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Original Article

Pharmacokinetic comparison between a fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg and a corresponding loose combination of fimasartan/amlodipine 60/25 mg and hydrochlorothiazide 25 mg in healthy subjects

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ABSTRACT

For the treatment of hypertension, fixed-dose combinations (FDCs) of antihypertensive drugs can provide complementary benefits from improved compliance and cost-effectiveness compared with loose combinations of corresponding drugs. A new FDC of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg is undergoing clinical development. A randomized, open-label, single-dose, 3-period, 3-sequence, partially replicated crossover phase 1 study was conducted to compare the pharmacokinetics (PKs) between the FDC of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg and a loose combination of a dual-combination FDC (fimasartan/amlodipine 60/10 mg) and hydrochlorothiazide 25 mg. Sixty healthy subjects were randomized, and 55 subjects completed the study. Serial blood samples were collected, and plasma concentrations of fimasartan, amlodipine and hydrochlorothiazide were measured to analyze PK parameters. The PK profiles of the FDC were similar to those of the loose combinations. The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of the FDC to loose combinations for the maximum plasma concentration (C_{max}) and area under the curve until the last measurable time point (AUC_{last}) were within the conventional bioequivalent range of 0.80 to 1.25. The GMRs and 90% CIs of fimasartan, amlodipine and hydrochlorothiazide were 1.0163 (0.8681–1.1898), 0.9595 (0.9256–0.9946), and 1.1294 (1.0791–1.1821) for C_{max} and 1.0167 (0.9347–1.1059), 0.9575 (0.9317–0.9841), and 1.0561 (1.0170–1.0967) for AUC_{last}, respectively. Both the FDC and loose combinations were well tolerated. In conclusion, the FDC of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg showed similar PK profiles to those of the corresponding loose combination, and both treatments were well tolerated.

Keywords: Fixed-dose Combination; Fimasartan; Amlodipine; Hydrochlorothiazide; Pharmacokinetics

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INTRODUCTION

Uncontrolled hypertension increases the risk of cardiovascular diseases, which may lead to sudden death [1]. Controlling blood pressure with proper treatments is important because it can decrease the risk of cardiovascular, cerebrovascular, and renal diseases caused by hypertension [2]. According to the 2018 ESC/ESH guidelines, a single pill with dual low-dose combination therapy is recommended as the first-line therapy for all kinds of hypertension. If a full-dose fixed-dose combination (FDC) is not sufficient to control hypertension, triple combinations of angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and thiazide-like diuretics are recommended [3,4]. Patients with hypertension often need multiple medications and frequently have other chronic diseases requiring additional medications [1].

Fimasartan is one of the ARBs commonly prescribed with other antihypertensive agents. The efficacy and safety of fimasartan for the treatment of hypertensive patients have been demonstrated in previous clinical studies [5-8]. Amlodipine, a CCB class agent, is frequently used with ARBs as combination therapy for hypertension. Additionally, hydrochlorothiazide, a thiazide-type diuretic class agent, is commonly used as an add-on drug to other antihypertensive therapies [9]. Moreover, combination therapy of thiazides with ARBs or CCBs can have a beneficial effect in terms of safety. ARBs and CCBs can cause sodium retention as a side effect, and thiazides can compensate for those effects by promoting the urinary excretion of sodium [10].

However, medical treatments with multiple medications cause patient nonadherence, resulting in treatment failure [11-13]. The FDC of antihypertensive drugs can provide complementary benefits from improved compliance and cost-effectiveness compared with loose combinations of corresponding drugs [14-16]. In terms of cost-effectiveness, FDC has the potential to lessen health costs by reducing the pill burden, referred to as polypharmacy [17].

Currently, FDCs of dual antihypertensive agents (fimasartan with amlodipine or fimasartan with hydrochlorothiazide) are approved as initial combination therapy in Korea [18-20]. According to the Korean society of hypertension when dual combination therapy of a CCB and an ARB is inadequate for blood pressure control, the next step is applied by adding another antihypertensive agent. Diuretic is recommended to add on the initial dual combination therapy [21]. To improve patient compliance with triple-combination therapy with antihypertensive drugs, the FDC of fimasartan, amlodipine, and hydrochlorothiazide is under clinical development.

Based on these understandings, this study aimed to compare the pharmacokinetic (PK) characteristics and tolerability profile of a triple-combination FDC (fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg) and a loose combination of a dual-combination FDC (fimasartan/amlodipine 60/10 mg) and hydrochlorothiazide 25 mg.

