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Pharmacokinetics of Purified Paeonol and Paeonol in Moutan Cortex Decoction and Rhubarbmoutan Decoction

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Abstract

180 KM male mice of 22~28g body weight were divided into three groups randomly and purified paeonol, Moutan Cortex decoction and Rhubarbmoutan decoction were orally administered at equivalent doses of 10 mg·kg^{-1} paeonol. A sensitive HPLC method was established and evaluated for determining the concentrations of paeonol in mice plasma. The main pharmacokinetic parameters of paeonol were as follows: $t_{1/2}$, (13.15± 2.48) min, (15.04±4.40) min and (21.83±6.21) min, T_{max}, 15 min, 15 min and 10 min, C_{max}, (69.41±4.50) ng·mL^{-1}, (82.90±6.10) ng·mL^{-1} and (123.32±5.55) ng·mL^{-1}, AUC_{0-t}, (1243.42±109.75)ng·min·mL^{-1}, (1412.74±97.72) ng·min·mL^{-1} and (2162.20±105.10) ng·min·mL^{-1}, $AUC_{0-\infty}$, (2192.46 ±472.18) ng·min·mL^{-1},(2659.57±1590.70) ng·min·mL^{-1} and (3423.36 ±465.40) ng·min·mL^{-1},respectively. All the results indicate that disposition in mice were affected by other components in Chinese herbs and in recipe.

Keywords: Paeonol; Moutan Cortex decoction; Rhuborbmoutan decoction; Pharmacokinetics; HPLC

Introduction

Paeonol is a major component extracted from Chinese herbs Moutan cortex [1], with the melting point of 51-52 [2]. Paeonol can relieve fever and promote blood flow, was widely used for its nonanalgesia-dependence, better tolerance and less side effects. Rhubarbmoutan decoction [3], composed of 3 g Rhubarb and 12 g Moutan cortex as principal, 9 g Peach seed and 9 g Glauber salt as ministerial, and 30 g Chinese Waxgourd seed as adjunctive, can relieve stagnant and detumescence and was clinically used in acute appendicitis.

Several methods were reported for determining paeonol in herbs or in traditional prescriptions for quality control. HPLC method was developed for determining paeonol in rat[4,5,6], dog [7] or human [8,9] plasma and pharmacokinetics of paeonol were also studied respectively. Chinese traditional herbs or compound recipe are complex systems with multiple components [10], in which synergistic or antagonism effects might exist. In this study, a sensitive HPLC method was established for paeonol determination and pharmacokinetic differences of paeonol, in Moutan cortex decoction and Rhubarbmoutan decoction were studied and evaluated.

Materials and Methods

Apparatus and reagents

Waters 515-2487 HPLC, LXJ High Speed Centrifuge, PK514BP Superwave Cleaner, and AX 205 Meteller-Toledo Scale were supplied by Waters, Agillent Technologies, the Shanghai Analysis Instrument Factory, and Metteler-Toledo Instrument (Shanghai) Co.Ltd, respectively. Paeonol tablets, 40mg per tablet, and paeonol standard (99%) were provided by Liu-Zhou (Guangxi) and Lu-Ye (Shandong) Co.Ltd, respectively.Methanol, acetonitrile and tetrahydrofuran, spectrum grade, were purchased from Tedia Company, USA. Phosphoric acid, analytical grade, and sodium chloride, from Tianjin Shen-Tai Chemicals and Weihai Ya-Tai Medcine Co.Ltd, respectively.

Decoction preparation

The paeonol, Moutan cortex decoction and Rhubarbmoutan decoction were prepared at the same concentration of 0.3 mg·mL^{-1} (paeonol). Reflux condenser was used for preparation of Moutan cortex decoction and Rhubarbmoutan decoction. The preparing flowcharts of those two decoction were shown in Figure 1 and Figure 2. No significant change was detected in paeonol concentration within 12 h under the conditions.

