Pharmacokinetics of Catechols in Human Subjects Intravenously Receiving XueBiJing Injection, an Emerging Antiseptic Herbal Medicine

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Running title: Pharmacokinetics of XueBiJing Catechols in Human Subjects

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ABSTRACT

XueBiJing injection, prepared from a five-herb combination, is extensively used as add-on therapy in routine sepsis care in China. Catechols, derived from the component herb *Salvia miltiorrhiza* roots (Danshen), are probably important because of their reported antiseptic properties. This study was designed to characterize pharmacokinetics of major circulating Danshen catechols in human subjects intravenously receiving the injection at the label doses. A total of 17 Danshen catechols were detected in XueBiJing injection (content level, 0.1–139.3 μM). After dosing, tanshinol and salvianolic acid B exhibited relatively high levels of systemic exposure with mean elimination half-lives of 0.38 and 0.29 hour, respectively. The total plasma clearance and apparent volume of distribution at steady state of tanshinol were 1.07 L/h/kg and 0.40 L/kg, respectively, whereas those of salvianolic acid B were 0.43 L/h/kg and 0.13 L/kg, respectively. Protocatechuic acid and five other catechols were also detected in plasma but at low exposure levels. Although protocatechuic aldehyde had the highest content level in the injection, like the remaining eight catechols, it was undetected in plasma. Protocatechuic aldehyde was extensively converted into protocatechuic acid and other metabolites. The information gained here facilitates understanding the roles of Danshen catechols in therapeutic actions of XueBiJing injection.

Keywords:

XueBiJing injection

Salvia miltiorrhiza roots

Danshen

Catechol

Pharmacokinetics

Sepsis

1. Introduction

Sepsis, an infection-induced systemic inflammatory response, is one of the most pressing clinical problems with significant mortality rate and poor prognosis [1]. In China, herbal medicines are often used as add-on therapy in the routine sepsis care [2]. One of such herbal medicines is XueBiJing injection, which was approved by the China Food and Drug Administration (China FDA; Beijing, China), in 2004, for treatment of sepsis and multiple organ dysfunction syndromes. The injection is prepared from a five-herb combination of *Carthamus tinctorius* flowers (Honghua in Chinese/Benibana in Japanese), *Paeonia lactiflora* roots (Chishao/Aka-shakuyaku), *Ligusticum chuanxiong* rhizomes (Chuanxiong/Senkyu), *Angelica sinensis* roots (Danggui/Toki), and *Salvia miltiorrhiza* roots (Danshen/Tanjin) and is a sterile and nonpyrogenic formulation for intravenous administration. Clinical studies show that treatment with XueBiJing injection reduces 28-day mortality and incidence of complications, improves acute physiology and chronic health evaluation II score and prognosis, and shortens stay in intensive care unit and ventilation time in septic patients with low incidence of side effects [3,4]. The herbal therapy improves microcirculation, alleviates coagulation and inflammation, protects the endothelium, and regulates immune response [5,6].

Four classes of compounds (including Honghua flavonoids, Chishao monoterpene glycosides, Chuanxiong/Danggui phthalides, and Danshen catechols) are probably important for XueBiJing injection, because they have been reported to have antiseptic and related properties. However, little is known about which of these herbal compounds are responsible for the injection's therapeutic actions. This is determined not only by the compounds' pharmacological properties and potency but also by their reachability for and concentrations at the sites of action. Accordingly,

pharmacokinetic research is required, which is based on the four classes of XueBiJing compounds. This study was designed to assess systemic exposure to Danshen catechols in human subjects intravenously receiving XueBiJing injection and to characterize the pharmacokinetics of major circulating compounds.

2. Materials and Methods

A detailed description of materials and methods is provided in the [Appendix A. Supplementary information](#), which is available online.

2.1. XueBiJing injection and Danshen

Samples of **eight** lots of XueBiJing injection (China FDA ratification number, GuoYaoZhunZi-Z20040033) and raw material samples of Danshen (*S. miltiorrhiza* roots) were obtained from Tianjin Chasesun Pharmaceutical Co., Ltd. (Tianjin, China).

