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Pharmacokinetics and safety profiles of tadalafil/tamsulosin HCl fixed-dose combination capsule under fasted and fed condition in healthy volunteers

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Co-administration of tadalafil and tamsulosin HCl in patients with benign prostate hyperplasia and erectile dysfunction is increasing in clinical settings. Development of fixed-dose combination (FDC) of tadalafil and tamsulosin HCl could contribute to improving patients' adherence and treatment efficacy. We evaluated the pharmacokinetics and safety profiles of a newly developed fixed-dose combination capsule of tadalafil 5 mg/tamsulosin HCl 0.4 mg in comparison with co-administration of each formulation in healthy volunteers under fasted and fed conditions. Two randomized, open-label, single-dose, two-way, crossover studies were completed in 29 subjects under fasted condition, and 33 subjects under fed condition. Serial blood sample collection for PK analysis was conducted up to 72 hours after dosing, and PK parameters were calculated using non-compartmental analysis. Geometric mean ratios and 90% confidence intervals of the C_{max} and AUC_{last} were used to evaluate comparative bioavailability. In both fasted and fed condition studies, the bioequivalence was established. The most common adverse drug reactions were orthostatic hypotension and headache with no statistical difference between treatment groups. All subjects with orthostatic hypotension recovered at follow-up test. Although changes in vital signs from baseline were statistically significant, there were no subjects with systolic blood pressure < 90 mmHg and there were no clinically meaningful signs or symptoms associated. FDC of tadalafil and tamsulosin HCl can be an alternative to co-administration of individual drugs for providing better compliance. Changes in blood pressure should be kept in mind when tadalafil and tamsulosin HCl are co-administered in clinical settings.

Introduction

Benign prostatic hyperplasia (BPH) is the proliferation of smooth muscle and epithelial cells in prostatic tissue resulting in lower urinary tract syndrome (LUTS).[1,2] Garraway et al. reported that the prevalence of BPH was 25.3% in total 699 subjects aged between forty and seventy and tended to increase as the age increased.[3,4] Erectile Dysfunction (ED) is defined as difficulty in gaining or keeping erected state enough to enjoy sex life.[5,6] LUTS is known as an independent risk factor of ED.[6] Suggested pathophysiologic mechanisms of LUTS and ED are decrease in nitric oxide synthase/nitric oxide production and overactivity of sympathetic nervous system.[7] Clinical studies have shown the prevalence of BPH in ED patients was as high as 72.2-85.2%.[6,8]

Tamsulosin hydrochloride (HCl) is a strong inhibitor of al-

pha-1 adrenoreceptor in the urogenital system and has been used in the treatment of dysuria caused by BPH.[9] Tadalafil inhibits phosphodiesterase-5 and increases nitric oxide activity which in turn increases penile blood flow resulting in enhancement of the erectile function.[10,11] Tadalafil also acts on the smooth muscle in urogenital system and reduces LUTS in patients with BPH. U.S. Food and Drug Administration also approved tadalafil for treating signs and symptoms of patients who are comorbid with both BPH and ED in 2011.[12] The signs and symptoms of detrusor overactivity and LUTS were improved with concomitant therapy with tadalafil and tamulosin HCl without the difference in safety in previous studies. There was also improvement in signs or symptoms related with ED accompanied with the LUTS in the treatment group that both tadalafil and tamsulosin HCl were co-used.[13,14] Thus, coprescription of tadalafil and tamsulosin HCl is increasing. Based on these findings, the development of fixed-dose combination (FDC) of tadalafil and tamsulosin HCl can be justified with the expectation of improving patients' adherence and treatment efficacy, especially in old aged patients with high incidence of BPH and ED.

