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ORIGINAL RESEARCH

No pharmacokinetic interactions between candesartan and amlodipine following multiple oral administrations in healthy subjects

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Purpose: To evaluate the pharmacokinetics and pharmacodynamics of candesartan and amlodipine in the absence and presence of each other in healthy subjects.

Methods: This study consisted of two parts: part 1, the effect of amlodipine on candesartan; part 2, the effect of candesartan on amlodipine. Each part was designed as a randomized, open-label, two-sequence, two-period, two-intervention crossover study with 20 subjects and performed separately in different populations. Pharmacokinetic assessments were performed over 48 hours for candesartan in part 1 and 72 hours for amlodipine in part 2 after drug administration on Day 10. Safety data included the results of physical examinations, clinical laboratory tests, vital signs, an electrocardiogram, and adverse events.

Results: For both candesartan and amlodipine, the 90% confidence intervals for the geometric mean ratios of area under the concentration-time curve from time zero to the time of dosing interval of 24 hours and maximum concentration after drug administration fell within the bioequivalence acceptance criteria. Although this study was conducted in normotensive subjects, blood pressure lowering effects were observed in all intervention groups and co-administration of candesartan and amlodipine reduced blood pressure more than amlodipine alone, but similar to candesartan alone. No serious adverse event was reported throughout the study, and all treatment emergent adverse events were mild to moderate in severity and were recovered without sequelae.

Conclusion: Co-administration of candesartan and amlodipine did not change the systemic exposure of each drug alone in healthy subjects. The administration of candesartan 32 mg alone, amlodipine 10 mg alone, and co-administration of candesartan and amlodipine were well tolerated during the study.

Keywords: interaction, candesartan, amlodipine, combination

Introduction

Hypertension is one of the most important risk factors of cardiovascular disease. For the management of hypertension, it is required to reduce blood pressure (BP) to target levels by using antihypertensive drugs. The antihypertensive drugs are divided into several classes such as thiazide-type diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker according to their action mechanisms.[1] Monotherapy with one class drug is usually not adequate for patients with high-risk conditions, and most hypertensive patients will require two or more drugs with different action mechanisms to achieve goal BP.[2]

Candesartan is one of the angiotensin receptor blockers (ARBs) and amlodipine is the most widely used calcium channel blocker for the treatment of hypertension.

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Since the action mechanisms of candesartan and amlodipine are quite different, combination therapy with these two drugs was effective for hypertensive patients.[3–5] Moreover, candesartan has shown more favorable tolerability in terms of developing peripheral edema compared to amlodipine.[6] For patients whose BP is uncontrolled by low dose amlodipine alone, it can be better to use candesartan in combination with amlodipine than to increase the dose of amlodipine. To facilitate this rational prescribing, fixed-dose combinations of candesartan and amlodipine have been available in Japan and Republic of Korea.[7,8]

A large number of drug interactions are attributable to the inhibition or induction of CYP/CYP450 (CYP) enzymes.[9] Since amlodipine is extensively metabolized by the CYP3A4, its systemic exposure may be affected by CYP inhibitors and inducers.[10] In contrast, candesartan is mainly excreted unchanged in urine and feces.[11] Although they have different disposition and elimination pathways, it is recommended to address the drug interaction potential if they are commonly used in combination.[12,13] The clinical efficacy of combination therapy with candesartan and amlodipine in hypertensive patients is well demonstrated; however, there is a lack of study explicitly reporting drug interactions between these drugs. The purpose of this study was to evaluate the pharmacokinetics and pharmacodynamics of candesartan and amlodipine in the absence and presence of each other in healthy subjects.

Materials and methods

Study design and subjects

This study consisted of two parts: part 1, the effect of amlodipine on candesartan; part 2, the effect of candesartan on amlodipine. Each part was designed as a randomized, open-label, two-sequence, two-period, two-intervention (administration of one drug with the absence or presence of the other drug) crossover study with 20 subjects and performed separately in different populations. In each part, subjects were randomized to receive either one drug with absence followed by presence of the other drug, or vice versa. Each intervention was separated by a 14-day washout period except when subjects received candesartan alone first and then candesartan with amlodipine after a washout period of 4 days in part 1 (Table 1).

