건강한 남성 자원자에서 탐스로신의 공복 투여 시 항정상태의 약동학적 특성 연구

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=Abstract=

Steady-State Pharmacokinetic Properties of Tamsulosin in Healthy Male Volunteers

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Background: To evaluate the pharmacokinetic properties of daily oral doses of tamsulosin administered to fasted healthy Korean male volunteers for 5 days.

Methods: In a randomized, open-label, multiple-dose, two-period, crossover study, all 44 subjects were randomly assigned in a 1:1 ratio to receive a newly developed generic capsule formulation (test) or a branded capsule formulation (reference) of tamsulosin 0.2 mg, followed by a 10-day washout period and administration of the other formulation. Plasma concentrations of tamsulosin were assessed after administration of five-day multiple doses, using HPLC-MS/MS. Clinical and laboratory adverse events (AE) were assessed.

Results: The mean (SD) pharmacokinetic properties with the test and reference formulations were as follows: $C_{ss, max}$, 9.0 (2.9) and 8.4 (2.6) ng/mL, respectively; median (range) t_{max}, 4 (2-6) and 5 (2-7) hours; AUC_τ, 93.7 (31.5) and 88.2 (29.3) ng $\times$ h/mL; and $t_{\frac{1}{2}}$, 9.5 (2.6) and 10.0 (2.7) hours. The volume of distribution and clearance after oral administration of tamsulosin were 0.5 L/kg, and 0.04 L/h/kg, respectively. The accumulation ratios for 0.2 mg once-daily dosing regimen were 1.2. The 90% CIs of the geometric mean ratios for the log-transformed AUC_τ (1.005-1.131) and $C_{ss, max}$ (1.000-1.136) values were within the acceptable range for bioequivalence. No serious AE was reported during the study. Both formulations were well tolerated.

Conclusion: The results demonstrate that the $C_{ss, max}$ and AUC_τ values in the fasted subjects were higher than those in the fed from other study, with a shorter t_{max} values.

Key words: Fasted state, Healthy volunteers, Multiple-dose, Pharmacokinetics, Tamsulosin.

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INTRODUCTION

Lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH), including urinary frequency, urgency, nocturia, incontinence, and hesitancy, increase with age[1,2] α_1-Adrenoceptor antagonists, muscarinic receptor antagonists, and 5α-reductase inhibitors have been prescribed for the treatment of LUTS/BPH.[3-5]

Tamsulosin HCl, chemically (−)-(R)-5-[2-[[2-(o-ethoxyphenoxy)ethyl]amino]propyl]-2-methoxy-benzenesulfonamide monohydrochloride), is a third-generation α_1-adrenoceptor antagonist.[6] Tamsulosin has a moderately higher affinity for the α_{1A}-adrenoreceptor subtype, which is predominantly distributed in the prostate, bladder neck, and urethra, than for the α_{1B} subtype in vascular tissues.[7,8] The chemical structure of tamsulosin is shown in Figure 1.

Tamsulosin is usually administered once daily as a capsule in a modified-release (MR) formulation, at a dose of 0.2 mg in Japan and other Asian countries and a dose of 0.4 mg in Europe and the US.[9] When administered orally to fasted humans, the absolute bioavailability of tamsulosin MR is approximately 100 %, with a time to reach peak plasma concentration (t_{max}) ranging from 2.9 to 5.6

h, and a mean terminal half-life of approximately 11.7–22.0 h.[6,10] Tamsulosin has been reported to exhibit linear pharmacokinetics following single and multiple doses.[9] Tamsulosin is highly bound to plasma proteins (98.9–99.1 %), with most binding to α_1-acid glycoprotein.[10-12] After absorption, tamsulosin in humans is extensively metabolized to inactive water-soluble metabolites, by cytochrome P450 (CYP) 3A4 and CYP2D6, with only 8.7–15 % of an oral dose being excreted in urine as the parent compound.[8,10,12,13] Because slightly shorter t_{max} values and higher C_{max} values have been reported in the fasted state compared with the fed state, ingestion of tamsulosin after a meal is recommended to decrease the risk of adverse events from high peak concentrations.[10] Although the single-dose pharmacokinetics of tamsulosin have been widely evaluated in the fasted and fed states, limited data are available investigating the multiple-dose pharmacokinetics of tamsulosin, especially in the fasted state.[10] The aim of the study was to investigate the pharmacokinetic (PK) properties of a newly developed generic capsule formulation (test) and a branded capsule formulation (reference) of tamsulosin after 0.2 mg/day oral doses administered to fasted healthy Korean male volunteers for 5 days.