2.2. Chemicals and reagents

Reference standards of Danshen catechols (purity, $\geq 98\%$ **by HPLC**) were obtained from Tauto Biotech (Shanghai, China). 3-*O*-Methyltanshinol and 4-*O*-methyltanshinol ($\geq 98\%$ **by HPLC**) were synthesized in-house using the methods by Tian *et al.* [7]

2.3 Human study

An ethics committee of clinical investigation at the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (Tianjin, China) reviewed and approved the protocol for human pharmacokinetic study of XueBiJing injection. Healthy volunteers (19–31 years) were recruited and gave their informed consent to participate in the study, which was implemented at a national clinical research center

of the Hospital (Tianjin, China). The human subjects were randomly divided into three groups (six male and six female subjects for each). The test dosage regimens of XueBiJing injection were set based on the injection's label dose (50 mL/person for treatment of sepsis or 100 mL/person for treatment of multiple organ dysfunction syndromes) as used in clinics; they were: a 75-minute intravenous infusion of 100-mL XueBiJing injection diluted in 100-mL NaCl injection (group I), a 150-minute intravenous infusion of 100-mL XueBiJing injection diluted in 200-mL NaCl injection (group II), and a 75-minute intravenous infusion of 50-mL XueBiJing injection diluted in 100-mL NaCl injection (group III). Each subject received one of the three regimens. After receiving the single dose of XueBiJing injection, the six male subjects of group III continued to receive the same dose of the injection each day for the following six days. Blood and urine were sampled.

2.4. Liquid Chromatography/Mass Spectrometry-Based Assays

An AB Sciex API 4000 Q Trap mass spectrometer (Toronto, Canada), interfaced via a Turbo V ion source with a Waters Acquity UPLC separation module, was used for detection and quantification of Danshen catechols and metabolites.

2.5. Data Processing

Pharmacokinetic parameters were estimated using non-compartmental analysis with Kinetica software (version 5.0; Thermo Scientific, Philadelphia, PA, USA) and are shown as means $\pm$ standard deviation. Statistical analysis was performed using IBM SPSS Statistics software (version 19.0; Somers, NY, USA). A *P* value <0.05 was considered statistically significant.

3. Results and Discussion

Cell- and animal-based studies showed that Danshen catechols have

antithrombotic, endothelial protective, vasodilating, cardioprotective, anti-inflammatory, and antioxidant properties [8], which could be important for XueBiJing therapy. A total of 17 Danshen catechols were detected in XueBiJing injection ([Appendix B. Supplementary data](#)). Different from raw materials of Danshen exhibiting predominant salvianolic acid B (**15**), XueBiJing injection contained higher content levels of protocatechuic aldehyde (**1**) and tanshinol (**3**) than **15**. Salvianolic acid B was reported to be converted into protocatechuic aldehyde, tanshinol and other catechols by heating in water [9]. This conversion probably occurred during the injection's preparation. The injection exhibited lot-to-lot variability in content levels of **1**, **3**, rosmarinic acid (**5**), isosalvianolic acid C (**9**), **15**, and protocatechuic acid (**2**) with relative standard deviations of 12.7–23.4%. Such values for the remaining minor catechols were 0.0–36.4%. The XueBiJing injection with a lot number of 1309301 was used in human PK study. The dose levels of catechols from this XueBiJing injection (100 mL/person) could be divided into three classes: >10 $\mu\text{mol/person}$ (**1**), 1–10 $\mu\text{mol/person}$ (**3**, **5**, **9**, **15**, and **2**), and <1 $\mu\text{mol/person}$ (the remaining minor catechols). The total dose level of the minor catechols was only 4.0% of the total dose of catechols present in the injection.

