Pharmacokinetic Comparison of Controlled-Release and Immediate-Release Oral Formulations of Simvastatin in Healthy Korean Subjects: A Randomized, Open-Label, Parallel-Group, Single- and Multiple-Dose Study

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ABSTRACT

Background: A controlled-release (CR) formulation of simvastatin was recently developed in Korea. The formulation is expected to yield a lower C_{max} and similar AUC values compared with the immediate-release (IR) formulation.

Objective: The goal of this study was to compare the pharmacokinetics of the new CR formulation and an IR formulation of simvastatin after single- and multiple-dose administration in healthy Korean subjects. This study was developed as part of a product development project at the request of the Korean regulatory agency.

Methods: This was a randomized, open-label, parallel-group, 2-part study. Eligible subjects were healthy male or female volunteers between the ages of 19 and 55 years and within 20% of their ideal weight. In part I, each subject received a single dose of the CR or IR formulation of simvastatin 40 mg orally (20 mg × 2 tablets) after fasting. In part II, each subject received the same dose of the CR or IR formulation for 8 consecutive days. Blood samples were obtained for 48 hours after the dose in part I and after the first and the last dose in part II. Pharmacokinetic parameters were determined for both simvastatin (the inactive prodrug) and simvastatin acid (the active moiety). An *adverse event* (AE) was defined as any unfavorable sign (including an abnormal laboratory finding) or symptom, regardless of whether it had a causal relationship with the study medication. *Serious AEs* were defined as any events that are considered life threatening, require hospitalization or prolongation of existing hospitalization, cause persistent or significant disability or incapacity, or result in congenital abnormality, birth defect, or death. AEs were determined based on patient interviews and physical examinations.

Results: Twenty-four healthy subjects (17 men, 7 women; mean [SD] age, 29 [7] years; age range, 22–50 years) were enrolled in part I, and 29 subjects (17 men, 12 women; mean age, 33 [9] years; age range, 19–55 years) were enrolled in part II. For simvastatin acid, C_{max} was significantly smaller (1.68 vs 3.62 ng/mL; $P < 0.013$) and T_{max} and apparent $t_{1/2}$ significantly longer (10.33 vs 4.04 hours [$P < 0.001$] and 11.41 vs 4.16 hours [$P < 0.011$]) for the CR formulation compared with the IR formulation, respectively, after the single-dose administration. After the multiple-dose administration, for simvastatin acid, the C_{max} for the CR formulation was significantly smaller (3.40 vs 5.16 ng/mL; $P < 0.037$), while the values for T_{max} and apparent $t_{1/2}$ were significantly longer (8.40 vs 4.57 hours and 13.09 vs 4.52 hours; both, $P < 0.001$) compared with the IR formulation. There was no significant difference between the CR and the IR formulations for AUC_{0-last} and $AUC_{0-\infty}$ during either the single- or multiple-dose testing. Both CR and IR formulations were well tolerated in all subjects, and no serious AEs or adverse drug reactions were found. No subjects reported any AEs during part I of the

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study. During part II, 6 subjects (3 from each formulation group) reported headache, 1 reported lumbago before the dose, and 1 subject had a hordeolum while receiving the CR formulation.

Conclusions: The C_{max} of the simvastatin CR formulation was found to be significantly smaller while the AUC of the active moiety did not differ significantly from that of the IR formulation in these healthy Korean subjects. The simvastatin CR and IR formulations were well tolerated, with no serious AEs observed. To evaluate the characteristics of the CR formulation, its clinical efficacy must be examined in patient populations. (*Clin Ther*. 2010;32:206–216) © 2010 Excerpta Medica Inc.

Key words: simvastatin, simvastatin acid, pharmacokinetics, controlled-release formulation.