Eligible subjects were males between 20–55 years old with body mass index of 18.5–27.0 and were healthy as determined by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests (hematology, blood chemistry, urinalysis, serology) within 28 days prior to enrolment in the study. Subjects were excluded if they had donated blood in the 2 months previous to the study or participated in any clinical trials in the month previous to the study or had received any drug that affects the pharmacokinetics of candesartan or amlodipine in the month previous to the study. During the study, subjects were required to abstain from strenuous physical exercise, smoking, and products, such as over-the-counter medications or beverages containing alcohol or caffeine.

The intra-subject coefficients of variation of the PK exposure of candesartan and amlodipine were assumed to be 18% and 10%, respectively, based on the results of a previous clinical study.[21,22] With a sample size of 16, a difference of 20% in the log-transformed PK parameters of candesartan and amlodipine could be detected with >90% test power at a significance level of 0.05. Assuming a drop-out, the total number of subjects for each part was 20 (10 subjects per sequence).

The protocol of this study was approved by the Samsung Medical Center Institutional Review Board and the Ministry of Food and Drug Safety in Republic of Korea before the initiation of the study. The study was conducted in accordance with the Declaration of Helsinki, Korean Good Clinical Practice. All subjects gave written informed consent prior to any study procedures.

Dosing and sampling schedules

Subjects received candesartan alone, amlodipine alone, or both candesartan and amlodipine for 10 days in each part. Candesartan 32 mg (Atacand®, AstraZeneca Korea, Seoul, Korea)

Table 1 Study design and drug administration scheme

Part	Sequence	Intervention	Washout	Intervention
1	1	Candesartan[a]	14 days	Candesartan + amlodipine[b]
	2	Candesartan + amlodipine[b]	14 days	Candesartan[a]
2	1	Amlodipine[c]	14 days	Amlodipine + candesartan[b]
	2	Amlodipine + candesartan[b]	14 days	Amlodipine[c]

Notes: [a]Administration of candesartan 32 mg alone for 10 consecutive days. [b]Co-administration of candesartan 32 mg and amlodipine 10 mg for 10 consecutive days. [c]Administration of amlodipine 10 mg alone for 10 consecutive days.

and amlodipine 10 mg (Norvasc®, Pfizer Korea, Seoul, Korea) were administered with 240 mL water regardless of meals, while the same were administered under fasted conditions on Day 10. Subjects visited the Samsung Medical Center for drug administration on Days 1, 4, 7, 8, and 9 and documented timing and administration of drugs with dosing diaries on Days 2, 3, 5 and 6. Pharmacokinetic assessments were performed over 48 hours for candesartan in part 1 and 72 hours for amlodipine in part 2 after drug administration on Day 10. For the pharmacokinetic analysis of candesartan, blood samples (8 mL) were collected at predose and at 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 hours postdose on day 10 in part 1. As for amlodipine, blood samples were collected at predose and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours postdose on Day 10 in part 2. Blood samples were centrifuged at 1,800 *g* for 10 minutes and plasma was collected and frozen at −70°C until analysis.

Determination of plasma concentrations

Plasma samples for PK analysis were determined using ultra performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS) with a validated methodology to determine plasma concentrations of candesartan and amlodipine.

In the candesartan assay, chromatography (Waters Acquity UPLC™ System; Waters Corporation, Milford, MA, USA) was performed with a Waters Acquity UPLC®BEH C18 column (1.7 µm, 2.1×50 mm; Waters) while the column temperature was maintained at 30°C ± 5°C. The standards for candesartan and the internal standard (IS), candesartan _d5, were provided by Toronto Research Chemicals Inc. (North York, ON, Canada). The mobile phase for candesartan consisted of a mixture of (A) 0.1% (vol/vol) formic acid in distilled water and (B) 0.1% (vol/vol) formic acid in acetonitrile (A:B=6:4, vol/vol) with a flow rate of 0.4 mL/min. Detection of candesartan was conducted by a Waters Micromass Quattro Premier™ XE Mass Spectrometer (Waters Corporation) with a positive electrospray ionization multiple reaction monitoring mode set to transmit at m/z 440.86 → 262.85 and 445.92 → 267.88 for candesartan and the internal standard, respectively. The assay was linear in the concentration ranges of 5–1,000 µg/L and the lower limit of quantification was 5.0 µg/L in the candesartan assay. A mixture of 50 µL aliquot of plasma sample and 10 µL of IS working solution (candesartan-d5 1.50 µg/mL in 70% methanol [vol/vol]) was prepared. The prepared mixture was deproteinized by 150 µL volume of pure acetonitrile. Then, each 100 µL of the supernatant was diluted with 200 µL of 0.1% formic acid. The 5 µL aliquot was injected into the LC/MS/MS system. The intrabatch and interbatch precision (%relative SD) for candesartan in plasma samples was less than 9.8% and 10.4%, respectively. The intrabatch and interbatch accuracy (%deviation of mean from theoretical) for candesartan in plasma samples ranged between 4.7% and 7.5%, and −3.4% and 7.1%, respectively.