METHODS

Study population and study design

A randomized, open-label, single-dose, partially replicated crossover study was performed in healthy subjects. Subjects aged 19 to 50 were recruited for the study. Subjects' health status

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was determined by physical examination, clinical laboratory tests, 12-lead ECG, serology (HBsAg, anti-HCV, anti-HIV antibody), and urinary drug screening. Subjects who had systolic blood pressure (SBP) ≤ 100 mmHg or ≥ 140 mmHg and diastolic blood pressure (DBP) ≤ 60 mmHg or ≥ 90 mmHg were excluded from the study. Eligible subjects were hospitalized in the Seoul National University Hospital clinical trial center on the day before administration of the study drug for each period. A triple-combination FDC (fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg, Boryung Pharmaceutical Co. Ltd. Seoul, Republic of Korea) tablet was used as the test drug (T), and the loose combination of a dual-combination FDC (fimasartan/amlodipine 60/10 mg, Boryung Pharmaceutical Co. Ltd. Seoul, Republic of Korea), and hydrochlorothiazide 25 mg (Yuhan, Seoul, Republic of Korea) was used as the reference drug (R). The study was conducted in two-treatment, three-period, three-sequence, partially replicated crossover design. Each of three sequences consisted of a single oral administration of the test drug (T) in one period and the reference drug (R) in the other two periods (Sequence A: Reference drug, Reference drug, Test drug; Sequence B: Reference drug, Test drug, Reference drug; Sequence C: Test drug, Reference drug, Reference drug in order). The subjects were randomly assigned to one of the three sequences (**Fig. 1**) and received the allocated treatment in each period with a 14-day washout.

For the PK analysis of fimasartan, amlodipine and hydrochlorothiazide, serial blood samples were obtained using sodium heparin tubes. Serial blood samples were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, and 48 hours of post-dose for fimasartan; at 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, and 144 hours of post-dose for amlodipine; and at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 12, 24, 36, and 48 hours of post-dose for hydrochlorothiazide. Blood samples were centrifuged at 3,000 rpm for 10 minutes at 4°C to aliquot the plasma. The plasma samples were stored below −70°C until assays were performed. Tolerability was assessed by monitoring adverse events (AEs), physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory tests. Serial SBP and DBP monitoring were performed at 0, 4, 8, 12, 24, 48, 72, 96, and 144 hours after dosing.

This study (NCT03629067) was approved by the Institutional Review Board of Seoul National University Hospital (Seoul, Republic of Korea). All procedures were performed in compliance with the Korean Good Clinical Practice and the principles of the Declaration of Helsinki. All the subjects provided written informed consent before participating in the study.

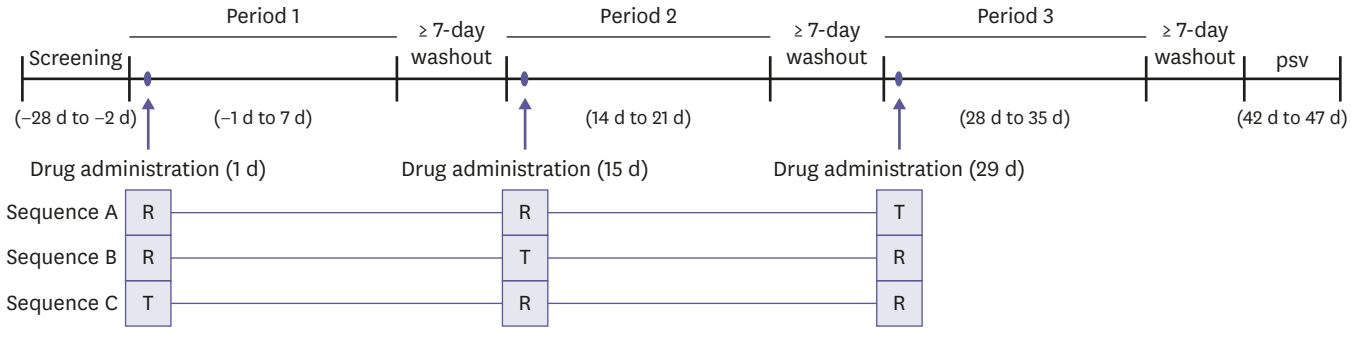

Figure 1. Study design.
T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg; R, loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; psv, post-study visit.