SUBJECTS AND METHODS

1. Subjects

Healthy Korean male volunteers, aged 19–50 years, with a body weight of > 55 kg and
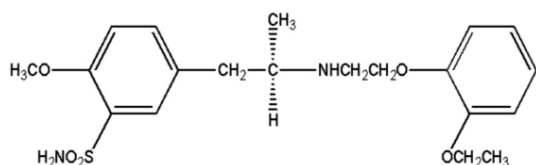
Figure 1. Chemical structure of tamsulosin.

within ± 20 % of ideal weight, were eligible for the study if they had no clinically significant findings on medical history, physical examination, routine clinical laboratory tests (blood hematology, biochemistry, urinalysis), 12-lead electrocardiography, and urinary drug testing for barbiturates, benzodiazepines, amphetamine, cocaine, and opiates.

Subjects were excluded if they had a history of allergy or hypersensitivity to any drug, had a history or evidence of cardiovascular, pulmonary, hepatic, renal, endocrine, musculoskeletal, central nervous system, hematologic, gastrointestinal or malignant disease, and/or a history of drug abuse. Subjects were also excluded if they had received any prescription drug or herbal remedy within 14 days or had used over-the-counter remedies within seven days prior to dosing, had participated in another investigational drug study within three months prior to dosing, had donated whole blood within two months or any blood product within one month prior to dosing, regularly drank > 21 units of alcohol per week, engaged in excessive smoking (> 10 cigarettes per day), had a systolic BP of > 150 or < 100 mmHg, had a diastolic BP of > 100 or < 60 mmHg, had serum aspartate aminotransferase or alanine aminotransferase levels > 1.5-fold the upper limit of normal, or had a positive test result for hepatitis (B or C) and/or human immunodeficiency virus (HIV) infection.

Use of any food known to induce or inhibit hepatic drug metabolism, and excessive exercise were prohibited seven days before and during the study period. Alcohol, grapefruit juice, and xanthine-containing substances were prohibited three days before and during the study period. Products containing nicotine were also prohibited during the admission period.

The study protocol was approved by the institutional review board at Kyungpook National University Hospital (KNUH), Daegu, Republic of Korea, in accordance with the ethical standards for studies in humans of the Declaration of Helsinki and its amendments, and the applicable guidelines for Good Clinical Practice. Before participating, all the subjects received written and oral information on the study and signed a consent document.

2. Study Design

This randomized, open-label, two-period, multiple-dose, crossover study was conducted at KNUH Clinical Trial Center. All eligible subjects received the test or reference formulation, separated by a 10-day washout period, in a crossover manner. Enrolled subjects were randomized in a 1:1 ratio to receive multiple 0.2-mg doses of tamsulosin as a newly-developed capsule (test) formulation (lot no. 10003; expiration date, May 2013; Hanmi Pharmaceutical Co. Ltd., Seoul, Republic of Korea) followed by a capsule (reference) formulation (lot no. C0401; expiration date, December 2012; Astellas Pharma Inc., China) or vice versa. An SAS code for randomization (ver. 8.2; SAS Institute Inc., Cary, NC) was used to randomize the 44 subjects into

two different groups. On days 1-4 of each period, all subjects arrived at the study center and received the 0.2 mg/day maintenance dose with 240 mL of water after a minimum overnight fast of 10 h. Subjects were admitted to the study center at 8 pm on day 4. After an overnight fast of 10 h, subjects received the last maintenance dose of the test or reference formulation with 240 mL of water in the morning of day five. Additional water intake was permitted 2 h after dosing, and food intake was allowed 4 h after dosing.