We evaluated the pharmacokinetics and safety profiles of a newly developed tadalafil/tamsulosin HCl FDC capsule (HCP1303, Hanmi Pharmaceutical Co. Seoul, Korea) and compared with concomitant administration of individual drugs under fasted and fed conditions. Studies under both conditions were conducted considering the food effect of tamsulosin HCl in previous study.[9]

Methods

Subjects

Healthy male volunteers who were aged between 19 and 50 years, weighed at least 55 kg, and had body mass index between 18.5 and 25.0 kg/m^2 were enrolled. Subjects agreed, voluntarily signed the informed consent forms and went through screening procedures such as past medical history, physical examination, and laboratory assessments including hematology, blood chemistry, serology and urine drug screening. Subjects with the following criteria were excluded: a history of clinically significant hypersensitivity reaction to drugs or foods, with a genetic problem such as galactose intolerance, a history of gastrointestinal diseases which would affect the absorption of investigational drugs, positive results on a urine drug screening or serology test, with an orthostatic hypotension, ocular disorders including cataract, priapism, cardiovascular disorders or a history of micturition syncope. The study participants were not allowed to take any prescription drugs or herbal medicines for 2 weeks prior to the study drug administration, nor any over-the-counter drugs or dietary supplements for 1 week prior to the study drug administration. The participants were also refrained from consuming alcohol, caffeinated beverages, and grapefruit products, as well as smoking, during the studies.

Study Design

Two clinical trials with the identical design were conducted independently either under fasted or fed condition. Both studies were as designed randomized, open-label, single-dose, two-treatment, two-period, crossover. A total of 30 participants in the fasted condition study and 36 participants in the fed condition study were randomized and assigned to one of the two treatment sequences (test drug - reference drug, or reference drug - test drug). Because there was a previous report that showed increased coefficient of variation (CV) value in AUC_{last} of tamsulosin HCl in fed state compared with fasted state, the sample size was increased in the fed study.[9] Each treatment period was separated by a 7-day washout period that was over five-fold longer than the previously reported terminal half-lives of tamsulosin HCl and tadalafil.[12,15]

These studies were approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and were approved by the Ministry of Food and Drug Safety.

Treatment and administration

The treatments consisted of a single oral dose of test drug [tadalafil 5 mg/tamsulosin HCl 0.4 mg FDC capsule (Hanmi Pharmaceutical Co., Seoul, Korea)] and reference drugs [tadalafil 5 mg tablet (Cialis®, Eli Lilly Korea) and tamsulosin HCl 0.4 mg capsule (Hanmi Pharmaceutical Co., Seoul, Korea) co-administered].

In the fasted condition study, all participants were kept fasted overnight for at least 10 hours and received one of the two treatments as per the randomization schedule. In the fed condition study, all participants were kept fasted overnight for at least 10 hours and were allowed to have high-fat meals (at least total 900 kcal, at least 35 percent fat) 30 minutes prior to the administration of investigational products and then were given the study drugs. The composition of high-fat meal was decided based on the guidance for food effect bioavailability of sustained-release products issued by the Ministry of Food and Drug Safety (MFDS).[16] Fluid intake was prohibited for 1 hour before and after administration of investigational products. Lunch and dinner were provided about 4 hours and 10 hours after administration of investigational products, respectively.

Blood sample collection and analysis

Serial blood samples were collected in anti-coagulated EDTA-K2 tubes at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 6, 7, 8, 10, 12, 24, 36, 48 and 72 h after dosing in the fasting condition study, and at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 24, 36, 48 and 72 h in the fed condition study to assess plasma tadalafil and tamsulosin HCl concentrations. Blood sampling points were determined considering T_{max} and elimination half-life of tadalafil and tamsulosin HCl.[9] Sampling times

were modified in the fed study because food intake delayed the Tmax of tamsulosin HCl.[9] Samples were centrifuged for eight minutes at 4°C, 1800 g and stored below -70°C until analysis. Plasma concentrations of tadalafil were measured using ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS). The linear calibration ranges were 1–500 ng/ml in tadalafil and 0.2–100 ng/ml in tamsulosin HCl. The coefficient of variation (CV) represents overall precision of the tadalafil and tamsulosin HCl assay was below 20.0% for LLOQ and 15.0% for other upper concentrations for calibration. Plasma concentrations of both tadalafil and tamsulosin HCl were analyzed by BioInfra Co., (Suwon, Korea).

Pharmacokinetic data assessment

PK parameters were evaluated using a non-compartmental model of Phoenix® WinNonlin® software version 6.4 (Certara, St.Louis, MO, USA). C_{max} and T_{max} were determined directly from the observed values. The area under the curve from the time of dosing to the last measurable concentration (AUC_{last}) was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The terminal elimination rate constant (λ_z) was estimated by linear regression of the terminal portion of the log-transformed plasma concentrations-to-time profile. The AUC from the last dosing time extrapolated to infinity (AUC_{inf}) was calculated by $AUC_{last} + C_{last}/\lambda_z$, where C_{last} represents the last measurable concentration.