INTRODUCTION

Simvastatin is a 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitor (ie, a statin) with beneficial effects on coronary diseases and mortality rates in patients with hypercholesterolemia.[1–5] It is administered as an inactive lactone prodrug and has 2 separate metabolic pathways. Oxidative biotransformation is one of the pathways mediated primarily by cytochrome P450 (CYP) 3A4,[6,7] and the hydrolyzation of simvastatin acid by carboxylesterases is another pathway that is nonenzymatically metabolized into an active competitive statin.[6–8] The simvastatin acid then reduces the amount of mevalonic acid, a precursor of cholesterol, thereby inhibiting de novo synthesis of cholesterol. Consequently, the synthesis of LDL receptors increases while cholesterol synthesis decreases, resulting in the increased clearance of LDL from the bloodstream.[8,9]

Most of the available statins, including simvastatin, were developed as immediate-release (IR) formulations.[10] Adverse reactions commonly reported with these formulations include upper respiratory tract infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).[8] Hepatotoxicity and myotoxicity are the most serious adverse events associated with the statins, with higher concentrations associated with a higher incidence of adverse events.[11–14] In addition, rhabdomyolysis and acute renal failure may be observed if myopathy is not recognized and administration of the drug is continued.[15,16] For the controlled-release (CR) formulation of lovastatin, a reduced peak concentration of the pharmacologically active components reportedly reduced the potential risk of adverse events.[14] Given the similar mechanism of action among statins, peak concentrations of simvastatin would be expected to be related to the incidence of adverse events.

The currently available CR formulations of the statins are designed to deliver drugs to the liver efficiently, in a more sustained manner than other conventional IR formulations. [17] It has been hypothesized that the CR formulations would avoid the saturation of oxidative biotransformation without sudden elevation of systemic drug concentrations.

In this study, the simvastatin 20-mg CR formulation, which was recently developed in Korea, was used as the test drug and the simvastatin 20-mg IR formulation was used as the reference drug. The goal of the present study was to compare the pharmacokinetics of the new CR formulation and an IR formulation of simvastatin after single- and multiple-dose administration in healthy Korean subjects. This study was developed as part of a product development project at the request of the Korean regulatory agency.

SUBJECTS AND METHODS

Subjects

Eligible subjects were healthy male or female volunteers between the ages of 19 and 55 years and within 20% of their ideal weight. Demographic data and a medical history were obtained, and physical examinations and routine laboratory (hematology, blood biochemistry, and urinalysis) and ECG tests were conducted.

Exclusion criteria included a history of cardiovascular, hepatic, renal, hematogenous, or pulmonary disorders; the use of any medication within 14 days before the study that had the potential to interact with the study medication and influence the study results (eg, verapamil, diltiazem, propranolol); or the use of any substance that could induce CYP3A4 synthesis (eg, St. John's wort, other herbal medications).

Female subjects were required to have a negative result on a serum pregnancy test before the study. They had to be of nonchildbearing potential or practicing a medically accepted method of contraception, including abstinence, documented tubal ligation at least 1 year before enrollment in the study, documented placement of an intrauterine device with

a proven failure rate of <1% per year, or double-barrier methods (a spermicide plus a male condom or female diaphragm).

All subjects were informed of the objectives and risks of the study, and gave written informed consent before study participation. The study was approved by the institutional review board of Yonsei University Severance Hospital (Seoul, Korea) and performed according to the Declaration of Helsinki (KFDA-Clinical-4186).

Study Design

This was a randomized, open-label, parallel-group study conducted in 2005. It comprised 2 parts: a single-dose phase (part I) and a multiple-dose phase (part II). The 2 parts of the study were conducted in sequence. A computer-generated randomization scheme (Compaq Visual Fortran version 6.5, IMSL Fortran library, Compaq Computer Corporation, Houston, Texas) was used to assign enrolled subjects to the test and reference groups in a 1:1 ratio for each part.

The simvastatin CR formulation of 20 mg was used as the test drug (developed by Hanmi Pharmaceutical Co., Ltd. [Gyeonggi-do, Korea][18]; lot number SCRC-001; batch date, 2005; expiration date, March 24, 2006), and the simvastatin IR formulation of 20 mg was used as the reference drug (developed by Merck Sharpe & Dohme [Whitehouse Station, New Jersey][19]; lot number 05139; batch date, 2005; expiration date, April 12, 2008).