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Pharmacokinetic concentration measurement

The plasma concentration of fimasartan was determined using high-pressure liquid chromatography (HPLC) (Agilent 1200 Series, Agilent, Santa Clara, CA, USA) coupled with tandem mass spectrometry (API 4000, Applied Biosystems, Framingham, MA, USA). BR-A-563 was used as the internal standard. The plasma sample was deproteinized using 100 μL of acetonitrile containing 50 ng/mL BR-A-563. In the HPLC system, a phenyl hexyl column (Luna, 5 μm, 50 mm × 2.0 mm, Phenomenex, USA) was used with a gradient mobile phase consisting of 0.1% formic acid in distilled water:acetonitrile (60:40 to 20:80, vol/vol) and a flow rate of 250 μL/min. The MS/MS system was used in positive ionization mode with electrospray and multiple reaction monitoring modes. Transition ions at m/z 502.4 to 221.0 and 526.4 to 207.1 were followed for fimasartan and BR-A563, respectively.

The plasma concentration of amlodipine was determined using the same liquid chromatography-mass spectrometry system as fimasartan. Amlodipine-d4 was used as the internal standard (TRC Companies, Windsor, USA). The plasma was mixed with 50 μL of 0.5 M NaOH and 50 ng/mL Amlodipine-d4 in 25 μL of 100% methanol. Then, for liquid–liquid extraction, 0.5 mL of diethyl ether:dichloromethane (80:20, vol/vol) was added to the sample and mixed for 10 minutes. The mixture was centrifuged at 3,500 rpm for 10 minutes to obtain the supernatant. After evaporating the organic solvent under reduced pressure, the remaining solids were reconstituted with 100 μL of 50% acetonitrile.

For the determination of the hydrochlorothiazide concentration in plasma, a Shimadzu Nexera X2 (Shimadzu, Kyoto, Japan) coupled with tandem mass spectrometry (API 4000, Applied Biosystems) was used. Hydrochlorothiazide-13C-d2 was utilized as the internal standard (TRC Companies, Windsor, CT, USA). The plasma was prepared by using 1.182 mL of 100% DMSO. For liquid-liquid extraction, 1.5 mL of methyl tertiary butyl ether was added, including 20 μL of hydrochlorothiazide-13C-d2, and mixed for 10 minutes. The mixture was centrifuged at 3500 rpm for 10 minutes to obtain the supernatant. After evaporating the organic solvent under reduced pressure, the remaining solids were reconstituted with 800 μL of 50% acetonitrile. The MS/MS system was applied in negative ionization mode with electrospray and multiple reaction monitoring modes.

The lower limits of quantification for fimasartan, amlodipine and hydrochlorothiazide were 1, 0.2, and 2 ng/mL, respectively. The intra- and interday accuracies were 90.1–110.5% and 98.1–102.1% for fimasartan, 92.9–104.6% and 99.9–100.6% for amlodipine, and 89.3–109.5% and 100.4–103.7% for hydrochlorothiazide. The calibration curves were linear in the range of 1–1,000 ng/mL for fimasartan, 0.2–20 ng/mL for amlodipine, and 2–500 ng/mL for hydrochlorothiazide.

Pharmacokinetic analysis

Phoenix WinNonlin® version 8.0 software (Pharsight corp., Sunnyvale, CA, USA) was used to calculate pharmacokinetic parameters by the noncompartmental method. The actual blood sampling times were used for calculation of the pharmacokinetic parameters. The maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained from the observed values. The area under the plasma concentration-time curve (AUC) was calculated using the log-linear trapezoidal rule. The terminal elimination half-life ($t_{1/2}$) was calculated as 0.693/λz, where λz is the terminal elimination rate constant. Apparent clearance (CL/F) was determined as the administered dose divided by the area under the plasma concentration-time curve from time zero to infinity (AUC_{inf}). The apparent volume of distribution (Vd/F)

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was also calculated by dividing the apparent clearance (CL/F) by the terminal elimination rate constant (λz).

Statistical analysis

Statistical analysis was performed using SAS® version 9.4. A mixed effect model was applied, and analysis of variance (ANOVA) was conducted. Period, sequence, treatment and dosing group were considered fixed effects, and subjects nested within sequence were considered random effects in the mixed effect model. The modified mixed effect model was also used to reflect the multigroup nature of the study. Geometric mean ratios (GMRs) and their 90% confidence intervals (CIs) for C_{max} and AUC_{last} were calculated to compare the PK parameters between treatments. For comparison of demographic characteristics between the sequence groups, ANOVA and Fisher's exact test were performed. McNemar's test was conducted to compare the frequency of AEs between treatment groups. A p value of < 0.05 was considered statistically significant.

