



Pharmacokinetic Properties of Single- and Multiple-Dose Pitavastatin Calcium Tablets in Healthy Chinese Volunteers



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ABSTRACT

Background: Pitavastatin is a newly developed 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor approved for the treatment of hyperlipidemia. Pharmacokinetic properties of pitavastatin have been studied previously.

Objective: To investigate the pharmacokinetic properties of pitavastatin in healthy Chinese volunteers after single-dose and multiple-dose administration.

Methods: An open-label, randomized, single-dose and multiple-dose study was conducted in healthy Chinese volunteers. The study included 4 stages, each separated with a 5-day washout period. A randomized, 3-way crossover design was carried out in Stages 1 to 3 for the single-dose study. Eligible subjects were randomized to receive a single 1 mg, 2 mg, or 4 mg pitavastatin calcium tablet. Blood samples were obtained predose and up to 36 hours following dosing. In Stage 4 the subjects received a 2-mg pitavastatin calcium tablet once daily for 6 days. At the last day of multiple dosing, blood samples were collected predose and up to 48 hours following dosing. Plasma pitavastatin was quantified by a validated liquid chromatography tandem mass spectrometry method. Tolerability was assessed by the adverse events, physical examination, 12-lead ECG, and laboratory tests.

Results: Twelve volunteers (6 male and 6 female) were enrolled in the study and 11 of them completed all 4 study stages. Following a single dose of 1 mg, 2 mg, and 4 mg, the mean (SD) T_{max} values were 0.63 (0.17) hours, 0.65 (0.17) hours, and 0.79 (0.36) hours, respectively; the corresponding C_{max} values were 66.80 (16.32) ng/mL, 106.09 (31.59) ng/mL, and 232.91 (66.42) ng/mL, respectively. AUC_{0-36} values were 190.04 (38.97) ng/mL/h, 307.87 (57.94) ng/mL/h, and 785.10 (166.08) ng/mL/h, respectively, whereas $t_{1/2}$ values were 10.99 (2.70) hours, 9.52 (2.58) hours, and 10.38 (4.28) hours, respectively. The AUC and C_{max} showed dose proportionality after single dosing according to linear-regression analysis. In the multiple-dose study, a rapid absorption (T_{max} of 0.68 [0.20] hours) and marked peak concentration of 90.99 (36.88) ng/mL were observed. AUC_{0-48} and AUC_{ss} were 306.28 (130.02) ng/mL/h and 256.16 (116.34) ng/mL/h, respectively. The elimination half-life after multiple dosing was significantly prolonged, which amounted to 13.31 (2.58) hours. Comparison of the pharmacokinetic parameters between the male and female groups revealed no significant differences.

Conclusions: In healthy Chinese volunteers, single dosing of 1 mg, 2 mg, and 4 mg pitavastatin resulted in linear plasma pharmacokinetic properties. Compared with single dosing, multiple dosing of pitavastatin showed different distribution and elimination characteristics. Sex did not appear to affect the pharmacokinetic properties of pitavastatin. Chict.org identifier: ChiCTR-OO-13004294.

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Introduction

Among the numerous medications for the treatment of hyperlipidemia, no class of drugs is so widely prescribed as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,

which are also known as statins.¹ Many previous studies have demonstrated the favorable efficacy and safety profiles of statins in modifying lipid levels and also the effects of lowering the morbidity and mortality of coronary heart disease.^{2–5} Pitavastatin is a newly developed HMG-CoA reductase inhibitor approved for the treatment of hyperlipidemia.⁶ Pitavastatin's effects on lipid parameters have been reported to be significant, and the safety profile comparable with those of other statins such as atorvastatin, simvastatin, and pravastatin.^{7–9} Pitavastatin calcium has been available for clinical use in Japan since 2003 and also has approval

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in China, Korea, and Thailand. In August 2009 it was approved for the treatment of hypercholesterolemia and combined dyslipidemia by the US Food and Drug Administration.¹⁰

Pharmacokinetic (PK) properties and clinical pharmacology of pitavastatin have been studied previously.¹¹ Pitavastatin's PK data are also available for a Chinese population, including female patients and those receiving multiple-dose administration.¹² To add more data to the already published literature, our study was conducted to investigate the PK properties of pitavastatin in healthy male and female Chinese volunteers receiving single- and multiple-dose administration. This was a registered study approved by the China Food and Drug Administration (approval No. 2005L04730).

Subjects and Methods

Study design

This was an open-label, randomized, single- and multiple-dose PK study that planned to enroll 12 (6 male and 6 female) healthy Chinese volunteers. The study included 4 stages, each separated with a 5-day washout period. Stages 1 to 3 are the single-dose study stages in which a randomized, 3-way crossover design was carried out. Based on a computer-generated table of random numbers, 12 subjects were allocated in a 1:1:1 ratio to receive a single 1 mg, 2 mg, or 4 mg pitavastatin calcium tablet in randomized sequence. Stage 4 is the multiple-dose study stage in which 12 subjects received a 2 mg pitavastatin calcium tablet once daily for 6 days.

