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The pharmacokinetic characters of simvastatin after co-administration with Shexiang Baoxin Pill in healthy volunteers' plasma

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ABSTRACT

To investigate the effect of Shexiang Baoxin Pill (SBP), a tranditional Chinese medicine, on the pharmacokinetic (PK) parameters of simvastatin in healthy volunteers' plasma, a quantitative method was developed using an Agilent G6410A rapid performance liquid chromatography (RPLC) coupled with triple quadrupole mass spectrometry system. The established method was rapid with high extraction recovery and successfully applied for the determination of simvastatin in plasma of 16 healthy volunteers. The results demonstrated that the $MRT_{(0-\infty)}$, $T_{1/2}$ and T_{max} value of simvastatin were significantly decreased, while the $AUC_{(0-t)}$ and C_{max} values of smivastatin were increased by SBP. The pharmacokinetic study demonstrated that the metabolism parameters of simvastatin could be affected by SBP and the potential drug–drug interaction should be noted in the future clinical practice.

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1. Introduction

Simvastatin is used to treat hyperlipidemia in clinic and has been recommended in the national cholesterol education program in USA [1–3]. As an inhibitor of HMG-CoA reductase, simvastatin shows satisfied effects to reverse the progression of coronary artery diseases (CAD) through improving endothelial function, reducing inflammation, and reducing thrombus formation [4–12]. With the large-scale application of simvastatin in clinic, the adverse effects of simvastatin were gradually observed such as myopathy and rhabdomyolysis [13,14]. To avoid the clinic adverse and monitor the concentration of simvastatin in plasma, the pharmacokinetic parameters of simvastatin were well studied. The clinical studies showed that the T_{max} values of simvastatin were various (from 1.3 to 2.4 h). Moreover, the elimination rate of simvastatin is rapid. The plasma concentration decreases to 10% of C_{max} at 4 h after administration. The bioavailability of simvastatin is as high as 85% [15]. Liver is the main organ for simvastatin distribution, and it is mainly metabolized by P450 [15,16].

As CAD is usually caused by multi-factors, the effectiveness of statins alone is limit. In clinical practice of China, traditional Chinese medicines (TCMs) were often used to treat CAD together with simvastatin such as Shexiang Baoxin Pill (SBP). The source of SBP formula is from "Taiping Huimin Heji Ju Fang" in Song Dynasty. It consists of seven medicinal materials including moschus, radix rhizoma ginseng, calculus bovis, cortex cinnamomi, styrax, venenum bufonis, and borneolum syntheticum and has been officially recorded in the Chinese pharmacopoeia since 1990s edition. SBP was used for chest pain caused by qi stagnation and blood stasis in TCM hospital for thirty-five years. Pharmacological studies demonstrated that SBP could reduced myocardial fibrosis [17,18], inhibited collagen proliferation of artery [19,20], and decreased infarct area in rat with coronary occlusion [21–24]. Until now, there were nearly 400 cases reported for co-administration of SBP and simvastatin [25–28].

Through identification of chemical components of SBP, hundreds of compounds, such as ginsenosides form radix rhizoma ginseng, bufadienolides from venenum bufonis, bile acids from

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calculus bovis and other volatile components were identified [29]. It has been reported that some components in SBP, such as bufalin, cinobufagin, and resibufogenin, were metabolized by CYP3A4 [30]. Thus, whether and how SBP change the PK parameters of simvastatin is worth of being studied.

In present study, we observed that the PK profile of simvastatin could be changed by SBP through analyzing the plasma of sixteen healthy volunteers. The direct clinical evidence indicated that the dosage of simvastatin should be adjusted when was co-administrated with SBP to prevent potential adverse effects induced by drug–drug interaction.

2. Material and method

2.1. Chemicals and reagents

HPLC grade acetonitrile was purchased from JT Baker (NJ, USA). HPLC grade *n*-butanol, hexane, ethyl acetate (EA) and methanol were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, P. R. China). Ion-free water from a Milli-Q50 SP Reagent Water System (Millipore Corporation, MA, USA) was used for the sample and mobile phase preparation. The standard simvastatin and lovastatin (structure shown in Fig. 1) were purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, P. R. China). SBP (bath number 20141208) was kindly offered by Shanghai Hutchison Pharmaceuticals Company (Shanghai, China). The finger printer similarities of volatile and nonvolatile components of SBP sample were both above 0.9 by comparing with the standard finger printers respectively [31,32]. The simvastatin tablet (10 mg/tablet) were purchased from Shanghai Sine Wanxiang Pharmaceutical Co., Ltd. (Shanghai, P. R. China).

