Research Article

Pharmacokinetics of Single-Dose and Multi-Dose of Lovastatin/Niacin ER Tablet in Healthy Volunteers

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An extended-release (ER) niacin and lovastatin fixed-dose combination has been developed for the treatment of primary hypercholesterolemia and mixed dyslipidemia. The purpose of the present study was to examine the drug interaction between niacin and lovastatin after multi-dose oral administration of lovastatin/niacin ER combination in healthy Chinese volunteers. A single-center, randomized, open-label, 5-period crossover study was conducted in thirty healthy volunteers aged 18 to 45 years with a washout period of 8 days. Subjects were randomized to receive multiple doses of treatment A (1 500 mg niacin ER tablet), B (1 20 mg lovastatin tablet), C (1 20 mg lovastatin and 500 mg niacin-ER tablet), D (2 10 mg lovastatin and 350 mg niacin-ER tablets) or E (2 10 mg lovastatin and 500 mg niacin-ER tablets) in 1 of 5 sequences (ABCDE, BCDEA, CDEAB, DEABC, EABCD) per period. Lovastatin, niacin and its metabolites (nicotinuric acid and nicotinamide) were determined in plasma by LC/MS method. Pharmacokinetic parameters were calculated, and least square mean ratios and 90% confidence intervals for C_{max} and $AUC_{(0-24)}$ were determined for lovastatin/niacin ER versus niacin ER or lovastatin. It revealed that the formulation had no potential drug interaction in healthy Chinese volunteers when the dosage was increased from 500 mg to 1000 mg.

1. Introduction

Niacin (nicotinic acid, 3-pyridine-carboxylic acid, NA), which belongs to the hydrophilic vitamin B complex, is widely used to treat a diverse range of lipid disorders and prevent clinical CVD [1]. It is well known for its effects in reducing total cholesterol, triglycerides (TGs), very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and lipoprotein (a) (L (pa)), and increasing high-density lipoprotein (HDL) level. NA is metabolized in two pathways: the first is the metabolic route to nicotinuric acid (NUA) through nicotinyl CoA by glycine conjugation, and the second is that to nicotinamide (NAM), which is utilized in NAD synthesis [2]. Lovastatin, as a fungal antibiotic, is a member of the drug class of statins and a specific and nonreversible competitive inhibitor of HMG-CoA reductase, used for lowering cholesterol (hypolipidemic agent) in the patients with hypercholesterolemia and so preventing cardiovascular disease [3]. Many clinical studies have shown that the combination tablet of extended-release (ER) niacin and lovastatin

decreases LDL-C and increases HDL-C greater than either treatment alone in patients with dyslipidemia [4–6].

Moreover, lovastatin was primarily metabolized by the cytochrome P450 isoenzyme, especially CYP3A4, with less than 10% being excreted renally [7]. And an in vitro study indicated that NA and NUA inhibited CYP2D6 and NA inhibited CYP3A4, which was responsible for lovastatin metabolism [8]. Genetic variation in those isoenzymes has been surveyed in an ethnically diverse population [9, 10]. Previous work has observed the lack of a pharmacokinetic interaction between niacin and lovastatin after single-dose administration in healthy Hispanic volunteers [11].

The most common adverse events of niacin and lovastatin were flushing, itch of skin, headache, abdominal pain, malaise, dyspepsia, nausea, and hepatic toxicity [3, 4]. And several clinical trials showed that the rates of adverse event with the ER niacin/lovastatin tablet were similar to those with the ER niacin or the lovastatin in Caucasian patients [12–14].

However, it is still unknown whether potential increased risks of adverse events or a pharmacokinetic interaction of lovastatin and niacin exist in Chinese people.

2. Experimental

2.1. Chemicals and Reagents. Lovastatin/niacin ER tablets were supplied by Kangde Pharmaceutical Group Co. Ltd., (Zhejiang, China). Niacin extended-release tablet was purchased from Beijing Second Pharmaceutical Co. Ltd., (China). Lovastatin tablet was obtained from Hisun Pharmaceutical Co. Ltd. (Zhejiang, China). Chemical reference substances of NA, NAM, lovastatin, and simvastatin were obtained from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). NUA was purchased from Sigma (St. Louis, MO), and 6-methyl nicotinic acid as an internal standard was supplied by Aldrich. HPLC grade methanol was obtained from Merck (Darmstadt, Germany), and other chemical reagents were of analytical grade, obtained from Nanjing Chemical Reagent Co., Ltd. (Nanjing, China). Water was deionized and purified by using a Milli-Q system (Millipore, Milford, MA, USA) and was used to prepare all aqueous solutions.