Inclusion and exclusion criteria

Healthy male and female Chinese volunteers aged 18 to 27 years and with a body mass index between 19 and 24 were eligible for recruitment. Additional inclusion criteria included a healthy status confirmed by medical history, physical examination, 12-lead ECG, laboratory tests (eg, hematology, blood biochemistry, hepatic function, urinalysis, hepatitis B surface antigen, and tests for alcohol and other drugs of abuse), and nonsmoking status.

Subjects were excluded from the study if they had any allergies or history of cardiac, pulmonary, renal, hepatic, gastrointestinal, or hematologic abnormality or any other acute or chronic disease. Other exclusion criteria included exposure to any investigational medication within 30 days of the first dose of study medication, pregnant or nursing women, and women of childbearing potential not using a highly effective method of birth control.

Ethics

The study was approved by the Independent Ethics Committee of West China Hospital, Sichuan University (Chengdu, China) and was conducted in accordance with the Declaration of Helsinki concerning medical research in human beings and the principles of the International Conference on Harmonisation Guideline for Good Clinical Practice. Written informed consent was obtained from each subject before screening procedures.

Drug administration and sample collection

The study drug administration and sample collection were performed in the Phase I Study Unit of West China Hospital, Sichuan University under direct medical supervision. The researched pitavastatin calcium tablets (batch No. 06100901; expiration date October 2008) were provided by Yangzi River Pharmaceuticals Co Ltd (Shanghai, China).

The subjects were admitted to the Phase I Study Unit 1 day before drug administration and were offered a standard dinner.

After an overnight fast (12 hours), subjects received a single dose of 1 mg, 2 mg, or 4 mg pitavastatin calcium tablet on dosing day in each single-dose study stage. The pitavastatin calcium tablets were administered with 200 mL water. Additional water intake was permitted 2 hours following dosing. Subjects were offered a standard meal (~900 kcal; 30% protein, 60% carbohydrate, and 10% fat) 4 and 10 hours following dosing. Blood samples (~4 mL) were collected from an indwelling catheter inserted in a forearm vein before and at 0.25 hours, 0.5 hours, 0.75 hours, 1 hours, 1.33 hours, 1.67 hours, 2 hours, 4 hours, 6 hours, 8 hours, 11 hours, 24 hours, and 36 hours following dosing. In the multiple-dose study stage, subjects received a 2-mg pitavastatin calcium tablet once daily for 6 days. At the third, fourth, and fifth day, blood samples (~4 mL) were collected before dosing. At the last day of multiple dosing, blood samples (~4 mL) were collected before and at 0.25 hours, 0.5 hours, 0.75 hours, 1 hour, 1.33 hours, 1.67 hours, 2 hours, 4 hours, 6 hours, 8 hours, 11 hours, 24 hours, 34 hours, and 48 hours following dosing. The blood sample was drawn into a plastic tube with heparin sodium as anticoagulant and then immediately centrifuged at 3500 revolutions/min for 10 minutes at 4°C. The supernatant plasma was transferred into a polypropylene tube and stored at -20°C until drug analysis.

The volunteers were instructed to abstain from taking any drug, including over-the-counter medications, for 2 weeks before and during the study period, and to abstain from alcohol, smoking, intense physical activity, and caffeine-containing beverages during the study.

Assays of pitavastatin

Plasma pitavastatin was quantified by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed and validated before the clinical study. Plasma pitavastatin quantification was conducted in the Research Center for Drug Metabolism of Jilin University. Chromatography was performed using an Agilent 1100 HPLC system (Agilent Technologies, Santa Clara, California) equipped with an Agilent Extend C18 column (150 mm × 4.6 mm; 5 μm) maintained at 30°C. The mobile phase consisted of acetonitrile-10 mM ammonium acetate in water (45:55 v/v) delivered at a flow rate of 1 mL/min. Mass spectrometric detection employed an API 4000 mass spectrometer (AB Sciex, Concord, Ontario, Canada) equipped with an electrospray ionization source operated in the negative ion mode. The curtain gases, Gas 1 and Gas 2, were nitrogen set at 15, 35, and 35 psi, respectively. The ion spray voltage was adjusted to 5000 V and the source temperature was set at 500°C. Detection was by multiple reaction monitoring at unit resolution for Q1 and unit resolution for Q3 with a dwell time of 200 ms/channel. Transitions of $[M+H]^+$ ions for multiple reaction monitoring were at m/z 421.9 → 290.1 for pitavastatin and m/z 515.2 → 276.1 for internal standard. Declustering potential and collision energy were 100 V and 38 eV for prostaglandin E1 and 90 V and 60 eV for internal standard. Mass spectrometric parameters were tuned to maximize the response of the precursor/product ion combinations. Data acquisition and integration were controlled by Applied Biosystems Analyst version 1.3 software (New York, USA).