Safety and tolerability assessments

Safety and tolerability were evaluated throughout the study. The assessments included monitoring of all adverse events based on physical examinations, vital signs, 12 lead electrocardiograms, routine hematology, serum chemistry, urinalysis, and orthostatic hypotension tests. Subjects were instructed to notify the study physician and/or nurses of any adverse events that occurred during the study. All AEs reported by subjects or detected in assessments were recorded and the investigators determined their relationship to the treatment.

Statistical analysis

Descriptive statistics were provided for baseline demographics, PK parameters and safety data by sequence group or treatment group. Baseline demographics of the treatment sequences were evaluated with Student's t-test using the IBM SPSS Statistics software version 23.0 (SPSS Incorporated, Chicago, IL, USA). To compare the PK parameters (AUC_{last} and C_{max}) between treatments, a general linear mixed effects model was developed using log-transformed data with period, sequence, and treatment as fixed effects and subjects nested within sequence as a random effect. The geometric mean ratio (GMR) and its 90% confidence interval (CI) of the AUC_{last} and the C_{max} between the FDC and co-administration of individual drugs were calculated, and the bioequivalence was demonstrated when the 90% CI entirely fell within the conventional bioequivalence range of 0.8-1.25. The incidence of major anticipated adverse drug reactions (ADRs) was statistically compared between treatment groups using chi-square test or McNemar's test using the IBM SPSS Statistics software version 23.0 (SPSS Incorporated, Chicago, IL, USA). Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline were compared between treatment groups using repeated mixed effects model.

Results

Demographics

A total of 31 subjects were enrolled in the fasted condition study. Two subjects withdrew consent during the study due to personal reasons, and 29 subjects completed the study and were included in the PK analysis. A total of 30 subjects who received at least one dose of any investigational products were included in the safety analysis. In the fed condition study, a total of 36 subjects were enrolled. One subject was removed from the study due to poor adherence before administration of any investigational products. Two subjects withdrew consent at the end of period 1 due to personal reasons. As a result, 33 subjects in total completed the study, but there was a subject whose pre-dose concentration at period 2 was higher than 5% of C_{max}, so 32 subjects were included in the PK analysis. A total of 35 subjects who received at least one dose of any investigational products were included in the safety analysis. Baseline demographics were similar and showed no statistical difference between sequence groups in both studies. The demographic information of study subjects was summarized in Table 1.

Pharmacokinetics

Bioequivalence in the fasted and fed condition studies

PK parameters and the plasma concentration-time profiles of tadalafil and tamsulosin HCl in the fasted condition study are shown in Table 2 and Figure 1, respectively. A single oral dose of tadalafil and tamsulosin HCl as the fixed-dose combination and the co-administration of individual drugs were bioequivalent. The GMRs (90% CI) of AUC_{last} and C_{max} between the test and the reference formulation of tadalafil were 0.98 (0.93–1.03) and 0.99 (0.92–1.07). Similarly the values were 1.03 (0.98–1.09) and 1.02 (0.96–1.08) for tamsulosin HCl, respectively. Furthermore, other PK parameters, including T_{max}, AUC_{inf}, t1/2, Vd/F and CL/F were also comparable between the two treatments.

PK parameters and the plasma concentration-time profiles of tadalafil and tamsulosin HCl in the fed condition study are shown in Table 2 and Figure 2, respectively. Single oral dose of tadalafil and tamsulosin HCl as the fixed-dose combination and the co-administration of individual drugs were bioequivalent. The GMRs (90% CI) of AUC_{last} and C_{max} between the test and the reference formulation of tadalafil were 0.99 (0.95–1.03) and 0.95 (0.91–1.00). The values were 0.99 (0.94–1.05) and 1.02

