Hindawi Publishing Corporation
Journal of Biomedicine and Biotechnology
Volume 2012, Article ID 386230, 4 pages
doi:10.1155/2012/386230

Research Article

The Difference in Pharmacokinetics and Pharmacodynamics between Extended-Release Fluvastatin and Immediate-Release Fluvastatin in Healthy Chinese Subjects

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Received 7 February 2012; Revised 28 April 2012; Accepted 14 May 2012

Academic Editor: Kazim Husain

The aim of this study was to evaluate the difference in pharmacokinetics and pharmacodynamics between extended-release (ER) fluvastatin tablet and its immediate-release (IR) capsule in Chinese healthy subjects. This was an open-label, single/multiple-dose, two-period, two-treatment, crossover, randomized trial with a minimum washout period of 7 days. Twenty healthy male adult subjects were given fluvastatin ER tablet 80 mg QD by oral administration or fluvastatin IR capsule 40 mg BID for seven days. Blood samples were collected up to 24 hours after dosing on day 1 and day 7. Serum concentrations of fluvastatin were determined by LC-MS/MS. For fluvastatin ER tablet 80 mg QD, C_{max} was 61.0 ± 39.0 and 63.9 ± 29.7 ng/mL, and $AUC_{0-24\,h}$ was 242 ± 156 and 253 ± 91.1 ng·h/mL on day 1 and 7, respectively. For fluvastatin IR capsule 40 mg BID, C_{max} was 283 ± 271 and 382 ± 255 ng/mL, and $AUC_{0-24\,h}$ was 720 ± 776 and 917 ± 994 ng·h/mL on day 1 and day 7, respectively. The relative bioavailability of fluvastatin ER tablet 80 mg QD to fluvastatin IR capsule 40 mg BID is (45.3 ± 23.9)% and (43.3 ± 24.1)% on day 1 and day 7, respectively. T_{max} for fluvastatin ER tablet was 2.50 and 2.60 h and for capsule was 0.78 and 0.88 h on day 1 and day 7, respectively. In the first period, compared to baseline, cholesterol decreased 15.3% in fluvastatin ER tablet 80 mg QD and 16.9% in fluvastatin IR capsule 40 mg BID. Triglyceride decreased 3.7% in fluvastatin ER tablet 80 mg QD and 19.1% in fluvastatin IR capsule 40 mg BID. The difference has no statistical significance at $P > 0.05$ in reduction percent of cholesterol and triglyceride between the two groups. No adverse events were recorded. The results indicated that C_{max} of fluvastatin ER tablet is reduced and T_{max} is prolonged compared with IR capsule. There is no accumulation for ER formulation after multiple doses.

1. Introduction

Fluvastatin, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is the first fully synthetic HMG-CoA reductase inhibitor and the well-established first-line agent for the treatment of hypercholesterolemia, primarily due to its marked lowering action of low-density lipoprotein cholesterol (LDL-C) levels (as discussed by Bruckert et al. [1]). The benefits of statin therapy on cardiovascular morbidity and mortality are thought to be related to both LDL-C lowering and pleiotropic effects such as modulation of inflammatory protein levels (as discussed elsewhere [2, 3]). Small increases in HDL-C and variable decrease in TG are also observed.

Fluvastatin is relatively hydrophilic, compared with the semisynthetic HMG-CoA reductase inhibitors, and, therefore, it is extensively absorbed from the gastrointestinal tract. After absorption, it is nearly completely extracted and metabolized in the liver to 2 hydroxylated metabolites and an N-desisopropyl metabolite, which are excreted in the bile. Approximately 95% of a dose is recovered in the faeces, with 60% of a dose recovered as the 3 metabolites (as discussed by Scripture and pieper [4]). An ER formulation of fluvastatin was developed as a starting and maintenance treatment for once-daily administration. It uses a hydrophilic cellulose matrix that swells when it is in contact with fluid in the intestine. Fluvastatin then diffuses through the matrix and is released over an 8-hour period. It was hypothesized that

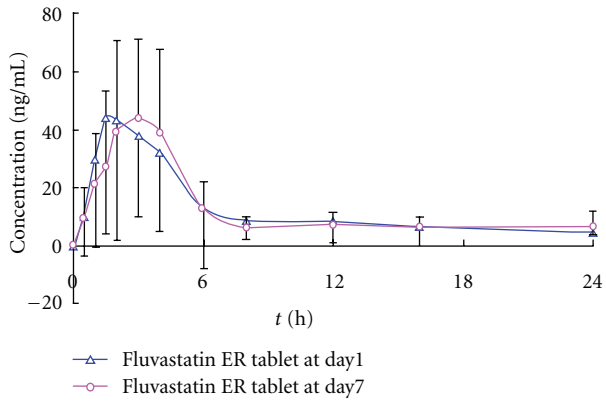

Figure 1: The mean serum concentration-time curves after single and multiple doses of fluvastatin extended-release tablet in Chinese healthy volunteers ($n = 20$).