Part I

After a 10-hour overnight fast, subjects received the test or the reference formulation orally (20 mg × 2 tablets) with 240 mL of water at 7 AM. Subjects were not permitted to lie down for 4 hours after dosing, and water intake was prohibited during the first 2 hours postdose. Standardized meals (2100 kcal/d; 300 g of carbohydrates, 95 g of protein, and 55 g of fat)[20] were served 5 and 11 hours after dosing.

Part II

The reported $t_{1/2}$ of the IR formulation of simvastatin ranges from 1.9 to 15.6 hours.[21] Assuming that the $t_{1/2}$ of the CR formulation of simvastatin is greater than or approximately the same as the largest value reported for the IR formulation (ie, 15.6 hours), the required length of the multiple-dose phase of the study was initially estimated to be ~3 days (~5 × 15.6 hours). Given the large interindividual variation of simvastatin (48% in CV), we further assumed that the required length of the multiple-dose phase could be as long as 6 days, twice the initial estimation. Finally, to schedule both the first and second pharmacokinetic samplings on the same day of the week for practical reasons, the length of the multiple-dose phase was fixed at 8 days.

On day 1, subjects received the test or the reference formulation orally (20 mg × 2 tablets) at 7 AM after a 10-hour overnight fast. Subjects were then given the same formulation at 7 AM for 7 consecutive days (with no overnight fasting). On day 8, after an overnight fast of 10 hours, subjects received the same formulation at 7 AM as a last dose. For days 1 and 8, subjects were not permitted to lie down for 4 hours after the dose, water intake was allowed from 2 hours postdose, and standardized meals (identical to those in part I of the study) were served 5 and 11 hours postdose.

Blood Sampling

Blood samples of 8 mL each were prepared in sodium heparin–containing tubes by using an indwelling venous catheter before and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 13, 17, 24, 36, and 48 hours after the dose in part I or after the first dose (day 1) and the last dose (day 8) in part II. Before collection of each blood sample, 2 mL of blood was drawn from the catheter and discarded. After each blood sample was drawn, 2 mL of normal saline was injected into the catheter. Plasma samples were put on ice after collection and were separated via centrifugation (2600*g* at 4°C for 10 minutes) within 30 minutes after sampling and stored at –20°C until assayed.

Bioanalysis

Plasma samples were analyzed to determine concentrations of simvastatin and simvastatin acid by the validated HPLC-MS/MS method.[22,23] This comprised use of an HPLC system (Waters 2795 Alliance HT, Waters Corporation, Milford, Massachusetts), with MS/MS detection (Micromass UK Ltd., Manchester, United Kingdom).

A total of 50 μL of the internal standard solution (lovastatin 10 ng/mL) was added to 200 mL of the plasma sample, and the solution was vortexed for 15 seconds. Then, 50 mL of the formic acid was added and the solution was vortexed again for 15 seconds. For the next step, 4 mL of the extraction mixture

(diethyl ether/hexane [70/30]) was added, and the solution was vortexed for 60 seconds and centrifuged at 840*g* at 4°C for 10 minutes. The organic layer was transferred to another tube and allowed to evaporate to dryness in a water bath at 40°C under a gentle stream of nitrogen. The residue or supernatant remaining was reconstituted with 200 mL of the acetonitrile/10-mM formic acid (90/10) and vortexed for 30 seconds, then centrifuged at 10770*g* at room temperature for 2 minutes. For the last step, 80 mL of the residue was injected into the column, where simvastatin, simvastatin acid, and the internal standard were separated from endogenous plasma substances.

Chromatographic separation was performed using a Genesis C_{18} column (3 μm, 4.6 × 150 mm; Grace Davison Discovery Sciences, Deerfield, Illinois). The mobile phase consisted of acetonitrile/10-mM formic acid (90/10) and was eluted at the flow rate of 1.0 mL/min at ambient temperature. Detection was identified by the multiple reaction monitoring transitions at m/z 419 → 285, 437 → 303, and 405 → 199 for simvastatin, simvastatin acid, and lovastatin, respectively. The peak area was measured, and the peak area ratio (simvastatin to internal standard and simvastatin acid to internal standard) and the concentration were calculated using MassLynx software version 3.5 (Micromass UK Ltd.).