RESULT

Demography

A total of sixty subjects were randomized, and two subjects withdrew their participation before dosing. The safety and tolerability were evaluated on 58 subjects who received the study drugs at least once. Two subjects were dropped out after dosing due to the consent withdrawal, reflected on the analysis of changes in systolic and diastolic blood pressure. A total of 55 subjects completed the study as planned and were included in the pharmacokinetic analysis set. The study included 46 males and 14 females. The mean ± standard deviation for age, height and body mass index (BMI) were 30.20 ± 6.57 years, 172.06 ± 8.58 cm, 69.52 ± 9.65 kg, and 23.42 ± 2.22 kg/m^2, respectively. None of the demographic characteristics were significantly different among the sequence groups (p > 0.05).

Pharmacokinetic results

The mean plasma concentration-time profiles and pharmacokinetic characteristics of fimasartan were similar between the test drug and the reference drug (**Fig. 2A** and **Table 1**). The C_{max} values of fimasartan were 74.04 μg/L in the reference drug and 75.25 μg/L in the test drug. The AUC_{last} values were calculated as 412.20 h·μg/L for the reference drug and 419.05 h·μg/L for the test drug (**Table 2**). Both geometric mean ratios (GMRs) for C_{max} and AUC_{last} fell within the conventional bioequivalent criteria of 0.8 to 1.25. The GMRs (90% CIs) of the test drug to the reference drug for the C_{max} and AUC_{last} of fimasartan were 1.0163 (0.8681–1.1898) and 1.0167 (0.9347–1.1059), respectively (**Table 2**). Multiple peaks were observed in the time-concentration profile of fimasartan (**Fig. 2A**). The C_{max} of fimasartan showed higher intraindividual variability than the C_{max} of amlodipine and hydrochlorothiazide (**Fig. 3** and **Table 2**).

The mean plasma concentration-time profiles of amlodipine were comparable in for test drug and the reference drug (**Fig. 2B** and **Table 1**). Pharmacokinetic parameters were also similar between the test drug and the reference drug. The C_{max} for amlodipine was 5.98 μg/L in the reference drug and 5.73 μg/L in the test drug. The AUC_{last} values were 258.71 h·μg/L and 247.72 h·μg/L, respectively (**Table 2**). Both geometric mean ratios (GMRs) for C_{max} and AUC_{last} fell within the conventional bioequivalent criteria of 0.8 to 1.25. The GMRs (90% CIs) of the test drug to the reference drug for the C_{max} and AUC_{last} of amlodipine were 0.9595 (0.9256–0.9946) and 0.9575 (0.9317–0.9841), respectively (**Table 2**).

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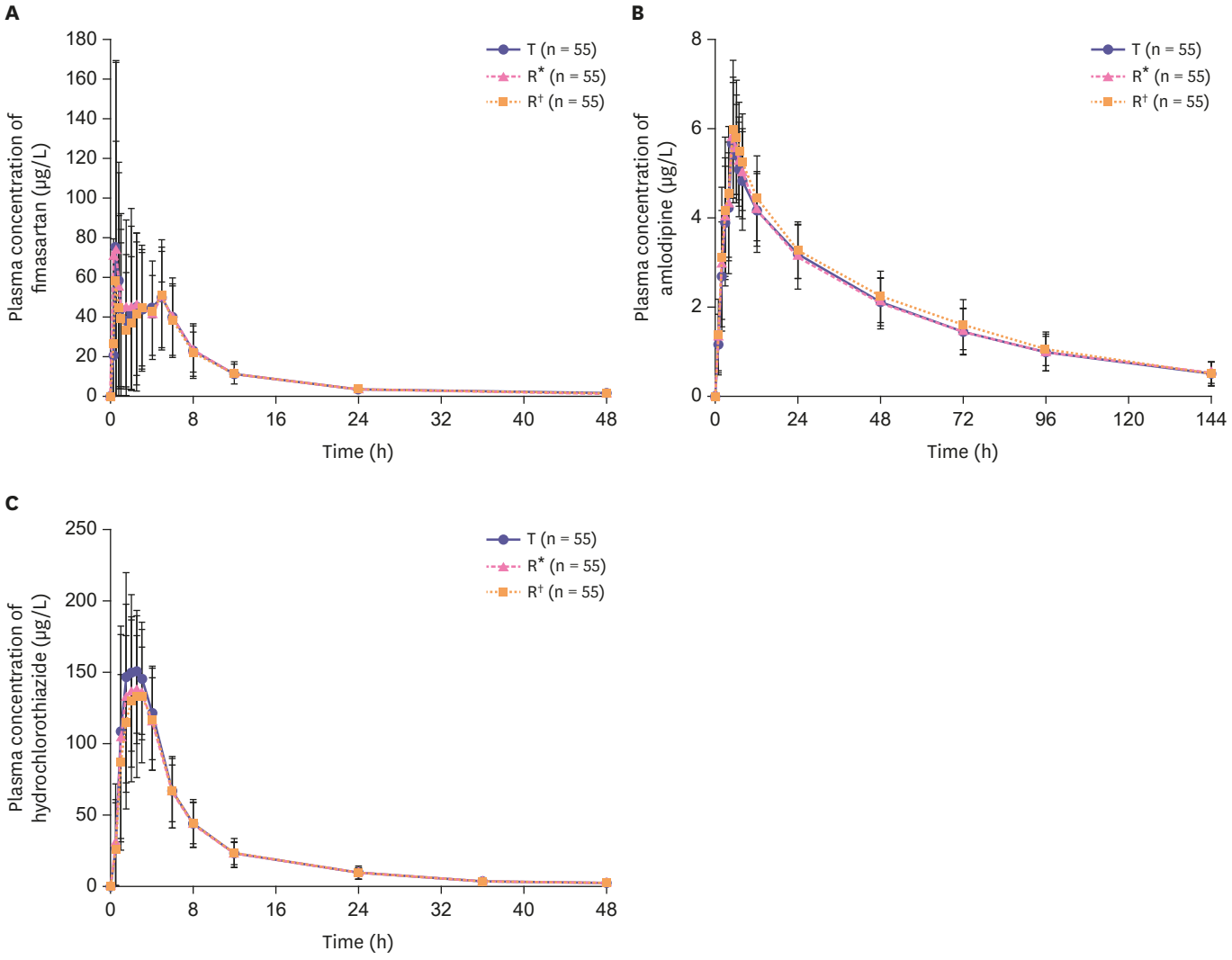