Eight unchanged Danshen catechols were detected in plasma during and after a single 75-minute intravenous infusion of 100 mL XueBiJing injection (diluted in 100 mL of NaCl injection) per subject ([Fig. 1A](#)); these compounds were undetected in plasma before dosing. The detected catechols were tanshinol (**3**), rosmarinic acid (**5**), isosalvianolic acid C (**9**), salvianolic acid B (**15**), protocatechuic acid (**2**), salvianolic acid C (**10**), lithospermic acid (**13**), and salvianolic acid D (**8**); they were also detected in urine ([Fig. 1B](#)). Unchanged protocatechuic aldehyde (**1**) was not detected in plasma; it was extensively converted into **2**, which was further methylated and glucuronized to

form **M2_{M-G-1}** and **M2_{M-G-2}**. Two methylated metabolites of **3** (**M3_{M-1}** and **M3_{M-2}**) and one dimethylated metabolite of **5** (**M5_{2M}**) were also detected in plasma (**Fig. 1C**). By comparing with the synthesized compounds, **M3_{M-1}** and **M3_{M-2}** were characterized as 3-*O*-methyltanshinol and 4-*O*-methyltanshinol, respectively. The preceding catechol metabolites were also detected in urine (**Fig. 1D**).

Figure 1 (E–G) shows plasma concentrations of tanshinol (**3**), salvianolic acid B (**15**), and protocatechuic acid (**2**) over time during and after an intravenous infusion of XueBiJing injection. **Table 1** summarizes the pharmacokinetic parameters of **3** and **15**. The plasma $C_{\max}$ values of **3** and **15** were measured just before stopping the infusion. After the infusion was stopped, their plasma concentration declined with mean $t_{1/2}$ values of 0.38 ± 0.14 and 0.29 ± 0.08 hour, respectively. The gender differences were insignificant for **3** and **15** with respect to $C_{\max}$ and $AUC_{0-\infty}$, when the doses were corrected for body weight ($P > 0.05$). **Although the levels of systemic exposure were XueBiJing-dose-dependent ($P = 0.0000005-0.005$),** the dosage regimens had no significant effect on the V_{SS} and $CL_{tot,p}$ of **3** ($P > 0.05$) or on those of **15** ($P > 0.05$). The mean V_{SS} of **3** for all the groups (0.40 ± 0.19 L/kg) was only slightly larger than the human total extracellular volume (0.26 L/kg), whereas that of **15** (0.13 ± 0.04 L/kg) was smaller. This suggested that both catechols had small volume of distribution. The mean $CL_{tot,p}$ of **3** for all the groups (1.07 ± 0.21 L/hour/kg) and that of **15** (0.43 ± 0.08 L/hour/kg) were 44% and 18% of human cardiac plasma output (2.4 L/hour/kg), respectively, suggesting the two catechols had high and moderate total clearance, respectively. Neither **3** nor **15** exhibited any gender differences in $t_{1/2}$, V_{SS} , or $CL_{tot,p}$ ($P > 0.05$). **Table 1** shows the mean C_{SS} and A_{SS} values of **3** and those of **15** for test dosage regimens of XueBiJing injection. No significant accumulation was observed for plasma **3** and **15** in $AUC_{0-\infty}$ during multiple infusions of XueBiJing injection

($P > 0.05$) and the R_{ac} values were 1.04 and 0.96, respectively. Elimination of **3** was mainly via renal excretion with $CL_R/CL_{tot,p}$ ratios of 63.0–73.8%. Renal excretion of tanshinol was found to be attributed mainly to OAT1/2/3-mediated tubular secretion [11]. Renal excretion of **15** was poor. Salvianolic acid B was reported to be eliminated, in rats, mainly via biliary excretion of its methylated metabolites [12].

Herein, we identified Danshen compounds, which exhibited relatively high levels of systemic exposure after dosing XueBiJing injection, and assessed their pharmacokinetics. This enabled us to compare the pharmacokinetic concentrations of Danshen catechols with the reported effective concentrations for exerting their antiseptic activities. The results suggested that the concentrations of Danshen catechols measured in human plasma after dosing XueBiJing injection might be too low, when compared with the reported effective concentrations [8]. Although the low concentrations do not result in ineffectiveness of XueBiJing injection in treatment of sepsis, they probably limit the contribution of Danshen to the current XueBiJing therapy. The differences in Danshen catechols' concentrations in human plasma between dosed XueBiJing injection and dosed DanHong injection [10] suggested that higher plasma concentrations are technically achievable for future XueBiJing therapy. This idea is important for design and development of new and superior antiseptic agents derived from the current XueBiJing injection.

