Pharmacokinetics of Rosuvastatin/Olmesartan Fixed-Dose Combination: A Single-Dose, Randomized, Open-Label, 2-Period Crossover Study in Healthy Korean Subjects

Hankil Son, MS[1,2]; Hyerang Roh, BS[1,2]; Donghwan Lee, MD[1,2]; HeeChul Chang, PhD[3]; JunKu Kim, MS[3]; Chohee Yun, BS[4]; and Kyungsoo Park, PhD, MD[1,2]

[1]*Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea;* [2]*Brain Korea 21 Project for Medical Science, Yonsei University, Seoul, Korea;* [3]*DDS Research Laboratory, Daewoong Pharmaceutical Co. Ltd., Seoul, Korea; and the* [4]*Medical Department, Daewoong Pharmaceutical Co. Ltd., Seoul, Korea*

ABSTRACT

Background: Rosuvastatin, a lipid-lowering agent, has been widely used with olmesartan, a long-acting angiotensin II receptor blocker, indicated for the treatment of dyslipidemia accompanied by hypertension. A fixed-dose combination (FDC) tablet of these 2 drugs was recently developed to enhance the dosing convenience and to increase patient compliance while yielding pharmacokinetic profiles comparable to coadministration of each drug as individual tablets.

Objective: The goal of present study was to compare the pharmacokinetic profiles of single-dose administration of an FDC tablet containing rosuvastatin/olmesartan 20/40 mg (test formulation) with coadministration of a rosuvastatin 20-mg tablet and a olmesartan 40-mg tablet (reference formulation) in healthy Korean male volunteers, for the purpose of determining bioequivalence.

Methods: This single-dose, randomized, open-label, 2-period crossover study enrolled subjects aged 20 to 50 years and within 20% of ideal body weight. Each subject received a single dose of the test and reference formulations orally in a fasted state, with a 7-day washout period between the administrations. Blood samples were collected up to 72 hours after dosing, and pharmacokinetic parameters were determined for rosuvastatin, its active metabolite (*N*-desmethyl rosuvastatin), and olmesartan. Bioequivalence was concluded if the 90% CIs of the geometric mean ratios for the primary pharmacokinetic parameters were within the predetermined range of 80% to 125%. Adverse events (AEs) were evaluated based on subject interviews and physical examinations.

Results: Among the 58 enrolled subjects, 54 completed the study. The 90% CIs of the geometric mean ratios of the primary pharmacokinetic parameters were as follows: rosuvastatin: AUC_{last}, 85.60% to 97.40% and C_{max}, 83.16% to 98.21%; *N*-desmethyl rosuvastatin: AUC_{last}, 82.08% to 93.45% and C_{max}, 79.23% to 93.41%; and olmesartan: AUC_{last}, 97.69% to 105.69% and C_{max}, 100.35% to 109.42%. The most frequently noted AE was headache, occurring in 3 and 6 patients with the test and reference formulations, respectively. All of the AEs were expected, and there was no significant difference in the prevalences of AEs between the 2 formulations.

Conclusions: The pharmacokinetic properties of the newly developed FDC tablet of rosuvastatin/olmesartan 20/40 mg suggest that it is bioequivalent to co-administration of each drug as individual tablets in these healthy Korean male subjects. The two formulations were well tolerated, with no serious AEs observed. ClinicalTrials.gov identifier: NCT01823900. (*Clin Ther.* 2013;35:915–922)

Key words: combination drug, dyslipidemia, hypertension, olmesartan, pharmacokinetics, rosuvastatin.

INTRODUCTION

Hypertension and dyslipidemia are highly prevalent chronic diseases in adults, the former characterized by

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elevated blood pressure in the circulatory system and the latter by elevated blood lipid levels. Dyslipidemia contributes to the buildup of plaque in the arteries, known as atherosclerosis, and is often accompanied by cardiovascular conditions, including hypertension. However, the cause of this association is still uncertain.[1] Because hypertension and dyslipidemia are both important risk factors for heart and vessel diseases, comorbidity from these conditions may increase the risk for ischemic or hemorrhagic stroke.[2]

Olmesartan is an angiotensin II receptor blocker (ARB) indicated for the treatment of hypertension.[3,4] The drug blocks the binding of angiotensin II to angiotensin II type 1 receptors in vascular muscle[5] and inhibits the negative regulatory feedback on renin secretion. As a result, aldosterone secretion is reduced, which lowers blood pressure by inducing vasodilation.

