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# Pharmacokinetics and bioequivalence of fixed-dose combination of candesartan cilexetil/amlodipine besylate (16/10 mg) versus coadministration of individual formulations in healthy subjects

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## ABSTRACT

This study compared the pharmacokinetics of a fixed-dose combination (FDC) of candesartan (16 mg) and amlodipine (10 mg) versus coadministration of individual formulations to clarify the bioequivalence of the FDC. In this randomized, open-label, single-dose, 2-treatment, 2-way crossover study, healthy Korean volunteers received a single dose of candesartan (16 mg) with amlodipine (10 mg) as either an FDC or single agents concomitantly administered, with a 2-week washout period. Serial blood samples were collected up to 72 hours after dosing for each treatment period, and plasma concentrations of candesartan and amlodipine were measured using a validated liquid chromatography-tandem mass spectrometry method. A total of 39 subjects completed the study. The geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the area under the plasma concentration-time curve from time 0 to the last measurement ($AUC_{0-t}$) and the peak plasma concentration ($C_{max}$) for candesartan were 1.0182 (0.9562–1.0841) and 0.9492 (0.8726–1.0324), respectively. The GMR and 90% CI for the $AUC_{0-t}$ and $C_{max}$ for amlodipine were 1.0552 (1.0255–1.0857) and 1.0668 (1.0259–1.1094), respectively. In conclusion, the new FDC formulation of candesartan (16 mg) and amlodipine (10 mg) was bioequivalent to the concomitant administration of single agents. A single dose of candesartan/amlodipine as the FDC or as single agents was well tolerated.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT02988362

**Keywords:** Hypertension; Pharmacokinetics; Bioequivalence; Candesartan; Amlodipine

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## INTRODUCTION

Hypertension is a major risk factor for cardiovascular morbidity and mortality worldwide [1]. From one year of follow-up after a 10-mmHg decrease in systolic blood pressure (SBP) or 5-mmHg decrease in diastolic blood pressure (DBP), 20% reduction in coronary heart disease and 32% reduction in stroke have been reported [2]. According to the guidelines for hypertension management, four classes of antihypertensive drugs are recommended as first-line therapy: calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), and thiazide-type diuretics [3]. For the majority of hypertensive patients, two or more antihypertensive agents are required for blood pressure (BP) control [4]. In several clinical trials, combination therapy using 2 or more antihypertensive drugs with complementary mechanisms of action exhibited more effective BP reduction, with no increase in adverse events (AEs), compared with high-dose monotherapy [5,6]. One of the preferred combinations of antihypertensive drugs from different classes is ARB/CCB, as peripheral edema and tachycardia due to CCBs are prevented by ARBs [7].

Candesartan, an ARB, lowers BP by selectively blocking the angiotensin II type 1 (AT1) receptor in the renin-angiotensin-aldosterone system, which maintains homeostasis of BP and body fluids [8]. With oral administration of candesartan cilexetil, conversion to the active compound, candesartan, occurs rapidly and completely by hydrolysis during gastrointestinal absorption [9]. Following oral administration, the absolute bioavailability of candesartan has been shown to be 15%, with a time to maximum plasma concentration ($t_{max}$) of 3.0–5.5 hours, and a terminal half-life ($t_{1/2}$) of 9–11.5 hours [9-11]. Candesartan is primarily excreted unchanged into feces and urine (67% and 33%, respectively, of radioactivity recovered following an oral dose of $^{14}$C-labeled candesartan cilexetil), with minor hepatic metabolism by O-deethylation to an inactive metabolite [9].

Amlodipine, a dihydropyridine-based CCB, inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, resulting in reduced peripheral vascular resistance and blood pressure [12]. Absolute bioavailability of amlodipine has been estimated to be 64%–90% after oral administration, with a $t_{max}$ of 6–12 hours and a $t_{1/2}$ of 30–50 hours [12,13]. About 90% of the orally administered amlodipine is converted to inactive metabolites via hepatic metabolism; in humans, cytochrome P450 (CYP) 3A4 accomplishes this metabolism [12,14]. The amounts excreted in urine are 60% of the metabolites and 10% of the parent drug.

