

## Original Article



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# Comparative pharmacokinetics between two tablets of tramadol 37.5 mg/acetaminophen 325 mg and one tablet of tramadol 75 mg/acetaminophen 650 mg for extended-release fixed-dose combination

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## ABSTRACT

An extended-release (ER) fixed-dose combination (FDC) of tramadol 37.5 mg/acetaminophen 325 mg was developed due to the demand for varying dosages. This study aimed to evaluate the pharmacokinetics (PKs) for two tablets of the new developed tramadol 37.5 mg/acetaminophen 325 mg ER FDC (DW-0920, Wontran Semi ER<sup>®</sup>) as test formulation compared to one tablet of the tramadol 75 mg/acetaminophen 650 mg ER FDC (DW-0919, Wontran ER<sup>®</sup>) as reference formulation. A randomized, open-label, 2-way crossover study was conducted in 30 healthy subjects. Subjects were orally administered one of 2 formulations followed by an alternate formulation with a 7-day washout period. Blood samples were collected up to 36 hours post-dose. Plasma concentrations of tramadol and acetaminophen were determined using a validated high-performance liquid chromatography with tandem mass spectrometric method. The geometric mean ratios (GMRs) and their 90% confidence intervals (90% CIs) of test formulation to reference formulation were calculated for the maximum plasma concentration ( $C_{max}$ ) and the area under the plasma concentration-time curve from zero to the last measurable time point ( $AUC_{last}$ ). The PK profiles of 2 formulations were comparable. The GMRs (90% CI) of  $C_{max}$  and  $AUC_{last}$  for tramadol were 1.086 (1.047-1.127) and 1.008 (0.975-1.042), respectively. The corresponding values for acetaminophen were 0.956 (0.897-1.019) and 0.986 (0.961-1.011), respectively. All the values were within the bioequivalence range of 0.80-1.25. Two tablets of DW-0920 were comparable to one tablet of DW-0919. The DW-0920 may be used for optimal pharmacotherapy for pain control with a lower dose.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT01606059

**Keywords:** Tramadol; Acetaminophen; Drug Combination; Pharmacokinetics; Extended Release Formulation

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**Author Contributions**

Conceptualization: Kim HC, Lee S, Hong JH, Kim J; Formal analysis: Kim HC; Investigation: Hong JH, Kim J; Methodology: Hong JH, Kim J; Project administration: Hong JH, Kim J; Supervision: Yoon DY, Lee S, Jang IJ, Hong JH, Kim J; Validation: Kim HC; Visualization: Kim HC; Writing - original draft preparation: Kim HC; Writing - review and editing: Yoon DY, Lee S, Jang IJ, Hong JH, Kim J.

**INTRODUCTION**

Tramadol and acetaminophen are often co-administered for moderate to severe pain control with rapid onset and long duration of analgesic effect. Tramadol is a centrally acting analgesic which acts on the opioid receptors and inhibits reuptake of the monoamines [1-3]. The bioavailability of tramadol is approximately 70% after the first-pass metabolism in the liver and tramadol is extensively metabolized in the liver via cytochrome 450 (CYP) 2D6, CYP 2B6 and CYP 3A4 [1,2,4]. Acetaminophen has the analgesic effects through both central and peripheral mechanisms [5,6]. Although the mechanisms of antinociception are uncertain, acetaminophen has been described that it inhibits the synthesis of prostaglandin and acts on endogenous neurotransmitter systems [6,7]. Approximately 90% of acetaminophen are removed by the metabolism through conjugation reaction such as glucuronidation and sulfation [6,8].

In the pharmacokinetics (PKs), the bioequivalence between the fixed-dose combination (FDC) and the loose combination of tramadol and acetaminophen was established and no significant differences in PK parameters of tramadol or acetaminophen after a single or multiple administration of FDC were observed when compared to each compound given alone [9-11]. In the pharmacodynamics, the FDC of tramadol and acetaminophen has been known to have the synergistically analgesic effects in the animal studies [12-14] and clinical trials [15-17]. Therefore, Ultracet<sup>®</sup> immediate-release (IR) tablet as the FDC of tramadol 37.5 mg and acetaminophen 325 mg, which is indicated for the management of acute pain that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate, was developed from Janssen Pharmaceuticals, Inc. [11]. Subsequently, Ultracet Semi<sup>®</sup> IR tablet (tramadol 18.75 mg/acetaminophen 162.5 mg) has been marketed for the need of various dosages, especially in geriatric patients or the patients who are sensitive to tramadol.

