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CLINICAL STUDY

Effect of naringenin in Qianggu capsule on population pharmacokinetics in Chinese women with primary osteoporosis

Wang Jiannong, Jiang Junjie, Xie Yanming, Wei Xu, Li Jianpeng, Duan Jingli, Xiong Xin

Wang Jiannong, Institute of Basic Medical Sciences, Xi Yuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100093, China

Jiang Junjie, Xie Yanming, Wei Xu, Li Jianpeng, Chinese Clinical Basic Institute, China Academy of Chinese Medical Sciences, Beijing 100700, China

Duan Jingli, Xiong Xin, Department of Pharmaceutics, Third Hospital Affiliated Peking University, Beijing 100083, China

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Correspondence to: Prof. Xie Yanming, Chinese Clinical Basic Institute, China Academy of Chinese Medical Sciences, Beijing 100700, China. Datamining5288@163.com

Telephone: +86-13911112416; +86-64014411-3302

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Abstract

OBJECTIVE: To characterize naringenin (NAR) population pharmacokinetics (PPK) in Chinese women with primary osteoporosis.

METHODS: Ninety-eight female patients with primary osteoporosis from the Jingshan, Beixinqiao, Jiaodaokou, Chaoyangmen, and Donghuamen communities in Beijing, China, aged 40 to 80 years, received oral Qianggu capsules (250 mg). Blood samples were collected before and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after administration. The concentration of NAR in the blood samples was measured using high performance liquid chromatography-tandem mass spectrometry. PPK analyses were performed with nonlinear mixed-effect modeling software (version 7.1.2, PsN3.2.12). The clearance (C1), central distribution volume (V), absorption rate constant (Ka1), peripheral distribution volume (VII), and inter-compartmental clearance (CLII) were set as parameters and estimated by the base model, covariate model, and final model. Kidney-*Yang* deficiency [Shenyangxu (SYAX)] and liver-kidney-*Yin* deficiency (Ganshenyinxu) are patterns of symptoms in Traditional Chinese Medicine that were set as covariates, along with age, height, blood urea nitrogen, serum creatinine, alanine transaminase, aspartate transaminase, and hyperlipidemia. Both stepwise forward and backward procedures were accomplished to build models. The final model was evaluated by internal and external validation, visual predictive check, bootstrap, and leverage analysis.

RESULTS: A one compartment open model with first order degradation was the best fitted to the concentration-time profiles following oral administration of NAR. The mean of population parameters of the final model, C1, SYAX on C1, V, Ka1, CLII, and VII, were measured to be 37.6 L/h, 0.427 L, 123 L/h, 0.12/h, 0.3056, and 1.446, respectively. Inter-individual variability was estimated and SYAX was identified as a significant covariate.

CONCLUSION: The population pharmacokinetic model described in this study could effectively characterize the pharmacokinetic profile of NAR following administration of a single dose of oral Qianggu capsules in Chinese women with primary osteoporosis. Among the tested covariates, only SYAX was a significant factor.

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Key words: Naringenin; Pharmacokinetics; Medicine, Chinese traditional; Qianggu capsule; Total flavonoids of Drynaria fortunei

INTRODUCTION

Qianggu capsules, which we developed in 2003, have been widely used in China for the treatment of women with primary osteoporosis. Naringenin (4′, 5, 7-trihydroxyflavanone, NAR), the active compound found in Qianggu capsules, has been reported to increase the bioavailability of other drugs, and have antioxidant,[1] anti-ulcer,[2] anti-tumor, anti-allergy, phlegm removing, cough suppressing, anti-inflammatory, and anti-hyperlipidemia activities.[3]

Various methods have been reported for quantification of NAR in biological samples to support preclinical and clinical studies. Most reported approaches involve long and tedious sample detection and preparation, such as solid phase extraction or protein precipitation, which involves multiple steps.[3-5] Further, there is limited plasma data or pharmacokinetic parameters of NAR in humans. Inter-subject variability in pharmacokinetics can also vary considerably among individual drugs and depends on a variety of factors. One potential factor involves Traditional Chinese Medicine (TCM) symptoms. We aimed to use HPLC-MS/MS assay method to assess the sensitivity of NAR population pharmacokinetics to TCM symptoms.

MATERIALS AND METHODS

The following diagnostic criteria, inclusion criteria, exclusion criteria, exclusion criteria, subject recruitment, drug administration and blood sampling, chemicals and reagents, instrumentation, HPLC, analysis conditions, and sample preparation methods are based on previous reported methods with some minor modifications.[6]

Subject recruitment

Ninety-eight female subjects, aged 40 to 80 years, were recruited from the communities of Jiangshan, Beixinqiao, Jiaodaokou, Chaoyangmen, and Donghuamen in Beijing, China between September 2010 and April 2011. All subjects gave informed consent before participation, and the study was approved by Ethics Committee of Chinese Clinical Basic Institute, China Academy of Chinese Medical Sciences (Approval number: 2010No13).

Diagnostic criteria

The diagnostic criteria for osteoporosis were mainly obtained from Guideline of Clinical Diagnosis: Subvolume of Osteoporosis and Bone Mineral Salt Diseases (First edition).[1] Subjects whose T-score was less than or equal to - 2.5 were considered to have osteopenia.[3]

Inclusion criteria

Patients were included if they volunteered to be a subject and signed an informed consent form. Those patients who were female, aged 40 to 80 years, and met the diagnostic criteria for osteoporosis were included.

Exclusion criteria

Men were excluded from the study, as were women who did not meet the diagnostic criteria for bone density (T-score > - 2.5).

Chemicals and reagents

Purified water was prepared by a Milli-Q water purification system (Millipore, Shanghai, China). Acetonitrile, methanol, formic acid, and ethyl acetate were all HPLC grade (American Fisher Chemicals Ltd., Waltham, MA, USA). Sodium acetate and ascorbic acid were all analytical grade (Beijing Chemical Agent Company, Beijing, China). β-glucuronidase was supplied by Sigma Co. (St. Louis, MO, USA). Naringenin standard (batch No. 10042231, naringenin content was 98.0%) was from Tong Tian Biotech Co., Ltd., (Shanghai, China), and hesperidin standard (batch No. 0721-9506, content hesperidin was 98.0%) was from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China).

Instrumentation

HPLC-MS/MS system (Agilent, Palo Alto, CA, USA) was used in this study. The HPLC-MS/MS system was comprised of a 6410 Triple Quadrapole mass spectrometer, and 1200 system was equipped with a 2170 binary system controller, a 1211 pump, a 1322-degasser, a 1329A auto-sampler, and a 1316A column oven. Data were collected and processed using MassHunter software B 01.03 (Agilent, Palo Alto, CA, USA).

Drug administration and blood sampling

Blood samples of volunteers were taken after a single oral dosage of Qianggu capsules (Beijing Qi Huang Pharmaceutical Co., Ltd.). The principle drug in each dose was 250 mg of total flavonoid of Drynaria fortunei (Kunze) J. Sm., which contains 75 mg of NAR. 2 mL blood samples were collected from their median cubital vein and stored in 4 mL ethylene diamine tetraacetic acid microcentrifuge tubes immediately before and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after oral administration. The samples were centrifuged at 10 000 ×*g* for 15 min at 4 ℃. A total of 500 μL of plasma were separated and kept frozen at – 80 ℃ until analysis. Blank plasma was purchased from the Red Cross Blood Center Warehouse of China and kept at a temperature of - 40 ℃.

HPLC analysis conditions and sample preparation

An Agilent XDB C18 (50 mm × 4.6 mm, 1.8 μm) was

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