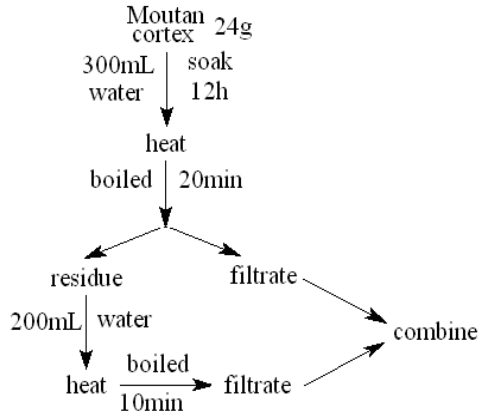

Figure 1: Flowchart of Moutan cortex decoction.

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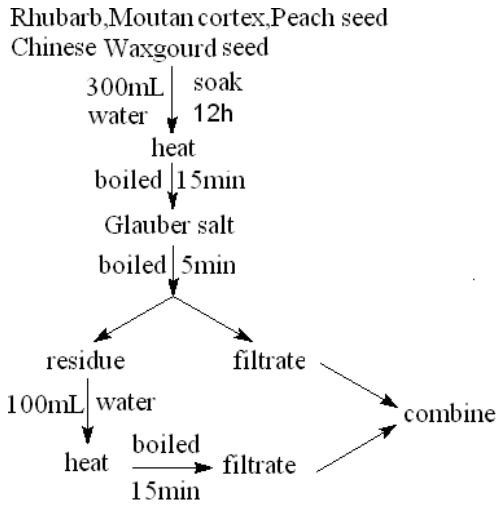

Figure 2: Flowchart of Rhuborbmoutan decoction.

Study design

180 KM male mice [11] of 22~28 g body weight were divided into three groups and purified paeonol, Moutan Cortex decoction and Rhuborbmoutan decoction equivalent to 10 mg·kg^{-1} of paeonol were orally administered. 0.3 mL blood was collected by the blood samples were taken in the studied mice by penetrating the retro-orbital sinus with a glass capillary at 5, 7, 10, 15, 20, 25, 30, 40, 50 and 60 min. One time point was corresponding to 6 mice for average. The concentration of paeonol in plasma was determined with HPLC method. The main pharmacokinetic parameters of paeonol were calculated by DAS 2.0 and the influences of other components in Moutan Cortex and Rhuborbmoutan decoction were evaluated.

Chromatographic conditions

Paeonol was separated by Hypersil C_{18} column (250mm×4.6mm i.d., 5μm) at 25 [8]. Isocratic elution of the analyte from the column was achieved with the mobile phase consisting of 1 mmoL·L^{-1} phosphoric acid (containing 1% triethylamine)-acetonitrile (40:60, v/v) at a flow rate of 1.0 mL·min^{-1}.