A stock solution of pitavastatin calcium (0.2 mg/mL) was prepared in water. Calibration standards of pitavastatin were prepared by diluting the stock solutions with blank plasma to concentrations of 0.287 ng/mL, 0.957 ng/mL, 2.87 ng/mL, 9.57 ng/mL, 28.7 ng/mL, 95.7 ng/mL, and 287 ng/mL. Quality control solutions were prepared independently at concentrations of 0.957 pg/mL, 9.57 pg/mL, and 95.7 pg/mL in the same way. A stock solution (0.2 mg/mL) of the internal standard, telmisartan in methanol-water (50:50 v/v), was diluted in methanol-water (50:50 v/v) to give a 50 ng/mL working internal standard solution. All solutions were stored at 4°C. To 200 μL plasma or calibration standard or quality control sample in a glass tube, 50 μL formic acid

and 50 μL internal standard working solution were added. The mixture was then shaken with 3 mL diethyl ether-dichloromethane (3:2 v/v), centrifuged for 5 minutes at 3500 g, and the organic layer was transferred to another glass tube and evaporated to dryness at 40°C under nitrogen. The residue was reconstituted in 150 μL mobile phase and the 10 μL was injected into the LC-MS/MS system.

Figure 1 shows the chromatograms of a blank plasma sample, a calibration standard, and plasma sample after pitavastatin administration. As Figure 1 shows, no significant interference was observed from endogenous substances in plasma at the retention times of pitavastatin and is the internal standard.

The calibration curve was linear over the range of 0.287 to 287 ng/mL with a typical equation of $y = 0.0157x + 0.000505$ ($r = 0.9980$). The inter- and intraday relative standard deviation of quality-control samples at concentrations of 0.957 ng/mL, 9.57 ng/mL, and 95.7 ng/mL were all < 15%; the relative error of the above 3 concentration-level quality control samples were between -1.25% and 1.92%, supporting the high precision and accuracy of the assay method. Extraction recoveries of pitavastatin for low-, medium-, and high-quality control samples were 89.0% (2.1%), 80.7% (0.92%), and 84.2% (3.7%), respectively. Stability tests showed the analyte was stable in human plasma under the following conditions: at -20°C for 80 days, after 3 freeze-thaw cycles (80°C to room temperature), and processed samples at room temperature for 8 hours.

PK parameters and statistical analysis

PK parameters were calculated using the noncompartmental analysis method with WinNonlin version 6.1 (Pharsight Corporation, Mountain View, California). C_{max} and T_{max} were obtained directly from the concentration time data of pitavastatin. AUC_{0-t} was calculated according to the linear trapezoidal rule. $\text{AUC}_{0-\infty}$ was calculated

as the sum of AUC_{0-t} and C_t/λ . C_t was the last measured concentration and λ was the slope of linear regression of the log-transformed concentration-time curve. Value of $t_{1/2}$ was calculated as the ratio of $0.693/\lambda$. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). Independent-samples t tests or nonparametric tests were used to determine statistically significant differences between the PK parameters. A linear-regression model was used to determine the dose proportionality. For all the analyses, $P < 0.05$ was considered statistically significant.

Tolerability assessment

The subjects were under continuous medical supervision in the Phase I Unit during the study. Data on adverse events were collected by trained study nurses or investigators using nonleading and open-ended verbal questioning. Vital signs were measured at screening, predose, and 0.5 hours, 1 hour, 2 hours, 4 hours, and 24 hours postdose on each dosing day. Physical examination was performed at screening, predose, and 24 hours postdose on each dosing day. All information was recorded in the case-report form. Twelve-lead ECG and laboratory tests, including hematology, blood biochemistry, hepatic function, and urinalysis were conducted at screening and at the end of the study. All laboratory tests were performed at the laboratory of West China Hospital, Sichuan University, which was authenticated by the College of American Pathologists.