To improve the prolongation of pain control and the convenience of patient compliance, an extended-release (ER) formulation of the FDC for tramadol and acetaminophen was developed. Whether the ER formulation of tramadol 75 mg/acetaminophen 650 mg (DW-0919, Wontran ER<sup>®</sup>) every 12 hours can be used as an alternative to Ultracet<sup>®</sup> IR tablet every 6 hours was confirmed through phase 1 and phase 3 studies (unpublished) and it has been marketed. The half-dose (tramadol 37.5 mg/acetaminophen 325 mg) ER formulation (DW-0920, Wontran Semi ER<sup>®</sup>) was developed from Daewon Pharmaceutical Co., Ltd. with the same approach as the relation between Ultracet<sup>®</sup> IR and Ultracet Semi<sup>®</sup> IR. Therefore, this study aimed to evaluate the PK profile for two tablets of DW-0920 as test formulation compared to one tablet of DW-0919 as reference formulation was conducted.

**METHODS**

The study was reviewed and approved by the Korean Ministry of Food and Drug Safety (MFDS) and the Institutional Review Board of Chungnam National University Hospital (ClinicalTrials.gov registry No. NCT01606059). The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Korean Good Clinical Practice.

**Subjects**

Healthy Korean male subjects aged 20 to 55 years who weighed more than 55 kg within  $\pm$  20% of ideal body weight were enrolled in the study. Their health status was evaluated based

on medical history, vital signs, physical examinations, and clinical laboratory tests within 4 weeks before the first drug administration.

Exclusion criteria included the contents as follows: a history of clinically significant hypersensitivity to tramadol, acetaminophen, or opioids; a history or presence of hepatobiliary, renal, neurological, psychiatric, respiratory, endocrine, hemato-oncological, or cardiovascular diseases; a history of gastrointestinal disease or surgery that may affect the absorption of drugs; systolic blood pressure  $\geq 150$  mmHg or  $\leq 90$  mmHg, or diastolic blood pressure  $\geq 95$  mmHg or  $\leq 50$  mmHg; a history of taking abuse drugs or test positive for abuse drugs in the urine drug screening test; excessive consumption of alcohol ( $> 21$  units/week) or cigarettes ( $> 20$  cigarettes/day); administration of any ethical-the-counter drug or over-the-counter drug within 14 days or 7 days respectively before the first drug administration; participation in any other clinical trials within 60 days prior to the first drug administration.

### Study design

This study had a randomized, open-label, 2-treatment, 2-sequence, 2-period, crossover design. A total of 30 subjects were randomly assigned to one of 2 sequences. Subjects were orally administered two tablets of DW-0920 as test formulation or one tablet of DW-0919 as reference formulation with 240 mL of water under fasted condition in the first period. After a 7-day washout period, subjects received an alternate formulation in the second period.

Blood samples for PK assessments were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 36 hours post-dose. The samples were centrifuged at 3,000 rpm for 10 minutes. The plasma was separated and dispensed each 1 mL into 2 Eppendorf tubes. The tubes were stored at below  $-70^{\circ}\text{C}$  until analysis.

Safety was assessed by monitoring adverse events (AEs), vital signs, physical examinations, 12-lead electrocardiograms and clinical laboratory tests.

### Bioanalytical analysis

Plasma concentrations of tramadol and acetaminophen were determined by a validated high-performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) method using an API 4000 (AB SCIEX, Framingham, MA, USA) on a Shiseido nanospace SI-2 HPLC system (Shiseido, Tokyo, Japan). Tramadol- $d_6$  hydrochloride and acetaminophen- $d_4$  manufactured by Toronto Research Chemicals were used as internal standard materials. Analytical materials were separated with a  $C_{18}$  column (2.1 mm, i.d.  $\times$  150 mm, particle size, 5  $\mu\text{m}$ ) using acetonitrile/10 mM ammonium acetate/formic acid (40/60/0.1, v/v/v) as mobile phase at a flow rate of 0.25 mL/min with 3 minutes of analysis time. The MS/MS system in positive ion mode was performed by monitoring transition ions at  $m/z$  264.4  $\rightarrow$  58.1 and 270.2  $\rightarrow$  64.2 for tramadol and tramadol- $d_6$ , 152.2  $\rightarrow$  110.1 and 156.1  $\rightarrow$  114.2 for acetaminophen and acetaminophen- $d_4$ , respectively. Calibration curves of the tramadol and acetaminophen were constructed in the range of 1 to 500 ng/mL and 30 to 20,000 ng/mL, respectively.

