

# Bioequivalence of the pharmacokinetics between two formulations of 0.2 mg tamsulosin hydrochloride in healthy subjects

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Tamsulosin is an effective therapeutic option for lower urinary tract symptoms, as it selectively blocks  $\alpha_{1A}$ - and  $\alpha_{1D}$ -adrenoceptors in the bladder and prostate. The purpose of this study was to evaluate the bioequivalence in the pharmacokinetics (PK) of two 0.2 mg tamsulosin formulations when administered as the reference formulation (Yuropa<sup>®</sup> sustained-release tablet) vs. the test formulation (Yutanal<sup>®</sup> capsule) in healthy male subjects. A randomized, open-label, single-dose, two-way, two-period, crossover study was conducted in 37 healthy volunteers. The 0.2 mg of tamsulosin as the test or the reference formulation were administered during each period, and serial blood samples were collected up to 36 hours after dosing for PK analyses. A non-compartmental analysis was used to estimate the PK parameters. Geometric mean ratios (GMR) and 90% confidence intervals (CIs) were calculated for the two formulations to compare the maximum concentration ( $C_{max}$ ) and the area under the concentration-time curve from time zero to the time of the last quantifiable concentration ( $AUC_{last}$ ). The mean  $C_{max}$  and  $AUC_{last}$  for the test formulation were 6.19  $\mu\text{g/L}$  and 71.30  $\mu\text{g}\cdot\text{h/L}$ , respectively, and 5.76  $\mu\text{g/L}$  and 70.38  $\mu\text{g}\cdot\text{h/L}$  for the reference formulation, respectively. The GMRs (90% CIs) of the  $C_{max}$  and  $AUC_{last}$  between the two formulations were 1.09 (1.01–1.17) and 1.03 (0.96–1.10), respectively. Tamsulosin 0.2 mg as the test formulation exhibited bioequivalent PK profiles to those of the reference formulation. Therefore, the test formulation is expected to be an alternative to the reference formulation without concerns about differences in drug exposure.

## Introduction

Lower urinary tract symptoms (LUTS) are a subjective indicator of benign prostatic hyperplasia or a bladder outlet obstruction. LUTS include storage symptoms (e.g., increased daytime frequency and nocturia), voiding symptoms (e.g., slow or intermittent stream during micturition), and post-micturition symptoms (e.g., feeling of incomplete emptying and postmicturition dribble), which increase with age.[1,2] The worldwide prevalence of LUTS is expected to increase, resulting in an estimated 2.3 billion individuals worldwide affected by at least one LUTS by 2018.[3,4] Considering that LUTS is closely as-

sociated with quality of life as well as economic and human burdens, effective management of this condition is required.[5]

$\alpha_1$ -adrenoceptor antagonists relax prostatic and urethral smooth muscle and have beneficial effect on LUTS in patients with benign prostatic hyperplasia.[6] Tamsulosin relieves LUTS not only by blocking  $\alpha_{1A}$ -adrenoceptors in the prostate but also by blocking  $\alpha_{1A}$ - and  $\alpha_{1D}$ -adrenoceptors in the bladder, which inhibit detrusor muscle contractions. Blocking these adrenoceptors causes relaxation of bladder neck and prostate smooth muscle, resulting in improved urine flow rate and reduced LUTS.[2,7,8]

Tamsulosin is available as sustained release (SR) or modified release oral formulations for once-daily dosing with almost 100% bioavailability.[2] The SR delivery system was developed to avoid dose-dependent side effects.[9,10] Furthermore, as many patients with LUTS are elderly with impaired cardio-

vascular regulation, the preferred tamsulosin hydrochloride formulation provides SR that modulates the release rate and absorption of the drug in the intestinal tract.[11,12]

Tamsulosin is recommended to be administered after a meal to produce consistent plasma drug concentrations.[2,8] Food decreases tamsulosin exposure and increases time to peak concentration ( $T_{max}$ ), which results in smaller fluctuations in plasma peak and trough concentrations. Tamsulosin is extensively metabolized mainly by CYP3A4 and CYP2D6, with possible minor contributions by other CYP enzymes.[8,13] Tamsulosin exhibits linear kinetics following single and multiple dosing and achieves steady-state concentrations by day 5 with once/day dosing.[8]

A generic SR tablet formulation of tamsulosin was developed by a Korean domestic pharmaceutical company to provide a therapeutic option. However, bioequivalence needs to be verified between two formulations for use as an alternative without concerns about differences in pharmacokinetics (PK), particularly the extent and rate of absorption. Thus, the purpose of this study was to evaluate the PK bioequivalence between the generic (test) formulation and the branded (reference) formulation of tamsulosin in healthy subjects.

