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# Gender Differences in Ondansetron Pharmacokinetics in Rats

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**ABSTRACT:** It has been reported that ondansetron is primarily metabolized via hepatic CYP2D and 3A1/2 in male Sprague–Dawley rats, and CYP2D1 and 3A2 are male dominant and male specific isozymes, respectively, in rats. Thus, it could be expected that the pharmacokinetics of ondansetron would be changed in male rats compared with those in female rats. Thus, gender-different ondansetron pharmacokinetics were evaluated after its intravenous or oral administration at a dose of 8 mg/kg to male and female Sprague–Dawley rats. After intravenous administration of ondansetron to male rats, the *AUC* and time-averaged non-renal clearance ($Cl_{nr}$) of the drug were significantly smaller (22.6% decrease) and faster (27.3% increase), respectively, than those in female rats. This probably could be due to faster hepatic blood flow rate in male rats. After oral administration of ondansetron to male rats, the *AUC* of the drug was also significantly smaller (58.8% decrease) than that in female rats, and this could have been due mainly to increased intestinal metabolism of ondansetron in addition to increased hepatic metabolism of the drug in male rats. Copyright © 2008 John Wiley & Sons, Ltd.

**Key words:** gender difference; ondansetron; pharmacokinetics; CYP2D and 3A1/2; rat

## Introduction

Since gender differences in the pharmacokinetics of drugs have been reviewed [1,2], reports in humans and animals are increasing [3,4]. Gender differences in the pharmacokinetics of drugs could have been due to the differences in the following factors; gastric emptying rate, intestinal transit time, gut enzyme, body water space, muscle mass, organ blood flow rate, organ function, body fat and hepatic metabolism between men and women [2]. Among the factors, differences in hepatic microsomal cytochrome P450 (CYP) systems play a significant role in the gender differences [2].

Ondansetron, a potent and selective 5-$HT_3$ (5-hydroxytryptamine) receptor antagonist, has been used in the treatment of chemotherapy- and/or radiotherapy-induced nausea and emesis. In rats, ondansetron was rapidly and extensively absorbed from the gastrointestinal tract and the extent of absolute oral bioavailability ($F$) was less than 10% as a result of the first-pass metabolism [5]. Yang *et al*. [6] reported that after intravenous, oral, intraportal, intragastric and intraduodenal administration of ondansetron at a dose of 8 mg/kg to male Sprague–Dawley rats, the unabsorbed fraction for up to 24 h is 1.58% of the oral dose, the $F$ value is 4.07%, and the hepatic and intestinal first-pass effects are 64.8% and 34.2%, respectively, of the oral dose. Yang *et al*. [7] also reported that ondansetron is primarily metabolized via hepatic CYP2D and 3A1/2 (not via CYP1A1/2, 2B1/2, 2E1 and 2C11) in male Sprague–Dawley rats; the time-averaged non-renal clearance ($Cl_{nr}$) of ondansetron (the $Cl_{nr}$ of ondansetron could represent the metabolic clearance of the drug in rats) was significantly slower in rats pretreated with

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quinine hydrochloride (48.9% decrease; a main inhibitor of CYP2D in rats) and troleandomycin (13.2% decrease; a main inhibitor of CYP3A1/2 in rats), but was significantly faster (18.2% increase) with dexamethasone (a main inducer of CYP3A1/2 in rats). Hepatic CYP2D1 and 3A2 are male dominant and male specific isozymes, respectively, in rats [8]. Thus, it could be expected that the pharmacokinetics of ondansetron would change in male rats compared with those in female rats. Differences in the pharmacokinetics of ondansetron between men and women have also been reported [9,10]. For example, Pritchard *et al*. [9] reported that after single intravenous (0.15 mg/kg) or oral (8 mg) administration of ondansetron to three different age groups of healthy male or nonpregnant female nonsmokers, such as young (21–38 years old), elderly (61–74 years old), and aged (75–82 years old) groups, men cleared ondansetron faster than women, resulting in a lower *F* in men. Additionally, Jann *et al*. [10] also reported that men have a consistently smaller total area under the plasma concentration–time curve from time zero to time infinity (*AUC*) of ondansetron for all the formulations (two extemporaneous 16 mg suppositories and 8 mg commercially available oral tablet) than that in women. However, the lower *F* [9] and smaller *AUC* [10] of ondansetron in men were not fully explained.

