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Pharmacokinetics of Depside Salts From *Salvia miltiorrhiza* in Healthy Chinese Volunteers: A Randomized, Open-Label, Single-Dose Study

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ABSTRACT

BACKGROUND: Depside salts from *Salvia miltiorrhiza*, with active components of lithospermic acid B (LSB), rosmarinic acid (RA), and lithospermic acid (LA), are a multicomponent drug marketed in China for the treatment of coronary heart disease.

OBJECTIVES: The aims of this study were to determine the concentrations of LSB, RA, and LA in human plasma and urine, and to compare the pharmacokinetic properties of depside salts from *S miltiorrhiza* in healthy Chinese volunteers.

METHODS: A randomized, open-label, single-dose study was conducted in healthy Chinese volunteers. Participants were randomly assigned to receive a single intravenous infusion of 100 or 200 mg of depside salts from *S miltiorrhiza*. Blood was collected through a venous cannula prior to study drug administration (0 min) and at 10, 20, 30, 60, 65, 70, 80, and 90 minutes and 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration. Urine samples were taken before study drug administration (0) and at 0 to 12 and 12 to 24 hours after study drug administration. LSB, RA, and LA concentrations in serum and urine were analyzed by an LC-MS/MS method. Tolerability was determined by clinical assessment; vital signs (ie, blood pressure, heart rate, breathing rate, body temperature) monitoring at baseline and at the end of the study, clinical laboratory tests (ie, hematology, blood biochemistry, hepatic function, renal function, urinalysis), 12-lead ECG measurements, and physical examinations at baseline and after completion of the study.

RESULTS: Twelve Chinese volunteers (6 males, 6 females; mean [SD] age, 25.2 [3.8] years; mean height, 165.7 [8.9] cm; mean body mass index, 21.6 [2.5] kg/m^2) were enrolled in the study. Peak plasma concentrations of LSB, RA and LA were observed at 0.3 to 1 hour following the 1-hour intravenous infusion, with respective mean (SD) C_{max} of 4925 (1861), 174 (61), and 361 (101) ng/mL for the 100-mg dose and 10,285 (2259), 308 (77), and 674 (85) ng/mL for the 200-mg dose. The AUC_{last} values for LSB, RA, and LA were 4537 (1265), 129 (28), and 1229 (330) ng/mL/h,

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respectively, for the 100-mg dose and 10,426 (2589), 260 (53), and 2792 (729) ng/mL/h for the 200-mg dose. No significant difference in pharmacokinetic parameters was observed between male and female subjects. Three metabolites were found in the plasma with low concentrations. The urinary excretion recoveries of LSB, RA, and LA were 0.58% (0.42%), 25.21% (20.61%), and 10.02% (7.72%) for the 100-mg dose and 0.38% (0.18%), 20.11% (10.50%), and 6.34% (3.20%) for the 200-mg dose. No adverse events were reported by the subjects or found by the investigators in the analysis of vital signs, 12-lead ECG measurements, physical examinations, or clinical laboratory tests.

CONCLUSIONS: Following single intravenous infusion of 100 or 200 mg of depside salts from *S miltiorrhiza* to healthy Chinese subjects, no statistical differences in pharmacokinetic parameters were observed between males and females. The 2 doses of depside salts from *S miltiorrhiza* were clinically well tolerated during the study. (*Curr Ther Res Clin Exp.* 2010;71:260–271) © 2010 Excerpta Medica Inc.

KEY WORDS: lithospermic acid B, rosmarinic acid, lithospermic acid, pharmacokinetics, healthy volunteers, liquid chromatography tandem mass spectrometry, LC-MS/MS.

INTRODUCTION

Depside salts from *Salvia miltiorrhiza* are a multicomponent drug used for the treatment of coronary heart disease. It was approved in 2005 by the State Food and Drug Administration (SFDA) of China as an injection. These components are derived from danshen, the dried roots of the medicinal plant *S miltiorrhiza*, a traditional Chinese medicine used for the treatment of hepatitis, blood circulation diseases, and other cardiovascular diseases.[1] Lithospermic acid B (LSB) and its analogues, rosmarinic acid (RA), and lithospermic acid (LA), are the main active components of depside salts from *S miltiorrhiza*.[2] Depside salts from *S miltiorrhiza* have been reported to improve myocardial microperfusion and cardiac output in rats.[3] LSB, also known as magnesium lithospermate B (MLB), is a strong antioxidant and free radical scavenger extracted from *S miltiorrhiza*.[4,5] Pharmacologic studies have indicated that MLB might protect against renal dysfunction, myocardial damage, and experimental hepatitis.[6–11] RA and LA are natural polyphenols with antioxidative, antibacterial, and antiviral activities.[12] A 2009 study indicated that LA was associated with inhibited vascular smooth muscle cell migration and proliferation in rats.[13] A clinical study found that intravenous infusion of depside salts from *S miltiorrhiza* was an efficacious treatment for coronary heart disease and angina pectoris with heart-blood stagnation syndrome.[14]

MLB is a component with oral absolute bioavailability of 0.0002 from the AUC values after both intravenous and oral administration in rats[15] and is rapidly excreted into the bile, mostly as methylated metabolites.[16] The elimination $t_{1/2}$ for LSB, RA, and LA is 1.04, 0.75, and 2.0 hours, respectively, in rats[2] and 0.71, 0.51, and 0.83 hour in dogs,[17] following intravenous administration of depside salts from *S miltiorrhiza*.