### PK analysis

PK parameters of tramadol and acetaminophen were calculated with plasma concentration-time curves by a noncompartmental method using WinNonlin<sup>®</sup> version 6.2 (Pharsight, Mountain View, CA, USA). The primary PK parameters were maximum plasma concentration ( $C_{\text{max}}$ ) and area under the plasma concentration-time curve from zero until the last measurable time point ( $\text{AUC}_{\text{last}}$ ). The secondary PK parameters included time to reach  $C_{\text{max}}$  ( $T_{\text{max}}$ ), area under

the plasma concentration-time curve from zero to infinity ( $AUC_{inf}$ ) and apparent total clearance of the drug from plasma after oral administration ( $CL/F$ ). Areas under the concentration-time curve were calculated using the linear trapezoidal linear interpolation method.

### Statistical analysis

Statistics for the PK parameters were analyzed by using SAS<sup>®</sup> version 9.2 (SAS Institute Inc., Cary, NC, USA). The geometric mean ratios (GMRs) of two tablets of DW-0920 as test formulation to one tablet of DW-0919 as reference formulation and its 90% confidence intervals (CIs) were estimated using the linear mixed model. The model for the analysis of log-transformed values of  $C_{max}$  and  $AUC_{last}$  considered formulation as a fixed effect and subjects nested within sequence as a random effect. It was assessed that no significant differences are observed for PK profiles between 2 formulations if 90% CIs of GMRs for  $C_{max}$  and  $AUC_{last}$  are within the conventional bioequivalence range of 0.80–1.25.

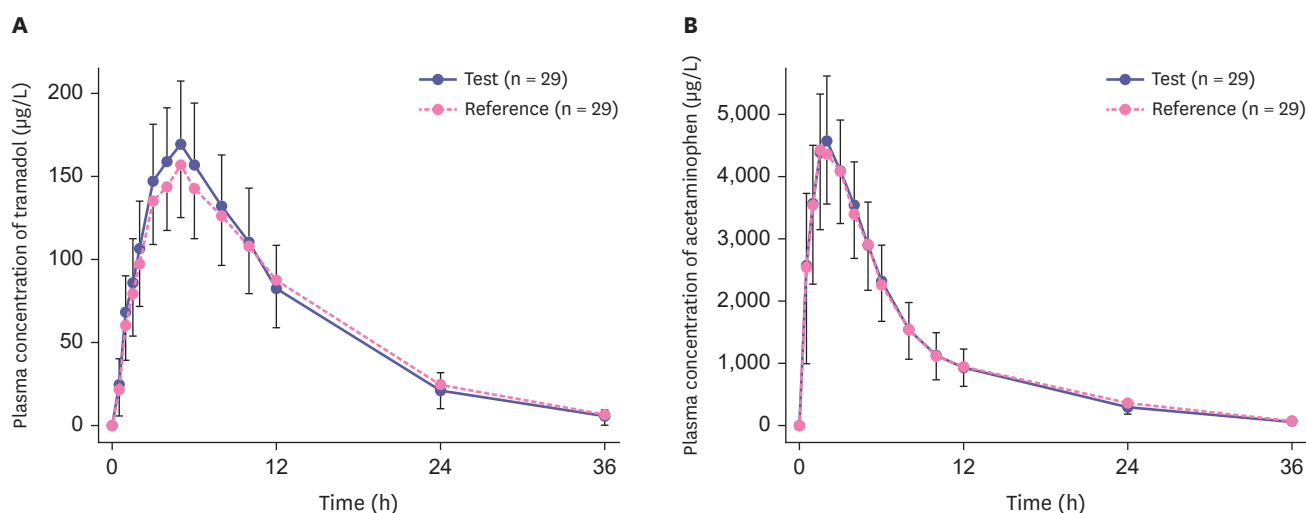
## RESULTS

### Subject characteristics

A total of 30 male subjects were enrolled and 29 subjects completed except 1 subject who withdrew the consent after the administration of one tablet of DW-0919 in first period. The age, height and weight of 30 subjects were  $23.8 \pm 2.0$  (mean  $\pm$  standard deviation) years,  $176.4 \pm 5.8$  cm and  $67.3 \pm 5.2$  kg, respectively. No statistically significant differences were observed in demographics between 2 sequences.