According to the report by Sohn et al. [6], combination therapy with candesartan and amlodipine more effectively reduced BP compared with either candesartan or amlodipine given alone. No drug-drug interactions have been reported following multiple-dose coadministration of candesartan and amlodipine [10]. The different disposition pathways of candesartan and amlodipine might explain this lack of pharmacokinetic (PK) interactions.

Fixed-dose combinations (FDCs) of 2 antihypertensive agents in a single pill can significantly improve medication compliance or persistence with therapy—and, consequently, have beneficial effects on BP control—compared with free combinations or monotherapy [15]. Recently, a new FDC formulation of candesartan cilexetil and amlodipine besylate 16 mg/10 mg was developed by HanAll BioPharma Co. Ltd. (Seoul, Korea). The aim of the current study was to compare the pharmacokinetic characteristics and bioequivalence of the FDC formulation of candesartan and amlodipine with those of coadministration of the 2 drugs (ClinicalTrials.gov: NCT02988362).


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## METHODS

This study was performed after the protocol was approved by the Institutional Review Board of Kyungpook National University Hospital (KNUH, Daegu, Korea) and the Korea Ministry of Food and Drug Safety (MFDS), in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice Guideline, and local laws and regulations. Written informed consent was obtained from all subjects prior to any study procedures.

### Study subjects

Healthy male volunteers aged 19–55 years with a body mass index of 18.5–27.0 kg/m$^2$ were eligible to participate. Subjects were excluded if there was evidence or a history of any of the following: clinically significant medical or neuropsychiatric disorders; clinically significant laboratory abnormalities for serum aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels; positive serologic tests; SBP ≥ 140 or < 115 mmHg, or DBP ≥ 90 or < 70 mmHg; a history of hypersensitivity to any drug, including candesartan and amlodipine; alcohol abuse; excessive smoking; donation of whole blood within 2 months; or ineligibility to participate at the discretion of the study investigator.

### Study design and procedure

This study was conducted as a randomized, open-label, single-dose, 2-period, 2-way crossover study at the KNUH Clinical Trial Center. Eligible participants were randomly assigned to one of two treatment groups in a 1:1 ratio. In each period, every subject received a single oral dose of candesartan/amlodipine (16 mg/10 mg) FDC (HanAll BioPharma Co. Ltd., Seoul, Korea) as the test treatment, or, as the reference treatment, the coadministration of candesartan (16 mg; Atacand®, Yuhan Corporation, Seoul, Korea) and amlodipine (10 mg; Norvasc®, Pfizer Korea, Seoul, Korea) as separate agents. The crossover study design included a 14-day washout period between the 2 treatments.

The subjects were hospitalized at the study center from 6 p.m. the day before dosing to 36 hours after dosing. After an overnight fast of 10 hours, subjects received the reference or the test formulation orally with 150 mL of water. No additional water intake was allowed for 1 hour before and 2 hours after each treatment administration, and fasting continued until 4 hours after dosing. Standard meals were provided at 4 and 10 hours after dosing.

Serial blood samples (8 mL) were taken from an indwelling catheter using a tube containing EDTA-K2. To determine the plasma concentrations of candesartan and amlodipine, serial blood samples were collected at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, and 36 hours after candesartan dosing, and at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, and 72 hours after amlodipine dosing. After blood collection, each tube was centrifuged at 3,000 rpm and 4°C for 10 minutes in order to separate the plasma. Following centrifugation, the plasma samples were transferred to three different tubes (1 mL to each tube) and stored at −70°C until analysis by BioCore Co., Ltd. (Seoul, Korea).

### Analysis of the plasma concentrations of candesartan and amlodipine

The plasma concentrations of candesartan were determined using ultra-fast liquid chromatography (UFLC, Shimadzu UFLC system, Shimadzu Corp., Kyoto, Japan) coupled to tandem mass spectrometry (MS/MS, API 5000, AB Sciex, Foster City, CA, USA). Chromatographic separation was performed on a C18 column (2.0 × 75 mm internal


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diameter, 3.0 μm particle size) at a flow rate of 0.2 mL/min. The mobile phase consisted of a 40:60:0.1 (v/v/v) mixture of 10 mM ammonium formate, acetonitrile, and formic acid. Multiple reaction monitoring transitions were performed at m/z ratios of 441.2 → 263.1 and 446.1 → 268.1 for candesartan and candesartan-$d_5$ (the internal standard [IS]), respectively.