In the amlodipine assay, chromatography (Waters Acquity UPLC™ System) was performed with a Waters Acquity UPLC®BEH C18 column (1.7 µm, 2.1×50 mm) while the column temperature was maintained at 30°C ± 5°C. The standards for amlodipine and the IS, amlodipine_d4 maleic acid salt, were provided by Hana Pharam Co., Ltd (Seoul, Korea) and Toronto Research Chemicals Inc., respectively. The mobile phase consisted of: (A) 0.1% (vol/vol) formic acid in distilled water and (B) 0.1% (vol/vol) formic acid in acetonitrile, under gradient condition was changed as follows: (A) 70% at 0.00 and 2.30 minutes; (A) 10% at 2.40 and 3.00 minutes; and (A) 70% at 3.10 and 3.50 minutes. Detection of candesartan was conducted by a Waters Xevo™ TQ-S Mass Spectrometer (Waters Corporation) with a positive electrospray ionization multiple reaction monitoring mode set to transmit at m/z 409.23 → 238.15 and 413.23 → 238.15 for amlodipine and the internal standard, respectively. The assay was linear in the concentration ranges of 0.05–50 µg/L and the lower limit of quantification was 0.05 µg/L in the amlodipine assay. Plasma (100 µL) was added to the IS working solution (amlodipine-d4 maleic acid salt, 10 µg of 20 µg/mL in 50% methanol [vol/vol]). The mixture sample was deproteinized by 250 µL volume of pure acetonitrile. Each 200 µL of the supernatant was diluted with 300 µL of 0.1% formic acid. The 20 µL of mixture was injected into the LC/MS/MS system. The intrabatch and interbatch precision for amlodipine in plasma samples was less than 3.0% and 6.0%, respectively. The intrabatch and interbatch accuracy for amlodipine in plasma samples ranged between −7.2% and −2.0%, and −2.0% and −0.7%, respectively.

Assessments

Noncompartmental analysis was used for the pharmacokinetics of candesartan and amlodipine. Under steady state conditions, the following pharmacokinetic parameters were determined using Phoenix WinNonlin 6.3 (Certara, St Louis, MO, USA): maximum concentration after drug administration (C_{max}); area under the concentration-time curve from time zero to the time of dosing interval of 24 hours (AUC_{τ}); time to reach C_{max} (t_{max}); terminal elimination

half-life ($t_{1/2}$); and the concentration at predose on Day 10 (C_{trough}). For evaluating the pharmacodynamics, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate (PR) were measured in sitting position at predose and 2, 4, 6, 8, 12, and 24 hours postdose on Day 10 as well as baseline on Day 1. Safety was assessed throughout the study by evaluating treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, physical examinations, and ECG. Particularly, BP decreased by more than expected in healthy subjects following a hypertensive drug administration was documented as a TEAE.

Statistical analysis

The pharmacokinetic parameters except t_{max} were log-transformed before analysis. The effect of co-administration of candesartan and amlodipine in comparison with each drug alone was analyzed using a linear mixed effects model. The statistical model included sequence, period and intervention as fixed factors, and subjects nested within sequence as a random factor. For C_{max} and AUC_{τ}, the geometric means ratios (GMR) and their 90% CI were obtained by back-transformation to the original scale to estimate an interaction effect. Lack of an interaction effect on the pharmacokinetics would be concluded if the 90% CIs of the GMRs were contained within 0.80 and 1.25 for both C_{max} and AUC_{τ}. The Wilcoxon signed-rank test was used to analyze the difference between interventions for t_{max}. As for SBP, DBP, and PR, maximum change from baseline and trend over time were compared using a linear mixed effects model for repeated measurements with first-order autoregressive covariance structure. Demographic characteristics were summarized using descriptive statistics and all pharmacokinetic parameters were summarized by intervention group. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA).

Based on the known pharmacokinetic profile of candesartan and amlodipine, the sample size of 20 subjects provided >90% power to discriminate 20% differences in exposures by pharmacokinetic equivalence test using a linear mixed effects model appropriate for a two-way crossover.