Pharmacokinetic Analysis

The pharmacokinetic parameters of simvastatin and simvastatin acid were determined from the plasma concentration data by a noncompartmental method using WinNonlin version 5.2 (Pharsight Corporation, Mountain View, California). C_{max} and T_{max} were determined by inspection of the observed data. $AUC_{0–last}$ was calculated by the linear trapezoidal rule, and $AUC_{0–\infty}$ was calculated as $AUC_{0–last} + C_t/\lambda_z$, where C_t is the last measurable concentration and λ_z is the decay rate constant estimated as the slope of the linear regression of the log-transformed plasma concentration–time data in the terminal phase. The $t_{1/2}$ (terminal decay $t_{1/2}$) was calculated as $0.693/\lambda_z$. The slope of the terminal decay was determined by the slowest process, and CR products were more likely to have terminal "absorption" rates rather than elimination ("flip-flop").[24]

Tolerability Assessments

Tolerability assessments included monitoring and evaluation of ECG results and adverse events, as well as vital signs (blood pressure, body temperature, and pulse rate) and laboratory tests (hematology, blood chemistry, and urinalysis) performed at 0 and 48 hours after the dose (part I) or after the last dose (part II) and at follow-up visits occurring 1 week later. Based on patient 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 *adverse event* and recorded on case-report forms. *Serious adverse events* were defined as any events that are considered life threatening, require hospitalization or prolongation of existing hospitalization, cause persistent or significant disability or incapacity, or result in congenital abnormality, birth defect, or death.

Statistical Analysis

Because it was a comparative pharmacokinetics study, with no hypothesis test or sample size estimation involved, 12 subjects per group were chosen for the single-dose case and 15 for the multiple-dose case, considering dropout subjects. Descriptive statistics were calculated for demographic data, as well as for pharmacokinetic parameters. Formulation differences in demographic characteristics were tested by χ^2 or Fisher exact tests for nominal values, and the *t* test for continuous values; differences in pharmacokinetic parameters were tested using the Wilcoxon rank sum test for T_{max} and the *t* test for the other parameters.

RESULTS

Study Subjects

Part I

Twenty-four healthy subjects (17 men, 7 women; mean [SD] age, 29 [7] years; age range, 22–50 years) were enrolled in part I, and all subjects completed the study. Their demographic characteristics are summarized in **Table I**.

Part II

Among the 30 healthy subjects eligible for part II of the study, 1 subject withdrew before the first dose. Thus, 29 subjects (17 men, 12 women; mean [SD] age, 33 [9] years; age range, 19–55 years) were enrolled and completed the study. Their demographic characteristics are summarized in **Table II**.

No subject was enrolled in both parts of the study. No significant differences in demographic characteris-

Table I. Demographic characteristics of subjects receiving a single 40-mg dose of simvastatin (N = 24).

Variable	Simvastatin CR (n = 12)	Simvastatin IR (n = 12)	*P**
Age, y			<0.930
Mean (SD)	29 (5.5)	29 (7.9)	
Range	23–40	22–50	
Sex, no. (%)			
Male	9 (75)	8 (67)	1.000
Female	3 (25)	4 (33)	
Weight, kg			<0.220
Mean (SD)	69.0 (8.0)	64.2 (10.2)	
Range	54.2–81.0	50.6–82.6	
Height, cm			<0.598
Mean (SD)	171.0 (5.7)	172.5 (7.7)	
Range	160.0–181.2	157.9–182.9	
Smoking, no. (%)			
Nonsmoker	4 (33)	7 (58)	<0.414
Smoker	8 (67)	5 (42)	
Drinking, no. (%)			
Nondrinker	3 (25)	7 (58)	<0.214
Drinker	9 (75)	5 (42)	

CR = controlled release; IR = immediate release.
*Formulation differences were tested using the Fisher exact test for nominal values and the *t* test for continuous values.

tics were found between the test and reference groups in either portion of the study.