The frozen plasma was thawed at room temperature and vortexed for 10 seconds. Following the addition of 10 μL of candesartan-$d_5$ (1,000 ng/mL) to 100 μL of plasma in a polypropylene tube, 500 μL of acetonitrile were added and vortexed for 1 minute. After the mixture was centrifuged at 13,000 rpm for 5 minutes, 100 μL of the upper layer were transferred to a polypropylene tube. Then, 100 μL of 50% acetonitrile were added and mixed. A 3-μL aliquot of this solution was injected into the liquid chromatography with tandem mass spectrometry (LC-MS/MS) system for analysis.

The plasma concentrations of amlodipine were determined using liquid chromatography (Shiseido Nanospace SI-2; Shiseido Co. Ltd., Tokyo, Japan) coupled with a 4000 QTRAP® tandem mass spectrometer (AB SCIEX, Foster City, CA, USA). Chromatographic separation was performed on an Atlantis dC18 column (2.1 × 100 mm internal diameter, 3.0 μm particle size; Waters Corp., Milford, MA, USA) at a flow rate of 0.2 mL/min. The mobile phase consisted of a 50:50:0.1 (v/v/v) mixture of acetonitrile, deionized water, and formic acid. Multiple reaction monitoring transitions were performed at mass-to-charge (m/z) ratios of 409.2 → 238.2 and 413.2 → 238.3 for amlodipine and amlodipine-$d_4$ (IS), respectively. The frozen plasma was thawed at room temperature and vortexed for 10 seconds. Following the addition of 10 μL of amlodipine-$d_4$ (100 ng/mL) to 200 μL of plasma in a polypropylene tube, 20 μL of 1 M sodium hydroxide were added and vortexed for 1 minute. After 1.5 mL of methyl *tert*-butyl ether were added and vortexed for 2 minutes, the mixture was centrifuged at 13,000 rpm for 5 minutes. The upper layer was dried with a stream of nitrogen gas, and then the residue was reconstituted with 150 μL of mobile phase and filtrated with a 0.2-μm filter. A 10-μL aliquot of this solution was injected into the LC-MS/MS system for analysis.

The linear calibration curves ranged between 2 and 500 ng/mL for candesartan ($r \geq 0.9996$), and between 50 and 20,000 pg/mL for amlodipine ($r \geq 0.9996$). The overall intraday accuracy ranged from 88.4% to 109.0% at concentrations of 2, 6, 40, and 400 ng/mL for candesartan, and from 94.7% to 101.9% at concentrations of 50, 150, 2,000, and 16,000 pg/mL for amlodipine. The overall inter-day accuracy ranged from 93.5% to 103.9% for candesartan, and from 97.3% to 99.7% for amlodipine. The intraday precision (% coefficient of variation, CV) ranged from 0.6% to 5.7% for candesartan, and from 1.5% to 8.7% for amlodipine. The inter-day precision (%CV) ranged from 1.6% to 7.6% for candesartan, and from 2.3% to 6.3% for amlodipine. The lower limit of quantification was 2 ng/mL for candesartan and 50 pg/mL for amlodipine.

### PK analysis

Noncompartmental pharmacokinetic analysis of candesartan and amlodipine was performed using the Phoenix WinNonlin software, version 6.4 (Pharsight Corporation, Sunnyvale, CA, USA) for the following parameters: maximum plasma concentration ($C_{max}$); $t_{max}$; area under the plasma concentration-time curve from time 0 to the last measurement ($AUC_{0-t}$); AUC from time 0 to infinity ($AUC_{0-\infty}$); $t_{1/2}$.