Table 1. Demographics of study participants

Variables	Fasted Study			Fed Study		
	T-R (N=15)	R-T (N=15)	P-value	T-R (N=17)	R-T (N=18)	P-value
Age (years)	24.5 ± 4.3	24.9 ± 3.5	0.82	27.0 ± 5.7	30.9 ± 6.5	0.07
Height (cm)	175.1 ± 4.8	175.5 ± 5.8	0.52	176.2 ± 5.2	174.7 ± 4.5	0.84
Weight (kg)	67.7 ± 6.0	69.1 ± 5.4	0.84	70.0 ± 4.9	70.4 ± 6.6	0.37
BMI (kg/m^2)	22.0 ± 1.8	22.4 ± 1.7	0.59	22.5 ± 1.1	23.0 ± 1.7	0.29

Notes: Data are summarized as arithmetic mean ± standard deviation. P-values were derived by Student's t-test. T-R, FDC followed by concomitant administration of individual drugs; R-T, concomitant administration of individual drugs followed by FDC

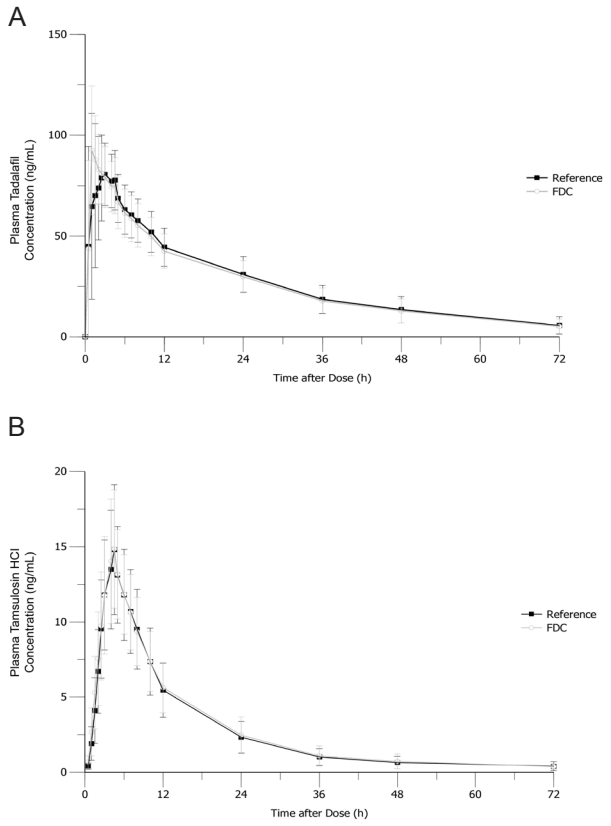

Figure 1. Plasma concentration-time profiles for (A) tadalafil, (B) tamsulosin HCl in fasted condition study as a fixed-dose combination or concomitant administration of individual drugs. Data are shown as mean ± SD. FDC, fixed-dose combination; Reference, concomitant administration of individual drugs.

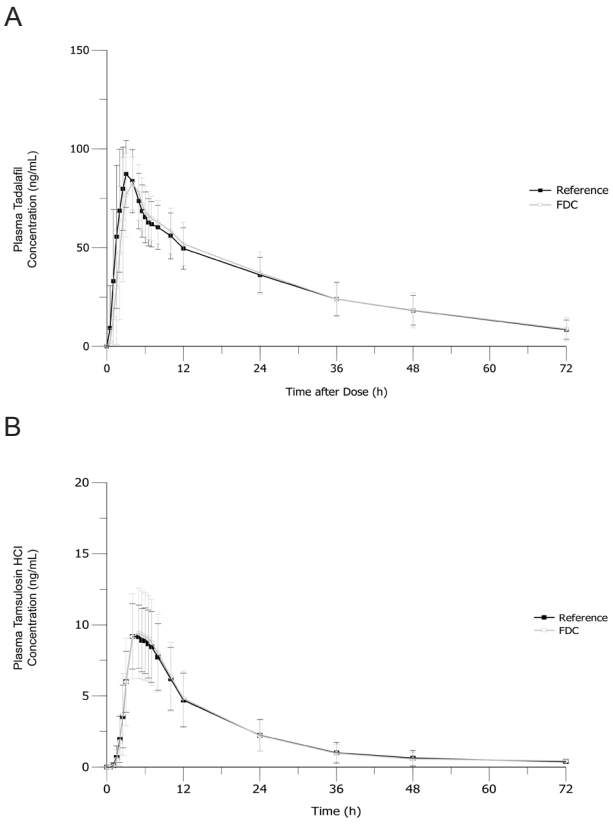

Figure 2. Plasma concentration-time profiles for (A) tadalafil, (B) tamsulosin HCl in fed condition study as a fixed-dose combination or concomitant administration of individual drugs. Data are shown as mean ± SD. FDC, fixed-dose combination; Reference, concomitant administration of individual drugs.