Pharmacokinetics

Part I

Figure 1 presents mean (SD) plasma concentration–time profiles of simvastatin and simvastatin acid after a single dose of the simvastatin CR or IR formulation, and **Table III** lists the pharmacokinetic data for the 2 formulations. For simvastatin, C_{max} was significantly smaller ($P < 0.002$) and T_{max} significantly longer ($P < 0.001$); there was no significant difference for apparent $t_{1/2}$. For simvastatin acid, C_{max} was significantly smaller ($P < 0.013$) and T_{max} and apparent $t_{1/2}$ significantly longer ($P < 0.001$ and $P < 0.011$, respectively) for the CR formulation compared with the IR formulation (**Table III**). For $AUC_{0–last}$ and $AUC_{0–\infty}$, there were no signficant differences between the CR formulation and the IR formulation.

Part II

Figure 2 presents mean (SD) plasma concentration–time profiles of simvastatin and simvastatin acid on day 8 after multiple doses of the simvastatin CR or IR formulation, and **Table IV** summarizes the pharmacokinetic data for the 2 formulations. For simvastatin, the CR formulation was significantly different from the IR formulation, with a larger $AUC_{0–last}$ and $AUC_{0–\infty}$, smaller C_{max}, and longer T_{max} (all, $P < 0.001$), while there was no significant difference in apparent $t_{1/2}$. For simvastatin acid, the C_{max} for the CR formulation was significantly smaller ($P < 0.037$), while the values for T_{max} and apparent $t_{1/2}$ were significantly longer (both, $P < 0.001$). $AUC_{0–last}$ and

Table II. Demographic characteristics of subjects receiving simvastatin 40 mg for 8 days (N = 29).

Variable	Simvastatin CR (n = 15)	Simvastatin IR (n = 14)	*P**
Age, y			<0.256
Mean (SD)	31 (8.8)	35 (9.3)	
Range	19–45	22–55	
Sex, no. (%)			<0.825
Male	9 (60)	8 (57)	
Female	6 (40)	6 (43)	
Weight, kg			<0.648
Mean (SD)	64.5 (10.1)	63.0 (7.9)	
Range	50.1–82.2	49.8–76.8	
Height, cm			<0.451
Mean (SD)	170.0 (8.4)	167.5 (8.5)	
Range	159.0–183.7	154.3–181.9	
Smoking, no. (%)			<0.848
Nonsmoker	7 (47)	8 (57)	
Smoker	8 (53)	6 (43)	
Drinking, no. (%)			<0.798
Nondrinker	10 (67)	9 (64)	
Drinker	5 (33)	5 (36)	

CR = controlled release; IR = immediate release.
*Formulation differences were tested using the χ^2 test for nominal values and the *t* test for continuous values.

$AUC_{0-\infty}$ values were not significantly different between the 2 formulations.

The peak–trough fluctuation ($[C_{ss,max} - C_{ss,min}]/C_{ss,ave}$) was smaller in the CR formulation ($P < 0.011$).

Tolerability

Both the CR and IR formulations were well tolerated in all subjects, and no serious adverse events or adverse drug reactions were found. No subjects reported any adverse events during part I. During part II, 6 subjects (3 from each formulation group) reported headache, 1 reported lumbago before the dose, and 1 subject had a hordeolum while receiving the CR formulation. All adverse events were mild, and the subjects recovered after a few hours without medication.

No clinically relevant changes were observed in vital signs, laboratory test results, or ECG results during part I or II of the study.

DISCUSSION

The purpose of this study was to compare the pharmacokinetics of CR and IR formulations of simvastatin in healthy Korean subjects, with the objective of marketing the CR formulation in Korea. The study comprised 2 phases—part I was performed with a single-dose design and part II used a multiple-dose design. All subjects received the simvastatin CR or IR formulation of 40 mg (20 mg × 2 tablets) for each dose.