## Subjects and Methods

This study protocol was approved by the institutional review board at Kyung Hee University Hospital, Seoul, South Korea. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and was approved by the Ministry of Food and Drug Safety.

### Subjects

Healthy Korean male volunteers (age, 19–55 years) were enrolled in this study if they presented no abnormalities based on medical history, a physical examination, and clinical laboratory tests. The participants provided written informed consent after a detailed explanation of the study and before the screening tests for eligibility. All the subjects were not allowed to take any medication or beverages containing xanthine or alcohol during the entire period of the study. The occurrence of adverse events (AEs) and vital signs were recorded by the study staffs during the study period. Data from all the study participants who were administered the test or reference formulations were included for tolerability assessment.

### Study design

This was a randomized, open-label, single-dose, two-sequence, two-period, two-treatment crossover study. The test formulation was Yuropa® SR tablet (tamsulosin hydrochloride 0.2 mg) manufactured by DongKoo Bio & Pharma Co., Ltd., Seoul, Republic of Korea. The reference formulation was Yutanal® capsule, containing coated pellets of active ingredients, manufactured by Kukje Pharmaceutical Industrial Co., Ltd., Seoul, Republic of Korea. Eligible subjects were randomly assigned

into two sequence groups, each group receiving a dose each of the test and the reference formulation in a reverse order. That is, the one sequence group which was given the test formulation in period 1 following the reference in period 2, and the other sequence group which was given the reference formulation in period 1 following the test in period 2. There was a 7-day period between period 1 and period 2 in order to allow sufficient time for washout, more than five times terminal half-life ( $t_{1/2}$ ) of tamsulosin hydrochloride reported previously ( $8.1 \pm 3.8$  h).[14] After a 10 h overnight fast, the subjects received either the test or reference drug with 240 mL of water in the morning. Food intake was allowed 4 h after dosing.

### Blood sample collection and analysis

Seven ml of serial blood samples were collected in heparinized tubes at 0 (i.e., pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, and 36 h post-dosing to assess plasma tamsulosin concentrations. The blood samples were centrifuged for 10 min at 3000 rpm and stored at  $-70^{\circ}\text{C}$  until analysis.

Plasma tamsulosin concentrations were analyzed by high performance liquid chromatography (Agilent 1200 series, Palo Alto, CA, USA) coupled with a API 4000 triple-quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX, Foster City, CA, USA) operated in positive ionization mode. Chromatographic separation was performed using a CapcellPak C18 column ( $5\ \mu\text{m}$ ,  $3.0 \times 150$  mm; Shiseido, Tokyo, Japan) at a flow rate of 0.25 mL/min as in a previous study.[14] The mobile phase was 0.1% formic acid-acetonitrile distilled water (50:50, v/v). The quadrupole mass spectrometer equipped with an electrospray ionization source that was used in positive ion selected ion monitoring (SIM) mode, and a drying gas ( $\text{N}_2$ ) flow of 10 L/min, nebulizer pressure of 40 psig, and a drying gas temperature of  $350^{\circ}\text{C}$ . Target ions were monitored at  $m/z$  228 for tamsulosin, and  $m/z$  222 for the internal standard in the SIM mode.

Linear calibration curves for tamsulosin were established between 0.2 and 40 ng/mL under these conditions ( $r^2 = 0.9966$ ). Intra-day precision and accuracy were determined by five repeated analyses of each quality control sample on 1 day, and inter-day precision and accuracy were determined by repeated analyses on 5 consecutive days using 0.2, 0.5, 32, and 40 ng/mL of tamsulosin. Intraday % coefficient of variation (CV) and accuracy were 4.11–5.97%, and 92.39–103.22%, respectively. Interday % CV and accuracy were 4.74–11.53%, and 92.93–96.69%, respectively.