(0.96–1.09) for tamsulosin HCl. Other PK parameters, including T_{max}, AUC_{inf}, $t_{1/2}$, Vd/F and CL/F were also comparable between the two treatments.

Post hoc cross-study evaluation of food effect on FDC

Post hoc evaluation of food effect on FDC was conducted using the same statistical method to assess the bioequivalence because both studies were performed in healthy male volunteers with the same design, used the same analytical methods although both studies were not specifically designed to be compared. The results are summarized in Table 3. T_{max} of both tadalafil and tamsulosin HCl were delayed under fed condition compared to fasted condition. AUC_{last} of tadalafil under the fed condition was increased by 16% compared to those under the fasted condition. However, AUC_{last} of tamsulosin HCl was decreased by 24% under fed condition compared to fasted condition. C_{max} of tadalafil

Table 2. Pharmacokinetic parameters of tadalafil and tamsulosin HCl after a single oral administration given as fixed-dose combination or concomitant administration of individual drugs in both studies

Study Type	Parameter	Tadalafil			Tamsulosin HCl		
		FDC	Reference	Geometric Mean Ratio[a](90% CI)	FDC	Reference	Geometric Mean Ratio[a](90% CI)
Fasted condition study (N=29)	T_{max} (h)	1.0 [0.5-4.5]	1.5 [0.5-4.5]		4.5 [3.0-6.0]	4.5 [3.0-6.0]	
	C_{max} (ng/ml)	103.80 ± 25.99	103.33 ± 21.24	0.99 (0.92-1.07)	15.38 ± 3.74	15.20 ± 4.12	1.02 (0.96-1.08)
	AUC_{last} (ng·h/ml)	1835.35 ± 442.93	1877.44 ± 469.36	0.98 (0.93-1.03)	185.96 ± 62.01	180.46 ± 61.64	1.03 (0.98-1.09)
	AUC_{inf} (ng·h/ml)	2005.80 ± 589.04	2078.39 ± 695.02		193.54 ± 64.56	188.83 ± 66.68	
	$t_{1/2}$ (h)	18.82 ± 5.61	19.56 ± 7.18		11.15 ± 2.87	12.45 ± 3.91	
	CL/F (L/h)	2.70 ± 0.79	2.63 ± 0.76		2.30 ± 0.77	2.37 ± 0.80	
	Vd/F (L)	69.51 ± 14.69	68.84 ± 11.55		35.98 ± 7.92	39.75 ± 10.27	
Fed condition study (N=32)	T_{max} (h)	4.0 [2.0-5.6]	2.75 [1.0-5.0]		5.0 [3.0-7.0]	5.0 [3.0-7.1]	
	C_{max} (ng/ml)	91.13 ± 15.48	95.94 ± 18.54	0.95 (0.91-1.00)	10.43 ± 3.37	10.03 ± 2.46	1.02 (0.96-1.09)
	AUC_{last} (ng·h/ml)	2144.83 ± 626.33	2146.43 ± 553.55	0.99 (0.95-1.03)	144.20 ± 61.90	144.24 ± 60.00	0.99 (0.94-1.05)
	AUC_{inf} (ng·h/ml)	2485.43 ± 930.43	2459.07 ± 777.79		152.14 ± 64.12	153.45 ± 61.06	
	$t_{1/2}$ (h)	22.43 ± 7.08	22.62 ± 6.19		12.47 ± 3.18	14.09 ± 10.19	
	CL/F (L/h)	2.28 ± 0.81	2.22 ± 0.66		3.03 ± 1.11	2.94 ± 0.97	
	Vd/F (L)	67.33 ± 11.29	68.22 ± 12.31		52.40 ± 19.91	56.54 ± 36.22	

Notes: Data are summarized as arithmetic mean ± standard deviation except for T_{max}, for which median [min-max] is presented. [a]Geometric mean ratio of fixed-dose combination to concomitant administration

