Pharmacokinetic Comparison of 2 Fixed-Dose Combination Tablets of Amlodipine and Valsartan in Healthy Male Korean Volunteers: A Randomized, Open-Label, 2-Period, Single-Dose, Crossover Study

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ABSTRACT

Background: Amlodipine and valsartan have different mechanisms of action, and it is known that the combination therapy with the 2 drugs increases treatment effects compared with the monotherapy with each drug. A fixed-dose combination (FDC) drug is a formulation including fixed amounts of active drug ingredients combined in a single dosage form that is expected to improve medication compliance.

Objective: The goal of this study was to compare the pharmacokinetic profiles of single administration of a newly developed FDC tablet containing amlodipine orotate 10 mg and valsartan 160 mg (test formulation) with the conventional FDC tablet of amlodipine besylate 10 mg and valsartan 160 mg (reference formulation) in healthy male Korean volunteers.

Methods: This was a randomized, open-label, single-dose, 2-way crossover study. Eligible subjects were between the ages of 20 and 50 years and within 20% of their ideal weight. Each subject received a single dose of the reference and the test formulations, with a 14-day washout period between formulations. Blood samples were collected up to 144 hours after the dose, and pharmacokinetic parameters were determined for amlodipine and valsartan. Adverse events were evaluated based on subject interviews and physical examinations.

Results: Forty-eight of the 50 enrolled subjects completed the study. For both amlodipine and valsartan, the primary pharmacokinetic parameters were included in the range for assumed bioequivalence, yielding 90% CI ratios of 0.9277 to 0.9903 for AUC_{0-last} and 0.9357 to 1.0068 for C_{max} in amlodipine, and 0.9784 to 1.1817 for AUC_{0-last} and 0.9738 to 1.2145 for C_{max} in valsartan. Dizziness was the most frequently noted adverse event, occurring in 4 subjects with the test formulation, followed by oropharyngeal pain occurring in 1 subject with the test formulation and 3 subjects with the reference formulation. All other adverse events occurred in <3 subjects.

Conclusions: These findings suggest that the pharmacokinetics of the newly developed FDC tablet of amlodipine and valsartan did not differ significantly from the conventional FDC tablet in these healthy Korean male subjects. Both formulations were well tolerated, with no serious adverse events observed. ClinicalTrials.gov identifier: NCT01823913. (*Clin Ther.* 2013;35:934–940)

Key words: amlodipine, combination drug, pharmacokinetic, valsartan.

INTRODUCTION

Data from the National Health and Nutrition Examination Survey 2005 to 2008 reported that $>30\%$ of US citizens aged >20 years have high blood pressure.[1] According to a national survey conducted in Korea in 2011, the medical cost associated with

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hypertension treatment ranked highest among common diseases.[2] Hypertension is known as one of the major risk factors for coronary heart disease, the incidence of which can be reduced through proper management of blood pressure.[3] The World Health Organization suggests that people with systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg begin treatment, because even low-risk patients with marginally elevated blood pressure are likely to benefit from proper medical intervention.[4] Amlodipine*, a class of dihydropyridines, blocks calcium influx into vascular smooth muscle and cardiac muscle, resulting in a decrease in peripheral vascular resistance.[5] Valsartan* selectively inhibits the binding of angiotensin II to the angiotensin I receptor in many tissues, including vascular smooth muscle and the adrenal gland, and blocks vasoconstriction and aldosterone-secreting effects of angiotension II, thereby reducing blood pressure.[6] Because these 2 agents have different mechanisms of action, combination therapy with amlodipine and valsartan can have synergistic effects, especially in patients with poorly controlled hypertension. According to the review article by Frampton et al,[7] combination therapy with amlodipine and valsartan more effectively reduced mean seated systolic and diastolic blood pressure than either amlodipine or valsartan given alone. Furthermore, it was well tolerated, displaying less frequent adverse events (AEs) such as peripheral edema and headache than amlodipine monotherapy. The recent study by Karpov et al[8] also reported the effectiveness of the combination of amlodipine and valsartan in 8336 patients who were suffering from high blood pressure. Irrespective of such evidence, however, an additional pill to take can significantly decrease medication compliance. Regarding such practicality, a fixed-dose combination (FDC) tablet comprising amlodipine besylate and valsartan in a single dosage form may be a more efficient treatment option than coadministration of each drug in a separate dose. This agent is available in different FDC formulations: 5 mg/160 mg, 10 mg/160 mg, and 5 mg/320 mg and 10/320 mg of amlodipine besylate and valsartan, respectively.[9]