Results

Subjects

Twenty subjects in each part were enrolled and completed without any drop-out. The demographic characteristics of subjects are summarized in Table 2. Particularly, baseline vital signs were similar between interventions in each part.

Candesartan pharmacokinetics

Plasma candesartan levels reached a peak at about 5 hours, and then declined with half-lives of about 10 hours (Figure 1A). The pharmacokinetic parameters of candesartan with and without amlodipine are presented in Table 3. The 90% CIs of the GMR for C_{max} and AUC_{τ} were contained within the predefined limits of 0.80–1.25. There was no statistically significant difference in t_{max}, $t_{1/2}$, and C_{trough} following co-administration of candesartan and amlodipine compared to candesartan alone (Table 3).

Amlodipine pharmacokinetics

Plasma amlodipine levels reached a peak at 6 hours, and then declined with half-lives of about 50 hours (Figure 1B). The pharmacokinetic parameters of amlodipine by intervention group are presented in Table 3. The 90% CIs of the GMR for C_{max} and AUC_{τ} were contained within the predefined limits of 0.80–1.25. There was no statistically significant difference in t_{max}, $t_{1/2}$, and C_{trough} following co-administration of candesartan and amlodipine compared to amlodipine alone (Table 3).

Table 2 Demographic and baseline characteristics of subjects

Variable	Part 1 (n=20)		Part 2 (n=20)	
Age (year)	30±7		31±8	
Weight (kg)	73.3±7.5		69.6±8.1	
Height (cm)	174.9±5.3		175.5±5.0	
Body mass index (kg/m^2)	24.0±2.3		22.6±2.4	
	Amlodipine + candesartan	**Candesartan**	**Candesartan + amlodipine**	**Amlodipine**
Systolic blood pressure (mmHg)	125.0±8.2	128.7±9.5	124.4±12.1	123.9±12.0
Diastolic blood pressure (mmHg)	76.0±7.3	75.0±7.0	72.8±8.8	71.7±7.8
Pulse rate (beats/min)	69.0±8.9	67.5±8.2	66.9±7.9	67.8±10.1

Note: Values are presented as arithmetic mean ± SD.