The aim of this study was to report significantly smaller *AUC* and significantly faster clearance of intravenous or oral ondansetron in male rats than those in female rats.

## Materials and Methods

### *Chemicals*

Ondansetron hydrochloride dihydrate was supplied from Dong-A Pharmaceutical Company (Yongin, Republic of Korea). Propranolol [internal standard for the high-performance liquid chromatographic (HPLC) analysis of ondansetron] and the reduced form of β-nicotinamide adenine dinucleotide phosphate (NADPH; as a tetrasodium salt) were purchased from Sigma–Aldrich Corporation (St Louis, MO). Other chemicals were of reagent grade or HPLC grade.

### *Rats*

Protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Seoul National University, Seoul, Republic of Korea. Male (weighing 235–340 g) and female (weighing 220–240 g) Sprague–Dawley rats, 8–10 weeks old, were purchased from the Samtako Bio Korea (Osan, Republic of Korea). Rats were maintained in a clean-room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University) at a temperature of $23 \pm 2^{\circ}$C with 12 h light (07:00–19:00) and dark (19:00–07:00) cycles, and a relative humidity of $55 \pm 5\%$. The rats were housed in metabolic cages (Tecniplast, Varese, Italy) under filtered, pathogen-free air, with food (Sam Yang Company, Pyeongtaek, Republic of Korea) and water available *ad libitum*.

### *Measurement of $V_{max}$, $K_m$, and $Cl_{int}$ for the disappearance of ondansetron in hepatic and intestinal microsomal fractions*

The procedures used for the preparation of hepatic [11] and intestinal [12] microsomal fractions were similar to reported methods. Microsomal protein content was measured using a reported method [13].

The $V_{\max}$ (the maximum velocity) and $K_{\mathrm{m}}$ (the apparent Michaelis–Menten constant; the concentration at which the rate is one-half of the $V_{\max}$) for the disappearance of ondansetron were determined after incubating the above microsomal fractions (equivalent to 0.5 and 1.0 mg protein for the hepatic and intestinal microsomes, respectively), a 5 µl aliquot of distilled water containing ondansetron hydrochloride dihydrate having the final ondansetron base concentrations of 0.05, 0.1, 0.2, 0.5, 1, 2 or 5 µM (for both hepatic and intestinal microsomes), and a 50 µl aliquot of 0.1 M phosphate buffer (pH 7.4) containing 1 mM NADPH in a final volume of 0.5 ml by adding 0.1 M phosphate buffer (pH 7.4) in a water-bath shaker [37°C, 50 oscillations per min (opm)]. All of the above microsomal incubation conditions were linear. The reaction was terminated by the addition of 0.5 ml of dichloromethane after 5 min incubation for both hepatic and intestinal microsomes.



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The kinetic constants ($K_m$ and $V_{max}$) for the disappearance of ondansetron were calculated using a non-linear regression method [14]. The intrinsic clearance ($Cl_{int}$) for the disappearance of ondansetron was calculated by dividing the $V_{max}$ by the $K_m$.

### *Measurement of rat plasma protein binding of ondansetron using equilibrium dialysis*

Protein binding values of ondansetron to fresh plasma from male and female rats ($n$=5, each) were measured using equilibrium dialysis [6]. Plasma (1 ml) was dialysed against 1 ml of isotonic Sørensen phosphate buffer (pH 7.4) containing 3% (w/v) dextran ('the buffer') in a 1 ml dialysis cell (Spectrum Medical Industries, Los Angeles, CA) using a Spectra/Por 4 membrane (mol. wt cutoff of 12–14 KDa; Spectrum Medical Industries). After 4 h incubation, two 50 μl aliquots were collected from each compartment and stored at −70°C until used for the HPLC analysis of ondansetron. The binding value of ondansetron to 4% human serum albumin was constant, 73.1 ± 2.30%, at ondansetron concentrations ranging from 0.2 to 5 μg/ml. Thus, an ondansetron concentration of 0.5 μg/ml was arbitrarily chosen for these plasma protein binding studies.