### PKs

PK profiles of 2 formulations were evaluated for 29 participants. The concentration-time profiles of tramadol and acetaminophen were similar between the 2 formulations (**Fig. 1**). The PK parameters between 2 formulations were also comparable (**Table 1**). The GMRs (90% CI) of  $C_{max}$  and  $AUC_{last}$  for tramadol were 1.086 (1.047–1.127) and 1.008 (0.975–1.042), respectively. The corresponding values for acetaminophen were 0.956 (0.897–1.019) and



**Figure 1.** Mean plasma concentration-time profiles of (A) tramadol, or (B) acetaminophen after a single oral administration of two tablets of DW-0920 (tramadol 37.5 mg/acetaminophen 325 mg ER FDC) as test formulation and one tablet of DW-0919 (tramadol 75 mg/acetaminophen 650 mg ER FDC) as reference formulation. Error bar represents standard deviation. ER, extended-release; FDC, fixed-dose combination.

**Table 1.** PK parameters of tramadol or acetaminophen after a single oral administration of two tablets of DW-0920 (tramadol 37.5 mg/acetaminophen 325 mg ER FDC) as test formulation and one tablet of DW-0919 (tramadol 75 mg/acetaminophen 650 mg ER FDC) as reference formulation

PK parameter	Tramadol		Acetaminophen	
	Test (n = 29)	Reference (n = 29)	Test (n = 29)	Reference (n = 29)
T <sub>max</sub> (hr)	5.00 (3.00–6.00)	5.00 (3.00–6.00)	1.50 (1.00–3.00)	1.50 (0.50–3.00)
C <sub>max</sub> (µg/L)	173.84 ± 38.71	159.19 ± 30.58	4,829.23 ± 1,003.52	5,077.56 ± 1,190.37
AUC <sub>last</sub> (hr·µg/L)	2,228.19 ± 598.95	2,217.83 ± 608.28	37,514.33 ± 8,747.74	38,097.76 ± 8,986.20
AUC <sub>inf</sub> (hr·µg/L)	2,276.39 ± 641.35	2,285.33 ± 678.26	38,591.44 ± 8,543.86	39,542.68 ± 8,410.44
t <sub>1/2</sub> (hr)	5.70 ± 0.99	6.02 ± 1.47	6.28 ± 1.54	6.83 ± 2.77
CL/F (L/hr)	35.40 ± 9.48	35.72 ± 10.73	17.68 ± 3.97	17.17 ± 3.64
V <sub>z</sub> /F (L)	281.48 ± 54.96	294.27 ± 53.52	162.11 ± 62.06	173.37 ± 98.70

All values are expressed as mean ± standard deviation. T<sub>max</sub> is expressed as median (min–max). PK, pharmacokinetic; ER, extended-release; FDC, fixed-dose combination; T<sub>max</sub>, time to reach maximum plasma concentration; C<sub>max</sub>, maximum plasma concentration; AUC<sub>last</sub>, area under the plasma concentration-time curve from zero until the last measurable time point; AUC<sub>inf</sub>, area under the plasma concentration-time curve from zero to infinity; t<sub>1/2</sub>, elimination half-life; CL/F, apparent total clearance of the drug from plasma after oral administration; V<sub>z</sub>/F, apparent volume of distribution during terminal phase after oral administration.

**Table 2.** Evaluation of bioequivalence for PK parameters of tramadol or acetaminophen

PK parameter	GMR (90% CI)*
Tramadol (n = 29)	
C <sub>max</sub>	1.086 (1.047–1.127)
AUC <sub>last</sub>	1.008 (0.975–1.042)
Acetaminophen (n = 29)	
C <sub>max</sub>	0.956 (0.897–1.019)
AUC <sub>last</sub>	0.986 (0.961–1.011)

PK, pharmacokinetic; GMR, geometric mean ratio; CI, confidence interval; C<sub>max</sub>, maximum plasma concentration; AUC<sub>last</sub>, area under the plasma concentration-time curve from zero until the last measurable time point; ER, extended-release; FDC, fixed-dose combination.

\*Geometric mean ratio of two tablets of DW-0920 (tramadol 37.5 mg/acetaminophen 325 mg ER FDC) as test formulation to one tablet of DW-0919 (tramadol 75 mg/acetaminophen 650 mg ER FDC) as reference formulation (90% CI).