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Figure Legends

Fig. 1. Systemic exposure to, renal excretion of, and pharmacokinetics of Danshen catechols and metabolites in human subjects receiving an intravenous infusion of XueBiJing injection.

For detection of unchanged and metabolized Danshen catechols (A–D), human subjects received a 75-minute intravenous infusion of 100-mL XueBiJing injection (diluted in 100-mL NaCl injection); the plasma samples of the same point of time ($n = 12$) were pooled for analysis, whereas the urine samples of the same period of time ($n = 12$) were also pooled. Red and black bars are used to show the plasma and urinary levels of the catechols, respectively. The detected plasma (A) and urine Danshen catechols (B) are ranked according to their content levels in XueBiJing injection and their chemical names are shown in [Appendix B. Table S1](#). The symbol “x” (in red) denotes the compound that was not detected. Panels E–G show the mean plasma concentrations of **3**, salvianolic acid B (**15**), and protocatechuic acid (**2**) over time, respectively. Unlike the sample treatment for detection of catechols, the human plasma samples of the same point of time were not pooled before being analyzed for determination of the compounds’ pharmacokinetics. Red lines: the subjects of group I receiving a 75-minute intravenous infusion of 100-mL XueBiJing injection (diluted in 100-mL NaCl injection); blue lines: the subjects of group II receiving a 150-minute intravenous infusion of 100-mL XueBiJing injection (diluted in 200-mL NaCl injection); and green lines: the subjects of group III receiving a 75-minute intravenous infusion of 50-mL XueBiJing injection (diluted in 100-mL NaCl injection). Solid and open circles are used to shown the plasma concentrations for male and female subjects, respectively. The plasma concentrations of **2** were quite low for Groups II and III, so the corresponding plasma concentration-time curves are not shown.

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Drug Metabolism and Pharmacokinetics

Appendix A. Supplementary Information

Materials and Methods

XueBiJing injection and Danshen: Samples of eight lots (1309271, 1309281, 1309291, 1309301, 1405301, 1406161, 1408191, and 1410081) of XueBiJing injection (China FDA ratification number, GuoYaoZhunZi-Z20040033) and raw material samples of Danshen (*S. miltiorrhiza* roots; lot number, 1206121, 1405181, and 1412071) were obtained from Tianjin Chasesun Pharmaceutical Co., Ltd. (Tianjin, China). The standard reference materials *S. miltiorrhiza* roots were obtained from the National Institutes for Food and Drug Control (Beijing, China).

Chemicals and reagents: Reference standards of tanshinol; protocatechuic aldehyde; protocatechuic acid; lithospermic acid; rosmarinic acid; and salvianolic acids A, B, C, and D (purity, $\geq 98\%$ by HPLC) were obtained from Tauto Biotech (Shanghai, China). 3-*O*-Methyltanshinol and 4-*O*-methyltanshinol ($\geq 98\%$ by HPLC) were synthesized in-house using the methods by Tian *et al.* [1] A 0.9% sodium chloride injection (NaCl injection; China FDA ratification number, GuoYaoZhunZi-H12020025) was manufactured by China Otsuka Pharmaceutical Co., Ltd. (Tianjin, China).