### *Pretreatment of rats for intravenous or oral study*

Early in the morning, the jugular vein (for drug administration in the intravenous study) and the carotid artery (for blood sampling) of each rat were cannulated with a polyethylene tube (Clay Adams, Parsippany, NJ) while each rat was under light ether anesthesia [15]. Both cannulae were exteriorized to the dorsal side of the neck, where each cannula was terminated with a long silastic tube (Dow Corning, Midland, MI). Both silastic tubes were inserted into a wire sheath to allow free movement of the rat. Then, each rat was housed individually in a rat metabolic cage (Daejong Scientific Company, Seoul, Republic of Korea) and allowed to recover from the anesthesia for 4–5 h before beginning the experiment. Thus, the rats were not restrained in the present study.

### *Intravenous study*

Ondansetron hydrochloride dihydrate (dissolved in distilled water) at a dose of 8 mg (2 ml)/kg as ondansetron base was infused over 1 min via the jugular vein of male ($n$=7) and female ($n$=8) rats. A blood sample (approximately 0.22 ml) was collected via the carotid artery at 0 (control), 1 (at the end of the infusion), 3, 7, 15, 30, 45, 60, 75, 90, 120, 150 and 180 min after the start of the intravenous infusion of ondansetron. A heparinized 0.9% NaCl-injectable solution (20 units/ml; 0.3 ml) was used to flush the cannula immediately after each blood sampling to prevent blood clotting. Blood samples were immediately centrifuged and a 100 μl aliquot of each plasma sample was stored at −70°C until used for the HPLC analysis of ondansetron [16,17]. At the end of 24 h, each metabolic cage was rinsed with 5 ml of distilled water and the rinsings were combined with the 24 h urine sample. After measuring the exact volume of the combined urine sample, two 100 μl aliquots of the combined urine sample were stored at −70°C until used for the HPLC analysis of ondansetron. At 24 h, each rat was exsanguinated and killed by cervical dislocation.

### *Oral study*

Ondansetron hydrochloride dihydrate (the same solution used in the intravenous study) at a dose of 8 mg (5 ml)/kg as ondansetron base was administered orally using a feeding tube to male ($n$=6) and female ($n$=5) rats. Blood sampling time schedules were 0, 3, 5, 10, 20, 30, 40, 50, 60 and 90 min after oral administration of ondansetron. Other procedures were similar to those for the intravenous study.

### *HPLC analysis of ondansetron*

Concentrations of ondansetron in the samples were determined using a slight modification of reported HPLC methods [16,17]. Briefly, a 50 μl aliquot of pH 9 buffer solution and a 20 μl aliquot of distilled water containing 50 μg/ml of propranolol (internal standard) were added to a 100 μl aliquot of sample. Then, the mixture was extracted with 0.5 ml of dichloromethane. After vortex-mixing for 30 s and centrifugation



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(15000 × *g*, 10 min), the upper aqueous layer was discarded. The organic layer was transferred into a new tube and evaporated (Dry Thermo Bath MG-2100; Eyela, Tokyo, Japan) under a gentle stream of nitrogen gas at room temperature. The residue was reconstituted in a 100 µl aliquot of the mobile phase and a 75 µl aliquot was directly injected onto a reversed-phase ($C_{18}$; Symmetry®; 100 mm, ℓ. × 4.6 mm, i.d.; particle size, 3.5 µm; Waters, Milford, MA) HPLC column. The mobile phase, 0.02 M sodium phosphate monobasic solution: acetonitrile [70:30 (v/v); adjusted pH to 4.0 with 85% phosphoric acid], was run at a flow rate of 1.0 ml/min, and the column eluent was monitored using an ultraviolet detector at 305 nm at room temperature. The retention times of ondansetron and propranolol (internal standard) were approximately 2.2 and 3.6 min, respectively. The detection limit of ondansetron in rat plasma and urine samples were all 0.02 µg/ml. The coefficients of variation (intra- and inter-day) were below 5.39%.

### *Pharmacokinetic analysis*

The *AUC* was calculated using the trapezoidal rule—extrapolation method [18]. The area from the last datum point to time infinity was estimated by dividing the last measured plasma concentration by the terminal-phase rate constant.