*Trademark: Exforge® (Novartis Pharmaceuticals Co, Ltd, Basel, Switzerland; lot number B1004; expiration date, July 2014).

*Trademark: G-0081 (Dong-A ST Co, Ltd, Seoul, Korea; lot number 1206002; expiration date, September 2012).

Recently, a new FDC tablet including amlodipine orotate 10 mg and valsartan 160 mg was developed. The current study was designed to compare the pharmacokinetic properties and tolerability of the newly developed FDC tablet with those of the conventional FDC tablet of amlodipine besylate 10 mg and valsartan 160 mg in healthy male Korean subjects.

SUBJECTS AND METHODS

Subjects

Eligible subjects were healthy male volunteers between the ages of 20 and 50 years and within 20% of their ideal body weight, with no congenital abnormality or chronic disease. Key exclusion criteria included history of hypersensitivity to amlodipine or valsartan; history of cardiovascular, pulmonary, renal, endogenous, gastrointestinal, hematologic, neurologic, or hemorrhagic disease; clinically significant findings on routine laboratory tests (serology, hematology, serum chemistry, and urinalysis); hypotension (systolic blood pressure ≤100 mm Hg or diastolic blood pressure ≤65 mm Hg) or hypertension (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥100 mm Hg); use of prescription drugs or herbal medications within 2 weeks or use of nonprescription drugs within 1 week before the study that had the potential to interact with amlodipine or valsartan; and use of drugs that induce or inhibit drug-metabolizing enzymes within 1 month before the study that had the potential to interact with study medications.

This study was approved by the institutional review board of Yonsei University Severance Hospital (Seoul, Korea) and performed in accordance with the Declaration of Helsinki[10] and Korean Good Clinical Practice.[11] All subjects gave written informed consent before study enrollment.

Study Design

This was a randomized, open-label, single-dose, 2-way crossover study. Subjects were randomly assigned into 2 groups according to a computer-generated randomization scheme (Compaq Visual Fortran 11.1; IMSL Fortran Library, Compaq Computer Corporation, Houston, Texas) and received the test and the reference formulations alternatively. The reference formulation was a single dose of the FDC tablet containing amlodipine besylate 10 mg and valsartan 160 mg and the test formulation was a single dose of the FDC tablet containing amlodipine orotate 10 mg and valsartan 160 mg.

The subjects in group 1 received the reference formulation in period 1 and the test formulation in period 2, and those in group 2 vice versa, with a 14-day washout period between periods 1 and 2. According to the guidelines of the Korea Food and Drug Administration (KFDA), after an overnight fast of 10 hours, subjects received the reference or the test formulation orally with 240 mL of water at 8 AM.[12] Subjects were prohibited from drinking water for 2 hours after drug administration. Standard meals containing ~700 kcal (carbohydrate, 60%; protein, 16%; and fat, 24%) were provided for lunch and dinner to both groups at 4 and 10 hours after the dose, respectively.

Blood Sampling

Venous blood samples were collected into K_2EDTA-containing tubes by an indwelling catheter inserted into the forearm at 0 (predose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96, 144, and 192 hours after the dose for the test and the reference drugs. Blood samples up to 48 hours were collected (6 mL each) for plasma concentration analysis of both amlodipine and valsartan and those sampled from 72 hours to 192 hours were collected (4 mL each) for plasma concentration analysis of amlodipine only.

Before collecting each blood sample, 1 mL of blood was drawn from the catheter and discarded. After each blood sample was drawn, 1 mL of normal saline was injected into the catheter. Separated via centrifugation (3500 rpm for 10 minutes) within 30 minutes after sampling, plasma samples were transferred to polyethylene tubes and stored at −70°C until assayed.