### Pharmacokinetic data assessment

A non-compartmental analysis using Phoenix® WinNonlin® software version 6.3 (Certara, St. Louis, MO, USA) was used to evaluate the PK parameters. The area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ( $\text{AUC}_{last}$ ) was calculated using the linear trapezoidal linear interpolation method. The observed values were used to estimate  $C_{max}$  and  $T_{max}$  for tamsulosin. The terminal elimination

rate constant ( $\lambda_z$ ) was estimated from a regression line of log-transformed plasma concentrations vs. time over the terminal log-linear portion, and  $t_{1/2}$  was calculated as the natural logarithm of 2 divided by  $\lambda_z$ . The plasma concentration-curve from time 0 to infinity ( $AUC_{inf}$ ) was calculated as  $AUC_{last} + C_{last} / \lambda_z$ , where  $C_{last}$  is plasma concentration measured at the last time point. Apparent clearance (CL/F) was calculated as the dose divided by the  $AUC_{inf}$ . The apparent volume of distribution (Vd/F) was estimated as the CL/F divided by the  $\lambda_z$ .

### Statistical analysis

The PK parameters were summarized using descriptive statistics. A general linear mixed effects model was developed using log-transformed data to compare the PK ( $AUC_{last}$  and  $C_{max}$ ) parameters between treatments, where period, sequence, and treatment were fixed effects and subjects nested in sequence was a random effect. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the  $AUC_{last}$  and the  $C_{max}$  between the two tamsulosin formulations were estimated for the PK parameters. Bioequivalence testing was concluded if the 90% CI of the GMR for the PK parameters was entirely contained within the

conventional bioequivalence range of 0.8–1.25. Statistical analyses were performed using the SPSS 18.0 (SPSS Korea, Seoul, Korea).