2.2. LC-MS Instrumentation and Analytical Conditions. An agilent (Agilent Technologies, USA) 1100 series LC system equipped with degasser and agilent 1100 MS was used to detect NA and lovastatin during the study. For detecting NA, NAM, and NUA [15], separation was carried out using a Dikma-C₁₈ column (dp 3 μ m, 2.1 $\times$ 150 mm ID, Dikma Technologies Inc.), with an isocratic elution system consisting of methanol (containing 0.1% acetic acid) and water (containing 0.3% isopropanol) (2/98, v/v) at a flow rate of 0.2 mL/min. Ion scan mode was with the following settings: the capillary voltage, 100 V; temperature, 350°C; drying gas, 600 L/h; nebulizer pressure, 40 psig. Quantitations of NA, NAM, NUA, and 6-methyl nicotinic acid were achieved by monitoring the ions at $[M + H]^+$, m/z 124.1, 123.1, 181.1, and 138.1, respectively (Figure 1). For detecting lovastatin [16], separation was carried out using a Lichrospher C₁₈ (dp 5 μ m), 200 mm $\times$ 4.6 mm ID with a gradient elution system consisting of methanol and water (containing 50 μ mol/L sodium acetate) (see Table 1) at a flow rate of 1 mL/min. The column temperature was kept at 25°C. Detection was performed by mass spectrometer (MS) in positive ion mode. Ion scan mode was with the following settings: the capillary voltage, 140 V; temperature, 350°C; drying gas, 600 L/h; nebulizer pressure, 40 psig. Lovastatin and simvastatin, ions at $[M + Na]^+$ m/z 427.2 and 441.3 (Figure 2), were monitored, respectively. All data were collected and analyzed using Agilent Chemstation software.

2.3. Study Design. The pharmacokinetics of Lovastatin/Niacin ER tablet was studied in healthy Chinese subjects in accordance with the Declaration of Helsinki for biomedical research involving human subjects and Good Clinical Practice. The protocol and associated informed consent statements were reviewed and approved by the Committee on Human Rights Related to Human Experimentation, Xijing

TABLE 1: Mobile phase program for lovastatin.

Time (min)	Water phase (B%)	Flow rate (mL/min)
0	12	1
6.5	12	1
6.6	0	1
10.6	0	1
10.7	12	1
16.0	12	1

Hospital, and the informed consent statements were signed by the volunteers. It was a single-center, randomized, open-label, crossover study with five treatment cycles separated by an eight-day washout cycle. Thirty healthy volunteers who aged from 18 to 45, body mass index (BMI) ranged 19 and 24 Kg/m², were enrolled in this study. All volunteers have passed an obtaining of complete medical history and physical examination before participate in the study. All subjects were fasted for at least 8 hours at last night before our study and were confirmed abstinence from other medications, alcohol, tobacco, and caffeinated products.

The subjects were randomly allocated into five groups (each group have 3 male and 3 female). Each group was randomized to receive multi-dose of treatment A (500 mg niacin ER, one tablet), B (20 mg lovastatin, one tablet), C (one lovastatin/niacin ER tablet (500/20)), D (two lovastatin/niacin ER tablet (350/10)), or E (two lovastatin/niacin ER tablet (500/10)) in 1 of 5 sequences (ABCDE, BCDEA, CDEAB, DEABC, EABCD) per period. Blood samples were collected in heparinized tubes before dosing at days 1, 4, 5, 6, and 7, and on the 1st and 7th day, and blood samples were also collected at 30, 60, and 90 minutes 2, 3, 4, 6, 5, 8, 10, 12, 15, and 24 hours after dosing. All samples were separated immediately by centrifugation at 3500 rpm for 10 min at 4°C and stored at -80°C until analysis.

2.4. Analytical Procedures

2.4.1. Preparation of Stock Solutions and Standard. Stock solutions of NA, NAM, and NUA were prepared by dissolving the drugs in methanol at the concentrations of 0.492, 0.508, 0.0993 mg/mL, respectively. Serial (working) dilutions of NA, NAM, and NUA were prepared from the stock solutions by appropriate dilution with methanol at the concentrations of 98.4, 9.84, 0.984, 0.0984 μ g/mL for NA; 102, 10.2, 1.02, 0.102 μ g/mL for NAM; 9.93, 0.993, 0.0993 μ g/mL for NUA, respectively. Stock solution of lovastatin was prepared by dissolving 10.34 mg drug in methanol at a concentration of 1.034 mg/mL. Serial (working) dilutions of lovastatin were prepared with methanol at the concentrations of 103.4, 10.34, 1.034, 0.1034, 0.01034 μ g/mL, respectively. Stock solutions of internal standards (IS) were prepared by dissolving the drug in methanol at concentrations of 0.500 mg/mL for 6-methyl nicotinic acid and 1.052 mg/mL for simvastatin. Working solutions of IS were prepared with methanol at concentrations of 2.0 μ g/mL for 6-methyl nicotinic acid and 0.2104 μ g/mL for simvastatin. All the stock

FIGURE 1: Electrospray product ion mass spectrum of the precursor ion of NA (a), NAM (b), NUA (c), and internal standard 6-methyl nicotinic acid (d).

and working solutions were stored at -20°C and prepared for calibration curve and quality controls.