Abbreviations: CI, confidence interval; T_{max}, time to C_{max}; C_{max}, the maximum concentration of drug; AUC_{last}, area under the plasma concentration-time curve from the time of dosing to the last measurable concentration; AUC_{inf}, area under the plasma concentration-time curve from dosing time extrapolated to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; Vd/F, apparent volume of distribution

Table 3. Comparison of pharmacokinetic parameters of tadalafil and tamsulosin HCl after a single oral administration as a fixed-dose combination capsule in the fasted and fed conditions

Parameter	Tadalafil			Tamsulosin HCl		
	Fasted Study (N=29)	Fed Study (N=32)	Fed/Fasted Geometric Mean Ratio (90% CI)	Fasted Study (N=29)	Fed Study (N=32)	Fed/Fasted Geometric Mean Ratio (90% CI)
T_{max} (h)	1.0 [0.5-4.5]	4.0 [2.0-5.6]		4.5 [3.0-6.0]	5.0 [3.0-7.0]	
C_{max} (ng/ml)	103.80 ± 25.99	91.13 ± 15.48	0.89 (0.81-0.97)	15.38 ± 3.74	10.43 ± 3.37	0.67 (0.59-0.75)
AUC_{last} (ng·h/ml)	1835.35 ± 442.93	2144.83 ± 626.33	1.16 (1.03-1.30)	185.96 ± 62.01	144.20 ± 61.90	0.76 (0.65-0.88)
AUC_{inf} (ng·h/ml)	2005.80 ± 589.04	2485.43 ± 930.43		193.54 ± 64.56	152.14 ± 64.12	
$t_{1/2}$ (h)	18.82 ± 5.61	22.43 ± 7.08		11.55 ± 2.87	12.47 ± 3.18	
CL/F (L/h)	2.70 ± 0.79	2.28 ± 0.81		2.30 ± 0.77	3.03 ± 1.11	
Vd/F (L)	69.51 ± 14.69	67.33 ± 11.29		35.98 ± 7.92	52.40 ± 19.91	

Notes: Data are summarized as arithmetic mean ± standard deviation except for T_{max}, for which median [min-max] is presented.
Abbreviations: CI, confidence interval; T_{max}, time to C_{max}; C_{max}, the maximum concentration of drug; AUC_{last}, area under the plasma concentration-time curve from the time of dosing to the last measurable concentration; AUC_{inf}, area under the plasma concentration-time curve from dosing time extrapolated to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; Vd/F, apparent volume of distribution

Table 4. The incidence of common adverse drug reactions

Adverse Drug Reaction	Treatment	Fasted Study	Fed Study	Total	*P*-value[#]
Orthostatic hypotension	FDC Reference	8/30 (26.7%) 7/29 (24.1%)	3/34 (8.8%) 4/34 (11.8%)	11/64 (17.2%) 11/63 (17.5%)	0.059
	Total*	12/30 (40.0%)	6/35 (17.1%)		
Headache	FDC Reference	3/30 (10.0%) 2/29 (6.9%)	2/34 (5.9%) 4/34 (11.8%)	5/64 (7.8%) 6/63 (9.5%)	0.659
	Total*	4/30 (13.3%)	6/35 (17.1%)		
Dizziness	FDC Reference	0/30 0/29	1/34 (2.9%) 1/34 (2.9%)	1/64 (1.6%) 1/64 (1.6%)	0.999
	Total*	0/30	2/35(5.7%)		

Notes: the number of subjects with ADRs / total subjects (percentage). P-values were derived by chi-square test. *Subjects whose ADRs occurred in both treatment groups were counted once. [#]Statistical difference in the incidence of ADRs between studies in fixed-dose combination group was estimated.

under fed condition was similar to those in fasted condition. On the other hand, C_{max} of tamsulosin HCl under the fed condition was 33% lower than the fasted condition.

Safety

Adverse events

The number of subjects included in the safety analysis set (the number of subjects who administered at least 1 dose of investigational products) was 30 in the fasted condition study and 35 in the fed condition study. A total of 24 AEs were reported by 15 subjects (50.0%) in the fasted condition study, and 30 AEs reported by 17 subjects (48.6%) in the fed condition study. AE profiles were similar for the FDC capsule and the co-administration of individual drugs in each of the fasted and fed condition studies. All AEs were mild or moderate in severity, and there were no deaths, serious AEs (SAEs), or withdrawals due to AEs.