Results

Study population

We enrolled 12 subjects (6 male and 6 female) into the study, with the mean age (SD) of 24.6 (1.0) years (range = 23–26 years),

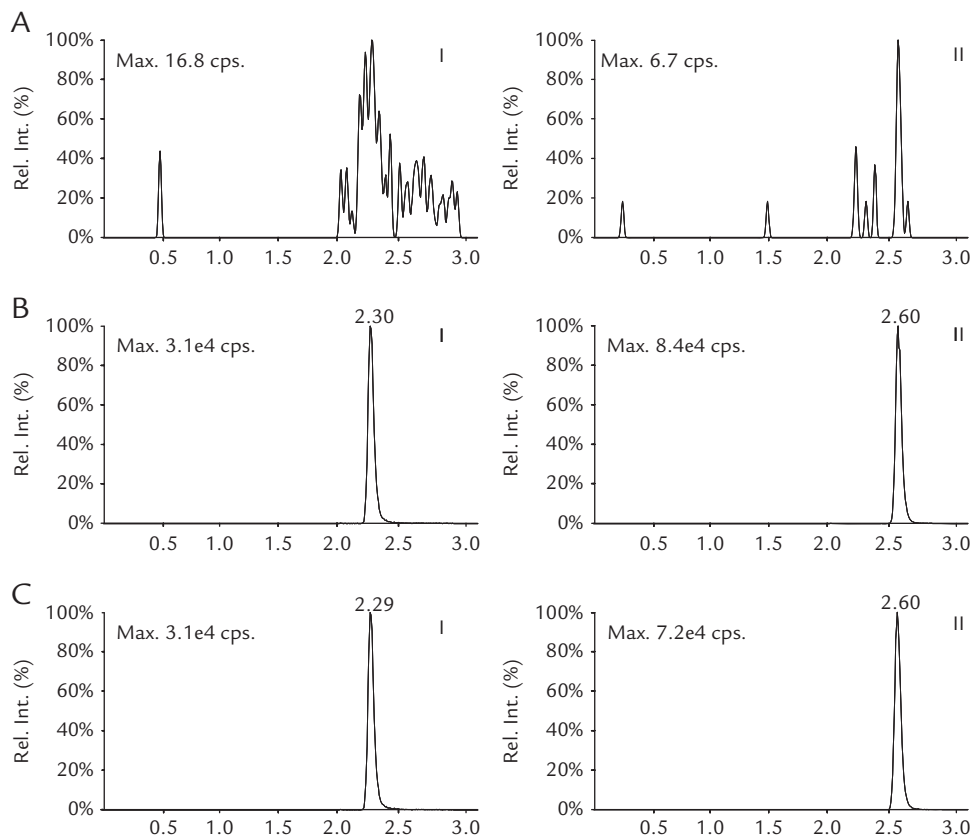


Figure 1. Representative chromatograms of (A) blank plasma sample, (B) plasma sample spiked with pitavastatin and telmisartan, and (C) plasma sample collected at 1.33 hours following dosing. I = pitavastatin. II = telmisartan.

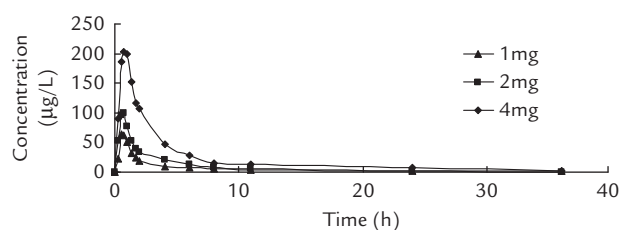


Figure 2. Mean plasma concentration-time curves of pitavastatin after single-dose administration of 1 mg, 2 mg, and 4 mg pitavastatin calcium tablets.

weight 57.0 (6.1) kg (range = 48.0–67.0 kg), and height 162.8 (5.1) cm (range = 155.0–169.0 cm). All subjects completed the 4 study stages except 1 male subject who withdrew from the study following the 1 mg and 2 mg single-dose stage because of withdrawing the informed consent. So, 12 subjects' PK data were obtained for the 1 mg and 2 mg single-dose study and 11 subjects' PK data were obtained for the 4 mg single-dose and multiple-dose study.

PK properties

The mean plasma pitavastatin concentration-time curves are shown in **Figures 2** and **3**. The primary PK parameters are presented in **Table I**. All measurements are stated as the resulting mean (SD) values. Following a single dose of 1 mg, 2 mg, and 4 mg pitavastatin, the drug was rapidly absorbed and the T_{max} values were 0.63 (0.17) hours, 0.65 (0.17) hours, and 0.79 (0.36) hours, respectively. For the 1 mg, 2 mg, and 4 mg dose levels, C_{max} values were 66.80 (16.32) ng/mL, 106.09 (31.59) ng/mL, and 232.91 (66.42) ng/mL, respectively; AUC_{0-36} values were 190.04 (38.97) ng/mL/h, 307.87 (57.94) ng/mL/h, and 785.10 (166.08) ng/mL/h, respectively; and $t_{1/2}$ values were 10.99 (2.70) hours, 9.52 (2.58) hours, and 10.38 (4.28) hours, respectively. The dose proportionality of C_{max} and AUC after single dosing was analyzed by linear regression. The linear regression equation for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were $y = 56.41x + 3.56$, $y = 203.55x - 47.80$, and $y = 213.23x - 46.61$, respectively. The correlation coefficient for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were 0.86, 0.92, and 0.91, respectively. P value was 0.000 for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ linear regression analysis, suggesting that single dosing of 1 mg, 2 mg, and 4 mg pitavastatin resulted in linear plasma PK parameters.