2.4.2. Sample Preparation. To determine the niacin and its metabolites, $50\ \mu\text{L}$ 6-methyl nicotinic acid ($2.00\ \mu\text{g/mL}$, IS) solution was added into $100\ \mu\text{L}$ plasma sample and vortex-mixed for 30 s and then $0.6\ \text{mL}$ methanol was added and vortex-mixed for 3 min. After centrifugation ($16000\ \text{r/min}$, 6 min), the upper organic layer was separated and evaporated to dryness using a gentle stream of nitrogen. The residuum was reconstituted using the mobile phase and centrifuged 6 min at $16000\ \text{r/min}$. A $5\ \mu\text{L}$ supernatant was autoinjected into the LC/MS system for analysis.

For lovastatin, $1\ \text{mL}$ plasmas sample and $75\ \mu\text{L}$ simvastatin solution ($0.2104\ \mu\text{g/mL}$, IS) were accurately added into $10\ \text{mL}$ centrifuge tube, and vortex-mixed adequately, then

$5\ \text{mL}$ redistillate acetidin was added, and, after centrifugation ($4000\ \text{r/min}$, 10 min), the upper organic layer was evaporated to dryness using nitrogen in a water bath at 30°C . The residuum was dissolved with $200\ \mu\text{L}$ mobile phase solution, and, after centrifugation ($16000\ \text{r/min}$, 6 min), a $20\ \mu\text{L}$ supernatant was transferred into the LC/MS system for analysis.

2.4.3. Calibration Curve. Calibration curves were prepared at the concentration levels of 0.00492, 0.0148, 0.0295, 0.0984, 0.295, 0.984, 1.97, 4.92, and $9.84\ \mu\text{g/mL}$ for NA; 0.00508, 0.0152, 0.0305, 0.102, 0.305, 1.02, 2.03, 5.08, and $10.2\ \mu\text{g/mL}$ for NAM; 0.00497, 0.0149, 0.0298, 0.0993, 0.298, 0.993, 1.99, 4.96, and $9.93\ \mu\text{g/mL}$ for NUA; 0.0517, 0.1551, 0.3102, 1.034, 3.102, 10.34, 20.68, and $41.36\ \text{ng/mL}$ for lovastatin by spiking an appropriate amount of the standard solutions

FIGURE 2: Electrospray product ion mass spectrum of the precursor ion of Lovastatin (a), and internal standard simvastatin (b).

in 1 mL blank plasma. The calibration curve was prepared and assayed along with quality control (QC) samples. QC samples were prepared in 1 mL blank plasma at three levels of 0.00984, 0.246, and 8.86 $\mu\text{g/mL}$ for NA; 0.0102, 0.254, and 9.14 $\mu\text{g/mL}$ for NAM; 0.00993, 0.248, and 8.94 $\mu\text{g/mL}$ for NUA; 0.1034, 2.585, 36.19 ng/mL for lovastatin, respectively. The plasma samples were stored at -20°C .

2.4.4. Specificity. The specificity of the method was tested by screening six different batches of blank human plasma. Each blank sample was tested for interferences in the MS channels using the proposed extraction procedure and chromatographic/MS conditions, and the results were compared with those obtained for water solution of the analytes at a concentration near to the lower limit of quantification (LLOQ).

2.4.5. Precision and Accuracy. The intrarun precisions and accuracies were estimated by analyzing five replicates containing NA, NAM, NUA, and lovastatin at three different QC levels. The interrun precisions were determined by analyzing QC samples on three different runs. The criteria for acceptability of the data included accuracy within $\pm 15\%$ deviation (DEV) from the nominal values and a precision of within $\pm 15\%$ relative standard deviation.

2.4.6. Extraction Recovery. The recoveries of NA, NAM, NUA, and lovastatin were determined by comparing the peak area obtained for QC samples that were subjected to the extraction procedure with those obtained from blank plasma extracts that were spiked after extraction to the same nominal concentrations (0.00984, 0.246, and 8.86 $\mu\text{g/mL}$ for NA; 0.0102, 0.254, and 9.14 $\mu\text{g/mL}$ for NAM; 0.00993, 0.248, and 8.94 $\mu\text{g/mL}$ for NUA; 0.1034, 2.585, 36.19 ng/mL for lovastatin).

2.4.7. Stability. The stability of NA, NAM, NUA, and lovastatin in plasma under different temperature and timing conditions was evaluated. Plasma samples were subjected to short-term conditions, to long-term storage conditions (-20°C), and to three freeze-thaw stability studies. The autosampler stability was conducted by reanalyzing extracted

samples kept under the autosampler conditions for 0 and 48 h. All the stability studies were conducted at two concentration levels with three determinations for each.