Standard methods [19] were used to calculate the following pharmacokinetic parameters using a non-compartment analysis (WinNonlin®; professional edition version 2.1; Pharsight, Mountain View, CA); the time-averaged total body, renal and non-renal clearances (*Cl*, $Cl_r$ and $Cl_{nr}$, respectively), the terminal half-life, the first moment of *AUC* (*AUMC*), the mean residence time (*MRT*), the apparent volume of distribution at steady states ($V_{ss}$), and the *F* [15]. The peak plasma concentration ($C_{max}$) and the time to reach $C_{max}$ ($T_{max}$) were directly read from the experimental data.

### *Statistical analysis*

A value of $p < 0.05$ was deemed to be statistically significant using an unpaired *t*-test. All data are expressed as mean ± standard deviation, except for as a median (ranges) for $T_{max}$.

## Results

### *Protein binding of ondansetron to plasma from male and female rats*

Protein binding values of ondansetron to fresh plasma from male and female rats (*n*=5, each) were 74.3 ± 7.09% and 73.9 ± 9.64%, respectively; they were not significantly different.

### *$V_{max}$, $K_m$ and $Cl_{int}$ for the disappearance of ondansetron in hepatic and intestinal microsomes of male and female rats*

The $V_{max}$, $K_m$ and $Cl_{int}$ for the disappearance of ondansetron in hepatic microsomes of male and female rats are listed in Table 1. The $V_{max}$ and the $K_m$ values were comparable between male and female rats, suggesting that the maximum velocity for the disappearance of ondansetron (primarily metabolism) and the affinity of the enzyme(s) for the ondansetron were not significantly different between male and female rats. However, the $Cl_{int}$ in male rats was significantly

Table 1. Mean (± SD) $V_{max}$, $K_m$ and $Cl_{int}$ for the disappearance of ondansetron in the hepatic and intestinal microsomes of male and female rats

| Parameter | Hepatic microsomes | | Intestinal microsomes | |
|---|---|---|---|---|
| | Male (*n*=5) | Female (*n*=5) | Male (*n*=5) | Female (*n*=4) |
| $V_{max}$ (nmol/min/mg protein) | 3.14 ± 1.02 | 2.26 ± 0.961 | 0.0505 ± 0.0446 | 0.0381 ± 0.0119 |
| $K_m$ (µM) | 33.0 ± 10.3 | 28.7 ± 12.9 | 2.92 ± 2.43 | 2.70 ± 0.965 |
| $Cl_{int}$ (µl /min/mg protein) | 0.0947 ± 0.00372 | 0.0796 ± 0.00329[a] | 0.0169 ± 0.00252 | 0.0144 ± 0.00161 |
| Total protein (mg/whole liver) | 127 ± 20.3 | 88.9 ± 13.4[a] | 6.41 ± 2.17 | 5.43 ± 1.46 |

[a] Significantly different ($p < 0.05$) from male rats.



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faster (19.0% increase) than that in female rats, suggesting that the formation of metabolite(s) of ondansetron was increased in male rats compared with that in the female rats. The total protein in male rats was significantly greater (42.9% increase) than that in female rats.

The $V_{max}$, $K_m$ and $Cl_{int}$ for the disappearance of ondansetron in intestinal microsomes of male and female rats are also listed in Table 1. The $V_{max}$ and the $K_m$ values were also comparable between male and female rats. The $Cl_{int}$ in male rats was faster (17.4% increase; $p$=0.123) than that in female rats. The total protein in male rats was greater (18.0% increase; $p$=0.306) than that in female rats.

### *Pharmacokinetics of ondansetron after intravenous administration*

For the intravenous administration of ondansetron to male and female rats, the mean arterial plasma concentration–time profiles of the drug are shown in Figure 1(a), and the relevant pharmacokinetic parameters are listed in Table 2. Compared with female rats, the *AUC* was significantly smaller (22.6% decrease), and the *Cl* and the $Cl_{nr}$ were significantly faster (26.8% and 27.3% increase, respectively) in male rats.

### *Pharmacokinetics of ondansetron after oral administration*

For the oral administration of ondansetron to male and female rats, the mean arterial plasma concentration–time profiles of the drug are shown in Figure 1(b), and the relevant pharmacokinetic parameters are also listed in Table 2. Compared with female rats, the *AUC* was significantly smaller (58.8% decrease), the terminal half-life was significantly shorter (18.2% decrease) and the percentage of the dose excreted in the 24 h urine as unchanged ondansetron ($Ae_{0-24\,h}$) was significantly smaller (62.3% decrease) in male rats.