Human study: An ethics committee of clinical investigation at the Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (Tianjin, China) reviewed and approved the protocol for human pharmacokinetic study of XueBiJing injection. In brief, 18 male and 18 female healthy volunteers (19–31 years) were recruited and gave their informed consent to participate in the study, which was implemented at a national clinical research center of the Hospital (Tianjin, China). The human subjects were randomly divided into three groups (six male and six female subjects for each), stratified by gender. The test dosage regimens of XueBiJing injection were set based on the injection's label dose (50 mL/person for treatment of sepsis or 100 mL/person for treatment of multiple organ dysfunction syndromes) as used in clinics; they were: a 75-minute intravenous infusion of 100-mL XueBiJing injection (lot number, 1309301) diluted in 100-mL NaCl injection (group I), a 150-minute intravenous infusion of 100-mL XueBiJing injection (1309301) diluted in 200-mL NaCl injection (group II), and a 75-minute intravenous infusion of 50-mL XueBiJing injection (1309301) diluted in 100-mL NaCl injection (group III). Each subject received one of the three dosage regimens. Serial blood samples (~3 mL) were collected from an antecubital vein catheter before and 0.17, 0.5, 1.25 (75 minutes), 1.42 (groups I and III only), 1.75 (groups I and III only), 2.25 (groups I and III only), 2.5 (150 minutes; group II only), 2.67 (group II only), 3 (group II only), 3.25 (groups I and III only), 3.5 (group II only), 4.5 (group II only), 5.25 (groups I and III only), 6.5 (group II only), 9.25 (groups I and III only), 10.5 (group II only), and 24 hours after starting the infusion and heparinized. Serial urine samples were also collected before and 0–3, 3–6, 6–10, and 10–24 hours after starting the infusion. After receiving the single dose of XueBiJing injection, the six male subjects of group III continued to receive the same dose of the herbal injection each day for the following six days. On days 2–6, blood sampling was performed before and 1.25 hour after the daily infusion was started; on day 7, blood and urine samples were collected according to the time schedule same as that on day 1. The human study was registered in Chinese Clinical Trials Registry (www.chictr.org) with a registration number of ChiCTR-ONRC-13003932.

Liquid Chromatography/Mass Spectrometry-Based Assays: An AB Sciex API 4000 Q Trap mass spectrometer (Toronto, Canada), interfaced via a Turbo V ion source with a Waters Acquity UPLC separation module, was used for detection and quantification of Danshen catechols and metabolites. Human plasma and urine samples (50 μ L) were acidified with 30 μ L formic acid, extracted with 500 μ L of ethyl acetate, and centrifuged; the supernatant were reduced to dryness and reconstituted with 50 μ L of 50% methanol before analysis. For detection of unchanged catechols and metabolites, chromatographic separation was achieved on a Waters Acquity UPLC HSS T3 1.8- μ m column (100 $\times$ 2.1 mm i.d.; Dublin, Ireland; kept at 40°C) using a mobile phase that consisted of solvent A (methanol/water, 1:99, v/v, containing 25 mmol/L formic acid) and solvent B (methanol/water, 99:1, v/v, containing 25 mmol/L formic acid). The mobile phase was delivered at 0.3 mL/min and a gradient program was used as follows: 0–2 minutes, at 2% solvent B; 2–32 minutes, from 2% to 98% solvent B; 32–37 minutes, at 98% solvent B; and 37–42 minutes, at 2% solvent B. For the quantification, the chromatographic method was modified by using a shortened gradient program (0–3 minutes, from 2% to 30% solvent B; 3–5 minutes, from 30% to 60% solvent B; 5–5.1 minutes, from 60% to 2% solvent B; and 5.1–6.5 minutes, at 2% solvent B). The precursor-to-product ion pairs for multiple-reaction monitoring of plasma tanshinol, salvianolic acid B, and protocatechuic acid was achieved using the precursor-product ion pair m/z 197 $\rightarrow$ 179, 717 $\rightarrow$ 519, and 153 $\rightarrow$ 109, respectively. Matrix-matched calibration curves (4.6–1111 nM) were constructed using weighted ($1/X^2$) linear regression of the analyte area (Y) against the corresponding nominal analyte concentration (X , nmol/L). Before use, the quantification assay was validated according to the US Food and Drug Administration guide on bioanalytical method validation (2013). **The lower limits of quantification were 4.6, 4.6, and 13.7 nmol/L for measurement of tanshinol, salvianolic acid B, and protocatechuic acid in plasma samples, respectively (the assay precision, < 20%; the assay accuracy, 80–120%).**

Data Processing: Pharmacokinetic parameters were estimated using non-compartmental analysis with Kinetica software (version 5.0; Thermo Scientific, Philadelphia, PA, USA) and are shown as means $\pm$ standard deviation. Statistical analysis was performed using IBM SPSS Statistics software (version 19.0; Somers, NY, USA). A P value <0.05 was considered statistically significant.

References

- 1) Tian D-D, Jia W-W, Liu X-W, Wang D-D, Liu J-H, Dong J-J, et al. Methylation and its role in the disposition of tanshinol, a cardiovascular carboxylic catechol from *Salvia miltiorrhiza* roots (Danshen). *Acta Pharmacol Sin* 2015;36:627–43.

