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Pharmacokinetics comparative study of a novel Chinese traditional herbal formula and its compatibility

Qin Zheng [1], Peng-Fei Yue [1], Bin Wu, Peng-Yi Hu, Zhen-Feng Wu, Ming Yang *

Key Lab of Modern Preparation of Traditional Chinese Medicine, Ministry of Education, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China

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ABSTRACT

Ethnopharmacological relevance: Da Chuan Xiong Decoction Compound preparation (DCXDCP), the formulation of a classical Chinese prescription recorded in "*Xuanminglunfang*", was clinically employed to treat migraine's disease.
Aim of the study: In order to investigate the influence of compatibility on the pharmacokinetics of the active ingredient Gastrodin (GAS), the comparative evaluations on pharmacokinetics of DCXDCP with various combinations of its constituent herbs in plasma after oral administration were studied.
Materials and methods: The rats were randomly assigned to four groups and orally administered with different prescription proportion of *Gastrodia elata* Bl. and *Ligusticum chuanxiong* Hort. (1:0; 1:0.25; 1:2.1; 1:4.2), respectively. At different predetermined time points after administration, the concentrations of GAS in rat plasma were determined by using HPLC, and main pharmacokinetic parameters were investigated.
Results: The results showed that the pharmacokinetic parameters, AUC and C_{max} of GAS were dramatically different ($p < 0.05$) after oral administration of *G. elata* Bl. and the different combinations of its constituent herbs.
Conclusions: These indicated that the compatibility effects of other ingredients present in DCXDCP could affect the pharmacokinetics of the prescription.

1. Introduction

The TCM formula is the predominant application mode of TCM (Bent and Ko, 2004; Drasar and Moravcova, 2004). Compatibility of two or more drugs is one of the characteristics of TCM formula. Therapeutic and pharmacological effects of TCM are usually attributed to synergism among multiple herbs and constituents, because the individual component in the compound prescription interact with other ingredients, termed "TCM formula compatibility", which might influence on ADME (absorption, distribution, metabolism and elimination) of some components in the formula *in vivo* (Park, 2002; Gao et al., 2006; Bochu et al., 2005; Di et al., 2006; Lu et al., 2007). For example, the C_{max} and AUC of wogonoside were increased after oral administration of Huangqin-Tang decoction compared with the single Huangqin decoction (Zuo et al., 2003). The bioavailability of ephedrine was increased after combination of *Ramulus Cinnamomi*, *Semen Armeniacae Amarum* and *Radix Glycyrrhizae* with *Herba Ephedrae* (He and Luo, 2005). On the other hand, there were also some reports of the negative influence of TCM compatibility on pharmacokinetics of active components in formula, for example, Shuang–Huang–Lian reduced the bioavailability of baicalein (Di et al., 2006) and components of the other herbs used in Longdan Xiegan Tang had a significant inhibitory effect on gentiopicroside absorption (Wang et al., 2007). Increasing attention is currently being paid to scientific evaluation of formula compatibility by means of pharmacokinetic study.

Da Chuan Xiong Decoction Compound preparation (DCXDCP) was recorded in "*Xuanminglunfang*", a well-known formula book edited by Yuan-Su Liu, a notable doctor in the Jin Dynasty. This is a classic TCM formula of an aqueous extract made from chuanxiong (*Ligusticum chuanxiong* Hort., umbelliferae) and Tianma (*Gastrodia elata* Bl., *Orchidaceae*). It has been widely used in both China and Japan to treat migraine and has been proved to be effective and of low toxicity through thousands of years' use. It was used clinically for the treatment of neurasthenia, dizzy, headache and adjunctive therapy to epilepsy for thousands of years in China (Zhao et al., 1999; Zheng et al., 1997; Chen and Chen, 1992).

L. chuanxiong Hort., a commonly used Chinese medicinal herb with haemodynamic and analgesic effects, has been widely used for treating cardiovascular diseases and migraine in China for centuries (State Pharmacopoeia Committee, 2010a,b). *Tianma* (*G. elata* Blume) is a notable Chinese medicine. Its roots have been widely used for the treatment of rheumatism, epilepsy, paralysis,

* Corresponding author. Tel.: +86 0791 7118658; fax: +86 0791 7118658.
E-mail addresses: yangming16@126.com, jxtcmi412@126.com (M. Yang).
[1] These authors contributed equally to this work as joint first author.

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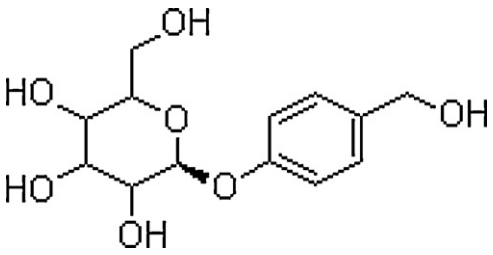

Fig. 1. The chemical structure of Gastrodin.

hemiplegia, lumbago, headache and vertigo (State Pharmacopoeia Committee, 2010a,b).

Gastrodin is the bioactive component of DCXDCP, which has sedative and anticonvulsant actions, neuroprotective effect, facilitating memory consolidation and retrieval, and antioxidant and free radical scavenging activities (Kim et al., 2001, 2003; Cao et al., 2001; Hsieh et al., 1997; Liu and Mori, 1992; Wang, 2005). The chemical structure of Gastrodin was shown in Fig. 1.