2.5. Pharmacokinetic Analysis. The noncompartmental model analysis was used in the data processing of NA, NUA, NAM, and lovastatin. The maximum and minimum observed serum concentrations at steady state ($C_{\text{max-ss}}$, $C_{\text{min-ss}}$) and time to $C_{\text{max-ss}}$ ($T_{\text{max-ss}}$) were taken from raw data. Ke was determined by linear regression of the terminal linear portion of the concentration-time curve, and $T_{1/2}$ was calculated as $\ln(2)/Ke$. AUC_{ss} (steady-state area under the curve during T (dosing interval) and AUC_{inf} (steady-state area under the curve from 0 to infinity) were calculated by the linear trapezoidal rule. C_{av} (mean concentration between 2 administrations) was calculated as AUC_{ss}/T . The degree of fluctuation (DF) value was calculated as $(C_{\text{max}} - C_{\text{min}})/C_{\text{av}} \times 100\%$ and actual accumulation factor $R = \text{AUC}_{\text{ss}}/\text{AUC}_{\text{inf}}$. Clearance (CL/F) was calculated as dose/ AUC_{inf} .

2.6. Safety Evaluation. Safety assessments included the recording of all adverse events, vital signs (blood pressure and heart rate), 12-lead electrocardiograms (ECG), laboratory investigations (including biochemistry, haematology, coagulation, and urinalysis), and full physical examinations.

3. Results and Discussion

3.1. Method Validation

3.1.1. Specificity and Selectivity. Good selectivity was observed, and there was no significant interference or ion suppression from endogenous substances observed at the retention time of the analytes. The retention time of NA, NAM, NUA, and 6-methyl nicotinic acid was 4.2, 7, 12, and 4.8 min, respectively. The retention time of lovastatin and simvastatin were 5.6 and 6.6 min, respectively.

3.1.2. Calibration Curve. NA and NAM can be both detected in the blank plasma samples therefore, the background level

TABLE 2: Intra- and interrune precision and accuracy of determination of NA, NAM, NUA, and lovastatin in human plasma.

	Concentration		RSD (%)	
	Nominal	Found C	Intrarun ($n = 5$)	Interrun ($n = 15$)
NA ($\mu\text{g/mL}$)	0.00984	0.0101	6.0	12.7
	0.246	0.237	4.2	8.3
	8.86	8.71	3.7	8.5
NAM ($\mu\text{g/mL}$)	0.0102	0.0103	5.5	12.0
	0.254	0.271	3.5	9.3
	9.14	9.58	3.2	13.5
NUA ($\mu\text{g/mL}$)	0.00993	0.0103	4.8	2.0
	0.248	0.268	2.3	11.3
	8.94	9.52	2.3	13.0
Lovastatin (ng/mL)	0.1034	0.1051	8.2	14.9
	2.585	2.688	5.0	8.6
	36.19	37.09	6.6	9.7

of peak area of NA and NAM will be deducted during the analysis process. Calibration curves of NA, NAM, and NUA in plasma were validated over the concentration ranges of 0.00492–9.84 $\mu\text{g/mL}$, 0.00508–10.2 $\mu\text{g/mL}$, and 0.00497–9.93 $\mu\text{g/mL}$, respectively. The r^2 values for the calibration curves were >0.99 . Typical equations of calibration curves were as follows: $y = 0.363 \times C - 0.000002$ ($r^2 = 0.9995$, $n = 5$) for NA, $y = 1.17 \times C - 0.00107$ ($r^2 = 0.9998$, $n = 5$) for NAM, and $y = 1.07 \times C - 0.000235$ ($r^2 = 0.9997$, $n = 5$) for NUA, respectively. Calibration curves of lovastatin in plasma were validated over the concentration ranges of 0.0517–41.36 ng/mL . The limit of quantification (LLOQ), defined as the lowest concentration on the standard curve that can be measured with acceptable accuracy and precision ($<20\%$), was established at 0.00492 $\mu\text{g/mL}$ for NA, 0.00508 $\mu\text{g/mL}$ for NAM, 0.00497 $\mu\text{g/mL}$ for NUA, and 0.0517 ng/mL for lovastatin, respectively (single-to-noise, $S/N \geq 10$).

3.1.3. Accuracy and Precision. The intra- and interrune precision and accuracy of the assay were assessed by running a single batch of samples containing a calibration curve and five replicates at each QC level. The precision was calculated by using one-way ANOVA. The results, which were summarized in Table 2, demonstrated that the precision and accuracy values were within the acceptable range and the method was accurate and precise.