Brief Description of Method for Preparation of XueBiJing Injection

XueBiJing injection was a 1:2 injectable solution, two milliliters of which was prepared from a combination of 0.2 g each of *Carthamus tinctorius* flowers (Honghua), *Paeonia lactiflora* roots (Chishao), *Ligusticum chuanxiong* rhizomes (Chuanxiong), *Angelica sinensis* roots (Danggui), and *Salvia miltiorrhiza* roots (Danshen). Honghua was first extracted with 30% ethanol and then the extract was diluted with ethanol and centrifuged. The supernatant was reduced followed by dilution with water. After centrifugation, the supernatant was reduced and precipitated with ethanol; after centrifugation again, the supernatant was reduced to yield “H-extract”. Chishao was first extracted with water. The aqueous extract was concentrated under reduced pressure, precipitated with ethanol, and filtered. The filtrate was then reduced and extracted with water-saturated n-butanol. After the n-butanol extract was reduced to dryness, the residual was dissolved in water to yield “C-extract”. Chuanxiong, Danggui, and Danshen were combined and extracted with water. The aqueous extract was treated, in the same way as the preparation of “C-extract”, to yield “CDD-extract”. The preceding H-extract, C-extract, and CDD-extract were combined, diluted with isotonic glucose solution, and fortified with Tween 80. The solution was adjusted to pH 5.8–6.2, ultrafiltered, and sterilized. The finished product of XueBiJing injection was standardized to contain 1.0–1.7 mg/mL concentration of paeoniflorin, 0.2–0.5 mg/mL concentration of hydroxysafflor yellow A, and 0.01–0.20 mg/mL concentration of benzoic acid.

Figure 1

Table 1

Table 1
Pharmacokinetics of Danshen catechols and metabolites in human subjects intravenously receiving XueBiJing injection.

Pharmacokinetic parameter ^a	Dosage regimen for group I ^b		Dosage regimen for group II ^c		Dosage regimen for group III ^d	
	Male (<i>n</i> = 6 ^e)	Female (<i>n</i> = 6)	Male (<i>n</i> = 6)	Female (<i>n</i> = 6)	Male (<i>n</i> = 6)	Female (<i>n</i> = 6)
Tanshinol (3)						
Plasma <i>C</i> _{max} (nmol/L)	87.3 ± 23.9	95.3 ± 17.1	52.1 ± 8.8	57.5 ± 11.4	43.5 ± 6.7	51.7 ± 12.6
Plasma AUC _{0-∞} (h·nmol/L)	109 ± 30	121 ± 27	109 ± 17	120 ± 24	56.5 ± 4.7	57.4 ± 14.8
Plasma <i>t</i> _{1/2} (h)	0.33 ± 0.07	0.31 ± 0.06	0.38 ± 0.14	0.46 ± 0.14	0.35 ± 0.13	0.36 ± 0.09
Plasma MRT (h)	0.48 ± 0.10	0.44 ± 0.09	0.55 ± 0.20	0.66 ± 0.19	0.51 ± 0.19	0.52 ± 0.12
Plasma CL _{tot, p} (L/h/kg)	1.03 ± 0.14	1.10 ± 0.21	1.03 ± 0.18	1.08 ± 0.19	0.96 ± 0.18	1.19 ± 0.33
Plasma <i>V</i> _{SS} (L/kg)	0.33 ± 0.06	0.33 ± 0.06	0.39 ± 0.17	0.49 ± 0.21	0.33 ± 0.09	0.38 ± 0.06
Plasma <i>C</i> _{SS} (nmol/L)	86.9 ± 24.2	97.1 ± 21.4	43.5 ± 6.7	51.1 ± 11.3	45.2 ± 3.8	45.9 ± 11.8
Plasma <i>A</i> _{SS} (nmol)	2690 ± 534	2478 ± 522	1367 ± 410	1699 ± 495	1429 ± 519	1459 ± 348
Urinary <i>Cum.A</i> _e (μmol)	5101 ± 1062	5415 ± 856	4779 ± 2029	4259 ± 1118	2161 ± 312	2261 ± 296
Urinary CL _R (L/h/kg)	0.76 ± 0.21	0.84 ± 0.11	0.72 ± 0.35	0.68 ± 0.25	0.63 ± 0.13	0.77 ± 0.23
Urinary <i>f</i> _{e-U} (%)	73.1 ± 15.2	77.6 ± 12.3	68.5 ± 29.1	61.0 ± 16.0	61.9 ± 8.9	64.8 ± 8.5
Urinary CL _R /(GFR× <i>f</i> _u)	6.94 ± 1.91	7.60 ± 1.02	6.53 ± 3.22	6.14 ± 2.26	5.69 ± 1.14	7.01 ± 2.08
Salvianolic acid B (15)						
Plasma <i>C</i> _{max} (nmol/L)	77.6 ± 11.7	87.3 ± 15.3	44.1 ± 4.1	54.6 ± 10.6	43.0 ± 5.3	48.1 ± 14.5
Plasma AUC _{0-∞} (h·nmol/L)	85.1 ± 19.2	101 ± 15	93.1 ± 15.5	105 ± 22	46.1 ± 5.2	56.8 ± 16.1
Plasma <i>t</i> _{1/2} (h)	0.26 ± 0.03	0.32 ± 0.12	0.29 ± 0.05	0.29 ± 0.01	0.27 ± 0.03	0.31 ± 0.14
Plasma MRT (h)	0.38 ± 0.05	0.46 ± 0.17	0.42 ± 0.07	0.42 ± 0.17	0.39 ± 0.04	0.44 ± 0.20
Plasma CL _{tot, p} (L/h/kg)	0.44 ± 0.08	0.46 ± 0.05	0.43 ± 0.09	0.41 ± 0.14	0.41 ± 0.03	0.43 ± 0.09
Plasma <i>V</i> _{SS} (L/kg)	0.11 ± 0.01	0.15 ± 0.07	0.13 ± 0.03	0.19 ± 0.05	0.11 ± 0.01	0.13 ± 0.05
Plasma <i>C</i> _{SS} (nmol/L)	68.1 ± 15.3	81.2 ± 11.7	37.2 ± 6.2	52.4 ± 18.9	36.9 ± 4.1	45.4 ± 12.9