Bioanalysis

Plasma amlodipine and valsartan concentrations were analyzed by BioInfra Co, Ltd (Suwon, Korea) by using a validated UPLC-MS/MS method. Plasma (100 μL) was added to the internal standard (for amlodipine, amlodipine-d_4 maleic acid salt, 10 μL of 0.0200 μg/mL in 50% methanol [vol/vol]; for valsartan, valsartan-d_3, 10 μL of 20.0 μg/mL in 50% methanol [vol/vol]) and was agitated at 1500 rpm for 3 minutes and centrifuged at 4000 rpm for 1 minute; 250 μL (amlodipine) and 400 μL (valsartan) of acetonitrile were then added. After mixing at 1500 rpm for 3 minutes, the mixture was centrifuged at 4000 rpm for 1 minute. The supernatant 200 μL (amlodipine) and 200 μL (valsartan) of the mixture was transferred in a 96-well round plate 1-mL master block. After adding 0.1% (vol/vol) formic acid to D.W. 300 μL (amlodipine) and 350 μL (valsartan), the diluted sample was agitated at 1500 rpm for 3 minutes and centrifuged at 4000 rpm for 1 minute.

For the sample analysis, chromatography was performed by using ACQUITY UPLC Systems (Waters Corporation, Milford, Massachusetts) with separation on an ACQUITY UPLC BEH C18, 1.7 μm (2.1 × 50 mm; Waters Corporation). 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. The mobile phase in UPLC under gradient condition of amlodipine 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. The mobile phase in UPLC under isocratic condition of valsartan was (A) 55%. The flow rate was 0.5 mL/min for amlodipine and 0.4 mL/min for valsartan, and mean column and sample tray temperatures were set at 30 (±5)°C and 15 (±5)°C for both agents, respectively. Detection and quantification were achieved by using XevoTQ-S MS mass spectrometer for amlodipine and Micromass Quattro micro API mass spectrometer (both, Waters Corporation) for valsartan with electrospray ionization interface in positive mode. Nitrogen was used as the cone gas/desolvation gas. The UPLC-MS/MS system was controlled by using MassLynx software (version 4.1, Waters Corporation), and the results were processed by using Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, Washington). A linear calibration curve was established in the range of 0.0500 to 50.0 ng/mL for amlodipine and 50.0 to 10,000 ng/mL for valsartan.

Pharmacokinetic Analysis

The plasma concentration–time profiles of amlodipine and valsartan of each subject were analyzed by a noncompartmental method using WinNonlin 5.3 (Pharsight Corporation, Mountain View, California). Pharmacokinetic parameters evaluated were AUC_{0-last}, C_{max}, $AUC_{0-\infty}$, T_{max}, and $t_{½}$ of amlodipine and valsartan. AUC_{0-last} was calculated by using the linear trapezoidal rule, $AUC_{0-\infty}$ as $AUC_{0-last} + (C_{0-last}/\lambda_z)$, where C_{0-last} was the last quantifiable concentration and λ_z the terminal elimination rate constant; and $t_{½}$ as $0.693/\lambda_z$. C_{max} and T_{max} were determined by searching the observed data. The primary parameters of interest were C_{max} and AUC_{0-last} of amlodipine and valsartan. All analyses were performed by using actual times of sampling rather than scheduled times.

