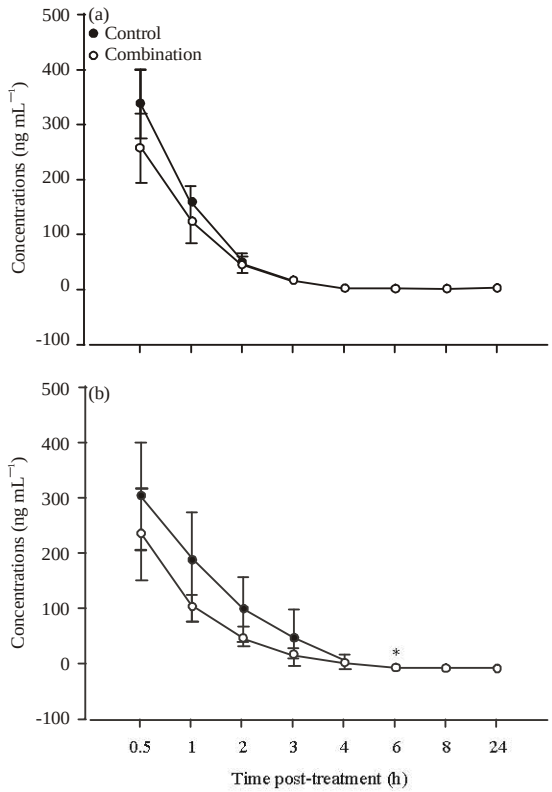


Fig. 3(a-b): Influences of Ijintang-gamibang on plasma concentration of ondansetron in repeated dosing after pretreatments with Ijintang-gamibang. As indicated study II in Fig. 1, 10 rats received repeated dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination, open circles) for 8 days after pretreatments with IJTGMB for 6 days or ondansetron with distilled water (control, closed circles) after pretreatments with distilled water for 6 days. The plasma concentration of ondansetron was assessed at the indicated time after the initial treatment of combination or control (A) and after the last treatment (B). All values are expressed as Means±SD and significant at $p<0.05$

concentration up to 3 h post-treatment compared to the control and recognizable detection up to 8 h post-treatment. There were significant differences in the ondansetron concentration between the combination and control at 6 h post-treatment, despites small amounts ($p<0.05$). In the further pharmacokinetic analyses, there were no significant differences in $C_{max}$, $T_{max}$, $t_{1/2}$ and $MRT_{inf}$ between the repeated dosing of combination and control. However, $AUC_{0-t}$ and $AUC_{0-inf}$ were significantly different between the both treatments ($p<0.05$). The $AUC_{0-t}$ was reduced by 39.0% in the repeated combination compared to the control and the $AUC_{0-inf}$ was also reduced by 38.4% in the combination compared to the control. The results suggest reduced bioavailability of ondansetron by repeated co-administration with IJTGMB for 8 days.

## DISCUSSION

Although ondansetron is a first-line drug for the management of NV involved in cancer chemotherapy and radiotherapy (Ye *et al*., 2001). It has adverse effects with potential QT interval prolongation and its safety is unclear for the use in states of pregnancy and lactation (Doggrell and Hancox, 2013). Various ondansetron combination may be available to reduce the ondansetron dose and enhance the efficacy but they should be well-monitored prior to use to avoid drug-drug interactions or possible adverse effects. To now, several drug-drug interactions have been evaluated in combination of ondansetron with other functioning drugs such as anesthetics (Dershwitz *et al*., 1992a; Lien *et al*., 1993), anti-cancer drugs (Tamaro *et al*., 1995; Gilbert *et al*., 1998; Cagnoni *et al*., 1999; Murren *et al*., 2000), hypnotic agents (Preston *et al*., 1996) and analgesics (Dursteler *et al*., 2006). However, there have been rare to report the interactions with other anti-emetic drugs for an adjunctive control. Considering that IJTGMB is one of the most famous Korean traditional medicines for the digestive impairments, ondansetron can be used in combination with IJTGMB to enhance its efficacy and reduce the unexpected adverse effects. Therefore, the drug-drug interactions between IJTGMB and ondansetron were examined in the oral co-administration within 5 min (Fig. 1).