To determine the plasma concentrations of tamsulosin, serial blood samples were drawn immediately before and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 36 h after administration of the last dose on day 5. A 20G, 0.75-inch indwelling catheter was inserted into an antecubital vein. After 1 mL of blood from the catheter was discarded, 8 mL of blood was collected into tubes containing sodium heparin (Vacutainer; BD BioSciences, Franklin Lakes, NJ). The line was flushed with 1.5 mL of normal saline to ensure patency. The samples were subjected to centrifugation (3000 rpm, 10 min), and the plasma samples were stored frozen at −70 °C until analysis by an analytical laboratory (Drug Development Supporting Service Division, Biocore Co., Ltd., Seoul, Republic of Korea).

3. Analysis of Tamsulosin Concentrations

Plasma concentrations of tamsulosin were determined using high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC/MS/MS). Briefly, 200 µL of plasma sample was pipetted into a polypropylene tube, and 10 µL of rac tamsulosin-methyl-d3 hydrochloride (30 ng/mL in acetonitrile) was added as an internal standard. The mixture was then vortexed. After addition of 500 µL acetonitrile, the mixture was vortexed for 5 min, and centrifuged (13,000 rpm, 5 min). The supernatant was transferred to a new glass tube and evaporated to dryness in a nitrogen evaporator. The residue was reconstituted in 500 µL acetonitrile, and 5 µL was injected for analysis.

Samples were analyzed by HPLC-MS/MS. MS using a Shiseido nanospace SI-2 HPLC system (Shiseido Co.. Ltd., Tokyo, Japan) coupled to TSQ Quantum Ultra mass spectrometer (Thermo Fisher Scientific Inc., Waltham, USA) operated in positive ionization mode. Chromatography was performed using a Unision UK C18 column (2.0×75-mm internal diameter, 3-µm particle size; Imtakt, Kyoto, Japan) at a flow rate of 0.2 mL/min. The mobile phase was acetonitrile-distilled water-formic acid (60:40:0.1, v/v/v), and the column temperature was maintained at 40 °C. The selected reaction monitoring (SRM) transitions for quantification were m/z 409.2 → 228.1 for tamsulosin and m/z 412.2 → 231.0 for tamsulosin-d3. Linear calibration curves were established between 0.1 and 20 ng/mL for tamsulosin ($r^2 = 0.9989$). Intraday % CVs were 12.5, 8.7, 3.7, and 4.4 for 0.1, 0.5, 5, and 20 ng/mL HTB, respectively. At the same respective

concentrations, interday % CVs were 14.8, 9.4, 7.2, and 2.6, respectively. The overall accuracy ranged from 102.9 to 114.2 % (intraday) and from 99.2 to 105.3 % (interday). The lower limit of quantification was 0.1 ng/mL.

4. Pharmacokinetic Analysis

The PK parameters of tamsulosin were determined by non-compartmental methods, using the WinNonlin Pro 5.2 software (Pharsight Corporation, Mountain View, CA), based on individual subject's tamsulosin plasma concentrations using actual sampling times after the administration of the final 0.2-mg maintenance dose.

The maximum plasma concentration ($C_{ss,max}$), minimum plasma concentration ($C_{ss,min}$), and time to reach maximum plasma concentration (t_{max}) were estimated directly from the observed plasma concentration-time data curve. The area under the plasma concentration-time curve over the dosing interval after multiple-dose administration (AUC_τ) was calculated using the linear trapezoidal method. The average steady-state concentration ($C_{ss,av}$) is calculated as AUC_τ / τ. The terminal elimination rate constant (k_e) was determined by linear regression of the log-linear decline of the final data points (at least three). The apparent elimination half-life ($t_{1/2}$) of tamsulosin was calculated as 0.693/ k_e. The fluctuation index was calculated as $(C_{ss,max} - C_{ss,min})/(AUC_\tau /\tau)$. All estimated pharmacokinetic parameters were summarized descriptively as means ± standard deviation (SD).