Tolerability Assessments

Tolerability was assessed by evaluating AEs, vital signs (blood pressure, body temperature, and pulse rate), laboratory tests (hematology, blood chemistry, and urinalysis), 12-lead ECG examination, and physical examination. Laboratory tests and physical examination were evaluated at baseline and at 24 and 192 hours after the dose in each period and at follow-up visits, with blood pressure and pulse rate being additionally evaluated at 1, 2, 4, 8, and 12 hours after drug administration. ECG examination was performed at baseline and 192 hours after dosing. The hematology test evaluated white blood cell (WBC), red blood cell count, hemoglobin, hematocrit, platelet, differential count of WBC (neutrophil, lymphocyte, monocyte, eosinophil, and basophil); the blood chemistry test evaluated calcium, inorganic phosphate, fasting glucose, blood urea nitrogen, creatinine, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, creatine kinase, lactate dehydrogenase, triglycerides, potassium, sodium, and chloride; and the urinalysis evaluated specific gravity, pH, protein, glucose, ketone, red blood cell, urobilinogen, bilirubin, nitrite, WBC, color, turbidity, sediment, and microscopy. Based on subject interviews and physical examinations, any unfavorable sign (including an abnormal laboratory finding) or symptom, regardless of whether it was causally related to the study medication, was defined as an AE and recorded on case-report forms.

Statistical Analysis

Assessment of comparative bioavailability was based on 90% CIs for geometric mean ratios (test to reference drug) for the primary pharmacokinetic parameters (C_{max} and AUC_{0-last}) of amlodipine and valsartan.

The 2 drugs were assumed to be bioequivalent, as defined by the KFDA, if 90% CIs for the treatment ratios of the primary parameters were within the range of 0.8 to 1.25.[12,13]

RESULTS

Study Subjects

A total of 50 healthy subjects were enrolled in the study. The sample size of 50 was obtained by the formulation used for a standard 2 × 2 crossover study,[14] on the assumption that type I and type II errors were 0.05 and 0.2, respectively; the dropout rate was 10%; and the intra-individual %CV of AUC_{0-last} and C_{max} was 32.35% according to the previous report.[15] Two of the 50 subjects withdrew after drug administration, 1 subject on day 3 of the first period, and the other in the washout period. Both subjects withdrew due to drinking alcohol, which was not allowed during the study. Thus, 48 subjects completed the study.

All subjects who were administered the study drug were included in the tolerability assessments, and only subjects who completed the blood sampling as scheduled were included in the pharmacokinetic analysis. Demographic characteristics of the enrolled subjects are summarized in Table I.

Pharmacokinetics

The mean (SD) plasma concentration–time profiles of amlodipine and valsartan after the test and the reference drugs are depicted in the Figure, and the pharmacokinetic parameters of amlodipine and valsartan are compared between the 2 formulations in

Table I. Demographic characteristics of the study subjects.

Characteristic	Group 1 (n = 25)	Group 2 (n = 25)
Age, y		
Mean (SD)	27.2 (6.6)	26.3 (5.4)
Range	20–45	20–41
Weight, kg		
Mean (SD)	67.5 (7.9)	69.6 (7.3)
Range	53.5–85.0	55.2–83.0
Height, cm		
Mean (SD)	174.2 (6.2)	174.4 (3.7)
Range	163.6–185.2	165.1–182.5
Smoking, no. (%)		
Smoker	7 (28)	14 (56)
Nonsmoker	18 (72)	11 (44)
Alcohol drinking, no. (%)		
Drinker	18 (72)	15 (60)
Nondrinker	7 (28)	10 (40)
Caffeine user, no. (%)		
Yes	13 (52)	10 (40)
No	12 (48)	15 (60)

Group 1 = received the reference formulation in period 1 and the test formulation in period 2;
Group 2 = received the test formulation in period 1 and the reference formulation in period 2.

Table II. The 90% CIs for the geometric mean ratio of the primary parameters were all within the comparative bioavailability range of 0.8 to 1.25 to assume bioequivalence of amlodipine and valsartan, yielding 90% CI ratios of 0.9277 to 0.9903 and 0.9784 to 1.1817 for AUC_{0-last} and 0.9357 to 1.0068 and 0.9738 to 1.2145 for C_{max}, respectively. In addition, the 90% CIs for the geometric mean ratios of the secondary parameters of amlodipine and valsartan, were 0.9256 to 0.9909 and 0.9711 to 1.1670 for $AUC_{0-\infty}$, 0.9636 to 1.0095 and 0.9084 to 1.1197 for $t_{1/2}$, and 0.9851 to 1.0777 and 0.8877 to 1.1236 for T_{max}, respectively, indicating that all the secondary parameters were also included in the comparative bioequivalence range. When tested at the significance level of 0.05, the sequence effect was not significant in any of the parameters.