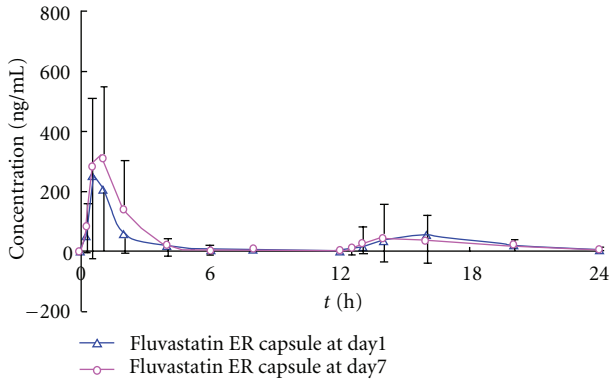

Figure 2: The mean serum concentration-time curves after single and multiple doses of fluvastatin immediate-release capsule in Chinese healthy volunteers ($n = 20$).

this new formulation would avoid hepatic saturation without elevating systemic drug levels and thus provide greater efficacy compared with the conventional formulation (as discussed elsewhere [5, 6]). Fluvastatin ER tablet 80 mg/d has been reported to provide comprehensive lipid management with a good safety profile similar to that of placebo in clinical trials (as discussed by Battantyne et al. [7]).

The pharmacokinetic properties of two fluvastatin formulations have been investigated in healthy white adult subjects (as discussed by Isaacsohn et al. [5]). Fluvastatin systemic exposure was less than 50% when administered as fluvastatin ER 80 mg qd compared with fluvastatin IR 40 mg BID (as discussed by Barilla et al. [6]). There is no pharmacokinetic data for fluvastatin ER tablet in Chinese subjects.

The purpose of the present study was to evaluate the difference in pharmacokinetics and pharmacodynamics between extended-release (ER) fluvastatin tablet and its immediate-release (IR) capsule after single and multiple doses in Chinese healthy subjects living in China. The study was conducted in accordance with the regulatory requirements for registration in China.

2. Materials and Methods

2.1. Study Populations. Twenty healthy male adult subjects were invited to participate in an open-label, randomized, single and multiple dose, two-period, two-treatment, crossover study. At the time of enrolment, the subjects were informed of the purpose, duration, and risks of the study, and they were requested to sign a written informed consent. They were also informed about the possibility of withdrawing from the study. They were prohibited to take food that contains xanthine or beverages from 48 h prior to the study until the end of the study. The subjects were also instructed to abstain from taking any medication except paracetamol in 2 weeks prior to the study. The evaluations and tests performed included physical examination, body height, body weight, vital signs (heart rate, systolic and diastolic blood pressure, and body temperature), hematology, blood chemistry, urinalysis, and electrocardiogram. The subjects were requested to report any abnormality occurring throughout and after the study. The results of clinical evaluations were documented in individual case report forms. The study protocol was approved by the Ethics Committee of Zhongshan Hospital.

2.2. Study Design. Healthy subjects were randomized in two groups of ten subjects, and each group received the two drug treatments at two different periods, with a 7-day interdose washout periods. Each volunteer received fluvastatin ER tablet 80 mg QD or fluvastatin IR capsule 40 mg BID for seven days. Each formulation was administered with 200 mL of water to subjects after a 10 h overnight fasting. Lunch and dinner were served at 4 and 10 h after dose, respectively. If the subject is receiving the fluvastatin IR BID treatment, the evening dose of fluvastatin IR 40 mg will be administered 12 hours following the morning dose. The evening meal should be consumed 3 hours prior to this dose. Blood samples were collected through an intravenous catheter in the Lescol IR 40 mg group before dose and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 16, 20, and 24 h after dose on day 1 and day 7. And for fluvastatin 80 mg ER tablet group, blood samples were drawn prior to dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 h following dose on day 1 and day 7. The blood samples were transferred to tubes and centrifuged (4°C) at 800 rpm for 15 min. The serum samples were stored at –20°C until chromatographic analysis.