3.1.4. Extraction Recovery and Matrix Effects. The extraction recoveries of the four analytes were NA $95.2 \pm 3.2\%$, $93.8 \pm 2.3\%$, and $96.7 \pm 2.9\%$ at the concentrations of 0.00984, 0.246, and 8.86 $\mu\text{g/mL}$, respectively; NAM $105.6 \pm 4.2\%$, $94.1 \pm 4.5\%$, and $98.5 \pm 4.3\%$ at the concentrations of 0.0102, 0.254, and 9.14 $\mu\text{g/mL}$, respectively; NUA $92.1 \pm 7.6\%$, $95.7 \pm 3.3\%$ and $101.7 \pm 5.2\%$ at the concentrations of 0.00993, 0.248 and 8.94 $\mu\text{g/mL}$ respectively; NUA $92.1 \pm 7.6\%$, $95.7 \pm 3.3\%$, and $101.7 \pm 5.2\%$ at the concentrations of 0.00993, 0.248, and 8.94 $\mu\text{g/mL}$ respectively; lovastatin $95.5 \pm 3.31\%$, $87.8 \pm 1.25\%$, and $82.8 \pm 1.81\%$ at the concentrations of 0.1034, 2.585, 36.19 ng/mL , respectively.

The matrix effect was defined as the direct or indirect alteration or interference in response due to the presence of unintended or other interfering substances in the samples. It was evaluated by comparing the peak area of the analytes (background subtraction for NA and NAM) dissolved in the blank plasma sample's reconstituted solution (the final solution of the blank plasma after extraction and reconstitution) with that dissolved in mobile phase. Three different concentration levels of analytes were evaluated by analyzing five samples at each level, and the blank plasma used in this study was from five different batches of blank plasma. If the peak area ratio is less than 85% or more than 115%, a matrix effect will be implied. In this study, the peak area ratios of the analytes were NA $87.2 \pm 1.6\%$, $107.8 \pm 4.6\%$, and $89.3 \pm 4.7\%$, NAM $99.1 \pm 10.8\%$, $96.8 \pm 3.1\%$ and $104.6 \pm 2.9\%$, NUA $104.9 \pm 4.0\%$, $97.1 \pm 3.4\%$, and $98.2 \pm 7.7\%$, respectively, at concentrations of 0.01, 0.25, and 9 $\mu\text{g/mL}$; 6-methyl nicotinic acid $95.5 \pm 10.5\%$ at the concentration of 2.0 $\mu\text{g/mL}$; lovastatin $94.5 \pm 3.21\%$, $89.8 \pm 1.35\%$, and $92.8 \pm 2.87\%$ at the concentrations of 0.10, 2.6, 36.2 ng/mL , respectively; simvastatin $94.5 \pm 7.8\%$ at the concentration of 0.2 $\mu\text{g/mL}$. The results showed that there was no matrix effect of the analytes and IS from the matrix of plasma in this study.

3.1.5. Stability. The stability of NA, NAM, NUA, and lovastatin in plasma was determined by assessing low- and high-QC samples ($n = 3$ for each concentration). The results are summarized in Table 3. All analytes were found to be stable in plasma samples for at least 12 h at room temperature, for 2 months at -20°C freezing condition, and following three freeze-thaw cycles.

3.2. Pharmacokinetics

3.2.1. NA, NAM, and NUA Plasma Analysis. Mean pharmacokinetic parameters of the treatment A and C were provided in Table 4 for NA, NAM, and NUA. Mean plasma concentration versus time profiles for NA, NAM, and NUA were presented in Figure 3.

TABLE 3: Stability of NA, NAM, NUA, and lovastatin under different storage conditions ($n = 3$).

Storage conditions	Drug	Concentration	
		Nominal	Mean found C
Stability at room temperature for 8 h	NA	0.00984	0.00904 ± 0.00059
		8.86	8.51 ± 0.10
	NAM	0.0102	0.00948 ± 0.00007
		9.14	9.11 ± 0.07
	NUA	0.00993	0.0105 ± 0.0007
		8.94	9.81 ± 0.13
	Lovastatin	0.1034	0.09808 ± 0.0117
		36.19	37.15 ± 3.08
Stability at -80°C for 2 months	NA	0.00984	0.00904 ± 0.00031
		8.86	0.00953 ± 0.00052
	NAM	0.0102	0.00925 ± 0.00072
		9.14	8.49 ± 0.18
	NUA	0.00993	8.53 ± 0.17
		8.94	8.79 ± 0.12
	Lovastatin	0.1034	0.1014 ± 0.0009
		36.19	34.10 ± 1.81
Freeze-thaw stability	NA	0.00984	0.00872 ± 0.00036
		8.86	7.98 ± 0.13
	NAM	0.0102	0.0109 ± 0.0002
		9.14	8.76 ± 0.22
	NUA	0.00993	0.0108 ± 0.0003
		8.94	8.46 ± 0.24
	Lovastatin	0.1034	0.09911 ± 0.0051
		36.19	34.71 ± 1.39
Autosampler stability at 4°C for 24 h	NA	0.00984	0.00955 ± 0.00096
		8.86	8.86 ± 0.16
	NAM	0.0102	0.0100 ± 0.0001
		9.14	9.58 ± 0.30
	NUA	0.00993	0.0100 ± 0.0010
		8.94	9.77 ± 0.139
	Lovastatin	0.1034	0.09931 ± 0.00437
		36.19	40.19 ± 0.31