Figure 2. Mean plasma concentration-time profiles of (A) fimasartan, (B) amlodipine, and (C) hydrochlorothiazide following a single administration of test drug (T) or reference drug (R* or R†).
T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg.
*First dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; †Second dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg. The error bars denote the standard deviations.

The pharmacokinetic results of hydrochlorothiazide were similar to those of fimasartan and amlodipine (**Table 1**). The mean plasma concentration-time profile of hydrochlorothiazide of the test drug was similar to that of the reference drug (**Fig. 2C**). The values of the pharmacokinetic parameters C_{max} and AUC_{last} calculated for the reference drug were 161.79 μg/L and 1076.21 h·μg/L, while those for the test drug were 182.73 μg/L and 1136.49 h·μg/L, respectively (**Table 2**). Both geometric mean ratios (GMRs) for C_{max} and AUC_{last} fell within the conventional bioequivalent criteria of 0.8 to 1.25. The GMRs (90% CIs) of the test drug to the reference drug for the C_{max} and AUC_{last} of hydrochlorothiazide were 1.1294 (1.0791–1.1821) and 1.0561 (1.0170–1.0967), respectively (**Table 2**).

Changes in systolic and diastolic blood pressure

The effects on lowering blood pressure were similar between the test drug and the reference drug (**Fig. 4**). The blood pressure after administration of both the test and reference drugs

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Table 1. Pharmacokinetic parameters of fimasartan, amlodipine, hydrochlorothiazide following a single administration of test drug (T) or reference drug (R* or R†)

Drug	Parameters	T (n = 55)	R* (n = 55)	R† (n = 55)
Fimasartan	T_{max} (h)	3.00 [0.25–8.00]	2.00 [0.25–8.00]	3.00 [0.25–6.00]
	C_{max} (μg/L)	102.75 ± 80.88	106.43 ± 88.67	91.17 ± 60.14
	AUC_{last} (h·μg/L)	485.40 ± 248.54	484.30 ± 241.47	472.21 ± 241.58
	AUC_{inf} (h·μg/L)	513.07 ± 251.02	508.39 ± 245.38	495.85 ± 242.28
	$t_{1/2}$ (h)	7.00 ± 2.06	6.50 ± 1.96	7.37 ± 2.58
	CL/F (L/h)	150.13 ± 91.61	159.08 ± 127.16	150.28 ± 72.97
	Vd/F (L)	1,481.47 ± 1,012.42	1,413.99 ± 978.33	1,613.60 ± 1,176.32
Amlodipine	T_{max} (h)	5.00 [3.03–8.00]	5.00 [3.00–12.00]	5.02 [2.00–8.00]
	C_{max} (μg/L)	5.92 ± 1.29	6.00 ± 1.22	6.36 ± 1.46
	AUC_{last} (h·μg/L)	257.87 ± 69.32	258.89 ± 68.30	276.99 ± 65.31
	AUC_{inf} (h·μg/L)	294.15 ± 94.11	293.10 ± 96.29	312.30 ± 83.81
	$t_{1/2}$ (h)	45.09 ± 10.13	43.53 ± 9.53	43.89 ± 10.81
	CL/F (L/h)	36.92 ± 10.35	36.66 ± 9.15	34.26 ± 9.08
	Vd/F (L)	2,299.59 ± 467.15	2,226.03 ± 442.08	2,100.80 ± 491.29
Hydro-chlorothiazide	T_{max} (h)	2.00 [1.00–4.00]	2.00 [1.00–4.00]	2.00 [1.00–6.00]
	C_{max} (μg/L)	190.93 ± 51.31	174.53 ± 43.68	166.96 ± 53.58
	AUC_{last} (h·μg/L)	1,152.84 ± 290.22	1,099.26 ± 280.63	1,096.52 ± 299.73
	AUC_{inf} (h·μg/L)	1,195.62 ± 290.41	1,139.97 ± 280.54	1,136.34 ± 298.73
	$t_{1/2}$ (h)	8.42 ± 1.73	8.88 ± 1.65	8.90 ± 2.20
	CL/F (L/h)	22.01 ± 4.91	23.28 ± 5.79	23.48 ± 6.31
	Vd/F (L)	264.70 ± 69.32	298.03 ± 93.07	306.46 ± 162.50