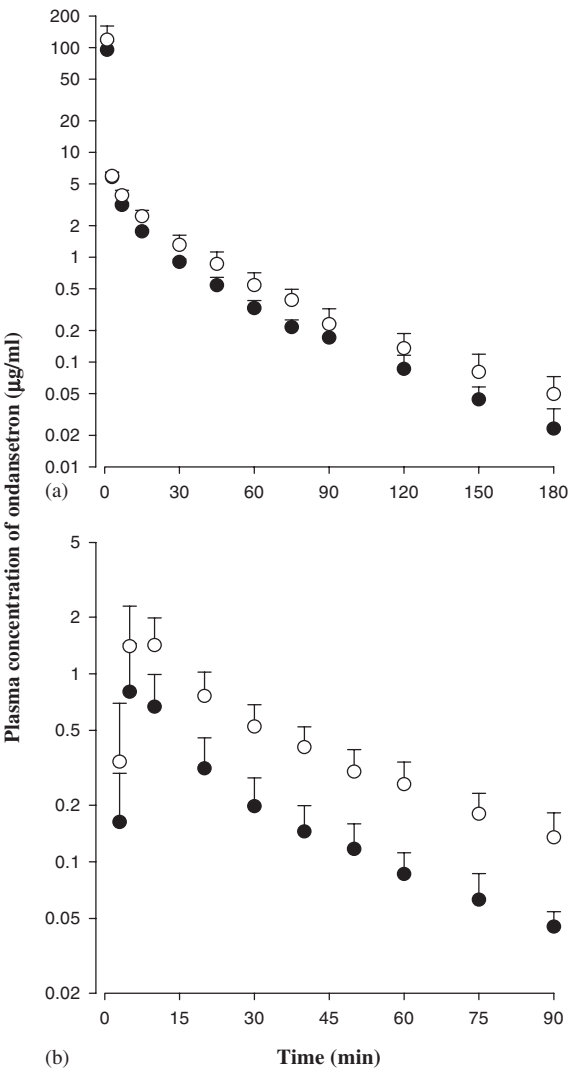


Figure 1. Mean arterial plasma concentration–time profiles of ondansetron after its intravenous infusion at a dose of 8 mg/kg to male (●; $n$=7) and female (○; $n$=8) rats (a), and its oral administration at a dose of 8 mg/kg to male (●; $n$=6) and female (○; $n$=5) rats (b). Bars represent standard deviation

## Discussion

After intravenous (at doses of 1–20 mg/kg) and oral (at doses of 4–20 mg/kg) administration of ondansetron to male Sprague–Dawley rats, the *AUC* values of ondansetron were dose-proportional [6]. Thus, an ondansetron dose of 8 mg/kg was arbitrarily chosen for the present study.

After intravenous administration of ondansetron, the contribution of the gastrointestinal (including the biliary) excretion of the unchanged ondansetron to the $Cl_{nr}$ of ondansetron was almost negligible; the percentages of the intrave-



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Table 2. Mean ( ± SD) pharmacokinetic parameters of ondansetron after its intravenous or oral administration at a dose of 8 mg/kg to rats

| Parameter | Female | Male |
|---|---|---|
| Intravenous | ($n$=8) | ($n$=7) |
| *AUC* (μg min/ml) | 257 ± 47.4 | 199 ± 21.1[a] |
| Terminal half-life (min) | 38.0 ± 5.28 | 33.2 ± 3.68 |
| *MRT* (min) | 19.4 ± 5.95 | 15.5 ± 2.98 |
| *Cl* (ml/min/kg) | 32.1 ± 5.97 | 40.7 ± 4.36[a] |
| $Cl_r$ (ml/min/kg) | 0.543 ± 0.270 | 0.618 ± 0.133 |
| $Cl_{nr}$ (ml/min/kg) | 31.5 ± 5.90 | 40.1 ± 4.38[a] |
| $V_{ss}$ (ml/kg) | 634 ± 262 | 632 ± 164 |
| $Ae_{0-24\,h}$ (% of dose) | 1.72 ± 0.746 | 1.54 ± 0.370 |
| Oral | ($n$=5) | ($n$=6) |
| *AUC* (μg min/ml) | 47.6 ± 15.6 | 19.6 ± 8.46[a] |
| Terminal half-life (min) | 34.0 ± 3.18 | 27.8 ± 4.46[a] |
| $C_{max}$ (μg/ml) | 1.62 ± 0.705 | 0.878 ± 0.600 |
| $T_{max}$ (min) | 10.0 (5.00–10.0) | 5.00 (5.00–10.0) |
| $Ae_{0-24\,h}$ (% of dose) | 0.642 ± 0.312 | 0.242 ± 0.156[a] |
| *F* (%) | 18.5 | 9.85 |