For the NA study, we found there was significant difference between $C_{\max}$, AUC_{0-24} , and $T_{\max}$ for NA on the multiple dose of the treatment A or C, compared with single-dose of treatment A (500 mg niacin ER tablet) or the treatment C (one lovastatin/niacin ER tablet (500/20)). And a higher $C_{\max}$ and AUC_{0-24} and longer $T_{\max}$ of NA were obtained for the multi-dose treatment A or C. And, for the NAM pharmacokinetic study, the mean NAM $C_{\max}$ and AUC_{0-24} values were about 3 times higher for multi-dose administration of 500 mg niacin ER tablet (treatment A or C), comparing with single-dose of 500 mg niacin ER tablet (treatment A or C). It was indicated the metabolism of NA and NAM may exit the accumulation phenomenon in human body. However, there was no significant statistical difference ($P > 0.05$) in the main pharmacokinetic parameters of NA, NAM, NUA

($C_{\max-SS}$, C_{av} , AUC_{0-24} , $T_{\max}$) between the two treatments (Figure 3). It was suggested that niacin had similar drug delayed release behavior in two treatments, and lovastatin had no effect on pharmacokinetic character of NA. The results initially indicated that no drug interaction existed between NA and lovastatin after multiple oral administration of lovastatin/niacin ER tablet in healthy Chinese volunteers.

For the multi-dose NA pharmacokinetic study, the mean pharmacokinetic parameters of NA, NAM, and NUA after multi-dose three different formulations (treatment C, D, E) were present in Table 5. The NA $C_{\max}$ and AUC_{0-24} were appropriately 30 times higher, when the dose was changed from 500 mg to 750 mg, but no big difference when the dose was changed from 750 mg to 1000 mg. It was indicated that there was a liver enzyme saturation phenomenon in NA

FIGURE 3: Plasma concentration-time curve of NA and NAM and NUA in 10 healthy volunteers after dose administration of lovastatin/niacin ER (20 mg/500 mg) and niacin ER (500 mg) ((a) single-dose; (b) multi-dose).

TABLE 4: The pharmacokinetic variables of NA, NAM, and NUA in volunteers after single- and multi-dose administration of the treatment A (niacin ER tablet, 500 mg) or the treatment C (lovastatin/niacin ER tablet, 20 mg/500 mg) (mean ± SD).

Treatment			NA			NAM			NUA			$t_{1/2}$ (h)
			$T_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/mL}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h/mL}$)	$T_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/mL}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h/mL}$)	$T_{\max}$ (h)	$C_{\max}$ ($\mu\text{g/mL}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h/mL}$)	
C	Single	Mean	1.1	0.079	0.104	7.2	0.148	2.09	1.5	0.404	0.94	1.9
		±s	0.8	0.061	0.067	4.3	0.061	0.79	0.4	0.114	0.32	0.6
	Multi	Mean	2.6	0.097	0.221	10.2	0.448	5.81	2.4	0.375	1.19	1.4
		±s	1.1	0.043	0.055	0.6	0.104	1.29	1.1	0.127	0.38	0.2
A	Single	Mean	2.1	0.0392	0.0761	5.1	0.176	1.82	2.8	0.232	0.743	1.8
		±s	1.6	0.0253	0.0385	0.6	0.068	1.10	1.4	0.062	0.217	0.4
	Multi	Mean	3.3	0.155	0.221	11.6	0.375	5.31	3.15	0.340	0.781	1.3
		±s	1.3	0.121	0.157	3.1	0.050	1.01	1.1	1.18	0.205	0.07
	Single	C/A		1.06	1.14		0.96	1.08		1.12	1.09	
		90%		0.94, 1.21	0.98, 1.29		0.80, 1.25	0.92, 1.24		0.96, 1.30	0.94, 1.24	
	Multi	C/A		1.03	1.06		1.09	1.10		1.11	1.06	
		90%		0.88, 1.22	0.96, 1.16		0.94, 1.26	0.99, 1.20		0.81, 1.21	0.93, 1.19	

TABLE 5: The pharmacokinetic variables of NA, NAM, and NUA in volunteers of group I after multi-dose administration of three different dosage of lovastatin/niacin ER.

Lovastatin/niacin ER	Variable	NA			NAM			NUA		
		AUC_{0-24} ($\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$)	$C_{\max}$ ($\mu\text{g/mL}$)	C_{av} ($\mu\text{g/mL}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$)	$C_{\max}$ ($\mu\text{g/mL}$)	C_{av} ($\mu\text{g/mL}$)	AUC_{0-24} ($\mu\text{g}\cdot\text{h/L}$)	$C_{\max}$ ($\mu\text{g/mL}$)	C_{av} ($\mu\text{g/mL}$)
20 mg/500 mg	Mean	0.221	0.097	0.00919	5.81	0.448	0.242	1.19	0.375	0.0496
	±s	0.055	0.043	0.00227	1.29	0.104	0.054	0.38	0.127	0.0159
20 mg/750 mg	Mean	7.15	3.54	0.298	7.16	0.804	0.298	4.31	1.38	0.179
	±s	3.76	1.90	0.157	1.26	0.168	0.052	0.96	0.35	0.037
20 mg/1000 mg	Mean	5.36	2.73	0.223	7.13	0.730	0.297	4.44	1.13	0.185
	±s	2.96	1.45	0.123	1.73	0.202	0.072	1.21	0.21	0.050

metabolism [11, 12] in Chinese healthy volunteers at the range of 500–1000 mg NA.