2.2. Instrumentation and parameters

2.2.1. Rapid performance liquid chromatography (RPLC)

RPLC analysis was carried on an Agilent-1200 (Agilent Technologies, Palo Alto, MA, USA) RPLC system included quaternary pump, vacuum degasser, autosampler and column heater–cooler. Separation was performed on a Agilent ZORBAX eclipse XDB-C_{18} column (2.1 × 100 mm, 1.8 μm) at 40 °C and 0.3 ml/min. The mobile phase consisted of water–0.1% formic acid (A) solution and acetonitrile (B) solution. The following gradient program was used: 0.0–5.0 min, 90.0% of B; 5.0–8.0 min, 95.0% of B; post time was 5.0 min. The injection volume was 10.0 μl.

2.2.2. MS parameters

An Agilent 6410A triple quadrupole LC/MS system (Agilent Corporation, MA, USA) was used for MS acquisition. The system was controlled by Mass Hunter software (Agilent Corporation, MA, USA). Ionization was achieved using electrospray in the positive mode. The MS parameters were set as follows: flow rate of desolvation gas (nitrogen) 10.0 l/min, temperature 350 °C, pressure of nebulizer gas 40 psi, capillary voltage 4000 V. Quantification was performed using multiple reaction monitoring (MRM) mode. Ion transitions from 441.3 to 325.2 and from 427.3 to 325.2 were used to detect simvastatin and lovastatin, respectively. The fragment voltages for both simvastatin and lovastatin were 210 V. CEs were set as 24 V and 20 V for simvastatin and lovastatin, respectively. The fragmentation schemes of simvastatin and lovastatin are shown in Fig. 1.

2.3. Subjects and study design

Sixteen male volunteers between 25 and 30 years old with weight range 60–70 kg were selected in this study. Each volunteer was in good health as assessed by physical examination.

Each volunteer was orally administered 20 mg of simvastatin followed by venous blood sampling (3 ml) at 0.00, 0.08, 0.17, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 11.0 h after drug administration. After a washout period of one week, all volunteers were given SBP (67.5 mg/day) for 7 days. At the eighth day, each volunteer was co-administration of simvastatin (20 mg) and SBP (67.5 mg), and then collected 3 ml blood samples at 0.00, 0.08, 0.17, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 11.0 h after drug administration. All subjects remained under close medical supervision and were supplied uniform diets. All blood samples were collected in micro-centrifuge tubes coated with heparin. Blood samples were centrifuged immediately at 4000 r/min for 15 min, then transferred the plasma into fresh tubes and stored in a −80 °C freezer until analysis. Blank plasma samples used for method establishment and validation were collected from vehicle-administrated human volunteers.

This study followed guidelines of the Helsinki Declaration of 1975 and the protocol was approved by the Ethics Committee of the Second Military Medical University.

2.4. Preparation of standard solution, working solution and quality control samples

As the similar chemical structure, chromatography profile, and mass response, lovastatin was chosen as the internal standard (IS). Standard stock solutions of simvastatin and IS were prepared in

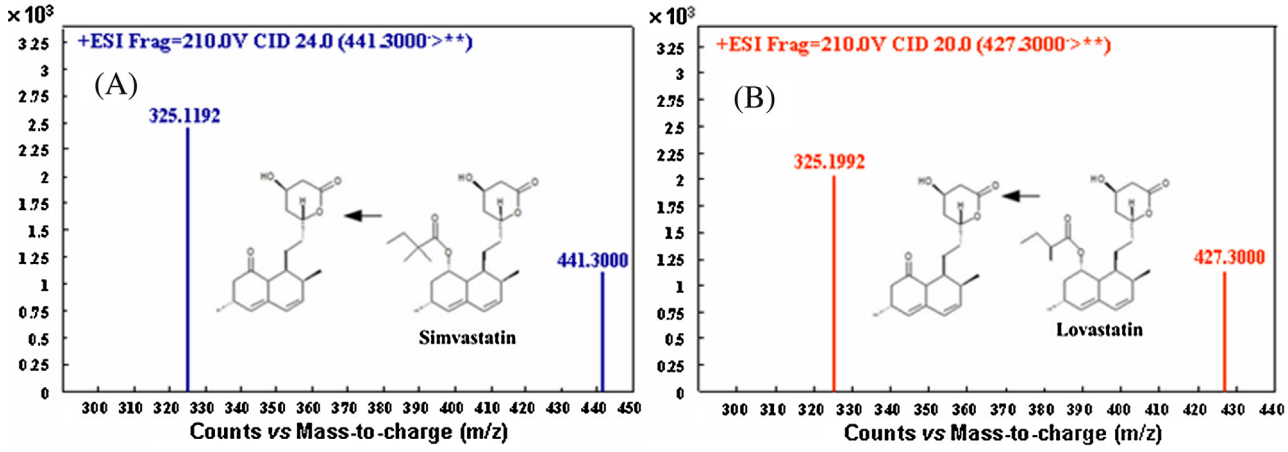

Fig. 1. The fragmentation scheme of simvastatin and lovastatin in mass spectrometry.

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