After repeated administration of pitavastatin, mean plasma concentrations attained predose on Day 4 and Day 5 of multiple dosing and at 24 hours postdose on Day 6 were similar, suggesting that a steady state of plasma pitavastatin concentration was achieved around Day 4 of multiple dosing. The steady-state concentration and steady-state trough concentration were 11.05 (4.85) ng/mL and 2.58 (0.92) ng/mL, respectively. Multiple-dose administration of pitavastatin was characterized by some similar PK parameters with single-dose administration. A rapid absorption

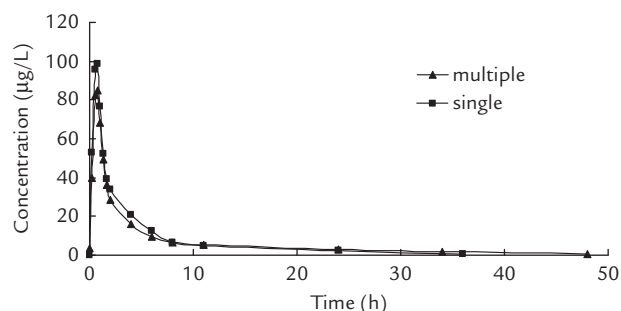


Figure 3. Mean plasma concentration-time curves of pitavastatin after single-dose and multiple-dose administration of 2 mg pitavastatin calcium tablets.

($T_{max} = 0.68$ [0.20] hours) and marked peak concentration 90.99 (36.88) ng/mL were observed. AUC_{0-48} and AUC_{ss} were 306.28 (130.02) ng/mL/h and 256.16 (116.34) ng/mL/h, respectively. Compared with single dosing, the elimination half-life after multiple dosing was significantly prolonged, which amounted to 13.31 (2.58) hours ($P = 0.002$). The mean apparent volume of distribution was 170.02 L and mean plasma clearance was 8.54 L/h after multiple dosing, both of which were also significantly different from those after single dosing ($P < 0.05$). However, the C_{max} or AUC_{0-t} did not increase after repeated administration and the accumulation index, which was calculated as $AUC_{single-dose}/AUC_{multiple-dose}$, was 0.98 (0.28), indicating no accumulation of pitavastatin.

Table II shows the comparison of the main PK parameters between the male and female subjects and reveals no significant differences between groups, suggesting that sex does not appear to affect the PK properties of pitavastatin.

Tolerability

Single doses of 1 mg, 2 mg, or 4 mg pitavastatin calcium tablets and multiple doses of 2 mg pitavastatin calcium tablets once daily for 6 days were well tolerated by all the subjects. One male subject reported a stuffy and running nose that was diagnosed as common cold by investigators. The above symptoms were rated as mild and considered unrelated to the study treatment. No other adverse events were observed or reported. Physical examination, electrocardiograms, and laboratory tests did not suggest any clinically significant abnormality.

Discussion

We investigated the PK properties of pitavastatin in healthy Chinese volunteers. We created and validated a LC-MS/MS method to quantify the plasma pitavastatin. The method validation results of specificity, precision, accuracy, recovery, and stability suggest that our method was suitable for the assay of pitavastatin in human plasma.

In our study, after single dosing of 1 mg, 2 mg, and 4 mg pitavastatin in healthy Chinese volunteers, the peak plasma concentration and AUC of pitavastatin were proportional to the dose, suggesting linear plasma PK properties. Our study revealed that pitavastatin is rapidly absorbed after oral administration, reaching peak concentration within 1 hour. The elimination half-life of pitavastatin after single dosing in healthy Chinese volunteers is about 10 hours. The PK findings from our study are in agreement with those from studies in the published literature.^{10–12} In our study, pitavastatin reached steady state around the fourth day on repeated daily administration, which is in accordance with the published literature.¹⁰

Interestingly, we found that pitavastatin showed somewhat different distribution and elimination characteristics after repeated administration compared with single dosing. The elimination half-life after multiple dosing was significantly prolonged compared with that following single dosing (from 9.52 [2.58] to 13.31 [2.58] hours). Furthermore, the mean apparent volume of distribution after multiple dosing increased to 170.02 L compared with that after single dosing (86.93 L); the mean plasma clearance increased from 6.48 L/h (single dosing) to 8.54 L/h following multiple dosing. Those differences were statistically significant ($P < 0.05$) and furthermore, in our opinion, clinically significant. Pitavastatin is reported to be highly protein bound, primarily to albumin and alpha-1-acid glycoprotein, with a binding ratio of 96%.^{13,14} Animal studies^{15,16} indicated that pitavastatin was widely distributed in tissue, achieving the highest levels in the liver, where levels of pitavastatin were approximately 54 times higher

Table I
Primary pharmacokinetic (PK) parameters of pitavastatin after single-dose administration of 1 mg, 2 mg, and 4 mg pitavastatin calcium tablets and multiple-dose administration of 2 mg pitavastatin calcium tablets in healthy Chinese volunteers.