5. Safety Assessment

The safety of tamsulosin was evaluated throughout the study period, based on the recordings of clinical and laboratory adverse events (AEs) collected and assessed after administration of tamsulosin. All subjective symptoms reported by subjects and objective signs observed by clinical investigators were collected and assessed after administration of tamsulosin and throughout the study period. Vital signs (blood pressure, pulse rate) were assessed at screening, days 1-4 (before dosing), day five (before and at 2, 6, 12, and 24 h after administration of the last dose), and follow-up visit. Body temperature was measured at screening, day five (before dosing), and the follow-up visit. A full physical examination was performed at screening, day one (before dosing), and at the follow-up visit. The following laboratory tests were conducted at screening, day one (before dosing) and follow-up visit, at an accredited laboratory (Department of Laboratory Medicine, KNUH, Daegu, Republic of Korea): blood hematology (hemoglobin, hematocrit, red blood cell, platelet, and white blood cells with lymphocyte, monocyte, eosinophil, and basophil counts), urinalysis (specific gravity, pH, protein, glucose, ketone, bilirubin, occult blood, urobilinogen, nitrite, and microscopic examination (red and white blood cells)), and serum chemistry (fasting glucose, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline

phosphatase, aspartate aminotransferase, alanine aminotransferase, ɣ-glutamyltransferase, creatine phosphokinase, lactate dehydrogenase). A 12-lead ECG was conducted at screening and at the follow-up visit.

Treatment-emergent adverse events (TEAEs) were defined as those occurring on or after administration of the first randomized dose. TEAEs were evaluated by the study physicians in terms of intensity (mild, moderate, severe), duration, severity, outcome, and relationship to the study drug administered.

6. Statistical Analyses

The results are expressed as means ± SD unless otherwise indicated, and a p-value below 0.05 was deemed to indicate statistical significance. The pharmacokinetic parameters were compared between the two tamsulosin formulations using paired t-tests or the Wilcoxon signed rank test. All statistical tests were performed using the SPSS software (ver. 18.0 for Windows; SPSS Korea Inc., Seoul, Republic of Korea).

RESULTS

In total, 44 healthy Korean male subjects (age, 24.3 ± 1.7 years; range, 20–28; weight, 68.9 ± 6.5 kg; range, 55.3–82.8; height, 175.4 ± 4.0 cm; range, 165.0–183.0) were enrolled. Three subjects dropped out. One subject dropped out on day three during period two because of
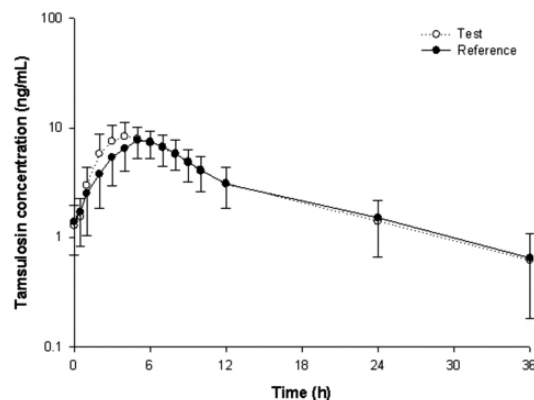
Figure 2. Mean (SD) plasma tamsulosin concentration-time profiles after administration of multiple 0.2-mg/day doses of two formulations of tamsulosin in 41 healthy Korean male volunteers.

drinking alcohol. Two subjects withdrew consent after study drug administration in periods one and two. All subjects were included in the safety analysis, and data from 41 subjects were included in the PK analysis.

The mean concentration-time profiles for tamsulosin after the five maintenance doses of the two tamsulosin formulations are shown in Figure 2. The PK parameters of tamsulosin for both formulations are summarized in Table 1. The mean (SD) PK values for the test and reference formulations, respectively, were as follows: $C_{ss,max}$, 9.0 (2.9) and 8.4 (2.6) ng/mL (p = 0.129), median (range) t_{max}, 4 (2–6) and 5 (2–7) h (p = 0.0002); AUC_{τ}, 93.7 (31.5) and 88.2 (29.3) ng × h/mL (p = 0.097), and $t_{1/2}$, 9.5 (2.6) and 10.0 (2.7) h (p = 0.172). The volume of distribution and clearance after oral administration of tamsulosin were 0.5 L/kg, and 0.04 L/h/kg, respectively. The accumulation ratios for 0.2 mg once-daily dosing

Table 1. Mean (SD) tamsulosin pharmacokinetic parameters following multiple doses of two tamsulosin formulations in healthy Korean male subjects (n = 41)