AEs reported after administration of investigational products were generally consistent with the known safety profile of tadalafil tablet and tamsulosin HCl capsule. Orthostatic hypotension and headache were the most common AEs. Other

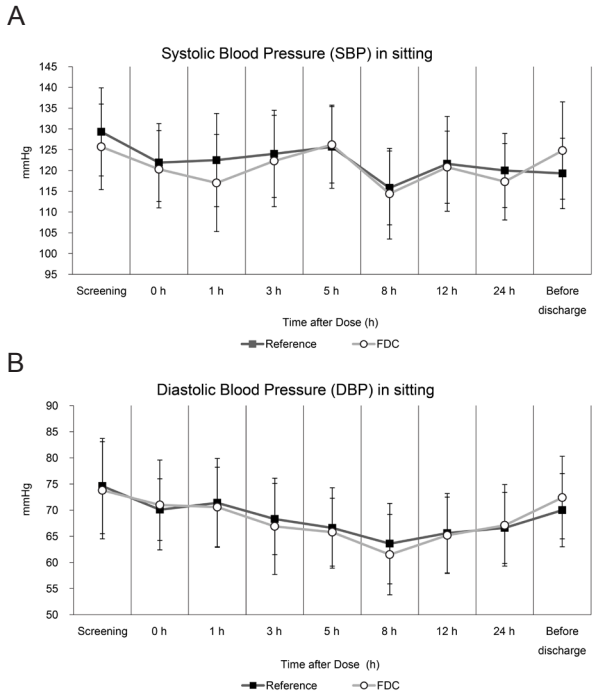

Figure 3. Changes in (A) systolic blood pressure, (B) diastolic blood pressure over time in fasted condition study. Data are shown as mean ± SD. R, concomitantly administrated as individual drugs; T, administered as a fixed-dose combination

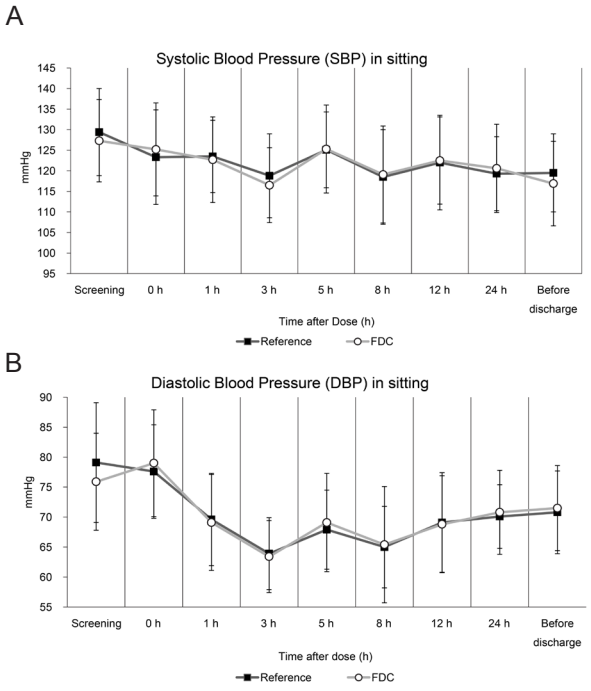

Figure 4. Changes in (A) systolic blood pressure, (B) diastolic blood pressure over time in fed condition study. Data are shown as mean ± SD. R, concomitantly administrated as individual drugs; T, administered as a fixed-dose combination

AEs were epigastric discomfort in fasted study, and dizziness (including postural dizziness), paresthesia, sinus pain, increased creatinine phosphokinase and nasal congestion in fed study. The number of subjects with orthostatic hypotension was similar between treatment groups in both studies (Table 4). Although the number of subjects with orthostatic hypotension seemed different for the FDC between fasted and fed conditions, the difference analyzed with chi-square test was not statistically significant (p-value = 0.059). The durations of orthostatic hypotension were transient in all cases and there was no subject whose orthostatic hypotension remained at the follow-up test.