[a] Significantly different ($p<0.05$) from female rats.

nous doses of ondansetron (1–20 mg/kg) recovered from the gastrointestinal tract (including its contents and feces) at 24 h ($GI_{24\,h}$) were almost negligible, less than 0.422% of the dose [6]. Moreover, the 24 h biliary excretion of unchanged ondansetron was less than 0.231% of the intravenous dose (8 mg/kg) in five male Sprague–Dawley rats with bile duct cannulation [6]. Thus, the $Cl_{nr}$ of ondansetron listed in Table 2 could represent the metabolic clearance of the drug. Additionally, changes in the $Cl_{nr}$ of ondansetron could represent changes in the metabolism of the drug in rats.

After intravenous administration of ondansetron to male rats, the $Cl_{nr}$ of the drug was significantly faster than that in female rats (Table 2). It has been reported that the hepatic first-pass effects of ondansetron after absorption into the portal vein is 68.4% after intravenous and intraportal administration of the drug at a dose of 8 mg/kg to male Sprague–Dawley rats [6]. Because, ondansetron is close to a high hepatic extraction ratio drug (hepatic extraction ratio of <70%) in rats, its hepatic clearance depends more on the hepatic blood flow rate and the free (unbound to plasma proteins) fraction of the drug in plasma rather than on the $Cl_{int}$ for the disappearance of ondansetron in rats [20]. Although gender difference in the hepatic blood flow rate in rats does not seem to have been published, it has been reported [21] that the liver weight in male rats was significantly heavier than that in female rats. For example, in 8 week old male rats, the liver weight was significantly heavier (15.6% increase) than that in female rats. In mouse, rat, rabbit, monkey, dog and human, the hepatic blood flow rate was approximately 1 ml/g liver/min [22]. The plasma protein binding values of ondansetron were comparable between male and female rats as mentioned earlier. Thus, the significantly faster (smaller) $Cl_{nr}$ (*AUC*) of ondansetron in male rats (Table 2) could possibly be due to the faster hepatic blood flow rate than that in female rats. Although it has been reported that hepatic CYP2D1 and 3A2 are male dominant and male specific isozymes, respectively, in rats [8], and the $Cl_{int}$ for the disappearance of ondansetron in hepatic metabolism of male rats are significantly faster than that in female rats (Table 1), the contribution of these factors to the significantly faster (smaller) $Cl_{nr}$ (*AUC*) of intravenous ondansetron in male rats (Table 2) did not seem to be considerable.

After oral administration of ondansetron to male rats, the *AUC* of the drug was also significantly smaller than that in female rats (Table 2). This could be due to increased intestinal metabolism of ondansetron in addition to increased hepatic metabolism of ondansetron in rats. It has been reported that the intestinal first-pass effect of ondansetron is 34.2% in male Sprague–Dawley rats after intraportal and intraduodenal administration of the drug at a dose of 8 mg/kg [6]. Because, ondansetron is close to a low intestinal clearance drug (intestinal extraction ratio of <30%), its intestinal clearance depends more on the $Cl_{int}$ for the disappearance of ondansetron in the intestine rather than on the intestinal blood flow rate, if the hepatic clearance concept [20] could also be applied to the intestinal clearance. The smaller *AUC* of oral ondansetron in male rats could be supported by the faster $Cl_{int}$ in the intestinal microsomes of male rats (Table 1). Although the $Cl_{int}$ in male rats was not significantly faster ($p$=0.123) than that in female rats (Table 1), the value could be considerably faster considering the large intest-



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inal surface area. It has been reported that CYP3A is most expressed [23], but CYP2D is little expressed [24] in the rat intestine. Aiba *et al*. [25] reported that protein expression of intestinal CYP3A1/23 and 3A9 did not differ in male and female rats and intestinal CYP3A2 was not detected in male and female rats. Although the $Cl_{int}$ for the disappearance of ondansetron in the intestinal microsomes of male rats was considerably faster than that in female rats (Table 1), the exact reason is not clear.