Tolerability

The test and the reference drugs were well tolerated in all subjects, and no serious AEs or drug reactions

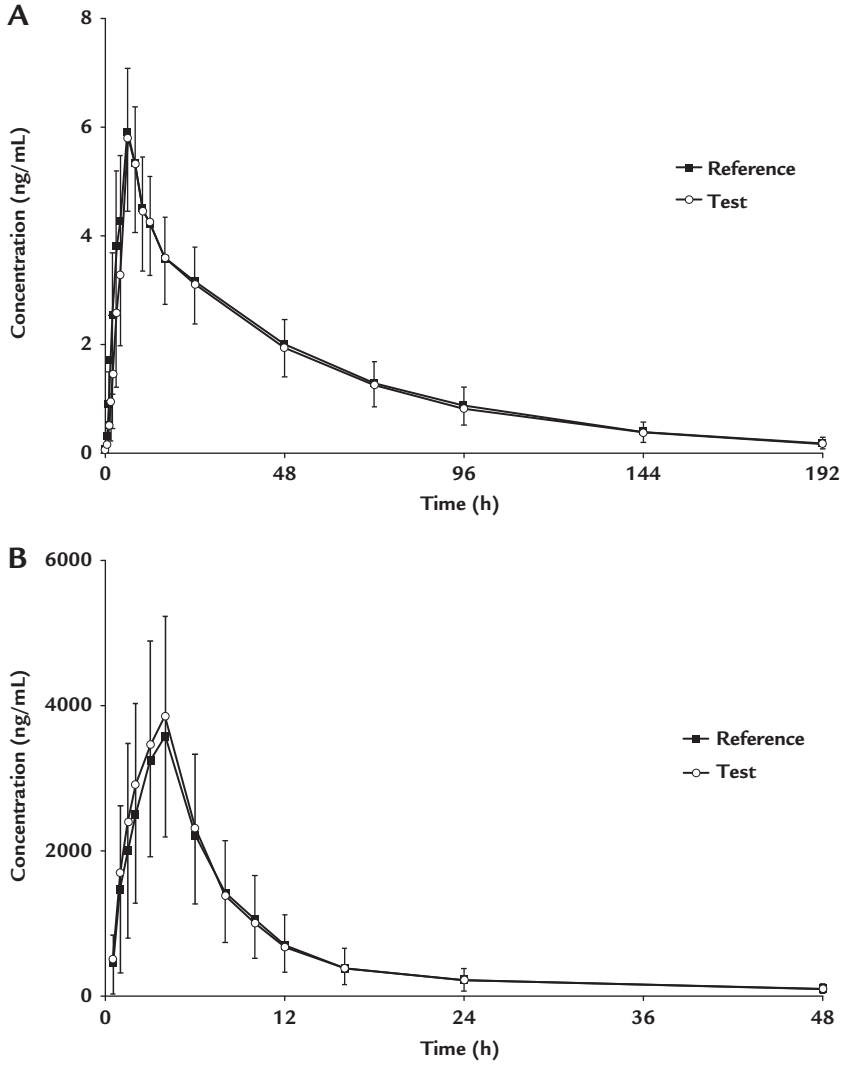

Figure. Mean (SD) plasma concentration–time profiles of (A) amlodipine and (B) valsartan after single-dose administration of the reference drug and the test drug. Reference drug = the fixed-dose combination tablet containing amlodipine besylate 10 mg and valsartan 160 mg (Exforge® [Novartis Pharmaceuticals Co, Ltd, Basel, Switzerland]); Test drug = the fixed-dose combination tablet containing amlodipine orotate 10 mg and valsartan 160 mg (G-0081 [Dong-A ST Co, Ltd, Seoul, Korea]).