Changes in vital signs

SBP did not increase or decrease over time in both studies. In the fasted study, the mean DBP in sitting position decreased maximally at 8 h after dosing by 8.1 mmHg compared with the baseline (pre-dose). The maximum decrease in the mean DBP was 14.7 mmHg and occurred 3 hours after dosing in the fed study (Fig. 3 and 4). Considering the mechanisms of action of tadalafil and tamsulosin HCl, this effect could be anticipated with the investigational products. Additionally, physiological effect due to keeping in bed-rested state and restricted physical activity could be considered for another reason. Although the change of DBP from baseline was statistically significant in both studies, the decrease was not judged to be clinically significant because there were no symptom and sign related to the changes of DBP. SBP and DBP had started to bounce back up from eight hours after dosing and stabilized to the baseline values in both studies. Other changes of vital signs could be explained with physiological effect due to restricted physical activity and diurnal variation. There were no statistically significant differences in vital signs between treatment groups in both studies.

Discussion

These studies were designed to evaluate the bioequivalence between FDC capsule of tadalafil 5 mg and tamsulosin HCl 0.4 mg to the co-administration of individual drugs in fasted and fed conditions respectively. The analysis of PK parameters in these two studies demonstrated that the FDC is pharmacokinetically comparable to the concomitant administration of each drug in fasted and fed condition, showing that the GMR and its 90% CI for FDC and concomitant administration of individual drugs falling entirely within the bioequivalence range (0.8–1.25). Other PK parameters of FDC were also pharmacokinetically comparable to those of concomitant administration of individual drugs.

Food affected the extent of exposure of tamsulosin HCl. Comparing with fasted condition, the C_{max} of tamsulosin HCl in fed condition decreased by 32% in FDC and the AUClast decreased by 24% in FDC. These results of FDC were quite similar with

the published data about fed condition study of tamsulosin HCl in which the C_{max} decreased by 41% and the AUC_{last} decreased by 24% under fed condition.[9] Our study showed that food increases slightly the variability in the exposure of tamsulosin HCl, which was demonstrated by AUC_{inf} (intra-subject CV of AUC_{inf}: 13% in fed study vs. 11% in fasted study). On the other hand, C_{max} and AUC_{last} of tadalafil in FDC under fasted and fed conditions were not within bioequivalence range. The result was conflicting with that of the previous study that tadalafil can be taken regardless of food.[12]

FDC capsule also showed comparable safety profile to the concomitant administration of each drug. Orthostatic hypotension is an adverse event that is mechanistically associated with α_1-antagonists such as tamsulosin HCl. The incidence of orthostatic hypotension was not different between FDC and individual drug administration in both studies (Table 4). The overall incidence of orthostatic hypotension was 40.0% in the fasted study and 17.1% in the fed study. This difference can be explained by the food effect on the exposure of tamsulosin HCl. However, there were no manifest symptoms or signs related to orthostatic hypotension, nor any subjects with SBP <90 mmHg in standing position. Although headache and dizziness were reported, these AEs were not associated with orthostatic hypotension in our studies. Although it has been reported that tamsulosin HCl, a selective antagonist of α_{1A}-adrenoceptors, which are not present in the blood vessels, shows less frequent orthostatic hypotension than conventional α1- antagonists,[17-19] our results show that administering tamsulosin HCl after meal is preferred to taking in fasted state in order to prevent orthostatic hypotension.

Our results also showed hypotensive potential of concomitant administration of tadalafil and tamsulosin HCl, but SBP was relatively less influenced than DBP, and dizziness, a symptom related to the decrease of DBP, was reported in 2 subjects (5.8%) only in fed study. Because it has been known that the exposure of tadalafil is not affected by fed condition and our analysis was post-hoc comparison of the two individual studies, placebo controlled systematic design of clinical trials is required to reveal the influence of tadalafil and tamsulosin HCl on the changes of vital signs and orthostatic hypotension. Although there were no subjects with a standing SBP <90 mmHg and no syncope following co-administration of investigational products was reported, paying attention to the changes of vital sign when tadalafil and tamsulosin HCl are co-prescribed in old-aged patients is desirable.

There is a limitation of this article. Both studies were conducted individually, not designed as crossover studies, therefore the result of evaluating statistically food effect could not be concluded corroboratively. Designing adequate study is required for more accurate evaluation for the food effect of FDC on pharmacokinetics and safety.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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