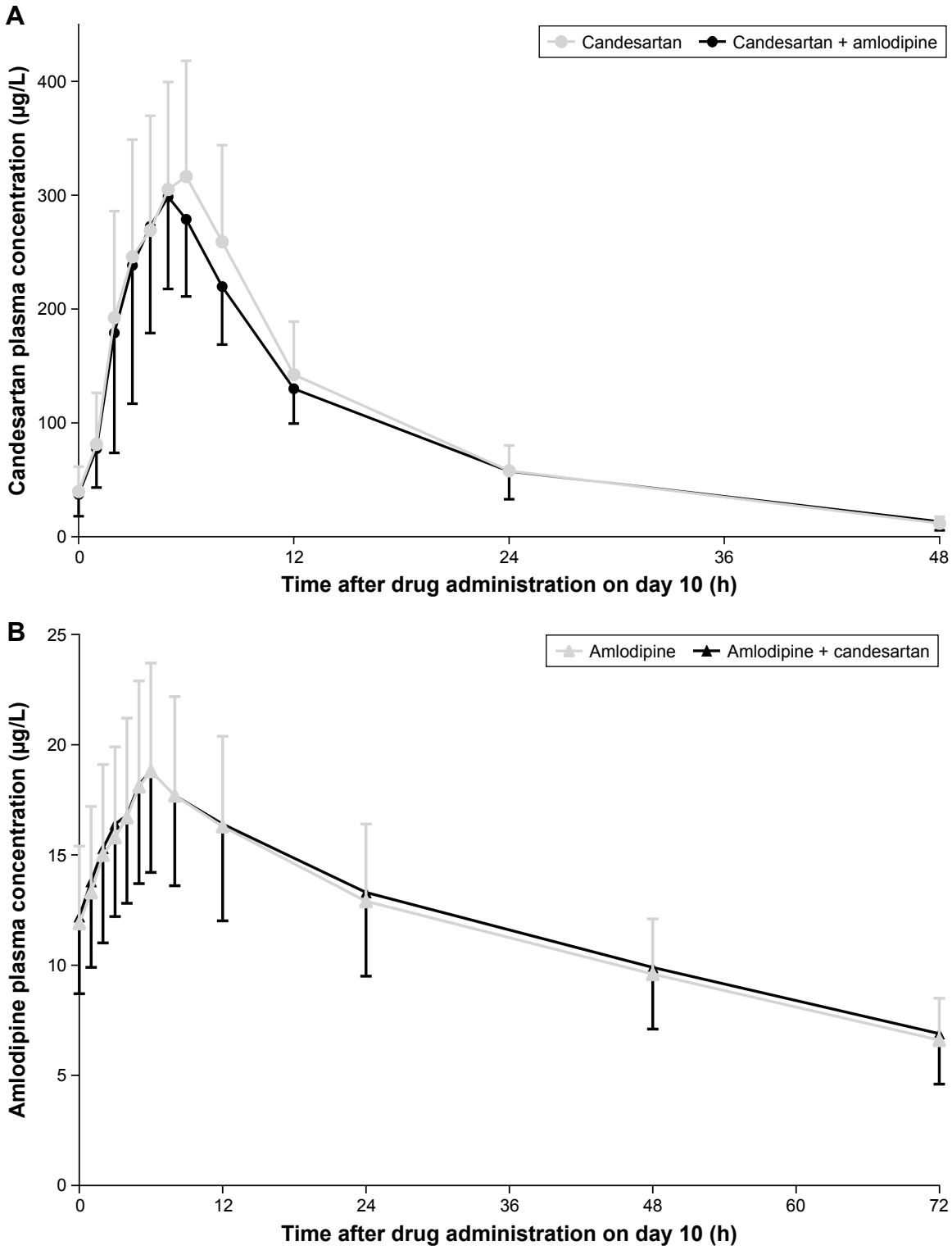

Figure 1 Mean (standard deviation) plasma concentration-time profiles of (**A**) candesartan and (**B**) amlodipine following multiple doses of the two drugs in the absence and presence of each other in healthy subjects.

Blood pressure and pulse rate

Candesartan, alone and in combination with amlodipine, showed similar profiles for the maximum change from baseline, although DBP was more decreased after combination with amlodipine than candesartan alone (Table 4). The maximum change in SBP and DBP on Day 10 were –19.5, –15.7 for amlodipine alone and –26.4, –21.3 for co-administration, respectively, and this difference reached statistical significance.

Table 3 Pharmacokinetic parameters following multiple doses of candesartan 32 mg and amlodipine 10 mg in the absence and presence of each other in healthy subjects

Variable	Geometric LSM (% CV)		GMR	90% CI	
	Combination	Alone		Lower	Upper
Candesartan					
AUC_{τ} (h·μg/L)	3,379.8 (23.8)	3,605.2 (28.0)	0.9375	0.8592	1.0229
C_{max} (μg/L)	303.7 (29.5)	330.7 (27.8)	0.9186	0.8126	1.0384
$t_{1/2}$ (h)	10.1 (28.3)	9.3 (29.5)			
C_{trough} (μg/L)	33.5 (51.5)	34.7 (55.0)			
t_{max} (h)[a]	5.0 (3.0–8.0)	5.5 (3.0–6.0)			
Amlodipine					
AUC_{τ} (h·μg/L)	366.4 (25.8)	361.2 (25.4)	1.0146	0.9747	1.0562
C_{max} (μg/L)	18.6 (24.2)	18.4 (25.7)	1.0128	0.9744	1.0528
$t_{1/2}$ (h)	48.0 (16.1)	46.3 (16.6)			
C_{trough} (μg/L)	11.7 (29.2)	11.3 (29.7)			
t_{max} (h)[a]	6.0 (5.0–8.0)	6.0 (2.0–12.0)			

Note: [a]Values are presented as median (range).
Abbreviations: LSM, least squares mean; CV, coefficient of variation; GMR, geometric mean ratio; AUC, area under the curve.

Trends over time in vital signs on Day 10 are shown in Figure 2. As with the maximum change from baseline, there were significant differences in SBP and DBP between amlodipine alone and in combination with candesartan. For PR, however, any differences were not shown between interventions in both parts.

Safety

No serious TEAE was reported throughout the study, and all TEAEs were mild to moderate in severity and were recovered without sequelae. None of subjects discontinued the study due to TEAEs. Although more subjects experienced low DBP when administered candesartan in combination with amlodipine, there was no apparent difference in TEAE profiles between interventions in each part (Table 5).