Parameter	Test	Reference
AUC_τ, ng × h/mL	93.7 (31.5)	88.2 (29.3)
AUC_∞, ng × h/mL	115.6 (46.5)	112.0 (45.4)
$C_{ss,max}$, ng/mL	9.0 (2.9)	8.4 (2.6)
$C_{ss,min}$, ng/mL	1.2 (0.7)	1.3 (0.7)
$C_{ss,av}$, ng/mL	3.9 (1.3)	3.7 (1.2)
FI	2.1 (0.4)	2.0 (0.4)
t_{max}, h†	4 (2-6)*	5 (2-7)
$t_{1/2}$, h	9.5 (2.6)	10.0 (2.7)
R	1.2 (0.1)	1.2 (0.1)
Cl/F, L/h/kg	0.04 (0.02)	0.04 (0.02)
Vd/F, L/kg	0.5 (0.2)**	0.5 (0.3)

AUC_τ, area under the plasma concentration-time curve over the dosing interval after multiple-dose administration, AUC_∞, area under the plasma concentration-time curve to infinity; $C_{ss,max}$, steady-state maximum plasma concentration, $C_{ss,min}$, steady-state minimum plasma concentration, $C_{ss,av}$, steady-state average plasma concentration, FI, fluctuation index, t_{max}, time to reach maximum plasma concentration, $t_{1/2}$, half-life, R, accumulation ratio, Cl/F, apparent oral clearance, Vd/F, apparent volume of distribution. †median (range). *P < 0.05 between the two groups by paired t-test. **P < 0.05 between the two groups by Wilcoxon signed rank test.

regimen were 1.2. There was no significant difference between the test and reference formulations in AUC_τ, AUC_∞, or $C_{ss,max}$ by paired t-test or $t_{1/2}$ or Cl/F by a Wilcoxon signed rank test, except t_{max} and Vd/F by paired t-test and a Wilcoxon signed rank test, respectively.

The 90 % CIs of the geometric mean ratios for the log-transformed AUC_τ (1.005-1.131) and $C_{ss,max}$ (1.000-1.136) values were within the acceptable range for bioequivalence (0.8-1.25).

Safety assessments were performed on the 44 subjects who received a study drug at least once. Overall, 32 subjects (72.7 %) experienced a total of 60 TEAEs (i.e., AEs occurring after the first dose of study medication) during the study period. Nine events were considered to be related to the medication, as follows (number of subjects): general malaise (2), sleepiness (1), dyspepsia (1), constipation (1), headache (1),

cheilitis (1), increase of ALT (1), and hyperbilirubinemia (1). All events resolved spontaneously with no specific treatment. The hyperbilirubinemia and the sleepiness were related to the administration of the reference drug. None of the TEAEs was considered to be serious or severe.

DISCUSSION

In this study, we evaluated the PK and safety profiles of two tamsulosin formulations–a newly developed generic capsule and an established conventional capsule–in healthy adult Korean male volunteers.

Although only 8.7-15 % of tamsulosin administered orally is excreted in the urine as the parent drug, the metabolites of tamsulosin resulting from extensive hepatic metabolism do

not contribute meaningfully to its safety and/or efficacy.[10,14] Accordingly, the metabolites of tamsulosin were not measured in our study.

The mean ratio of AUC_t (area under the plasma concentration-time curve to the last measurable concentration)/AUC_∞ for all subjects and for both products were around 92 % in our study, indicating that the sampling schedule was adequate to provide a reliable estimate of the extent of exposure (e.g., at least 80 % of AUC_∞). The mean $C_{ss,max}$ and AUC_τ values of 8.4 ng/mL and 88.2 ng × h/mL, respectively after oral administration of tamsulosin (reference formulation) 0.2 mg/d for 5 days from the present study were higher than those in the fed and multiple-dose study reported by Wolzt et al. (if normalized to 0.2 mg, 5.0 ng/mL and 74 ng × h/mL, respectively).[15] A plausible explanation for the differences of the mean $C_{ss,max}$ and AUC_τ values is the sampling schedule. The sampling times to determine the plasma concentrations of tamsulosin in our study were 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, and 36 h after administration of the last dose on day 5. However, in the study by Wolzt et al., the sampling times were every 2h up to 12h, with the resultant mean (SD) t_{max} value of 4.6 (2.1) h.[15] Accordingly, t_{max} and $C_{ss,max}$ values for some subjects may be inaccurate in the study by Wolzt et al. Another possible factor is the food-related changes (higher C_{max} values in the fasted state compared to with the fed state), because subjects took the study medication after breakfast in the multiple-dose study conducted by Wolzt et al.