Table II. Pharmacokinetic comparison of amlodipine and valsartan after single-dose administration of test and reference drugs.*

Substance	Geometric Mean		Geometric Mean Ratio (Test/Reference)		
	Test (n= 24)	Reference (n= 24)	% Ratio	90% CI	*P*
Amlodipine					
C_{max}, ng/mL†	5.75	5.92	0.9706	0.9357–1.0068	0.1775
AUC_{0-last}, ng · h/mL†	245.35	255.98	0.9585	0.9277–0.9903	0.0346
$AUC_{0-\infty}$, ng · h/mL†	255.44	266.73	0.9577	0.9256–0.9909	0.0385
$t_{1/2}$, h†	40.40	40.96	0.9863	0.9636–1.0095	0.3240
T_{max}, h†	6.62	6.42	1.0304	0.9851–1.0777	0.2694
Valsartan					
C_{max}, ng/mL†	4128.89	3796.73	1.0875	0.9738–1.2145	0.2087
AUC_{0-last}, ng · h/mL†	27346.26	25432.01	1.0753	0.9784–1.1817	0.2032
$AUC_{0-\infty}$, ng · h/mL†	28859.19	27109.18	1.0646	0.9711–1.1670	0.2592
$t_{1/2}$, h†	6.61	6.56	1.0085	0.9084–1.1197	0.8925
T_{max}, h†	2.91	2.92	0.9987	0.8877–1.1236	0.9857

Test drug = the fixed-dose combination tablet containing amlodipine orotate 10 mg and valsartan 160 mg (G-0081 [Dong-A ST Co, Ltd, Seoul, Korea]); Reference drug = the fixed-dose combination tablet containing amlodipine besylate 10 mg and valsartan 160 mg (Exforge® [Novartis Pharmaceuticals Co, Ltd, Basel, Switzerland]).
*Subjects who withdrew were excluded from the analysis.
†WinNonlin bioequivalence test (Pharsight Corporation, Mountain View, California).

occurred. Dizziness was the most frequently noted AE, occurring in 4 subjects with the test drug, followed by oropharyngeal pain (1 with the test drug and 3 with the reference drug). The other AEs were headache (2 with the test drug), ocular hyperemia, fatigue, feeling abnormal, injury associated with device, oral herpes, back pain, nasal congestion, and neurogenic shock (each occurred in 1 subject with the reference drug), and hordeolum, dyspepsia, toothache, neck pain, pain in extremity, cough, and rhinorrhea (each occurred in 1 subject with the test drug). All AEs were mild or moderate, with no serious AEs being observed. Most of the subjects who reported to have an AE recovered spontaneously within a few hours or a few days of drug administration. No clinically significant change was found in results of physical examinations, vital signs, laboratory tests, or ECG results when judged by clinicians (performed unmasked because it was an open-label study).

DISCUSSION

This study was conducted to compare the pharmacokinetic profiles and safety of a newly developed FDC tablet of amlodipine orotate 10 mg and valsartan 160 mg with the conventional FDC tablet containing amlodipine besylate 10 mg and valsartan 160 mg in healthy Korean male subjects. Pharmacokinetic analyses showed that the newly developed FDC tablet of amlodipine and valsartan was bioequivalent to the conventional FDC tablet of amlodipine and valsartan in this healthy population under the studied conditions, based on the KFDA's regulatory criteria for bioequivalence.

AEs were mild to moderate, and no serious AEs were reported. Among the subjects who withdrew from the study, none was for reasons considered by the investigators to be related to the study medication. The incidence of AEs was not significantly different between the 2 formulations.

As in most bioavailability and pharmacokinetic studies, this study has a limitation because it was conducted in a small number of healthy, young subjects selected with very narrow inclusion and exclusion criteria. More studies with larger number of subjects, including patients and the elderly, are needed.

CONCLUSIONS

The newly developed FDC tablet containing amlodipine orotate 10 mg and valsartan 160 mg did not significantly differ in pharmacokinetic profiles compared with the conventional FDC tablet containing amlodipine besylate 10 mg and valsartan 160 mg. The new FDC formulation met the criterion of assumed bioequivalence with the conventional FDC formulation in both amlodipine and valsartan. Both drugs were well tolerated in the study, with no serious AEs reported. These results indicate that the new FDC formulation can be used interchangeably with the conventional formulation.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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