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### Statistical analyses

Regarding intrasubject variability %CVs of $AUC_{0-t}$ values and $C_{max}$ values in earlier PK studies, the highest values were 27.3% for candesartan and 22.0% for amlodipine [11,16-18]. From these values, a sample size of 17 subjects in each group was calculated for this study to detect a 20% or more difference in the log-transformed PK parameters between the 2 treatments (FDC vs. coadministration of the individual tablets) with 80% power and a 5% level of significance. Therefore, a total of 40 subjects were to be enrolled, assuming an estimated attrition rate of 15%.

Demographic characteristics were summarized using descriptive statistics and all pharmacokinetic parameters were summarized by treatment group. The results were presented as the mean ± standard deviation (SD), except for the $t_{max}$ values, which were expressed as the median, maximum, and minimum values. The differences in baseline demographics between the 2 groups were determined by the Mann-Whitney U test or independent t-test using SPSS software for Windows OS (ver. 18.0; SPSS Korea, Seoul, Republic of Korea). The differences in PK parameters between the two treatments were compared using a mixed-effects model analysis of variance (ANOVA), with subject-within-sequence considered a random effect, and sequence, period, and treatment considered fixed effects, except the $t_{max}$ values using the Wilcoxon signed-rank test. A *p*-value below 0.05 indicated statistical significance.

To assess the bioequivalence between the test and reference treatments, the ln-transformed $C_{max}$ and $AUC_{0-t}$ of candesartan and amlodipine were compared using SAS software (ver. 9.4.; SAS Institute Inc., Cary, NC, USA). The two treatments were determined to be bioequivalent if the 90% confidence interval (CI) of the geometric mean ratios (GMRs; FDC/single agents) for the ln-transformed $C_{max}$ and $AUC_{0-t}$ were within the predetermined range of 0.8000–1.2500, according to the standard used by the Korea MFDS [19].

### Assessment of safety and tolerability

Safety and tolerability were assessed in every subject who received at least one or more doses of the study drugs throughout the study period. Clinical adverse events (AEs) or AEs identified in the laboratory after dosing including vital signs (BP, heart rate, and body temperature), routine laboratory tests (hematology, urinalysis, and serum chemistry), and 12-lead electrocardiograms.

The AEs were monitored and recorded using the Medical Dictionary for Regulatory Activities (version 16.0), and were summarized according to the number of events, number of subjects, severity, seriousness, and causality. All laboratory tests were performed at the Department of Laboratory Medicine, KNUH.

## RESULTS

### Demographic characteristics

In total, 40 healthy subjects were enrolled in this study and randomized in a 1:1 ratio into one of 2 groups. Two subjects were withdrawn from the study before drug administration in period I and replaced by other subjects from the waiting list. Just before admission in period II, another subject withdrew consent. Accordingly, 39 subjects (group A, n = 20; group B, n = 19) completed the study. The baseline demographic characteristics of the subjects are summarized in **Table 1**.


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**Table 1.** Demographics characteristics of the subjects who completed this study

| Demographic variables | Overall (n = 39) | Group A (n = 20) | Group B (n = 19) | *p*-value |
|---|---|---|---|---|
| Age (yr) | | | | |
| Mean ± SD | 24.7 ± 3.5 | 25.4 ± 3.8 | 24.1 ± 3.1 | 0.2715* |
| Range | 19–35 | 19–35 | 19–30 | |
| Height (cm) | | | | |
| Mean ± SD | 173.7 ± 5.4 | 173.8 ± 6.6 | 173.6 ± 4.0 | 0.8991* |
| Range | 159.7–187.5 | 159.7–187.5 | 163.7–181.8 | |
| Weight (kg) | | | | |
| Mean ± SD | 69.1 ± 8.6 | 69.8 ± 9.1 | 68.4 ± 8.2 | 0.6213* |
| Range | 55.3–95.0 | 57.9–95.0 | 55.3–85.6 | |
| SBP | | | | |
| Mean ± SD | 129.7 ± 6.1 | 128.1 ± 6.4 | 131.4 ± 5.4 | 0.0693† |
| Range | 115–138 | 118–138 | 115–138 | |
| DBP | | | | |
| Mean ± SD | 77.4 ± 5.0 | 78.1 ± 5.1 | 76.6 ± 4.9 | 0.3473* |
| Range | 70–89 | 71–89 | 70–85 | |

Group A = reference, test (RT); Group B = test, reference (TR); R = coadministration of candersartan 16 mg and amlodipine 10 mg; T = FDC formulation of candesartan 16 mg and amlodipine 10 mg.
SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Compared between 2 groups by *independent t-test and †Mann-Whitney U test.