Pritchard *et al*. [9] also reported that the clearance of intravenous ondansetron was faster in men than that in women. Although the hepatic first-pass effect of ondansetron in humans does not seem to have been published, the effect was 'indirectly' estimated by dividing the hepatic clearance of the drug by the hepatic blood flow rate [26]. The effect was estimated based on the hepatic blood flow rate of 1450 ml/70 kg/min and the hematocrit of 0.45 in humans [22], and the intravenous ondansetron clearance of 702 ml/min and 95% of the ondansetron dose was cleared in the liver in humans [27]. The hepatic first-pass effect of ondansetron thus estimated was 85.2%. Because ondansetron is a high hepatic extraction ratio drug in humans, its hepatic clearance depends more on the hepatic blood flow rate and free fraction of the drug in plasma rather than on the $Cl_{int}$ [20]. It has been reported [28] that the hepatic blood flow rate was faster in men than that in women. Thus, the slower clearance and smaller *AUC* of ondansetron after intravenous administration of the drug to men [9] could be due possibly to the faster hepatic blood flow rate than that in women [28]. Gender-different plasma protein binding of ondansetron in humans does not seem to have been published. It has been reported that in humans, hepatic CYP1A1/2 plays the most important role, whereas CYP2D6 plays a relatively minor role, and involvement of CYP3A seems important only at relatively high concentrations of ondansetron for the metabolism of ondansetron [28]. Although it has been reported that the activity of CYP1A2 was higher in men [25,29], the contribution of this factor to the faster clearance of intravenous ondansetron [9] does not seem to have been considerable. However, George *et al*. [30] reported no gender difference in the protein expression of hepatic CYP1A2, 2C, 2E1, and 3A in humans.

In conclusion, the significantly faster (smaller) $Cl_{nr}$ (*AUC*) of ondansetron after intravenous administration of the drug to male rats (Table 2) could be possibly due to faster hepatic blood flow rate in male rats. The significantly smaller AUC of ondansetron after oral administration of the drug to male rats (Table 2) could be due to increased intestinal metabolism of ondansetron (faster $Cl_{int}$ for the disappearance of ondansetron), in addition to increased hepatic metabolism of ondansetron in male rats.

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## References

1. Wilson K. Sex-related differences in drug metabolism in man. *Clin Pharmacokinet* 1984; **9**: 189–202.
2. Harris RE, Benet LZ, Schwarts JB. Gender effects in pharmacokinetics and pharmacodynamics. *Drugs* 1995; **50**: 222–239.
3. Ohtsuka H, Fujita K, Kobayashi H. Pharmacokinetics of fentanyl in male and female rats after intravenous administration. *Arzneimittelforschung* 2007; **57**: 260–263.
4. Zhu X, Lee DY, Shin WG. Gender difference in the pharmacokinetic interaction between oral warfarin and oxolamine in rats: inhibition of CYP2B1 by oxolamine in male rats. *Biopharm Drug Dispos* 2007; **28**: 125–133.
5. Saynor DA, Dixon CM. The metabolism of ondansetron. *Eur J Cancer Clin Oncol* 1989; **25**: S75–S77.
6. Yang SH, Bae SH, Lee MG. Dose-independent pharmacokinetics of ondansetron after intravenous and oral administration to rats: contribution of hepatic and intestinal first-pass effects to low bioavailability. In *Biopharmaceutics & Drug Disposition*. In press.
7. Yang SH, Lee MG. Effects of CYP inducers and inhibitors on the ondansetron pharmacokinetics in rats: involvement of CYP2D subfamily and 3A1/2 for the ondansetron metabolism. *J Pharm Pharmacol* 2008; **60**: 853–861.
8. Lewis DFV. Substrate specificity and metabolism. In *Cytochrome P450. Structure, Function and Mechanism.* Taylor & Francis: Bristol, 1996; 115–167.
9. Pritchard JF, Bryson JC, Kernodle AE, Benedetti TL, Powell JR. Age and gender effects on ondansetron pharmacokinetics: evaluation of healthy aged volunteers. *Clin Pharmacol Ther* 1992; **51**: 51–55.
10. Jann MW, ZumBrunnen TL, Tenjarla SN, Ward ES Jr, Weidler DJ. Relative bioavailability of ondansetron 8-mg