0.986 (0.961–1.011), respectively (**Table 2**). All the GMRs and its 90% CIs of C<sub>max</sub> and AUC<sub>last</sub> were within the bioequivalence range of 0.80–1.25 (**Table 2**).

## Safety

Safety was evaluated for 30 subjects who administered the drug at least once. A total of 4 AEs (nausea, vomiting, blood sampling site irritation, dry cough) occurred in 3 subjects after administration of the test formulation and 5 AEs (diarrhea, fever, blood sampling site urticaria, dizziness, somnolence) occurred in 4 subjects after administration of the reference formulation. All the AEs were considered mild in intensity and resolved spontaneously. No clinically significant findings were observed in vital signs, physical examinations, 12-lead electrocardiograms and clinical laboratory tests.

## DISCUSSION

DW-0919, DW-0920, Ultracet ER<sup>®</sup> and Ultracet ER Semi<sup>®</sup> are the FDC ER formulations of tramadol and acetaminophen, which consist of an IR layer and a sustained-release (SR) layer for the respective ingredients. Although each dose of tramadol and acetaminophen are same for DW-0919 and Ultracet ER<sup>®</sup> and for DW-0920 and Ultracet ER Semi<sup>®</sup>, the higher dose of acetaminophen in the IR layer and tramadol in the SR layer of DW-0919 and DW-0920 compared to those of Ultracet ER<sup>®</sup> and Ultracet ER Semi<sup>®</sup> suggests that it can be used for the management of acute pain as well as chronic pain. After conducting additive phase

3 study which compared DW-0919 to Ultracet® IR tablet in acute toothache patients after teeth extraction surgery (NCT01920386), DW-0919 and DW-0920 were approved for the management of acute pain as well as chronic pain which is moderate to severe.

FDC formulation has been developed in various therapeutic areas with many advantages [18,19]: co-administration of 2 or more molecules with complimentary mechanisms of action or synergistic effects in one tablet; improvement to patient compliance with reduction in pill burden. However, it may have limitations such as less flexible dose adjustment and difficulty in identifying ingredients causing the adverse drug reactions [18,19]. Meanwhile, the FDC formulation of tramadol and acetaminophen is recommended to use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [11]. In addition, tramadol, one of the opioid analgesics, should be gradually reduced in dose during the discontinuation in patients who may be physically dependent on opioids [11]. Therefore, the FDC formulation of tramadol and acetaminophen requires the development of varying dosages, and DW-0920, which is the half-dose formulation of DW-0919, can be an option for appropriate dosage use taking into account many factors such as the patient's pain severity, adverse reactions and response.

We also suggest that DW-0920 would provide more options in dose selection according to the patient condition. Specifically in patients with hepatic and renal impairment, individual dosage regimens should be adjusted considering the characteristics of tramadol and acetaminophen which are substantially excreted by the kidney after extensive metabolism in the liver [10,16,20]. In patients with renal insufficiency, the exposure of tramadol and its metabolite M1 is increased with prolonged half-lives [2,16,21,22] and the increased concentration of acetaminophen conjugates can lead to the accumulation of potentially toxic substances [23,24]. Patients with hepatic impairment are also recommended to use tramadol and acetaminophen by reducing the doses or extending dosage intervals because of significantly higher exposure and prolonged half-lives of tramadol and acetaminophen [2,21,25].

This study was well-designed with sufficient time period in calculating PK parameters of tramadol and acetaminophen. The standard on pharmaceutical bioequivalence study issued by the Korean MFDS recommends that blood collection shall be conducted with sufficient time period of  $AUC_{last}$  to reach at least 80% of  $AUC_{inf}$ . The lowest value of  $AUC_{last}/AUC_{inf}$  ratio for individual subject was 0.91 for tramadol and 0.82 for acetaminophen, respectively. Therefore, all the values of  $AUC_{last}/AUC_{inf}$  ratio for tramadol and acetaminophen satisfied the criteria of time period for blood collection recommended in the regulatory agency.

In conclusion, this study showed that PK profile of two tablets of DW-0920 (tramadol 37.5 mg/acetaminophen 325 mg ER FDC) as test formulation was not significantly different to one tablet of DW-0919 (tramadol 75 mg/acetaminophen 650 mg ER FDC) as reference formulation in the fasted state. We expect that DW-0920, which is the half-dose formulation of DW-0919, may be used flexibly for optimal pharmacotherapy for pain control with a lower dose.

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