All 40 subjects who received candesartan and/or amlodipine at least once were included in the safety assessment, and only subjects who completed the blood sampling as scheduled (n = 39) were included in the PK analysis.

## PK data

The mean (SD) plasma concentration versus time profiles of candesartan and amlodipine following a single oral administration of an FDC formulation and the coadministration of candesartan and amlodipine as separate tablets are illustrated in the **Fig. 1**, and the PK parameters for the 2 formulations of candesartan and amlodipine are summarized in **Table 2**. The 90% CIs for the ratio (FDC/coadministration) of the geometric means fell within the predetermined acceptance range of 0.8000 to 1.2500 to assume bioequivalence of candesartan and amlodipine, yielding 90% CI ratios of 0.9562–1.0841 and 1.0255–1.0857 for $AUC_{0\text{-}t}$, 0.9547–1.0736 and 1.0140–1.1076 for $AUC_{0\text{-}\infty}$, and 0.8726–1.0324 and 1.0259–1.1094 for $C_{max}$, respectively (**Table 3**).

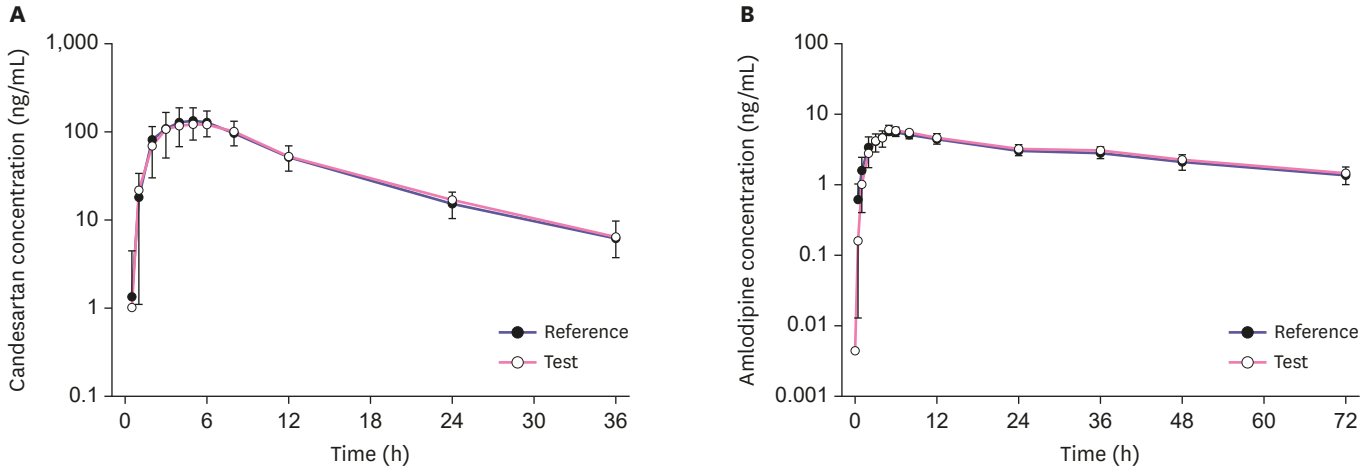


**Figure 1.** Mean (SD) plasma concentration-time profiles for (A) candesartan and (B) amlodipine following administration of a single dose of a candesartan/amlodipine (16 mg/10 mg) FDC tablet (○) and individual coadministration of single doses of candesartan (16 mg) and amlodipine (10 mg) (●) in 39 healthy subjects.
SD, standard deviation; FDC, fixed-dose combination.