PK parameter	Single dose		Multiple dose	
	1 mg (n = 12)	2 mg (n = 12)	4 mg (n = 11)	2 mg (n = 11)
C _{max} , ng/mL	66.80 (16.32)	106.09 (31.59)	232.91 (66.42)	90.99 (36.88)
T _{max} , h	0.63 (0.17)	0.65 (0.17)	0.79 (0.36)	0.68 (0.20)
t _{1/2} , h	10.99 (2.70)	9.52 (2.58)	10.38 (4.28)	13.31 (2.58)
AUC _{0–t} , ng/mL/h	190.04 (38.97)	307.87 (57.94)	785.10 (166.08)	306.28 (130.02)
AUC _{0–∞} , ng/mL/h	205.67 (45.62)	321.25 (64.02)	827.59 (190.55)	321.68 (130.56)
Volume of distribution, L	79.86 (26.16)	86.93 (21.82)	72.45 (19.56)	170.02 (89.75)
Mean plasma clearance, L/h	5.09 (1.13)	6.48 (1.41)	5.13 (1.45)	8.54 (2.90)
C _{av} , ng/mL	–	–	–	11.05 (4.85)
C _{min} , ng/mL	–	–	–	2.58 (0.92)
AUC _{ss} , ng/mL/h	–	–	–	265.16 (116.34)

* All values are mean (SD).

than those found in plasma. The wide distribution and high hepatoselectivity of pitavastatin following oral administration makes it minimally exposed to peripheral tissue. Our findings about the change of apparent volume of distribution suggest that pitavastatin is more widely distributed after repeated dosing compared with a single administration. The mechanism of such change might be as follows: after single dosing, the plasma pitavastatin is still in the dynamic distribution processing from peripheral tissue (blood) to liver, and multiple dosing made the distribution saturated. Therefore, pitavastatin is more widely distributed following repeated dosing compared with single dosing. Furthermore, although the plasma clearance of pitavastatin following multiple dosing increased, it could not offset the effect of distribution increase, resulting in a prolonged elimination half-life compared with single dosing. However, the peak plasma concentration and AUC did not increase after repeated administration. The accumulation index, calculated as $AUC_{\text{multiple-dose}}/AUC_{\text{single-dose}}$ and $C_{\text{max, multiple-dose}}/C_{\text{max, single-dose}}$, was 0.98 (0.28) and 0.85 (0.23), respectively. These facts indicated no accumulation of pitavastatin following repeated administration and even smaller exposure of the drug in plasma, minimizing drug toxicity and ensuring the safety of multiple dosing in clinical treatment.

In our study, the comparison of the PK parameters between the male and female subjects revealed no significant differences between groups, suggesting that sex did not appear to affect the PK properties of pitavastatin. Dose adjustments based on sex in the Chinese population are not anticipated.

Pitavastatin is a new HMG-CoA reductase inhibitor with a novel cyclopropyl moiety, which results in several differences compared with other statins. For example, pitavastatin does not undergo significant hepatic metabolism through the cytochrome P450 system. Instead, pitavastatin's cyclopropyl group diverts the drug away from metabolism by cytochrome P3A4 and allows only a small amount of clinically insignificant metabolism by cytochrome P2C9, minimizing its potential to cause many drug–drug interactions.¹⁷ Pitavastatin is rapidly taken up into the liver through organic anion transporting polypeptide 1B1 (OATP1B1)^{18,19} and the polymorphism of OATP1B1 plays an important role in the disposition of pitavastatin in the human body. Chung et al²⁰ reported AUC and C_{max} of pitavastatin to be 1.4- and 8-fold higher, respectively, in subjects heterozygous for the OATP*15 allele compared with those without this allele. A study by Wen et al²¹ showed that the disposition of pitavastatin is significantly altered by the 388A > G genetic variation; that is, the AUC and C_{max} values in the OATP 388GA + 388GG mutant group were about 80% and 71% higher than corresponding values for the 388AA wild-type group and the oral elimination of pitavastatin in the OATP 388GA + 388GG mutant group was about 35% lower than in the 388AA wild-type group. A study²² showed that the OATP1B1*15 allele frequencies differed statistically between Asian populations. Meanwhile, Xu et al²³ reported the frequencies of 388A > G and 521T > C variant alleles in the Chinese population are similar to those in the Japanese population, but significantly different from those in whites and blacks. The OATP1B1 polymorphism may explain the interindividual variations of pitavastatin PK properties

Table II
Comparison of pharmacokinetic (PK) parameters in male and female subjects after single-dose administration of 1 mg, 2 mg, 4 mg pitavastatin calcium tablets and multiple-dose of 2 mg pitavastatin calcium tablets.