Compared with IR formulations, it is expected that CR formulations usually display a smoother plasma concentration–time profile, with a lower C_{max}, delayed T_{max}, and prolonged $t_{1/2}$.[17,25–27] This enables the frequency of dosing to be reduced, which was also observed in our study. The peak–trough fluctuation was also smaller for the CR formulation, as expected. Given that peak concentrations of simvastatin would be related to

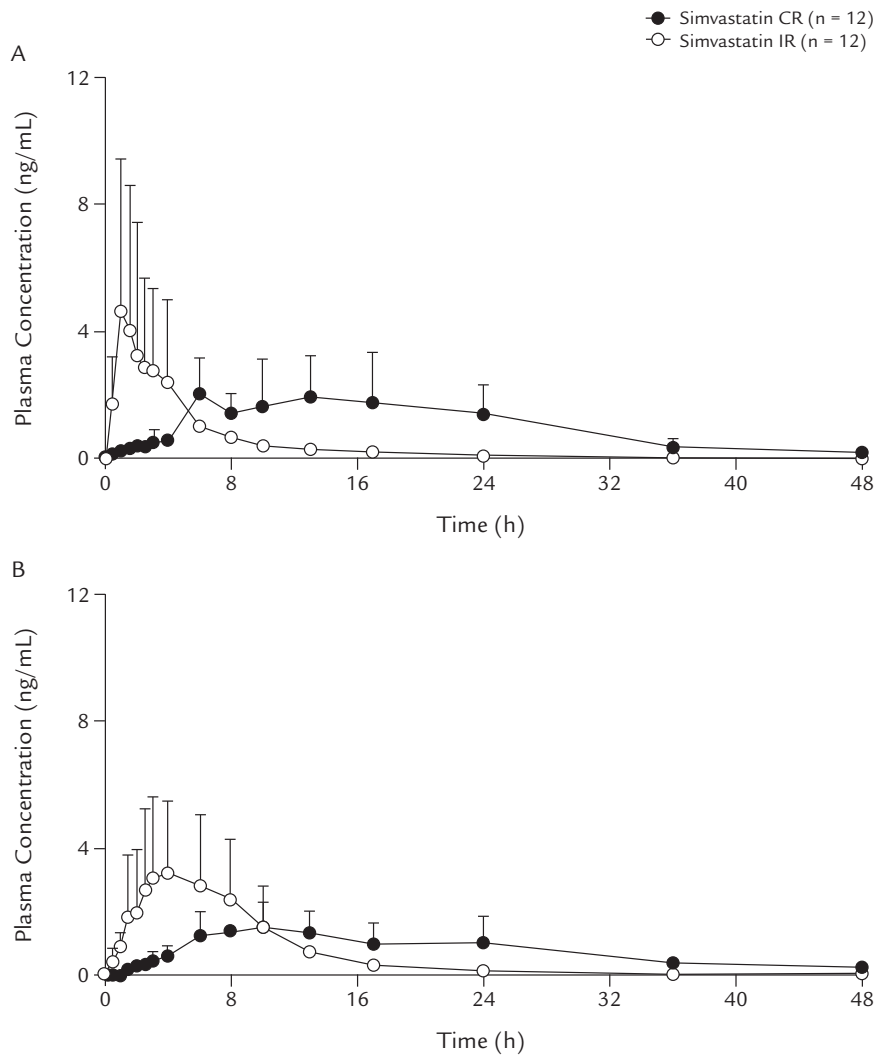

Figure 1. Mean (SD) plasma concentration–time curves of (A) simvastatin and (B) simvastatin acid after administration of a single 40-mg dose of simvastatin. CR = controlled release; IR = immediate release.

the incidence of adverse events, these findings for the CR formulation, along with its AUC values that were not significantly different from the IR formulation, may be potentially useful in reducing the incidence of adverse events while maintaining the efficacy of the drug. In the case of the reference formulation, overall, the pharmacokinetic parameters of simvastatin were found to be similar to those found in previous studies.[8,25,28]

AUC values between the 2 formulations, based on AUC_{0-last} and $AUC_{0-\infty}$, were not significantly different for simvastatin acid and were statistically larger in the CR formulation for simvastatin in both parts of the study. These findings indicate that the systemic bioavailability with the CR formulation becomes greater in the inactive prodrug (simvastatin) whereas it remains similar in the active moiety (simvastatin acid), which is consistent with the findings reported with other statins.[14]

In this study, for simvastatin acid, interindividual variations of AUC_{0-last} and C_{max} for the IR formulation,

Table III. Pharmacokinetic data (mean [%CV]) of simvastatin and simvastatin acid after subjects received a single dose of 40 mg (N = 24).