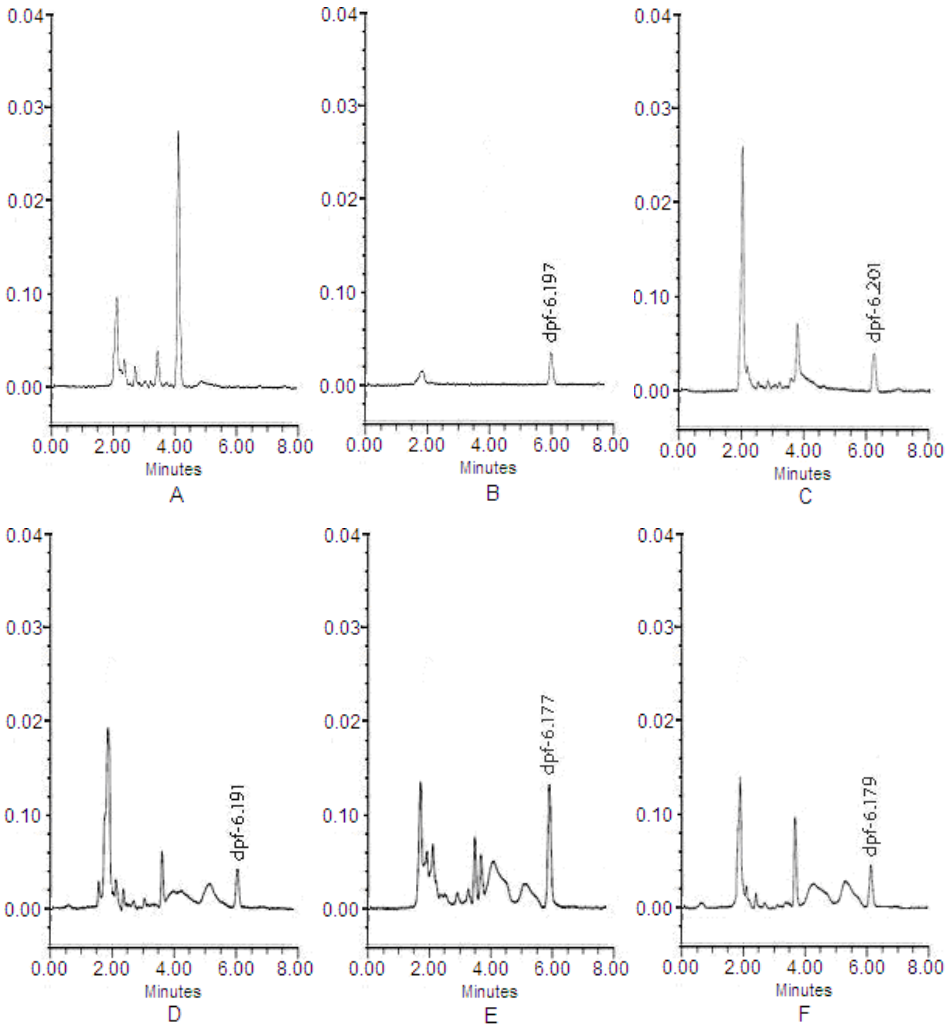

Figure 3: The chromatograms of blank plasma (A), 200 ng·mL^{-1} paeonol standard (B), blank plasma spiked with 250 ng·mL^{-1} paeonol standard (C) , plasma sample 5 min after intragastric administration of purified paeonol (D), Moutan cortex decoction(E) and Rhubarbmoutan decoction (F).

Sample disposition

0.2 mL plasma sample plus 0.2 mL acetonitrile were vortex-mixed for 30 s, then centrifuged at 10080 rpm (revolutions per minute) for 5 min. The upper organic layer was transferred into tubes containing 40~50 mg sodium chloride, then vortex-mixed for 30 s and incubated at room temperature for 10 min, centrifuged again at 10080 rpm for 5 min, and 5 mL of the upper organic layer was directly injected for analysis.

Quality control

The quality control (QC) samples were analyzed in each analytical run at concentrations of 25,100,400 ng·mL^{-1}.The relative standard deviation (RSD) of QC samples were all less than 15%.

Statistics

The main pharmacokinetic parameters ($t_{1/2}$,AUC_{0-t} ,$AUC_{0-\infty}$) of paeonol were calculated by DAS 2.0.The C_{max} and T_{max} were as observed.

Results

Specificity

The chromatograms of blank plasma (A), 200 ng·mL^{-1} paeonol standard (B), blank plasma spiked with 250 ng·mL^{-1} paeonol standard (C), plasma sample 5 min after intragastric administration of purified paeonol (D), Moutan cortex decoction(E) and Rhubarbmoutan decoction (F) were shown in Figure 3.

Calibration and LOQ

The calibration curve for plasma assay was constructed with the peak area of paeonol versus its concentration. The weighted regression equation ($1/x^2$) of the calibration curve was Y= -11652.36607+5207.71572X with a correlation coefficient (r) of 0.9998. The linear range was 10~500 ng·mL^{-1} and the limit of quantity (LOQ) was 10 ng·mL^{-1}.

Recovery, accuracy and precision

The recovery, accuracy and precision of method were evaluated and dates were shown in Table 1. The recoveries were ranged from 92.28% to 97.44%. The intra-day and inter-day precisions were ranged 3.59%~13.72% and 1.21%~4.56%. These results suggested that the procedures described as above were satisfactory with respect to both accuracy and precision.

Nominal concentration (ng·mL^{-1})	Intra-day		Inter-day		Extraction recovery (%)
	RSD(%)	Accuracy(%)	RSD(%)	Accuracy (%)	
25	4.56	99.88±4.56	13.72	95.60±13.04	92.28±5.90
100	1.21	97.92±1.97	3.59	97.91±1.70	97.44±3.46
400	2.34	89.86±2.10	3.77	88.30±3.33	97.34±3.05

Table 1: Precision and recovery of paeonol (n = 5).