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**Table 2.** Pharmacokinetic parameters of candesartan and amlodipine following administration of candesartan 16 mg and amlodipine 10 mg as a fixed-dose combination vs separate agents under fasting conditions in 39 healthy male subjects

| Drug | Pharmacokinetic parameter | FDC | Separate agents | ANOVA *p*-value* | Intra-CV (%) |
|---|---|---|---|---|---|
| Candesartan | $AUC_{0-t}$ (ng·hr/mL) | 1,579.5 ± 435.1 | 1,559.4 ± 472.0 | 0.6312 | 16.54 |
| | $AUC_{0-\infty}$ (ng·hr/mL) | 1,651.2 ± 448.5 | 1,635.4 ± 475.8 | 0.7241 | 15.45 |
| | $C_{max}$ (ng/mL) | 138.8 ± 43.9 | 148.9 ± 56.3 | 0.3018 | 22.27 |
| | $t_{1/2}$ (hr) | 7.4 ± 1.1 | 7.3 ± 2.2 | 0.3030 | 15.37 |
| | $t_{max}$‡ (hr) | 5.00 (2.00–8.00) | 5.00 (3.00–8.00) | 0.309† | 24.48 |
| Amlodipine | $AUC_{0-t}$ (ng·hr/mL) | 212.7 ± 43.0 | 201.9 ± 41.7 | 0.0030 | 7.47 |
| | $AUC_{0-\infty}$ (ng·hr/mL) | 291.3 ± 90.1 | 272.9 ± 69.5 | 0.0327 | 11.59 |
| | $C_{max}$ (ng/mL) | 6.3 ± 1.0 | 6.0 ± 1.1 | 0.0083 | 10.27 |
| | $t_{1/2}$ (hr) | 35.7 ± 9.7 | 35.0 ± 5.6 | 0.9118 | 14.39 |
| | $t_{max}$‡ (hr‡) | 5.00 (3.00–12.00) | 5.00 (2.00–12.00) | 0.236† | 22.79 |

FDC, fixed dose combination; ANOVA, analysis of variance; Intra-CV, intra-subject coefficient of variation; $AUC_{0-t}$, area under the plasma concentration versus time curve from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity; $C_{max}$, maximum plasma concentration; $t_{1/2}$, elimination half-life; $t_{max}$, time to reach $C_{max}$; SD, standard deviation.
*Compared between 2 groups by ANOVA, except for $t_{max}$ values by †Wilcoxon signed ranks test. Data are presented as arithmetic means ± SD, ‡except for $t_{max}$ values as median (range).

**Table 3.** Geometric mean ratios and 90% CIs for the $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ following administration of candesartan 16 mg and amlodipine 10 mg as a fixed-dose combination vs separate agents under fasting conditions in 39 healthy male subjects

| Pharmacokinetic parameter | Geometric mean ratio (90% CI) | |
|---|---|---|
| | Candesartan | Amlodipine |
| $AUC_{0-t}$ | 1.0182 (0.9562–1.0841) | 1.0552 (1.0255–1.0857) |
| $AUC_{0-\infty}$ | 1.0124 (0.9547–1.0736) | 1.0598 (1.0140–1.1076) |
| $C_{max}$ | 0.9492 (0.8726–1.0324) | 1.0668 (1.0259–1.1094) |

CI, confidence interval; $AUC_{0-t}$, area under the plasma concentration versus time curve from time 0 to the last quantifiable time point; $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity; $C_{max}$, maximum plasma concentration.

### Safety and tolerability assessments

In total, 11 AEs were experienced by 10 subjects (25.00% of the 40 subjects). Of these AEs, seven were determined to be possibly related to the study drugs: four AEs (2 cases of upper respiratory infection, and one case each of proteinuria and decreased white blood cell count) for the test drug and three AEs (one case each of diarrhea, hematuria, and decreased white blood cell count) for the reference drug. All AEs were transient and resolved spontaneously without any specific treatment; there were no severe or serious AEs.

**Fig. 2** shows the changes in mean SBP, DBP, and pulse rate in the 2 treatment groups from baseline (0 hours) to 72 hours after administration of a single dose of the FDC or the coadministration of the individual formulations. The changes in vital signs showed no statistical differences between the 2 groups.