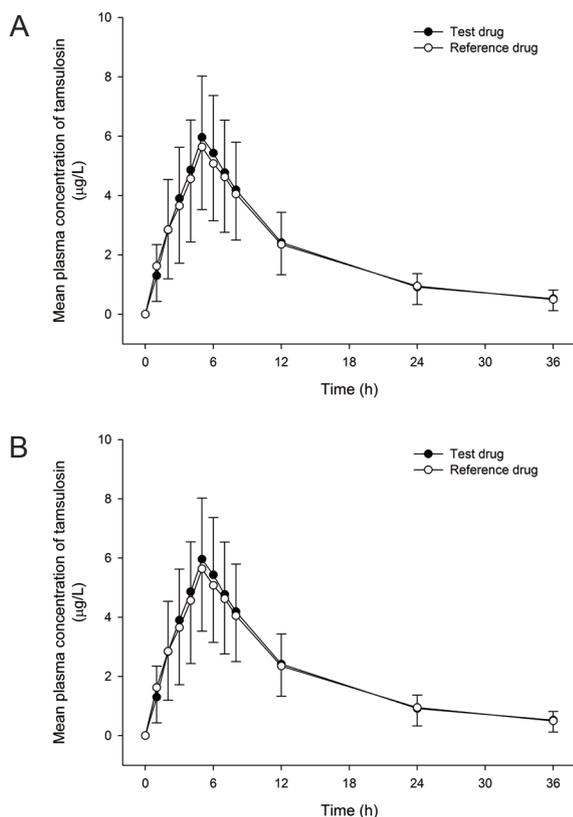
## Results

### Demographic characteristics

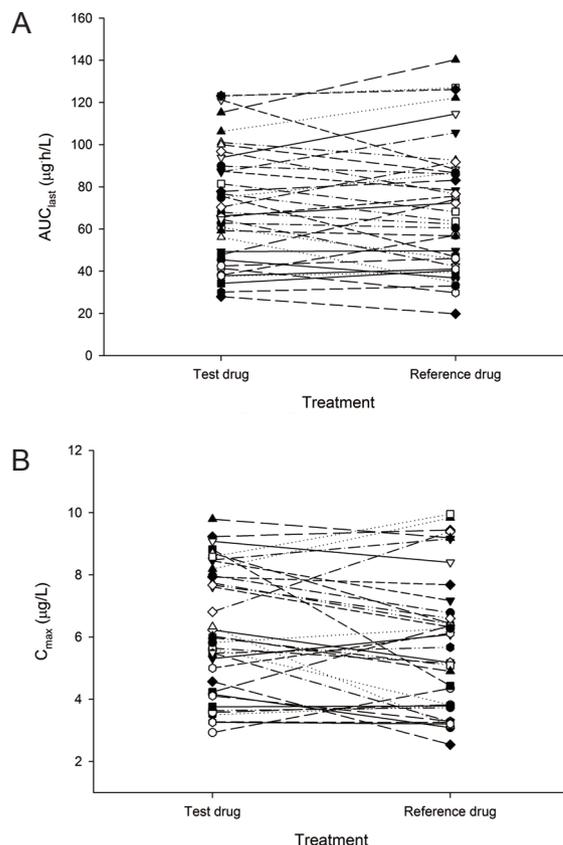
A total of 40 subjects were assigned into one of the two sequence groups. Two subjects (one subject for each sequence group) withdrew consent due to personal reasons, and one from the second sequence group withdrew after the 1 h sampling during the first period due to hypotension; thus, 37 subjects completed the study without clinically significant AEs. Mean  $\pm$  standard deviation (range) of age, height, and weight values were  $22.1 \pm 2.3$  (19–26) years,  $174.3 \pm 5.8$  (161.6–188.0) cm, and  $67.8 \pm 8.4$  (53.0–88.0) kg, respectively.

### Pharmacokinetics

Systemic exposure to tamsulosin after single dose oral administration of the tamsulosin hydrochloride 0.2 mg as the test and the reference formulations was bioequivalent. The GMRs (90%



**Figure 1.** Mean  $\pm$  SD plasma concentration-time profiles of tamsulosin after single doses of the test (black circles) and the reference formulations (white circles) of tamsulosin hydrochloride 0.2 mg in healthy subjects (A: linear scale B: log scale).



**Figure 2.** Individual (A)  $AUC_{last}$  and (B)  $C_{max}$  of tamsulosin after single doses of the test and the reference formulations of tamsulosin hydrochloride 0.2 mg in healthy subjects.

**Table 1.** Pharmacokinetic parameters of tamsulosin in 37 subjects after they received a single dose of tamsulosin hydrochloride 0.2 mg of the test and the reference formulations

	Test formulation	Reference formulation	Geometric mean ratio (90% confidence interval)
$T_{max}$ (h) <sup>a</sup>	5.0 [2.0-7.0]	5.0 [3.0-6.0]	
$C_{max}$ (µg/L)	6.19±2.04	5.76±2.21	1.09 (1.01-1.17)
$AUC_{last}$ (µg·h/L)	71.30±27.55	70.38±30.52	1.03 (0.96-1.10)
$AUC_{inf}$ (µg·h/L)	78.04±30.89	77.66±37.58	
$t_{1/2}$ (h)	8.67±2.03	8.85±2.98	
CL/F (L/h)	3.01±1.28	3.23±1.63	
Vd/F (L)	36.30±15.38	36.85±12.52	

Data are mean ± standard deviation. <sup>a</sup>Median [range].  $T_{max}$ , time to reach the maximum blood concentration after administration of drug;  $C_{max}$ , maximum plasma concentration of drug;  $AUC_{last}$ , area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration;  $AUC_{inf}$ , area under the plasma concentration-time curve from time 0 to infinity;  $t_{1/2}$ , terminal elimination half-life; CL/F, apparent clearance; Vd/F, apparent volume of distribution.

CI) of the test and the reference formulation were 1.09 (1.01–1.17) and 1.03 (0.96–1.10), respectively, and the  $C_{max}$  and  $AUC_{last}$  fell within the bioequivalence range of 0.8–1.25 (Table 1). The mean plasma concentrations-time profiles for tamsulosin were superimposable between the two formulations (Fig. 1). Furthermore, other PK parameters, including  $T_{max}$ ,  $AUC_{inf}$ ,  $t_{1/2}$ , and CL/F were also comparable between the two formulations (Table 1).