Data are presented as mean ± standard deviation, except for T_{max} which is presented as median [minimum–maximum].
T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg; T_{max}, time to reach C_{max}; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve from zero until the last quantifiable time point; AUC_{inf}, area under the plasma concentration-time curve from time zero to infinity; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; Vd/F, apparent volume of distribution.
*First dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; †Second dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg.

Table 2. Pharmacokinetic parameters of fimasartan, amlodipine, hydrochlorothiazide following a single administration of test drug (T) or reference drug (R*)

Drug	Parameters	Geometric mean		Geometric mean ratio† (90% CI)	Intra-subject CV (%)‡
		T (n = 55)	R† (n = 55)		
Fimasartan	C_{max} (μg/L)	75.25	74.04	1.0163 (0.8681–1.1898)	62.64
	AUC_{last} (h·μg/L)	419.05	412.20	1.0167 (0.9347–1.1059)	31.44
Amlodipine	C_{max} (μg/L)	5.73	5.98	0.9595 (0.9256–0.9946)	13.17
	AUC_{last} (h·μg/L)	247.72	258.71	0.9575 (0.9317–0.9841)	10.00
Hydrochlorothiazide	C_{max} (μg/L)	182.73	161.79	1.1294 (1.0791–1.1821)	16.76
	AUC_{last} (h·μg/L)	1,136.49	1,076.21	1.0561 (1.0170–1.0967)	13.83

T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg; CI, confidence interval; CV, coefficient variation (intra-individual coefficient of variation); C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve from zero until the last quantifiable time point.
*Sum of pharmacokinetic data collected after the first and second co-administration of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; †The ratio of the test drug to reference drug; ‡Intra-subject CV (%) was calculated with PK data of reference drug.

recovered to baseline within 48 hours. The overall mean ± standard deviation of SBP and DBP from the test drug group were 110.78 ± 13.28 and 66.91 ± 9.08 mmHg, respectively, while they were 110.46 ± 12.93 and 67.02 ± 9.69 mmHg in the reference drug group, respectively.

Safety results

A total of 114 cases of treatment emergent adverse events (TEAEs) were reported from 31 subjects. Among them, 46 cases of TEAEs were reported from 21 subjects in the test drug group, while there were 68 cases from 21 subjects in the reference drug group. A total of 89 adverse drug reactions (ADRs) were reported from 27 subjects, among which 36 ADRs were reported from 18 subjects in the test drug group, while 53 ADRs were reported from 18 subjects in the reference drug group. The most common adverse reaction was dizziness (25.86%), followed by headache (17.24%), nausea (13.79%), and hypotension (10.34%), as already described in previous studies [22-24]. All of the TEAEs were mild except for one moderate case (postural orthostatic tachycardia syndrome), and no serious adverse