## DISCUSSION

This randomized, open-label, 2-sequence, 2-period, two-treatment crossover study conducted in healthy volunteers indicates that the FDC formulation of candesartan (16 mg) and amlodipine (10 mg) is bioequivalent to coadministration of the individual tablets. In addition, both the FDC and individual tablets were well tolerated in this study.

According to the full prescribing information, the maximum limits of the dosing regimens for candesartan and amlodipine are 32 and 10 mg, respectively [9,12]. In a study to explore the optimal dosage of a FDC of candesartan cilexetil and amlodipine besylate in patients with essential hypertension, the 8-week combination therapy of candesartan/ amlodipine (8 mg/5 mg, 16 mg/5 mg, and 16 mg/10 mg) showed a significantly greater BP reduction and the achievement


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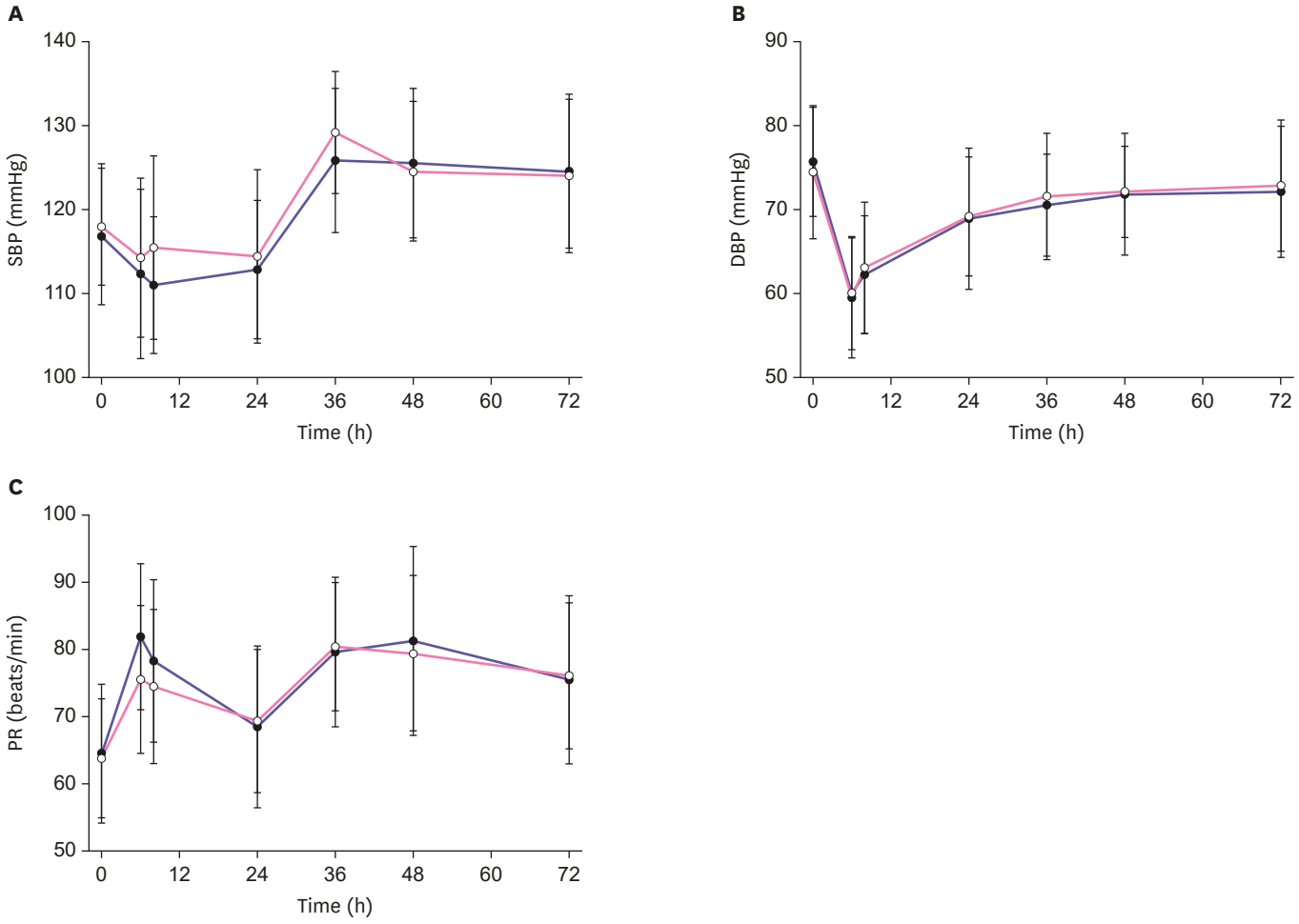


