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.