Parameter	CR	IR	*P*
Simvastatin			
AUC_{0-last}, ng · h/mL*	44.17 (63)	20.47 (93)	<0.007
$AUC_{0-\infty}$, ng · h/mL*	47.29 (67)	21.64 (89)	<0.015
C_{max}, ng/mL*	2.45 (52)	5.69 (79)	<0.002
T_{max}, h†	13.08 (57)	1.71 (58)	<0.001
$t_{1/2}$, h‡	7.95 (59)	5.85 (51)	<0.108
Simvastatin acid			
AUC_{0-last}, ng · h/mL*	29.88 (60)	28.11 (73)	<0.927
$AUC_{0-\infty}$, ng · h/mL*	36.33 (60)	28.96 (71)	<0.613
C_{max}, ng/mL*	1.68 (51)	3.62 (74)	<0.013
T_{max}, h†	10.33 (31)	4.04 (33)	<0.001
$t_{1/2}$, h‡	11.41 (85)	4.16 (68)	<0.011

CR = controlled release; IR = immediate release.
*Comparison of the mean of log-transformed values using the *t* test.
† Comparison of the mean of observed values using the Wilcoxon rank sum test.
‡ Comparison of the mean of calculated values using the *t* test.

as calculated from **Tables III** and **IV** (73% and 74%, respectively, in part I; 53% and 56%, respectively, in part II) were not substantially different from those found in another study (41%–86%).[29] These large interindividual differences in simvastatin acid pharmacokinetics have been associated with genetic polymorphisms of CYP3A4, the P-glycoprotein encoded by the multidrug resistance 1 gene (*MDR1/ABCB1*), and the organic anion-transporting polypeptide C encoded by *SLCO1B1*.[30–32] Wang et al[30] suggested that *CYP3A4*4* decreased CYP3A4 activity, thereby increasing the lipid-lowering effects of simvastatin in 211 Chinese patients. Conversely, *MDR1* polymorphisms have been associated with the lipid-lowering effect and tolerability of simvastatin in a Western population of 97 patients.[31] *CYP3A4* and *MDR1* polymorphisms are likely to affect simvastatin pharmacokinetics because CYP3A4 is a primary metabolic pathway for simvastatin, and P-glycoprotein is an important protein in drug disposition, which involves considerable interindividual variation that may need to be genetically determined.[32,33] In a study of 66 Japanese patients,[34] the *SLCO1B1* polymorphism reportedly markedly affected the pharmacokinetics of simvastatin acid without significantly interfering with that of the parent drug. Therefore, it would be worthwhile to investigate whether similar associations exist between genetic polymorphisms of these genes and pharmacokinetic variations of simvastatin in Korean populations.

One limitation in a study such as this with healthy volunteers, however, is that the results may be difficult to extrapolate to patient populations.

CONCLUSIONS

The C_{max} of the simvastatin CR formulation was found to be significantly smaller while the AUC of the active moiety did not differ significantly from that of the IR formulation in these healthy Korean subjects. The simvastatin CR and IR formulations were well tolerated, with no serious adverse events observed. To better understand the characteristics of the CR formulation, a clinical efficacy study in actual patient populations is clearly needed.