However, Comparative studies on pharmacokinetics of GAS of DCXDCP with various combinations of its constituent herbs in plasma after oral administration of chuanxiong, Tianma and their compound preparation, have scarcely been reported. Thus, it is important to compare the pharmacokinetics in the plasma following different proportion of formula compatibility, which has not yet been reported. The aim of this research was to study the possible pharmacokinetic differences of the compounds after oral administration of Rhizoma Gastrodiae aqueous extract and DCXDCP to rats, and explore whether there were some herb-herb interactions on Gastrodin in by determining the absorbed Gastrodin in DCXDCP.

2. Materials and methods

2.1. Materials and reagents

Rhizoma Chuanxiong extract and Rhizoma Gastrodiae extract were purchased from Zelang Co. (Nanjing, China). Gastrodin (purity > 99%) were supplied by the National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China. Water was double distilled. Acetonitrile and methanol were of HPLC grade.

2.1.1. Animals

Female Wistar rats (weight: 200 ± 20 g) were purchased from the animal laboratory of JiangXi University of Traditional Chinese Medicine (Jiangxi, China, Certificate No. JZDW20100131). The studies were approved by the Animal Ethics Committee of Jiangxi University of Traditional Chinese Medicine.

2.1.2. Preparation of Gastrodin and DCXDCP suspension

Rhizoma Gastrodiae suspension was prepared by mixing Rhizoma Gastrodiae extract 0.16 g in 20 ml water with magnetic stirring apparatus. Different DCXDCP suspensions (Table 1) were prepared by mixing different proportion of Rhizoma Chuanxiong extract and Rhizoma Gastrodiae extract, which were suspended with magnetic stirring apparatus in 20 ml water containing 1 g arabic gum as suspending agent. The different DCXDCP suspensions were shaked uniformly before administration.

Table 1
Different proportion formulas of Chuanxiong and Tianma.

Suspension	Rhizoma Gastrodiae (g)	Rhizoma Chuanxiong (g)	Prescription proportion
Formula 1	0.16	–	1:0
Formula 2	0.16	0.04	1:0.25
Formula 3	0.16	0.34	1:2.1
Formula 4	0.16	0.68	1:4.2

2.2. Animal treatment

The rats were randomly assigned into four groups (1–4). Each group contained six rats. The groups of experiment were listed in Table 1. The animals were fasted for 12 h with free access to water prior to the oral administration of the extracts prepared with a dose of 20 mg/kg based on the content of GAS. Blood samples (0.5 ml) were collected from the eyes at 5, 10, 15, 30, 45, 60, 90, 120, 180, and 240 min after administration, and immediately transferred into a heparinized EP tube. The blood samples were then centrifuged at 10,000 × *g* for 20 min. The plasma samples were stored at −20 °C for later analysis.

2.3. Blood sample preparation

The thawed plasma sample (0.2 ml) was transferred to another EP tube, added 0.8 ml acetonitrile. The mixture was vortexed for 2 min, and centrifuged at 10,000 × *g* for 15 min. The supernatant was transferred into a clean EP tube, and evaporated to dryness under the stream of nitrogen at 40 °C. The residue was dissolved in 200 μl of water and centrifuged at 18,000 × *g* for 20 min. The supernatant was injected into the HPLC system with a 20 μl fixed loop.

2.4. Determination of GAS in plasma

2.4.1. Apparatus

The high performance liquid chromatographic system comprised an LC-10AD pump (Shimadzu, Kyoto, Japan), a Rheodyne model 7725 injector with 20 μl loop (Rheodyne Inc., Cotata, CA, USA), an SPD-10A UV–visible detector (Shimadzu, Kyoto, Japan) and an LC-10AD workstation.

2.4.2. Chromatographic conditions

A Phenomenex C_{18} column (250 mm × 4.60 mm; 5 μm) from Feiluomen Co. (Tianjin, China) was used. A binary mixture of acetonitrile–water (5:95, v/v) was applied as mobile phase with a flow rate of 1.0 ml/min. The detector was set at 221 nm and all the measurements were performed at 33 °C.

2.4.3. Preparation of standard solution

The standard stock solution was prepared by dissolving 2.54 mg of Gastrodin in 25 ml methanol to yield a nominal concentration of 101.6 μg/ml. All the stock solutions were kept at 4 °C before use. Gastrodin standard samples (0.1016, 0.4064, 0.8128, 1.016, 2.032, 4.064, 10.16 μg/ml) were prepared by spiking blank plasma with appropriate amounts of standard stock solution prepared above after blow-dried by N_2 in 40 °C water bath. Quality control (QC) samples to determine the recovery, accuracy and precision of the method were independently prepared at low (0.10 μg/ml), medium (1.0 μg/ml) and high (10.0 μg/ml) concentrations. The rest operations were followed by blood sample preparation. All samples were stored at −20 °C until analysis.

2.4.4. Calibration curve

Stock solutions (10 μl) were pipetted respectively into 1 ml centrifuge tube and mixed to prepare seven concentrations of standard plasma samples. The samples were treated according to the method described above.