In the present study, the median (range) t_{max} values of the test and reference formulations in the fasted state were 4 (2-6) h and 5 (2-7) h, respectively. This result is consistent with previous findings of several investigators, who reported that the mean (SD) t_{max} in the fasted state ranged from 4.5 to 8.0 (0.7-1.05) h.[6,9,16,17] In the present study, the t_{max} of the test formulation was shorter, with statistical significance, than that of the reference formulation (p = 0.0002). This finding might have been the result of differences in the preparation technologies between the test and reference formulations.

The mean $t_{1/2}$ obtained in this study was 9.5 - 10.0 h for the two formulations. These findings are consistent with those previously reported.[8,9] Individual half-lives ranged from 6.1 to 19.7 h, so the 10-day washout period was sufficient because it was longer than five half-lives for all subjects.

The present study has some limitations that should be considered, including the small sample size, short duration of follow-up, open-label design, and data from only healthy male subjects.

Our study demonstrates that the $C_{ss,max}$ and AUC_τ values in the fasted subjects were higher than those in the fed from other study, with a shorter t_{max} values. Plasma clearance of tamsulosin was slow (0.04 L/h/kg) and accumulation at steady state was negligible.

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건강한 남성 자원자에서 탐스로신의 공복 투여 시 항정상태의 약동학적 특성 연구

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배경: 본 연구는 건강한 한국인 자원자를 대상으로 공복상태에서 5일간 탐스로신을 투여한 뒤 약동학적 특성을 평가하고자 하였다.

방법: 무작위배정, 공개, 반복 투여, 2기 교차 시험 설계로 수행된 본 연구는, 총 44명의 시험대상자를 1:1로 무작위 배정하여 제 1기에 시험약으로 탐수로이신® 캡슐 0.2 mg 또는 대조약인 하루날® 캡슐 0.2 mg을 각각 투여하고 10일간의 휴약기를 거친 후 제 2기에는 1기와 반대로 해당 임상시험용 의약품을 투여하였다. 탐스로신의 혈장 농도는 HPLC-MS/MS를 사용하여 측정하였다. 안전성 평가를 위하여 임상실험실 검사, 이상반응 모니터링, 신체검진 등을 수행하였다.

결과: 시험약과 대조약의 약동학적 파라미터는 다음과 같았다(평균(표준편차)). $C_{ss,max}$는 시험약이 9.0 (2.9) ng/mL, 대조약은 8.4 (2.6) ng/mL이었고, t_{max}(중앙값(최소값-최대값))는 시험약이 4 (2-6), 대조약은 5 (2-7) hours이었다. AUC_τ는 시험약이 93.7 (31.5) ng × h/mL, 대조약은 88.2 (29.3) ng × h/mL이었으며, $t_{1/2}$의 경우 시험약은 9.5 (2.6), 대조약은 10.0 (2.7) hours이었다. 탐스로신 경구 투여 후 volume of distribution 과 clearance는 각각 0.5 L/kg, 0.04 L/h/kg이었고, 탐스로신 0.2 mg 1일 1회 용법에 대한 accumulation ratio는 1.2 였다. 로그 변환한 AUC_τ와 $C_{ss,max}$ 변수의 대조약에 대한 시험약의 기하평균비의 90 % 신뢰구간은 각각 1.005-1.131, 1.000-1.136으로 동등성 범위 이내에 속하였다. 시험기간 동안 중대한 이상반응은 발생하지 않았고 시험약과 대조약 모두 내약성이 우수하였다.

결론: 공복상태에서 탐스로신을 투약한 후 $C_{ss,max}$와 AUC_τ는 타 연구에서 음식물과 함께 탐스로신을 복용한 경우보다 증가하였고 t_{max}는 감소하였다.

Key words: 탐스로신, 반복투여, 약동학, 공복 상태, 건강한 자원자