No trend or systematic deviation was found for the tamsulosin  $AUC_{last}$  and  $C_{max}$  after single oral administration of the test and the reference formulations (Fig. 2).

## Discussion

We showed that the test formulation of tamsulosin hydrochloride 0.2 mg had bioequivalent PK characteristics to the reference formulation. This bioequivalence after systemic exposure of both drugs was supported by the finding that the  $C_{max}$  and  $AUC_{last}$  GMRs (90% CI) were within the conventional bioequivalence criteria following administration of 0.2 mg of each formulation. In addition, the mean plasma concentrations-time profiles were superimposable between the two formulations from pre-dose to 36 h after dosing (Fig. 1). Furthermore, no trend or systematic deviation was found in the individual comparison of tamsulosin  $AUC_{last}$  and  $C_{max}$  values after the single dose oral administration of the test and the reference formulations (Fig. 2). These results indicate that the test formulation of tamsulosin can be used as an alternative to the reference formulation without concern about differences in systemic exposure. Finally, the PK parameters, including  $T_{max}$ ,  $t_{1/2}$ , CL/F, Vd/F,  $C_{max}$ , and  $AUC_{last}$  were comparable between the two formulations (Table 1).

The PK characteristics observed in this study demonstrated that approximately 50% of the drug exposure presented as the  $AUC_{inf}$  with a consistent  $T_{max}$  when compared with those in a previous study using a 0.4 mg tamsulosin SR tablet in 24 healthy

male volunteers; the mean  $AUC_{inf}$  of 162.88 µg/L was achieved with a median  $T_{max}$  of 5 h after dosing 0.4 mg tamsulosin hydrochloride as a SR tablet.[15] This result supports the linear PK characteristics of tamsulosin.[2]

The test drug formulation we investigated was a SR tablet for once daily dosing. SR formulation offers several advantages, such as an increased safety margin, reduced intensity of local or systemic side effects, improved patient convenience, and compliance.[16] The tamsulosin SR formulation exhibited longer  $T_{max}$  and  $t_{1/2}$  values with a smaller  $C_{max}$  and AUC in the current study, compared to values determined for the 0.2 mg immediate-release tablet in a previous study with healthy volunteers;  $AUC_{inf}$  = 85.5±15.8 ng·h/mL;  $C_{max}$  = 12.8±2.2 ng/mL;  $t_{1/2}$  = 5.25±0.93 h; and  $T_{max}$  = 1.6±0.6 h.[17,18] Therefore, the SR formulation maintained plasma tamsulosin concentrations within the therapeutic range for the desired duration with less potential to cause adverse effects, resulting in improved patient convenience.

The PK characteristics of tamsulosin observed here could be different from those in clinical settings. Tamsulosin is commonly prescribed to elderly patients with benign prostatic hyperplasia. Older patients show diminished intrinsic clearance of tamsulosin, resulting in a 40% overall higher exposure (AUC) in subjects aged 55–75 years than that in subjects aged 20–32 years.[8] Despite these PK differences, overall safety and effectiveness are not different between elderly and younger patients.[8] However, there is potential for a significant increase in systemic exposure when tamsulosin is co-administered with either a CYP3A4 or CYP2D6 inhibitor, as tamsulosin is metabolized mainly by CYP3A4 and CYP2D6.[8,13] Food intake decreases the AUC and  $C_{max}$  of tamsulosin and increases  $T_{max}$ .[8] Therefore, the SR formulation should be prescribed with caution for adverse effects and monitoring efficacy in a clinical setting (i.e., elderly patients receiving polypharmacy at the fed state).

Although safety profiles of the two formulations could not be compared in the current single-dose study for healthy volunteers, the tolerability and safety profiles of the test formulation are expected to be comparable to those of the reference formulation, which can be predicted based on the comparable PK characteristics shown in this study.

## Conclusion

The PK profiles of tamsulosin after single oral administration in healthy males were bioequivalent between the test and the reference formulations of tamsulosin hydrochloride 0.2 mg. Therefore, the test formulation can be used as an alternative therapeutic option for the reference formulation.

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## Conflict of interest

None of the authors have any conflicts of interest to disclose.

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