2.3. Determination of Serum Fluvastatin Concentrations. Serum fluvastatin concentrations were determined by using an LC-MS/MS method developed by personnel at Zhongshan Hospital, Shanghai, China, in which 6-methyl-fluvastatin sodium was used as the internal standard. The method included 0.2 mL serum, 0.1 mL of internal standard solution(6-methyl-fluvastatin 200 ng/mL), 0.4 mL saturation sodium chloride solution, and 0.8 mL acetonitrile. These constituents were mixed together in a 2.0 mL centrifuge tube for 30 s. The tube was centrifuged for 15 min at 18000 rpm and 4°C. The supernatant was filtered by 0.45 μm membrane and injected into the chromatographic system (SIL-HTc, Shimadzu Corporation, Kyoto, Japan). Fluvastatin concentration was determined with a 5.0 cm × 3.0 mm

Table 1: Pharmacokinetic parameters of fluvastatin of two fluvastatin formulations after single and multiple doses in healthy volunteers (Mean ± SD).

	Parameter	Test (extended-release tablet)	Reference (immediate-release capsule)
Single dose	C_{max} (ng/mL)	61.0 ± 39.0	283 ± 271
	T_{max} (h)	2.50 ± 1.34	0.78 ± 0.38
	MRT (h)	4.98 ± 2.28	1.45 ± 0.44
	AUC_{0-24} (ng·h/mL)	242 ± 156	720 ± 776
	F (%)	45.3 ± 23.9	
Multiple doses	C_{max} (ng/mL)	63.9 ± 29.7	382 ± 255
	C_{min} (ng/mL)	1.94 ± 4.16	0.574 ± 1.63
	C_{av} (ng/mL)	12.2 ± 7.76	52.5 ± 45.2
	T_{max} (h)	2.60 ± 0.87	0.88 ± 0.36
	MRT (h)	5.57 ± 2.40	1.43 ± 0.30
	AUC_{0-24} (ng·h/mL)	253 ± 91.1	917 ± 994
	R	1.39 ± 0.77	2.07 ± 1.42
	DF (%)	566 ± 214	811 ± 213
	F (%)	43.3 ± 24.1	

internal diameter column of 3.5 μm particle size (XTerra RP18 column, Shiseido Corporation, Tokyo, Japan) and eluted with a mobile phase consisting of a mixture of 1‰ formic acid in water and methanol (25 : 75 v/v). The column temperature was 40°C. Flow rate was maintained at 0.30 mL/min, and fluvastatin was detected by MS/MS detector (Sciex API 3000, Foster City, CA, USA). The mass analyzer was operated in multiple reaction mode; m/z for fluvastatin and 6-methyl-fluvastatin were 410.2 → 348.1 and 424.2 → 362.0, respectively. Typical retention time for fluvastatin and internal standard were 2.16 and 2.52 min, respectively. Data acquisition and analysis were carried out using Sciex Analyst 1.4 software. The fluvastatin peak area was used for quantification. Under these conditions, the method was linear in the range of 2 to 2000 ng/mL (2, 5, 10, 20, 50, 100, 200, 500, 1000, 2000 ng/mL). Accuracy was between 91.50% and 100.85%; the relative SD (RSD) of the method was always <11%. The method was considered suitable by study investigators for the pharmacokinetic study of fluvastatin.

2.4. Pharmacokinetic and Pharmacodynamic Evaluation and Statistical Analyses. Pharmacokinetic parameters were calculated by a noncompartmental method. The actual time of sample collection was used for pharmacokinetic analyses of fluvastatin ER tablet and IR capsule. The area under the serum concentration versus time curve AUC_{0-t} was obtained by the linear trapezoidal method. Mean residence time (MRT) is the average total time of a given dose spent in the body, which may be calculated as MRT = AUMC/AUC. The average steady-state concentration (C_{av}) is calculated as $C_{av} = AUC_{0-\tau}/\tau$. The C_{max} and T_{max} were obtained directly from the data. The degree of peak-trough fluctuation at steady state (DF) was calculated using the following equation: $DF(\%) = (C_{max,ss} - C_{min,ss})/C_{av,ss} \times 100\%$, where $C_{max,ss}$, $C_{min,ss}$, and $C_{av,ss}$ are the maximum, minimum, and average serum concentration, respectively, during a dosing interval at steady state. The accumulation ratio (R) was calculated as $C_{max,ss}/C_{max}$. An accumulation ratio of 1 indicated no or minimal accumulation.

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and was performed using the F ratio, where F was the ratio of AUC_{0-24} for fluvastatin ER tablet versus fluvastatin IR capsule. Ratios of $\ln(C_{max})$ and $\ln(AUC_{0-t})$ for all formulations were calculated, and 90% CIs were obtained. An analysis of variance (ANOVA, SPSS16.0) for cholesterol and triglyceride was carried out to evaluate the pharmacodynamic difference between fluvastatin ER tablet and fluvastatin IR capsule after continuous 7-day administration.