The current pharmacokinetic analyses revealed little effects of IJTGMB on ondansetron pharmacokinetics in a single dose (Fig. 2 and Table 3) and even after the pretreatments with IJTGMB for 6 days (Fig. 3a and Table 4). However, there were significant differences in the kinetics of ondansetron concentration between the repeated dosing of combination and control for 8 days (Fig. 3b); ondansetron kinetics in the combination showed decreased concentration up to 3 h post-treatment and long remaining up to 8 h post-treatment. Further analyses revealed reduced AUC in the repeated dosing of combination compared to control (Table 5). Since AUC is usually used for estimating bioavailability of drugs and total clearance, it suggests reduced bioavailability of ondansetron in the repeated co-administration with IJTGMB. Ondansetron is generally absorbed in gastrointestinal tract via oral administration and it has degradation process with a hepatic cytochrome P450 in the liver (Jann *et al*., 1998; Yang and Lee, 2008). Here, the fact that there were no differences in $C_{max}$ and $T_{max}$ between the both treatments of combination and control, mean little effect of IJTGMB on the absorption of ondansetron. It suggests that the reduced bioavailability of ondansetron may be involved in increases of ondansetron degradation by activation of the cytochrome P450 in the liver. Although many studies have shown various components of natural herbs interacting with

Table 5: Influences of Ijintang-gamibang on pharmacokinetic parameters of ondansetron in repeated dosing

| Parameters | Control | Combination |
|---|---|---|
| $C_{max}$ (ng $mL^{-1}$) | 327.60±57.35 | 237.60±72.96 |
| $T_{max}$ (h) | 0.60±0.22 | 0.50±0.00 |
| $AUC_{0-t}$ (ng h $mL^{-1}$) | 460.82±150.84 | 281.15±60.21* |
| $AUC_{0-inf}$ (ng h $mL^{-1}$) | 473.32±164.17 | 291.54±59.10* |
| $t_{1/2}$ (h) | 0.66±0.19 | 0.78±0.15 |
| $MRT_{inf}$ (h) | 1.35±0.29 | 1.33±0.25 |

A total of 10 rats received repeated dosing of ondansetron with Ijintang-gamibang (IJTGMB) (combination) for 8 days or ondansetron with distilled water (control) for 8 days. The plasma samples used at Fig. 3b were analyzed for pharmacokinetic parameters including peak concentration ($C_{max}$), time to reach the $C_{max}$ ($T_{max}$), area under the ondansetron concentration-time curve ($AUC_{0-t}$), AUC zero to infinity ($AUC_{0-inf}$), terminal half-life ($t_{1/2}$) and mean residence time to infinity ($MRT_{inf}$). Values are expressed as Means±SD in 5 rats and asterisks denote statistical significance at $p<0.05$

cytochrome P450 (Zhou *et al*., 2003), there are no data about the interaction between each 8 herbs consisting IJTGMB and cytochrome P450. Furthermore, since the ondansetron degradation in combination with IJTGMB may be results s from the interaction with the herbal complex, IJTGMB as cytochrome P450 agonists or antagonists, the exact mechanisms regarding about how ondansetron was interacted with specific components of IJTGMB are difficult to be speculated. Further study is needed for proper dosing interval or dosing off between IJTGMB and ondansetron, based on the degradation of ondansetron in co-administration with IJTGMB.

Establishment of dosing regimen for the combination therapy needs careful consideration about various elements such as protein binding, age, health conditions and so on. Ondansetron bioavailability is slightly enhanced by the presence of food probably because of 70-76% protein binding (Bozigian *et al*., 1994; Lewis *et al*., 2010). While $T_{max}$ of ondansetron is relatively consistent with 0.5-2.2 h when administered orally in human (Roila and del Favero, 1995), $t_{1/2}$ appears variable with ages and biological conditions (Simpson and Hicks, 1996; De Alwis *et al*., 1998). In addition, alterations of ondansetron pharmacokinetics have been reported in the hepatic impairment (Figg *et al*., 1996), renal impairment and geriatric diseases (Roila and del Favero, 1995; Mondick *et al*., 2010). This study suggests possibility to use IJTGMB with ondansetron by single dosing or pretreatments. In addition, the combination therapy needs further clinical studies for proper dosing regimen depending on various conditions in patients.

## CONCLUSION

Pharmacokinetic analysis is prerequisite for the first monitoring of drug combination and dosing regimen. Ondansetron in combination with IJTGMB within 5 min had little interaction in single dosing with or without pretreatments with IJTGMB for 6 days. However, the repeated dosing of combination treatments for 8 days resulted in reduced bioavailability of ondansetron. IJTGMB may be co-administered with ondansetron at interval gap above ondansetron $MRT_{inf}$ in control for avoiding the drug-drug interaction but proper dosing regimen needs further clinical and subclinical studies.

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