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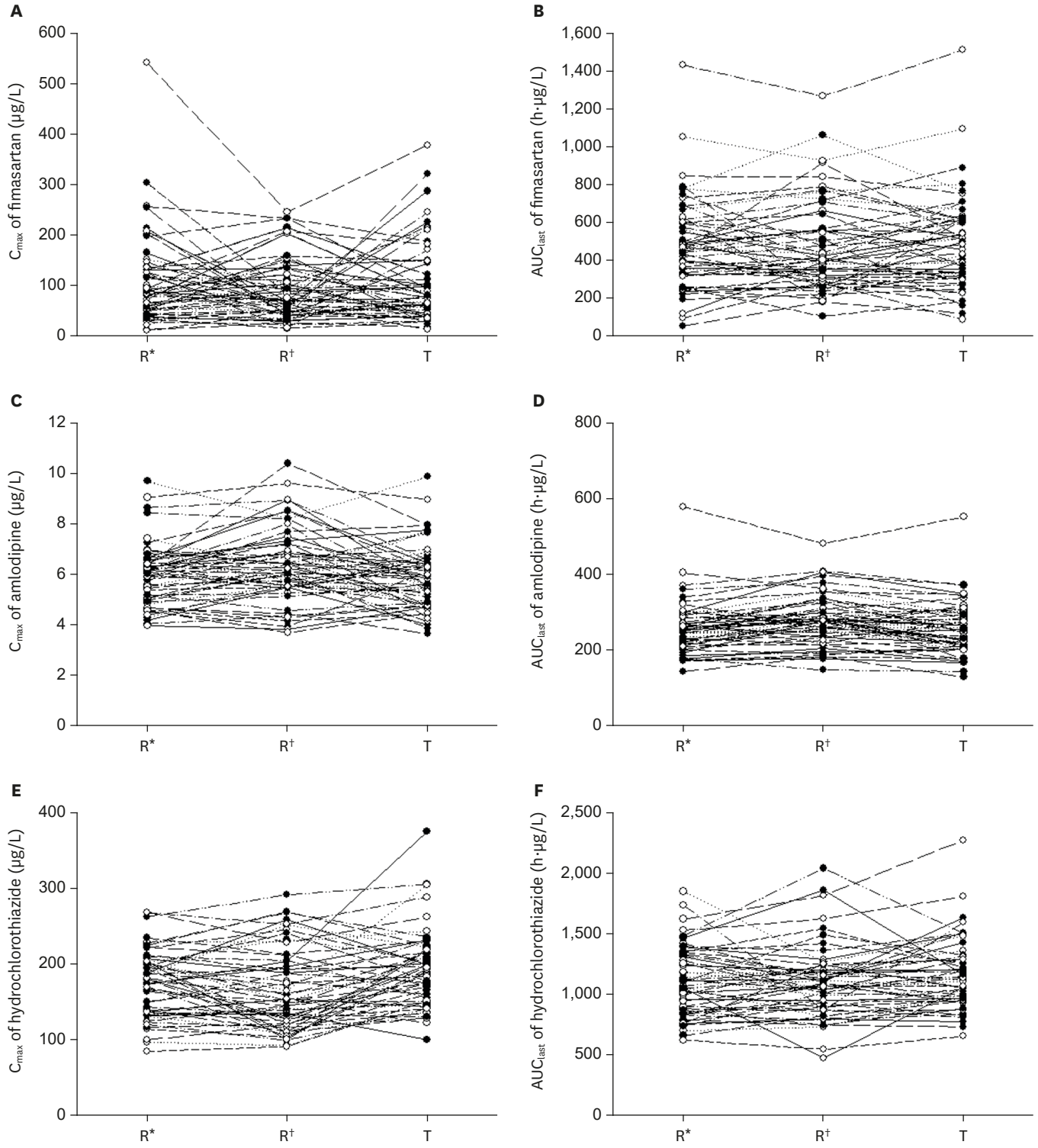

Figure 3. Individual comparison of (A) C_{max} and (B) AUC_{last} of fimasartan, (C) C_{max} and (D) AUC_{last} of amlodipine, and (E) C_{max} and (F) AUC_{last} of hydrochlorothiazide following a single administration of test drug (T) or reference drug (R* or R†).
T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg.
*First dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; †Second dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg. Open and solid circles represent the individual values of C_{max} or AUC_{last}.

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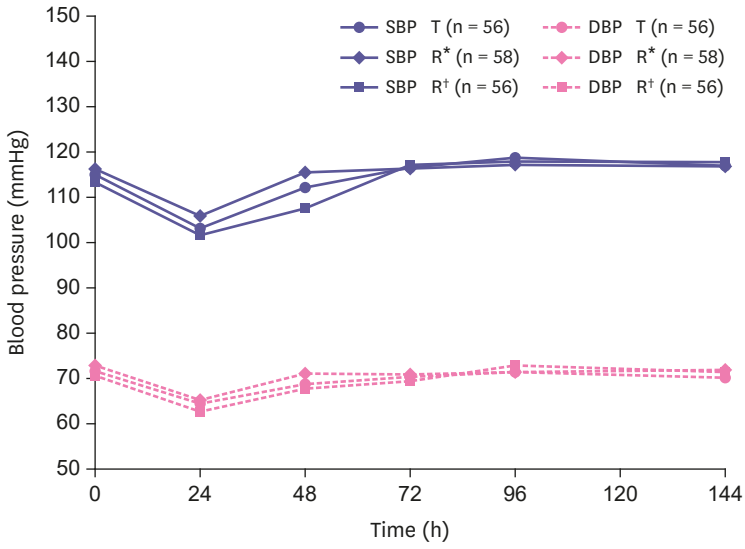