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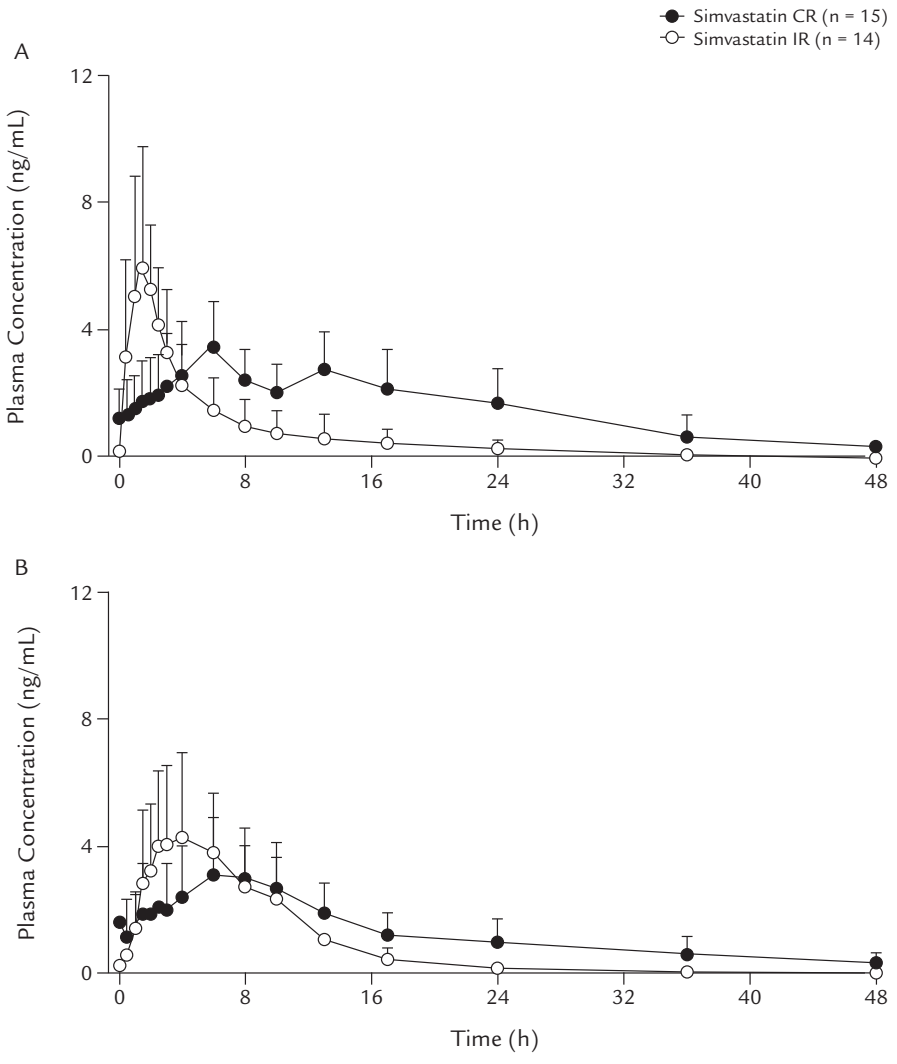

Figure 2. Mean (SD) plasma concentration–time curves of (A) simvastatin and (B) simvastatin acid after administration of simvastatin 40 mg for 8 days. CR = controlled release; IR = immediate release.

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Table IV. Pharmacokinetic data (mean [%CV]) of simvastatin and simvastatin acid after administration of 40 mg for 8 days (N = 29).

Parameter	CR	IR	*P*
Simvastatin			
AUC_{0-last}, ng · h/mL*	71.40 (45)	30.19 (50)	<0.001
$AUC_{0-\infty}$, ng · h/mL*	80.29 (41)	32.29 (48)	<0.001
C_{max}, ng/mL*	3.95 (45)	7.33 (45)	<0.001
T_{max}, h†	7.93 (59)	1.68 (35)	<0.001
$t_{1/2}$, h‡	12.18 (109)	8.45 (50)	<0.163
Simvastatin acid			
AUC_{0-last}, ng · h/mL*	57.59 (61)	41.44 (53)	<0.226
$AUC_{0-\infty}$, ng · h/mL*	68.77 (64)	42.59 (52)	<0.086
C_{max}, ng/mL*	3.40 (53)	5.16 (56)	<0.037
T_{max}, h†	8.40 (38)	4.57 (39)	<0.001
$t_{1/2}$, h‡	13.09 (64)	4.52 (60)	<0.001

CR = controlled release; IR = immediate release.
*Comparison of the mean of log-transformed values using the *t* test.
† Comparison of the mean of observed values using the Wilcoxon rank sum test.
‡ Comparison of the mean of calculated values using the *t* test.

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