Discussion

For the treatment of hypertensive patients, a rational combination of two antihypertensive drugs with different modes of action may be complicated by their drug–drug interactions. This study was performed to determine the potential for a drug interaction between candesartan and amlodipine in healthy subjects.

The present study demonstrated that amlodipine did not influence the rate and extent of candesartan absorption at steady state. In addition, the pharmacokinetics of amlodipine was not affected by multiple oral administrations of candesartan. Several studies have investigated pharmacokinetic interactions between ARBs and amlodipine. Multiple co-administrations of olmesartan 20 mg and amlodipine 5 mg,[14] valsartan 320 mg and amlodipine 10 mg,[15] and fimasartan 120 mg and amlodipine 10 mg[16] did not show any clinical relevant change in the systemic exposure of both ARBs and amlodipine. Similar results were observed when S-amlodipine, an enantiomer of amlodipine, was co-administered with telmisartan.[17] It should be noted that candesartan showed the relatively smallest degree of alteration in the pharmacokinetics of amlodipine among ARBs.

Table 4 The maximum change from baseline (CFB) in vital signs on Day 10 after co-administration of candesartan 32 mg and amlodipine 10 mg and after administration of each drug alone in healthy subjects

Variable	Combination	Alone	Difference (95% CI)	*p*-value
Part 1 (candesartan)				
Maximum CFB in SBP (mmHg)	–26.2	–25.8	–0.5 (–3.6~2.7)	0.7642
Maximum CFB in DBP (mmHg)	–23.6	–22.0	–1.5 (–2.8~–0.3)	0.0176
Maximum CFB in PR (beats/min)	6.4	6.2	0.2 (–3.2~3.5)	0.9232
Part 2 (amlodipine)				
Maximum CFB in SBP (mmHg)	–26.4	–19.5	–6.9 (–11.4~–2.4)	0.0053
Maximum CFB in DBP (mmHg)	–21.3	–15.7	–5.6 (–8.7~–2.6)	0.0012
Maximum CFB in PR (beats/min)	2.0	1.7	0.3 (–4.2~4.8)	0.8964

Note: Values are least squares means.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.