DOI: 10.1002/bdd

oral tablets versus two extemporaneous 16-mg suppositories: formulation and gender differences. *Pharmacotherapy* 1998; **18**: 288–294.
11. Moon YJ, Lee AK, Chung HJ, *et al*. Effects of acute renal failure on the pharmacokinetics of chlorzoxazone in rats. *Drug Metab Dispos* 2003; **31**: 776–784.
12. Peng JZ, Remmel RP, Sawchuk RK. Inhibition of murine cytochrome P4501A by tacrine: *in vitro* studies. *Drug Metab Dispos* 2004; **32**: 805–812.
13. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein–dye binding. *Anal Biochem* 1976; **72**: 248–254.
14. Duggleby RG. Analysis of enzyme progress curves by nonlinear regression. *Methods Enzymol* 1995; **249**: 61–90.
15. Kim SH, Choi YM, Lee MG. Pharmacokinetics and pharmacodynamics of furosemide in protein–calorie malnutrition. *J Pharmacokinet Biopharm* 1993; **21**: 1–17.
16. Bauer S, Stormer E, Kaiser R, Tremblay PB, Brockmoller J, Roots I. Simultaneous determination of ondansetron and tropisetron in human plasma using HPLC with UV detection. *Biomed Chromatogr* 2002; **16**: 187–190.
17. Depot M, Leroux S, Caille G. High-resolution liquid chromatographic method using ultraviolet detection for determination of ondansetron in human plasma. *J Chromatogr B Biomed Sci Appl* 1997; **693**: 399–406.
18. Chiou WL. Critical evaluation of potential error in pharmacokinetic studies using the linear trapezoidal rule method for the calculation of the area under the plasma level–time curve. *J Pharmacokinet Biopharm* 1978; **6**: 539–546.
19. Gibaldi M, Perrier D. *Pharmacokinetics* (2nd edn). Marcel Dekker: New York, 1982.
20. Wilkinson GR, Shand DG. A physiological approach to hepatic drug clearance. *Clin Pharmacol Ther* 1975; **18**: 377–390.
21. Tateishi T, Watanabe M, Nakura H, Tanaka M, Kumai T, Kobayashi S. Sex- or age-related differences were not detected in the activity of dihydropyrimidine dehydrogenase from rat liver. *Pharmacol Res* 1997; **35**: 103–106.
22. Davies B, Morris T. Physiological parameters in laboratory animals and humans. *Pharm Res* 1993; **10**: 1093–1095.
23. Kaminsky LS, Fasco MJ. Small intestinal cytochromes P450. *Crit Rev Toxicol* 1991; **21**: 407–422.
24. Okabe N, Hashizume N. Drug binding properties of glycosylated human serum albumin as measured by fluorescence and circular dichroism. *Biol Pharm Bull* 1994; **17**: 16–21.
25. Aiba T, Yoshinaga M, Ishida K, Takehara Y, Hashimoto Y. Intestinal expression and metabolic activity of the CYP3A subfamily in female rats. *Biol Pharm Bull* 2005; **28**: 311–315.
26. Lee MG, Chiou WL. Evaluation of potential causes for the incomplete bioavailability of furosemide: gastric first-pass metabolism. *J Pharmacokinet Biopharm* 1983; **11**: 623–640.
27. Simpson KH, Hicks FM. Clinical pharmacokinetics of ondansetron. A review. *J Pharm Pharmacol* 1996; **48**: 774–781.
28. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol* 2004; **44**: 499–523.
29. Pritchard JF. Ondansetron metabolism and pharmacokinetics. *Semin Oncol* 1992; **19**: 9–15.
30. George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. *Biochem Pharmacol* 1995; **50**: 727–730.



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