3.2.2. Lovastatin Plasma Analysis. For lovastatin study, mean pharmacokinetic parameters of lovastatin (treatment B and C) were provided in Table 6. Mean plasma concentrations versus time profiles for lovastatin were presented in Figure 4. Lovastatin was eliminated with a half-life of approximately 5 h, and peak plasma concentrations of lovastatin were reached within 0.7–1.8 h. These findings are in agreement with the previously reported pharmacokinetic parameters of lovastatin [16–20]. For both treatment B and C comparisons, the ratios ranged from 101% to 124% for $C_{\max}$, 104% to 126% for $\text{AUC}_{(0-24)}$. The 90% CI for the ratios of both comparisons was within the 80% to 126% interval. It was indicated that there was no drug interaction between monotherapy and coadministration.

For multi-dose pharmacokinetics study of lovastatin, mean pharmacokinetic parameters of lovastatin (treatment C, D, and E) were provided in Table 7. No significant statistical difference was observed in the pharmacokinetic parameters of lovastatin among the three treatments. The

results suggested that different doses of NA have no effect on the pharmacokinetic character of lovastatin and indicated that no drug interaction existed between NA and lovastatin after multiple oral administration of lovastatin/niacin ER tablet in healthy Chinese volunteers.

3.3. Adverse Events. Some subjects in the treatment A (1 subject), C (1 subjects), D (3 subjects), E (4 subjects) reported the adverse events of erubescence, slight fever, pruritus on the skin or mild stomach discomfort. Overall, all adverse events were mild and the volunteers recovered without treatment.

More detail information needs to be collected and analyzed from the phase-two clinical trials of the lovastatin/niacin ER tablet in Chinese patients.

4. Discussion and Conclusion

The study was completed with a sufficient number of subjects to meet the PK objectives. Although there are not observed mean PK differences between monotherapy and coadministration, the overall variability of the study was relatively high,

TABLE 6: The pharmacokinetic variables of lovastatin in volunteers after single-dose administration of lovastatin/niacin ER (20 mg/500 mg) and lovastatin (20 mg) (mean ± SD).

Variable	Lovastatin/niacin ER (treatment C)		lovastatin (treatment B)	
	Single-dose	Multi-dose	Single-dose	Multi-dose
$T_{\max}$ (h)	1.3 ± 0.5	1.3 ± 0.6	1.4 ± 0.2	1.5 ± 0.3
$C_{\max}$ (ng/mL)	10.94 ± 3.51	10.25 ± 3.12	9.54 ± 4.47	8.45 ± 2.77
AUC_{0-24} (ng·h/mL)	26.97 ± 6.2	29.85 ± 10.25	27.78 ± 10.33	26.86 ± 8.53
$t_{1/2}$ (h)	3.9 ± 0.8	4.6 ± 1.4	3.8 ± 1.5	5.1 ± 0.5
	Single (C/B, 90%)		Multi (C/B, 90%)	
$C_{\max}$	1.12, (1.00, 1.24)		1.14, (1.04, 1.24)	
AUC_{0-24}	1.13, (1.01, -1.24)		1.15, (1.04, 1.25)	

TABLE 7: The pharmacokinetic variables of lovastatin in volunteers after multi-dose administration of three different formulations of lovastatin/niacin ER (mean ± SD).

Variable	One	Two	Two
	Lovastatin/niacin ER tablet (500/20)	Lovastatin/niacin ER tablets (375/10)	Lovastatin/niacin ER tablets (500/10)
$T_{\max}$ (h)	1.3 ± 0.6	0.9 ± 0.3	1.3 ± 0.4
$C_{\max}$ (ng/mL)	10.25 ± 3.12	10.45 ± 3.85	12.67 ± 6.09
$C_{\min}$ (ng/mL)	0.02719 ± 0.02879	0.03676 ± 0.02553	0.05462 ± 0.02128
C_{av} (ng/mL)	1.244 ± 0.427	1.389 ± 0.411	1.552 ± 0.567
DF	8.42 ± 1.48	7.51 ± 1.37	7.98 ± 1.39
AUC_{0-24} (ng·h/mL)	29.85 ± 10.25	33.33 ± 9.86	37.25 ± 13.61
$t_{1/2}$ (h)	4.6 ± 1.4	4.7 ± 1.1	5.8 ± 1.5
K (h ⁻¹)	0.167 ± 0.065	0.155 ± 0.043	0.127 ± 0.035
CL/F (L/h)	742.8 ± 247.2	667.3 ± 269.4	616.8 ± 263.6
V_d/F (L)	5001.4 ± 2196.6	4556.9 ± 1911.9	5122.4 ± 2488.6

FIGURE 4: Plasma concentration-time curve of lovastatin after single- and multiple-dose administration of lovastatin/niacin ER (500 mg/20 mg) and lovastatin (20 mg) (mean ± SD) ((a) single-dose; (b) multi-dose).

particularly during ER niacin coadministration. This high variability in conjunction with the small number of subjects and apparently little or no effect on the exposure to the parent drugs makes it difficult to establish cause relationships for the potential interactions.