Rosuvastatin, a competitive inhibitor of HMG-CoA reductase ("statin"), is commonly used to treat hypercholesterolemia and to prevent cardiovascular disease.[6–8]

A regimen that combines a HMG-CoA reductase inhibitor (statin) and an ARB is well known for its synergistic vascular protective properties. Hence, statin + ARB has become one of the most commonly prescribed combinations, and the necessity of developing a fixed-dose combination (FDC) of statin/ARB has been gradually increasing.

An FDC is a formulation including fixed amounts of 2 or more active drug ingredients combined in a single dosage formulation.[9] Recently, many FDCs have been approved for the treatment of various diseases and disorders that require long-term therapy, such as hypertension and dyslipidemia. One example is amlodipine/atorvastatin,[10] which contains atorvastatin to treat hypercholesterolemia and amlodipine to treat hypertension. The advantages of FDCs include convenient prescription and consumption, improved medication compliance from reducing the pill burden of patients, and less expense compared with purchasing each ingredient drug separately.

In this context, the present study was designed to compare the single-dose pharmacokinetic properties and tolerability of a newly developed FDC tablet containing rosuvastatin 20 mg + olmesartan 40 mg to those of coadministration of each drug as individual tablets in healthy Korean male volunteers, for the purpose of determining bioequivalence.

SUBJECTS AND METHODS

Subjects

The enrolled subjects were healthy Korean male volunteers aged between 20 and 50 years who were within 20% of ideal body weight, with no congenital abnormalities or chronic diseases.

Exclusion criteria were as follows: a history of cardiovascular, pulmonary, renal, endogenous, gastrointestinal, hematologic, neurologic, or hemorrhagic disease; clinically significant findings on routine laboratory testing (serology, hematology, serum chemistry, and urinalysis) or 12-lead ECG; history of hypersensitivity reaction to rosuvastatin and/or olmesartan; or the use of prescription drugs within 14 days before the start of the study that could interact with rosuvastatin or olmesartan.

The study protocol was approved by the institutional review board of Yonsei University Severance Hospital (Seoul, Korea) and performed in accordance with the Declaration of Helsinki[11] and Korean Good Clinical Practice.[12] All subjects provided written informed consent before study enrollment.

Study Design

This single-dose, randomized, open-label, 2-period crossover study was conducted between January and March 2012. Eligible subjects were randomly assigned to 2 groups in a 1:1 ratio before the initiation of the study by a computer-generated randomization scheme (Compaq Visual Fortran 11.1; IMSL Fortran library, Compaq Computer Corporation, Houston, Texas) and received a single dose of the test and the reference formulations alternatively. The test formulation was an FDC tablet containing rosuvastatin 20 mg and olmesartan 40 mg.* The reference formulation was the coadministration of a rosuvastatin 20-mg tablet† and a olmesartan 40-mg tablet.‡

According to the guidance from the Korean Food and Drug Administration (KFDA) on bioequivalence studies for a single dose of an orally administered product,[15] the study was conducted as follows. The subjects in group 1 received a single dose of the reference drug in period 1 and a single dose of the test

*DWJ1276 (Daewoong Pharmaceutical Co., Ltd., Seoul, Korea; lot no. 964564; expiration date, March 2012).
†Trademark: Crestor® (AstraZeneca Co., Ltd., Södertälje, Sweden; lot no. HX714; expiration date, March 2013).[13]
‡Trademark: Olmetec® (Daiichi Sankyo Co., Ltd., Tokyo, Japan; lot no. 063724; expiration date, July 2013).[14]