3. Results and Discussion

3.1. Pharmacokinetic Results. A total of 20 subjects (male; mean (SD) age, 22.6 (1.1) years (range, 21–25 years); weight, 65.6 (7.6) kg (56–80 kg); height, 1.74 (0.62) m (1.62–1.85 m); BMI, 21.7 (1.7) kg/m^2 (18.7–24.0 kg/m^2)) were included in and completed the study. Ten subjects received fluvastatin ER tablet once daily first, and the others received fluvastatin IR capsule twice daily first.

Mean serum concentration-time curves of fluvastatin formulations on day 1 and day 7 are shown in Figures 1 and 2, and the pharmacokinetic properties (C_{max}, T_{max}, MRT, AUC_{0-24}) are summarized in Table 1. Ninety percent confidence intervals of AUC_{0-24} ratios were 0.306, 0.494 (ratio 0.388) and 0.293, 0.466 (ratio 0.370) for fluvastatin ER tablet versus fluvastatin IR capsule on day 1 and at day 7, respectively. Ninety percent confidence intervals of C_{max} ratios were 0.184, 0.376 (ratio 0.263) and 0.158, 0.233 (ratio 0.192) for fluvastatin ER tablet versus fluvastatin IR capsule on day 1 and at day 7, respectively.

3.2. Pharmacodynamic Results. The mean baseline of cholesterol and triglyceride of ten subjects who received fluvastatin

ER tablet once daily first was 3.70 ± 0.70 and 0.67 ± 0.16 mmol/l. The mean reduction of cholesterol and triglyceride after continuous 7-day administration was 0.58 ± 0.24 and 0.05±0.16 mmol/l, respectively. The percent of reduction was 15.3 ± 5.4% and 3.7 ± 19.8%, respectively. The mean baseline of cholesterol and triglyceride of ten subjects who received fluvastatin IR capsule twice daily first was 3.84±0.87 and 0.87 ± 0.39 mmol/l. The mean reduction of cholesterol and triglyceride after continuous 7-day administration was 0.71 ± 0.56 and 0.23 ± 0.31 mmol/l, respectively. The percent of reduction was 16.9 ± 11.2% and 19.1 ± 20.4%, respectively. The difference has no statistical significance at $P > 0.05$ in baseline of cholesterol and triglyceride between group of 80 mg fluvastatin ER tablet and group of 40 mg fluvastatin IR capsule. The difference has also no statistical significance at $P = 0.681$ and $P = 0.104$ in reduction percent of cholesterol and triglyceride between the two groups, respectively.

3.3. Tolerability. No adverse events occurred throughout the study.

3.4. Discussion. The ER formulation of fluvastatin was developed to decrease the frequency of dose administration and to reduce the incidence of AEs by reducing peak serum concentrations after drug administration. Because these concentrations may be related to the extent in which patients experience common AEs, the use of an ER formulation may help reduce these effects and improve tolerability.

Results from the single and multiple dose study showed that in Chinese healthy subjects, the mean C_{max} of 80 mg fluvastatin ER tablet once daily at single dose and multiple doses was 61.0 and 63.9 ng/mL, which was 78.4% and 83.3% lower compared with that of 40 mg fluvastatin IR capsule twice daily at single dose and multiple doses, respectively. The mean exposure with ER tablet (single dose and multiple dose $AUC_{0-24\,h}$) was 242 and 253 ng·h/mL, which were 66.4% and 72.5% lower compared with IR capsule, respectively. However, the difference has no statistical significance at $P > 0.05$ in reduction percent of cholesterol and triglyceride between group of 80 mg fluvastatin ER tablet and group of 40 mg fluvastatin IR capsule. The possible reason was that the time of effective concentration for 80 mg fluvastatin ER was no shorter than that for 40 mg fluvastatin IR.

The peak concentration was delayed for ER formulation of fluvastatin. In addition, there was less fluctuation from C_{max} to C_{min} for ER formulation of fluvastatin compared with IR formulation of fluvastatin.

4. Conclusion

The LC-tandem mass spectrometry method established for the determination of fluvastatin in human serum following administration of fluvastatin is simple, rapid, and showed to be highly reproducible and accurate. Compared with immediate-release formulation, C_{max} of fluvastatin extended-release tablet is reduced and T_{max} is prolonged, respectively. There is no accumulation for extended-release formulation after multiple doses. The difference has no statistical significance at $P > 0.05$ in reduction percent of cholesterol and triglyceride between the two groups. Fluvastatin was well tolerated following single and multiple doses.

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