Pharmacokinetic Interaction Between Rosuvastatin, Telmisartan, and Amlodipine in Healthy Male Korean Subjects: A Randomized, Open-label, Multiple-dose, 2-period Crossover Study

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ABSTRACT

Purpose: Rosuvastatin, a hydroxy methylglutaryl coenzyme A reductase inhibitor; telmisartan, an angiotensin receptor blocker; and amlodipine, a calcium channel inhibitor, are commonly prescribed together for the treatment of hypertension nonresponsive to monotherapy and accompanied by dyslipidemia. However, the pharmacokinetic interactions among these 3 substances are not well understood. The aim of this study was to investigate the pharmacokinetic drug–drug interactions among rosuvastatin, telmisartan, and amlodipine in a healthy Korean male population.

Methods: In both parts of this randomized, open-label, multiple-dose, 2-part, 2-period crossover study, subjects aged 19 to 55 years were enrolled. In part 1, each subject received rosuvastatin 20 mg with and without 2 fixed-dose combination (FDC) tablets of telmisartan/amlodipine 40/5 mg, once daily for 9 consecutive days. In part 2, each subject received 2 FDC tablets of telmisartan/amlodipine 40/5 mg with and without rosuvastatin 20 mg, once daily for 9 consecutive days. In both parts, there was a 13-day washout period between treatments. Pharmacokinetic samples were collected up to 72 hours after the last dose in subjects who received rosuvastatin only, and up to 144 hours after the last dose in subjects who received telmisartan/amlodipine with or without rosuvastatin. Adverse events (AEs) were assessed via interviews and physical examinations.

Findings: Forty-eight subjects were enrolled, of whom 19 in part 1 and 22 in part 2 completed the study. In Part 1, the 90% CIs of the geometric mean ratios (GMRs) (coadministration of rosuvastatin and telmisartan/amlodipine to monotherapy with rosuvastatin) of the primary pharmacokinetic parameters (AUC_{τ} and $C_{max,ss}$) were: rosuvastatin, 1.1436 to 1.3059 and 1.8970 to 2.3514, respectively; and *N*-desmethyl rosuvastatin, 0.8441 to 1.0200 and 1.1971 to 1.5457. In part 2, the 90% CIs of the GMRs (coadministration to monotherapy with telmisartan/amlodipine) were: telmisartan, 1.1204 to 1.4228 and 0.9940 to 1.5940; amlodipine, 0.9705 to 1.0636 and 0.9813 to 1.0779. There were no significant differences in the prevalences of AEs between the treatments, and all reported AEs were mild or moderate.

Implications: These results demonstrate that when rosuvastatin, telmisartan, and amlodipine are coadministered to healthy male subjects, pharmacokinetic exposure increases with respect to rosuvastatin and telmisartan, whereas no change occurs with respect to amlodipine. However, based on previous analyses, the degree of increase in the exposure observed was not regarded as clinically significant. All treatments were well-tolerated. (*Clin Ther.* 2016;38:1845–1857)

Key words: amlodipine, drug–drug interaction, pharmacokinetic properties, rosuvastatin, telmisartan.

Accepted for publication June 10, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.06.011
0149-2918/$ - see front matter

INTRODUCTION

Dyslipidemia, a disorder of lipoprotein metabolism, is a major risk factor for atherosclerosis that contributes to the risk for ischemic heart disease.[1] Rosuvastatin is a medicine widely used for treating dyslipidemia via the inhibition of the enzyme hydroxymethylglutaryl coenzyme A reductase.[2,3]

According to the World Health Organization, essential hypertension is a chronic condition characterized by elevated resting arterial blood pressures >140 mm Hg (systolic; SBP) and/or >90 mm Hg (diastolic; DBP).[4] Telmisartan, an angiotensin II receptor blocker, is given alone to control high blood pressure[5,6] or in combination with other antihypertensive agents, including amlodipine, a calcium channel blocker, when monotherapy with telmisartan is not effective.