**Figure 2.** Mean (A) SBP, (B) DBP, and (C) PR before (0 hours) and at 6, 8, 24, 36, 48, and 72 hours after administration of a single dose of a candesartan/amlodipine (16 mg/10 mg) FDC tablet (○) and single doses of candesartan (16 mg) and amlodipine (10 mg) individually coadministered (●) in 39 healthy subjects.
SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; FDC, fixed-dose combination.

of BP goals compared with either drug monotherapy [6]. Accordingly, the doses selected in this study for a new FDC formulation were 16 mg/10 mg for candesartan/amlodipine.

As recommended by the guidelines for bioavailability and bioequivalence studies, the sampling schedule should cover at least three or more times the $t_{1/2}$ in order to capture 90% of the relevant AUCs, but a sampling period longer than 72 hours is not considered necessary irrespective of the $t_{1/2}$ for drugs with low intrasubject variability in distribution and clearance [19]. Accordingly, blood samples in our study were collected for up to 36 hours for candesartan and 72 hours for amlodipine after dosing (at least three or more times the terminal elimination half-lives of candesartan and amlodipine, which are 9–11.5 hours, and 30–50 hours, respectively) [11,16-18]. In our study, the mean ratio (SD) values of $AUC_{0\text{-}t}$ for candesartan and amlodipine accounted for 95.2% (4.4%) and 74.8% (5.4%) of the total $AUC_{0\text{-}\infty}$, respectively. The 14-day washout period in this study, which was calculated from the longer $t_{1/2}$ of amlodipine (30–50 hours) in earlier PK studies, was adequate for the complete elimination of the study medications from the blood after period I, as candesartan and amlodipine were not detectable in the pre-dose plasma samples in period II, except for in one subject. The pre-dose amlodipine concentration for that subject in period II was 171.2 pg/


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mL, and the $C_{max}$ value was 8,395.9 pg/mL. According to the guidelines for bioavailability and bioequivalence studies, the data of the subject whose pre-dose concentration is within 5% of $C_{max}$ can be included in all PK evaluations [19].

All of the intra-subject variability (%CV) values of the $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ obtained in our study (15.45%–22.27% for candesartan, and 7.47%–11.59% for amlodipine) were less than the value used to calculate the sample size (27.3% for candesartan) and comparable to those reported by other studies [11,16-18]. In our study, ANOVA of the $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ values of amlodipine between the 2 treatments showed statistically significant differences, but all the 90% CIs of the GMRs fell within the predetermined bioequivalence range.

During this study, all the AEs were mild to moderate, with no serious AEs reported. The incidence of AEs did not significantly differ between the 2 treatments.

As in most bioavailability and pharmacokinetic studies, the present study has several limitations that need to be considered. First, only healthy young male volunteers who met very narrow inclusion and exclusion criteria were included in this study. The second limitation is the relatively small sample size. Third, only a single dose was administered in this study. As these conditions are not representative of the general hypertensive patient population, a further long-term study with a larger number of subjects, including hypertensive patients and the elderly, is needed to generalize this result to other populations.

In conclusion, the FDC formulations comprised of candesartan (16 mg)/amlodipine (10 mg) were bioequivalent to the individual drugs coadministered in healthy subjects under fasting conditions. Administration of candesartan/amlodipine FDC tablets and coadministration of candesartan and amlodipine as individual tablets were well tolerated by healthy subjects.

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