Lovastatin and ER-niacin in a fixed-dose combination (Advicor) is approved for the treatment of dyslipidemia [12]. In single-dose studies of ADVICOR, rate and extent of niacin and lovastatin absorption were bioequivalent under fed conditions to that from NIASPAN (niacin extended-release tablets) and Mevacor (lovastatin) tablets, respectively. After administration of two ADVICOR 1000 mg/20 mg tablets, peak concentrations averaged about 18 $\mu\text{g/mL}$ and occurred about 5 hours after dosing. And peak lovastatin concentrations averaged about 11 ng/mL and occurred about 2 hours after dosing. It was shown that coadministration of NA and lovastatin did not significantly influence C_{max} and AUC_{0-t} of lovastatin, NA, NUA, and total urinary recovery of niacin and metabolites. Although both drugs are extensively metabolized, genetic variation in those isoenzymes has been surveyed in an ethnically diverse population [9, 10]. Compared with Advicor, the pharmacokinetic profile of NA and lovastatin was similar. But in our study, the mean increase in NA, NAM, and NUA was 30 times, when the dose was changed from 500 mg to 750 mg, but no big difference when the dose was changed from 750 mg to 1000 mg. It was indicated that there was a liver enzyme saturation phenomenon in NA metabolism [11, 12] in Chinese healthy volunteers at the range of 750–1000 mg NA. Meanwhile, the recommended dosage of lovastatin/ER-niacin tablets may be better at the range of 350–500 mg for Chinese volunteers.

In the study of Advicor [12], it was also shown that a 22 to 25% decrease in lovastatin C_{max} was observed, when it was coadministered with NA. Lovastatin appears to be incompletely absorbed after oral administration. Because of extensive hepatic extraction, the amount of lovastatin reaching the systemic circulation as active inhibitors after oral administration is low (<5%) and shows considerable interindividual variation. Peak concentrations of active and total inhibitors occur within 2 to 4 hours after Mevacor administration. But, in our study, there was no significant difference on pharmacokinetic parameters of C_{max} , $\text{AUC}_{(0-24)}$ between single use and coadministration and 90% CI of both C_{max} and $\text{AUC}_{(0-24)}$ were at the range of 100–125% that is typically established for bioequivalence, considering the small sample size and moderate variability. But it was interesting that the pharmacokinetic parameters for 500 mg, 700 mg, and 1000 mg dose of lovastatin were 10.25 ± 3.12 ng/mL, 10.45 ± 3.85 ng/mL, and 12.67 ± 6.09 ng/mL for C_{max} and 29.85 ± 10.25 ng·h/mL, 33.33 ± 9.86 ng·h/mL, and 37.25 ± 13.61 ng·h/mL for $\text{AUC}_{(0-24)}$. It was indicated that lovastatin may have the nonlinear pharmacokinetic profile in Chinese healthy volunteers, when it was coadministered with NA. It also suggested the metabolism of NA and lovastatin may exit competitive in human body.

On the basis of these results, no dose adjustment for lovastatin should be necessary when lovastatin is administered in combination with sustained-release niacin. The same would be true for the ER niacin. These statements would be

true if indeed the patient was equal to a subject displaying near mean plasma levels of drug in this study. Given the wide variability in the results for all the drugs when administered together, caution in the form of close monitoring of the patient by blood tests and safety evaluations would be reasonable.

The treatment emergent adverse events that occurred during coadministration were similar in incidence and severity to those reported during the administration of sustained-release niacin alone or lovastatin alone and to those reported in registration documents, that is, the package insert. The notable changes from baseline in laboratory parameters after coadministration of sustained-release niacin and lovastatin were also expected from previous experience with sustained-release niacin or lovastatin administered alone. The adverse events observed are similar in type and degree to those observed in clinical trials testing the efficacy of combinations of ER niacin and lovastatin. These results, which demonstrate high intra- and intersubject variability due to high-dose ER niacin, have to be tempered by the fact that the individual medications alone and in combination can increase the risk of myopathy and rhabdomyolysis.

In conclusion, the data suggest that there is small PK drug interaction between ER niacin and lovastatin and that, although this is not considered to be clinically significant, the concomitant use of these drugs should be appropriately monitored, especially during the prescribed niacin titration period.

Authors' Contribution

S. Ying and Y. Jia contributed equally to this study.

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