Dyslipidemia and hypertension are common comorbidities[7] and both are involved in cardiovascular disease. Therefore, the combined treatment of hypertension and dyslipidemia has been recommended for over a decade.[8,9] However, when hypertension accompanied by dyslipidemia does not respond to a single medication, treatment usually involves a 3-drug combination of 1 antidyslipidemic agent and 2 antihypertensive agents.

Rosuvastatin, telmisartan, and amlodipine, which are investigated in this work, are among the medications widely prescribed in such 3-drug combination treatments, with known pharmacokinetic properties as follows. With rosuvastatin, ~10% of the absorbed amount is cleared via the urine; another 10% is metabolized by cytochrome P450 (CYP) 2C9 to its active metabolite, *N*-desmethyl rosuvastatin; and the rest is transported to the liver by organic anion-transporting polypeptides (OATPs) 1B1/1B3 and 2B1 and then is excreted to the bile by the actions of breast cancer resistance protein (BCRP), multidrug resistance protein 1 (MDR1), and multidrug resistance protein 2 (MRP2).[3,10–14] *N*-desmethyl rosuvastatin is known to have only one sixth to one half the pharmacologic effect of rosuvastatin.[15] As for telmisartan, its hepatic uptake and biliary excretion are associated with OATP1B3 and MRP2, and the biliary excretion of its metabolite telmisartan acylglucuronide, which is formed through a conjugation not involving CYP enzymes, is associated with BCRP, MDR1, and MRP2.[5,13,16–18] These transporters involved in the biliary excretion of telmisartan and its metabolite are also related to that of *N*-desmethyl rosuvastatin.[14] Amlodipine is extensively metabolized via CYP3A4, with only 5% to 10% renally excreted.[19,20] It has been reported that when amlodipine is coadministered with simvastatin, which is also metabolized via CYP3A4, simvastatin exposure increases as a consequence of the CYP3A4 inhibition effect of amlodipine.[19,21–24] The elimination half-lives of rosuvastatin, telmisartan, and amlodipine have been reported as ~19, 24, and 30 to 50 hours, respectively.[5,14,19] Thus, based on the pharmacokinetic characteristics of the 3 drugs, one can conjecture a potential interaction between telmisartan and rosuvastatin due to their common transporters OATP1B3, BCRP, MDR1, and MRP, but that there is no interaction between telmisartan and amlodipine or between rosuvastatin and amlodipine due to the lack of common enzymes/transporters involved. The potential interaction between telmisartan and rosuvastatin has been supported by data from our previous interaction study,[25] wherein the pharmacokinetic exposures of both drugs were increased when they were coadministered, whereas an interaction between telmisartan and amlodipine was not supported in studies reported elsewhere.[26,27] However, to the best of our knowledge, the pharmacokinetic influences between amlodipine and rosuvastatin have not been studied, nor have the pharmacokinetic interactions among the drugs when the 3 drugs are coadministered.

Given this background, the present study aimed to investigate the pharmacokinetic drug–drug interactions among rosuvastatin, telmisartan, and amlodipine in healthy Korean male volunteers.

SUBJECTS AND METHODS

Subjects

The enrolled subjects were healthy male volunteers aged between 19 and 55 years with a body mass index between 18 and 27 kg/m^2, with no congenital anomalies or chronic diseases. Exclusion criteria included a history of biliary, renal, gastrointestinal, cardiovascular, pulmonary, hematologic, neurologic, endocrine, musculoskeletal, psychiatric, and/or cancerous disease; clinically significant findings on clinical laboratory testing (serology, hematology, serum chemistry, and/or urinalysis) and/or 12-lead ECG; low blood pressure (SBP ≤100 mm Hg and/or DBP ≤65 mm Hg) or high blood pressure (SBP ≥150 mm Hg and/or DBP ≥100 mm Hg); low heart rate (≤40 beats/min) or high heart rate (≥100 beats/min); history of