PK parameter	1 mg single dose			2 mg single dose			4 mg single dose			2 mg multiple dose		
	Male (n = 6)	Female (n = 6)	P	Male (n = 6)	Female (n = 6)	P	Male (n = 5)	Female (n = 6)	P	Male (n = 5)	Female (n = 6)	P
C _{max} , ng/mL	62.63 (9.71)	70.98 (21.21)	0.401	98.40 (18.73)	113.78 (41.27)	0.425	209.00 (38.03)	252.83 (81.35)	0.299	86.18 (8.56)	98.82 (51.18)	0.714
T _{max} , h	0.58 (0.13)	0.67 (0.20)	0.465	0.63 (0.14)	0.67 (0.20)	0.789	0.65 (0.22)	0.90 (0.44)	0.286	0.60 (0.14)	0.75 (0.22)	0.237
t _{1/2} , h	12.28 (2.73)	9.69 (2.13)	0.098	9.08 (3.34)	9.95 (1.76)	0.585	8.72 (1.32)	11.78 (5.48)	0.273	13.77 (1.50)	12.93 (3.33)	0.619
AUC _{0–t} , ng/mL/h	175.64 (39.53)	204.44 (35.79)	0.215	285.77 (41.22)	329.96 (67.19)	0.200	689.53 (157.68)	764.74 (136.13)	0.145	288.83 (51.74)	320.83 (176.38)	0.706
Volume of distribution, L	86.44 (21.96)	73.28 (9.03)	0.419	86.41 (18.82)	87.45 (26.32)	0.938	72.19 (10.03)	72.67 (26.16)	0.465	164.54 (35.65)	174.59 (122.63)	0.715
Mean plasma clearance, L/h	5.52 (1.28)	4.65 (0.84)	0.194	6.85 (1.08)	6.11 (1.69)	0.200	5.91 (1.57)	4.98 (1.04)	0.120	8.25 (1.27)	8.78 (3.93)	0.782
C _{av} , ng/mL	–	–	–	–	–	–	–	–	–	10.32 (1.86)	11.65 (6.58)	0.674
AUC _{ss} , ng/mL/h	–	–	–	–	–	–	–	–	–	247.74 (44.61)	279.67 (157.86)	0.674

* All values are mean (SD).

in our study to some extent. However, we lacked the volunteers' genetic polymorphism data, which is 1 of the limitations of the study.

Lactonization is the major metabolic pathway of pitavastatin in the human body.²⁴ In our study, we measured plasma pitavastatin, but did not include its main metabolite (pitavastatin lactone [Pi-LAC]) for measurement, which is another limitation of our study. In a recent study in Chinese healthy volunteers, simultaneous determination of pitavastatin and Pi-LAC was conducted.¹² The authors reported the interconversion of pitavastatin and Pi-LAC in human plasma. Interestingly, the authors found pitavastatin is stable and did not convert to Pi-LAC. That is the reason why the interconversion phenomenon has been ignored in most reports of quantification of pitavastatin.^{25,26}

Conclusions

In healthy Chinese volunteers, both single and multiple dosing of pitavastatin are characterized by rapid absorption and sustained concentration of pitavastatin. Linear PK data can be used to describe the PKs from single-dosing data. We found that pitavastatin steady-state concentrations were reached around the fourth day of repeated daily administration. Although multiple dosing of pitavastatin showed different distribution and elimination characteristics compared with single dosing, pitavastatin exhibited no accumulation after repeated administration. Sex did not appear to affect the PK properties of pitavastatin. All the pitavastatin doses tested were well tolerated.