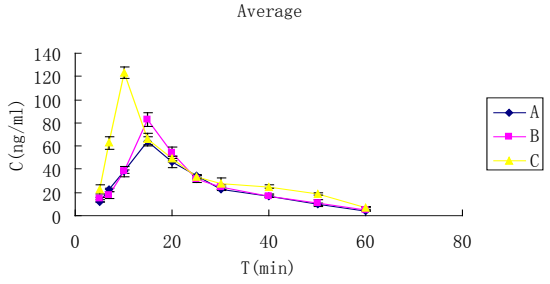

Figure 4: Mean plasma concentration-time curves after intragastric administration (10 mg·kg^{-1}) of purified paeonol (A), Moutan cortex decoction(B) and Rhubarbmoutan decoction(C).

Parameters	Purified paeonol	Moutan cortex decoction	Rhubarb moutan decoction
T_{max}/min	15	15	10
$t_{1/2}$/min	13.15±2.48	15.04±4.40	21.83±6.21
C_{max}/ng·mL^{-1}	69.41±4.50	82.90±6.10	123.32±5.55
AUC_{0-t} /ng·mL·min^{-1}	1243.42±109.75	1412.74±97.72	2162.20±105.10
$AUC_{0-\infty}$/ng·mL·min^{-1}	2192.46±472.18	2659.57±1590.70	3423.36±465.40

Table 2: Main pharmacokinetic parameters of Paeonol ($\bar{x}\pm s$, n = 6).

Time-plasma concentration curves

Mean plasma concentration-time curves after intragastric administration (10 mg·kg^{-1}) of purified paeonol (A), Moutan cortex decoction(B) and Rhubarbmoutan decoction(C) were as shown in Figure 4.

Pharmacokinetic parameters

Paeonol pharmacokinetics of the main pharmacokinetic parameters of paeonol were calculated by DAS 2.0 after administration of purified paeonol, Moutan cortex decoction and Rhubarbmoutan decoction in mice were as shown in Table 2.

Discussion

Paeonol is easy to evaporate during decorating, extracting or drying processes because of its lower melting point. In order to decrease the loss of paeonol as much as possible, reflux condenser was applied to prepare for Moutan cortex decoction and Rhubarbmoutan decoction. In our study, 0.2 mL acetonitrile was used for protein precipitation and 40~50 mg sodium chloride was added to improve the extraction and the organic phase was directly injected for analysis. The mobile phase, phosphoric acid (containing 1% triethylamine)-acetonitrile (40:60, v/v),was stable and suitable for the determination of paeonol. The paeonol was well separated from endogenous substances at above chromatographic conditions.

The linear range of the paeonol was 10~500 ng·mL^{-1} and the determination limit was 10 ng·mL^{-1}.The extraction recoveries of paeonol determined in high, medium and low concentrations were more than 92.28%. RSD of intra-day and inter-day analysis were <13.72%. The method established here is simple, sensitive, accurate and suitable to determine the low plasma levels of paeonol and applied to its pharmacokinetic studies in mice.

The feature of Traditional Chinese Medicine theory is to emphasize the human overall view, which can regulate the whole process. Modern Pharmacology studies have proved the efficacy of Traditional Chinese Medicine is not simply the sum of the single herbs or toxicity subtraction, it also includes the synergy restriction or modified and others in various drugs. In the boiling process, the interaction among Chinese herbs will bring about chemical changes or transform into new products.

The differences of paeonol pharmcokinetics were existed in purified paeonol, Moutan cortex decoction and Rhubarbmoutan decoction in mice. The paeonol elimination speed is decreased ($t_{1/2}$ was longer), and the absorption amount is increased (C_{max} and AUC were larger), in Rhubarbmoutan decoction than those of purified

paeonol while in Moutan cortex decoction were between purified paeonol and Rhubarbmoutan decoction. On the contrary, T_{max} of paeonol in Rhubarbmoutan decoction was much shorter than those of others, indicating that paeonol disposition in mice were affected by other components in Moutan cortex, a Chinese Medicinal Herb, and Rhubarbmoutan, a Chinese Traditional Prescriptions.

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