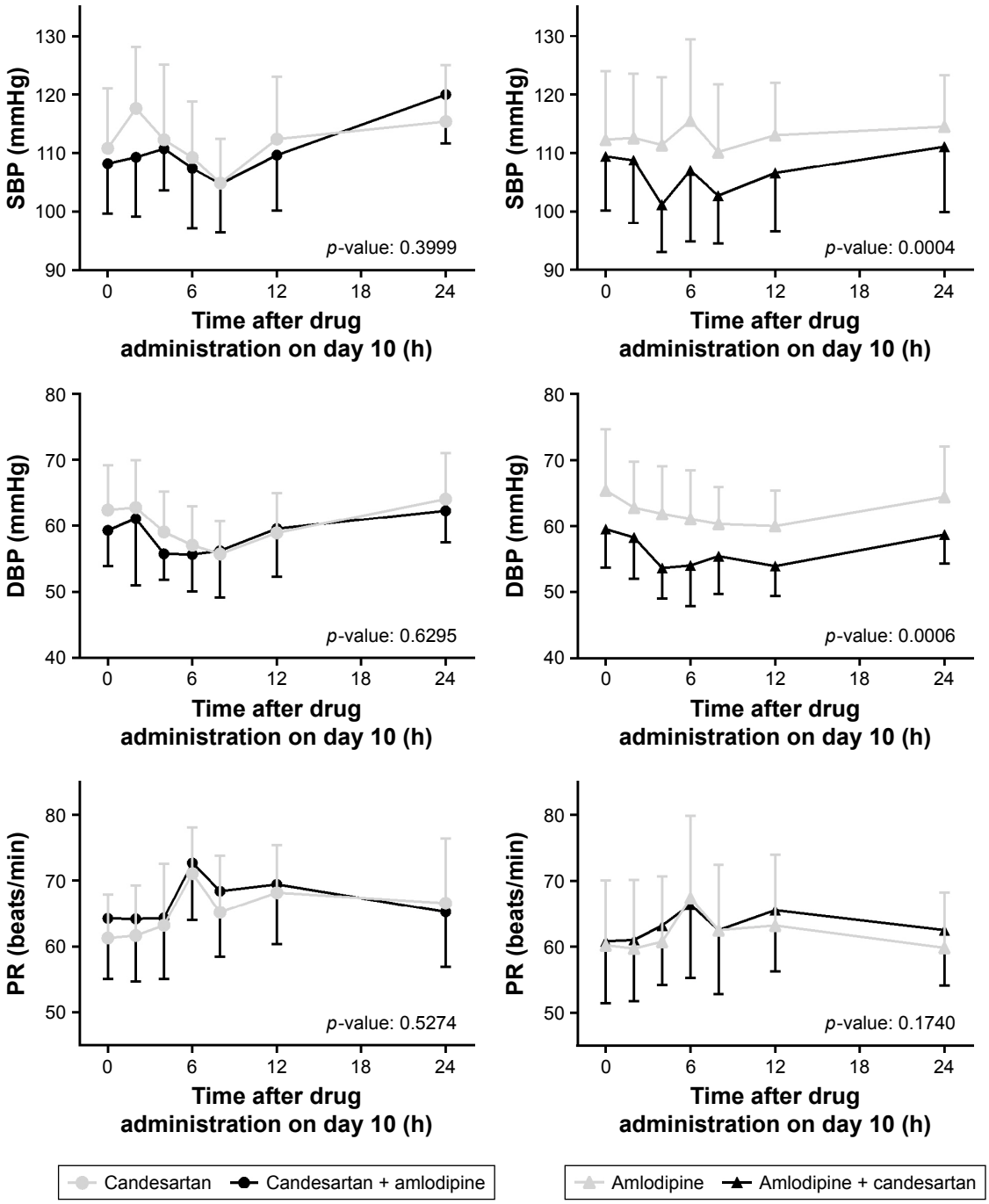

Figure 2 Trends over time in vital signs after co-administration of candesartan 32 mg and amlodipine 10 mg and after administration of each drug alone in healthy subjects (left panel: part 1, right panel: part 2).
Abbreviations: DBP, diastolic blood pressure; PR, pulse rate; SBP, systolic blood pressure.

The lack of pharmacokinetic interactions between candesartan and amlodipine can be attributed partly to their different disposition pathways. Candesartan is eliminated by renal and biliary excretion,[11] while CYP enzymes, mainly CYP3A4, are involved in amlodipine metabolism.[10] There are few drugs that affected the systemic exposure of amlodipine, except CYP3A4 inhibitors.[10] Candesartan has no effects on CYP enzymes at therapeutic concentrations,[11] meaning candesartan is not considered as a CYP3A4 inhibitor. In addition, P-glycoprotein (P-gp) is well known to play a significant role in drug absorption from the gastrointestinal lumen, indicating the modulation of P-gp can mediate drug–drug interactions.[18] Candesartan is reported as a P-gp substrate,[19] but amlodipine might be devoid of P-gp inhibiting

Table 5 Treatment-emergent adverse event (TEAE) profiles after co-administration of candesartan and amlodipine and after administration of each drug alone in healthy subjects

Symptom and sign	Combination (n=20)	Alone (n=20)
Part 1 (candesartan)		
Blood pressure diastolic decreased	3 (3)	2 (2)
Dizziness postural	1 (1)	2 (2)
Headache	2 (2)	–
Somnolence	2 (2)	–
Part 2 (amlodipine)		
Palpitations	1 (1)	1 (1)
Blood pressure diastolic decreased	6 (6)	–
Headache	1 (1)	4 (4)
Rhinorrhoea	–	2 (2)

Note: TEAEs that were reported at least twice are presented as number of subjects (number of events).

properties.[20] Therefore, significant pharmacokinetic alterations both in amlodipine by candesartan and in candesartan by amlodipine are unlikely.

Although this study was conducted in normotensive subjects, BP lowering effects were observed in all intervention groups. Furthermore, co-administration of candesartan and amlodipine reduced BP more than amlodipine alone, but similar to candesartan alone. In patients with essential hypertension, however, it was found that the combination therapy of candesartan and amlodipine for 8-weeks reduced a mean sitting DBP more than candesartan or amlodipine alone.[5] It should be noted that the administered dose in the present study was 32 mg candesartan, not 16 mg. Considering the short period of 10 days in normotensive subjects, the interaction effects on lowering BP need to be interpreted with caution.

Conclusion

To our knowledge, this study is the first to investigate the pharmacokinetic interactions between candesartan and amlodipine. Co-administration of candesartan and amlodipine did not change the systemic exposure of each drug alone in healthy subjects. The administration of candesartan 32 mg alone, amlodipine 10 mg alone, and co-administration of candesartan and amlodipine were well tolerated during the study.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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