Plasma A_{SS} (nmol)	779 ± 116	926 ± 345	427 ± 67	425 ± 174	393 ± 38	446 ± 197
Urinary $Cum.A_e$ (μmol)	5.18 ± 1.58	5.61 ± 2.27	5.14 ± 2.35	6.60 ± 3.22	—	—
Urinary CL_R (L/h/kg)	0.001 ± 0.000	0.001 ± 0.000	0.001 ± 0.000	0.001 ± 0.000	—	—
Urinary f_{e-U} (%)	0.21 ± 0.06	0.22 ± 0.09	0.26 ± 0.03	0.22 ± 0.13	—	—
Urinary $CL_R/(GFR \times f_u)$	0.008 ± 0.002	0.007 ± 0.001	0.009 ± 0.003	0.007 ± 0.002	—	—

^a C_{max} , maximum concentration; $AUC_{0-\infty}$, area under the concentration-time curve from zero to infinity; $t_{1/2}$, elimination half-life; MRT, mean residence time; $CL_{tot,p}$, total plasma clearance; V_{SS} , apparent volume of distribution at steady state; C_{SS} , calculated concentration at steady state; A_{SS} , calculated amount at steady state; $Cum.A_e$, cumulative amount excreted into urine; CL_R , renal clearance; f_e , fraction of dose excreted into urine; GFR, glomerular filtration rate.

^b Dosage regimen for group I: a 75-minute intravenous infusion of 100-mL XueBiJing injection (diluted in 100-mL NaCl injection).

^c Dosage regimen for group II: a 150-minute intravenous infusion of 100-mL XueBiJing injection (diluted in 200-mL NaCl injection).

^d Dosage regimen for group III: a 75-minute intravenous infusion of 50-mL XueBiJing injection (diluted in 100-mL NaCl injection).

^e The human plasma samples of the same point of time were not pooled before being analyzed for determination of the compounds' pharmacokinetics, whereas the human urine samples of the same period of time were also not pooled.