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Zhu Luo and Ping Feng designed this study and provided medical care to the subjects, Zhu Luo wrote the manuscript, Yunhui Zhang and Jingkai Gu performed the assays of pitavastatin, Ying Wang performed blood sampling.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

- [1] Yee LL, Wright EA. Pitavastatin calcium: clinical review of a new antihyperlipidemic medication. *Clin Ther.* 2011;33:1023–1042.
- [2] Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383–1389.
- [3] Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001–1009.
- [4] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267–1278.
- [5] Heart Protection Study Collaborative Group. MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 20536 high risk individuals: a randomized placebo-controlled trial. *Lancet.* 2002;360:7–22.
- [6] Aoki T, Nishimura H, Nakagawa S, et al. Pharmacological profile of a novel synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. *Arzneim Forsch.* 1997;47:904–909.
- [7] Sang HL, Namsik C, Jun K, et al. Comparison of the efficacy and tolerability of pitavastatin and atorvastatin: An 8 - week, multi-center, randomized, open-label, dose - titration study in Korean patients with hypercholesterolemia. *Clin Ther.* 2007;29:365–373.
- [8] Sungha P, Hyun JK, Se JR, et al. A randomized, open - label study to evaluate the efficacy and safety of pitavastatin compared with simvastatin in Korean patients with hypercholesterolemia. *Clin Ther.* 2005;27:1074–1082.
- [9] Toi T, Taguchi I, Yoneda S, et al. Early effect of lipid-lowering therapy with pitavastatin on regression of coronary atherosclerotic plaque: comparison with atorvastatin. *Circ J.* 2009;73:1466–1472.
- [10] *Livalo (pitavastatin) product information.* Montgomery, AL: Kowa Pharmaceuticals America, Inc; 2010.
- [11] Mukhtar RY, Reid J, Reckless JP. Pitavastatin. *Int J Clin Pract.* 2005;59:239–252.
- [12] Qi X, Ding L, Wen A, et al. Simple LC-MS/MS methods for simultaneous determination of pitavastatin and its lactone metabolite in human plasma and urine involving a procedure for inhibiting the conversion of pitavastatin lactone to pitavastatin in plasma and its application to a pharmacokinetic study. *J Pharm Biomed Anal.* 2013;72:8–15.
- [13] Kajinami K, Mabuchi H, Saito Y. NK-104: A novel synthetic HMG-CoA reductase inhibitor. *Expert Opin Invest Drugs.* 2000;9:2653–2661.
- [14] Suzuki H, Yamazaki H, Aoki T, et al. Lipid-lowering antiatherosclerotic effect of NK-104 (nisvastatin), a new synthetic HMG-CoA reductase inhibitor, in WHHL rabbits. *International Symposium on Drugs Affecting Lipid Metabolism (DALM).* 1998;13:53 (Abstract).
- [15] Kimata H, Fujino H, Koide T, et al. Studies on the metabolic fate of NK-104, a new inhibitor of HMG-CoA reductase (1): Absorption, distribution, metabolism and excretion in rats. *Xenobiot Metab Dispos.* 1998;13:484–498.
- [16] Fujino H, Yamada I, Shimada S, Kojima J. Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase - Effect of cMOAT deficiency on hepatobiliary excretion in rats and of mdr 1a/b gene disruption on tissue distribution in mice. *Drug Metab Pharmacokinet.* 2002;17:449–456.
- [17] Baker WL, Datta R. Pitavastatin: a New 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitor for the Treatment of Hyperlipidemia. *Adv Ther.* 2011;28(1):13–27.
- [18] Hirano M, Maeda K, Shitara Y, Sugiyama Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. *J Pharmacol Exp Ther.* 2004;311:139–146.
- [19] Nakai H, Nakagomi R, Furuta Y, et al. Human liver-specific organic anion transporter, LST-1, mediates take of pitavastatin by human hepatocytes. *J Pharmacol Exp Ther.* 2001;297:861.
- [20] Chung JY, Cho JY, Yu KS, et al. Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. *Clin Pharmacol Ther.* 2005;78:342–350.
- [21] Wen J, Xiong Y. OATP1B1 388A > G polymorphism and pharmacokinetics of pitavastatin in Chinese healthy volunteers. *J Clin Pharm Ther.* 2010;35:99–104.
- [22] Kim EY, Cho DY, Shin HJ. Duplex pyrosequencing assay of the 388A > G and 521T > C SLCO1B1 polymorphisms in three Asian populations. *Clin Chim Acta.* 2008;388:68–72.
- [23] Xu LY, He YJ, Zhang W. Organic anion transporting polypeptide-1B1 haplotypes in Chinese patients. *Acta Pharmacol Sin.* 2007;28:1693–1697.
- [24] Yamada I, Fujino H, Shimada S, Kojima R. Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: similarities and difference in the metabolism of pitavastatin in monkeys and humans. *Xenobiotica.* 2003;33:789–803.
- [25] Chen Y, Tan ZR, Zhou G, et al. LC-MS determination of pitavastatin in human plasma and its application. *J Clin Pharmacol.* 2011;46:134–137.
- [26] Deng JW, Kim KB, Song IS, et al. Determination of two HMG-CoA reductase inhibitors, pravastatin and pitavastatin, in plasma samples using liquid chromatography-tandem mass spectrometry for pharmaceutical study. *Biomed Chromatogr.* 2008;22:131–135.