Figure 4. Mean SBP and DBP following a single administration of test drug (T) or reference drug (R* or R†).
T, fixed-dose combination of fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg.
*First dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg; †Second dosing of loose combination of fimasartan/amlodipine 60/10 mg + hydrochlorothiazide 25 mg.

events occurred during the entire study period. Clinically significant changes in physical examination, vital signs, clinical laboratory tests, and 12-lead ECG were not observed during the whole study period.

DISCUSSION

This study compared the pharmacokinetic characteristics and tolerability profile of a triple-combination FDC (fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg) to the corresponding loose combination of a dual-combination FDC (fimasartan/amlodipine 60/10 mg) and hydrochlorothiazide 25 mg. The pharmacokinetic characteristics of fimasartan, amlodipine and hydrochlorothiazide were similar between the triple-combination FDC and the loose combination (**Fig. 2** and **Table 1**). The GMRs and their 90% CIs of the triple-combination FDC to the loose combination for C_{max} and AUC_{last} of the three antihypertensive drugs fell within the conventional bioequivalent range of 0.8 to 1.25 (**Table 2**, **Supplementary Table 1**). In addition, both treatments were well tolerated in healthy subjects.

For drugs with an expected within-subject variability greater than 30%, either a partially or fully replicated design is proposed for the trials [25]. Fimasartan is considered a highly variable drug; therefore, a replicated study design is recommended [26-29]. Based on the recommendation, this study was designed in a three-period, partially replicated, crossover study design. In this study, the intracoefficient of variability for the C_{max} of fimasartan was highly variable (62.6%), as reported in a previous study (68%) [30].

The effects of FDC on lowering blood pressure were similar to those of the loose combination (**Fig. 4**). Concerning the incidence of blood pressure-related AEs, the frequency of AEs was comparable between the FDC and loose combination treatment groups. In 6 subjects (2 from the loose combination group and 4 from the FDC group, $p = 0.2568$), 7 cases of hypotension were reported as AEs, and they recovered naturally without any posttreatments. Furthermore,

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no other clinically significant symptoms regarding changes in blood pressure, such as lightheadedness, dehydration or blurred vision, were observed.

The design of this study was appropriate for evaluating the PK characteristics of fimasartan, amlodipine and hydrochlorothiazide. The study was performed using a partially replicated design with consideration of the high intrasubject variability of fimasartan, and this study design met with recommendations from regulatory agencies [25]. Additionally, the number of subjects for this study was sufficient to identify the statistical significance of the study results. A minimum sample size of 54 subjects was estimated to evaluate the bioequivalence with 80% statistical power at a 5% level of significance, assuming that the highest intra-subject variability of fimasartan was 68% [30]. Considering the dropout rate, the total number of 60 subjects was chosen to enroll in this study. In addition, the sampling time points were sufficiently long to ensure an adequate description of the elimination phase. The ratios of AUC_{last} to AUC_{inf} for fimasartan, amlodipine and hydrochlorothiazide in most of the subjects were higher than 80%.

In this study, we used a loose combination of a dual-combination FDC (fimasartan/amlodipine 60/10 mg) and hydrochlorothiazide 25 mg as comparator drugs to the triple-combination FDC. Similar PK profiles between the FDC of fimasartan and amlodipine and the loose combination of each drug were demonstrated in a previous study, and dual-combination FDC has already been widely used for the treatment of hypertension [31]. Since an add-on treatment of hydrochlorothiazide to the dual-combination FDC is commonly used in the clinic, that regimen was set as the reference treatment group for this study. The triple-combination FDC is expected to improve medication compliance in patients who need the triple-combination therapy of fimasartan, amlodipine, and hydrochlorothiazide.

In conclusion, pharmacokinetic characteristics and the tolerability profile were similar between the triple-combination FDC of fimasartan, amlodipine, and hydrochlorothiazide (fimasartan/amlodipine/hydrochlorothiazide 60/10/25 mg) and the loose combination of dual-combination FDC (fimasartan/amlodipine 60/10 mg) and hydrochlorothiazide 25 mg in healthy subjects.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Pharmacokinetic parameters of fimasartan, amlodipine, hydrochlorothiazide following a single administration of test drug (T) or reference drug (R*)

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