This study aimed to investigate the pharmacokinetic (PK) parameters of LSB, RA, and LA after intravenous infusion of depside salts from *S miltiorrhiza* in healthy Chinese subjects.

SUBJECTS AND METHODS

STUDY DESIGN

A randomized, open-label, single-dose study design was conducted in healthy male and female volunteers at the Shanghai Xuhui Central Hospital (Shanghai, China). The study was approved by the ethics committee of Shanghai Xuhui Central Hospital, and carried out in accordance with Chinese ethical guidelines for biomedical research on human subjects. Informed written consent was obtained from all volunteers prior to study initiation. Medical history, physical examination results (including vital signs and 12-lead ECG), and analyses of laboratory parameters (including complete blood count, differential cell count, liver and renal function tests, and urinalysis) were recorded no more than 28 days prior to the commencement of the study. Subjects were to be nonsmokers, with no history of alcohol abuse, or family history of diabetes mellitus. Subjects had to have not taken medication or consumed alcohol for ≥2 weeks prior to the study and during the study period. They were allowed to engage in normal activities but were instructed to avoid severe physical exertion. Volunteers were recruited through an advertisement and compensated for their participation.

Individuals were randomly divided evenly into 2 groups with random number table and each group received either a 100- or 200-mg intravenous dose of depside salts from *S miltiorrhiza*, in accordance with a predetermined schedule (dose amount, meal timing, and sample collection). In each group, depside salts from *S miltiorrhiza* (LSB ≥87.7%, RA ≥4.5%, and LA ≥0.9%) were dissolved in 250 mL of glucose solution (5%) and intravenously infused at a flow rate of 250 mL/h for 1 hour.

A standardized meal was served to all subjects at 4, 6, and 12 hours after the 1-hour intravenous infusion. Venous blood samples (4 mL) were collected through a venous cannula prior to study drug administration (0) and at 10, 20, 30, 60, 65, 70, 80, and 90 minutes and 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration. The actual collection time of each blood sample and any protocol deviations were recorded. To obtain plasma, blood samples were heparinized and centrifuged at 3000 rpm for 10 minutes as soon as possible.

Fractionated urine samples were collected to measure the urinary excretion levels of both groups before and after dosing at the following time points: before study drug administration (0), 0 to 12 hours, and 12 to 24 hours after infusion.

Both plasma and urine samples were stored in labeled tubes at –80°C until analysis.

CHEMICALS AND REAGENTS

Depside salts from *S miltiorrhiza* (100 or 200 mg) were provided by Green Valley Co. Ltd. (Shanghai, China). MLB, RA, LA, and silibinin (internal standard [IS]) were provided by the Department of Phytochemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China). The purity of these compounds was

verified to be >99% by using a validated HPLC method. HPLC-grade acetonitrile and methanol were purchased from Fisher Scientific Co. (Fair Lawn, New Jersey). Double-distilled water was used for the preparation of all solutions. All other reagents were of analytic grade and used as received.

LIQUID CHROMATOGRAPHY MASS SPECTROMETRY

Plasma and urine samples were analyzed by LC-MS/MS as previously described.[2] The system was composed of an HPLC (Shimadzu, Japan) coupled to a triple-quadruple mass spectrometer (Perkin-Elmer API-3000, Sciex, Concord, Ontario, Canada) equipped with an electrospray ionization source. The separation was achieved using a 5-μm C_{18} column (Capcell Pak, 50 × 2.0 mm internal diameter; Shiseido, Japan) with the mobile phase of 60% water (containing 0.5% formic acid) and 40% acetonitrile. The negative ionization mode was selected for the determination and the mass spectrometer was operated in the multiple reaction monitoring mode, with monitoring of the precursor-to-product ion transitions of m/z 717→519 for LSB, m/z 359→160 for RA, m/z 537→493 for LA, m/z 731→533 for metabolite M1, m/z 745→547 for M2, m/z 759→547 for M3, and m/z 481→301 for silibinin (IS). These samples were isolated by the same liquid–liquid extraction method as previously described.[16] Linear ranges of calibration curves were 8 to 2048 ng/mL for all analytes with a lower limit of quantitation of 8 ng/mL.

PHARMACOKINETIC ANALYSIS

PK analysis was performed for plasma concentrations of each compound using Drug and Statistics, version 2.0 (Anhui Provincial Center for Drug Clinical Evaluation, Anhui, China). The AUC from 0 to 24 hours (AUC_{last}), C_{max}, T_{max}, mean residence time (MRT), and plasma elimination $t_{1/2}$ were calculated. Actual sampling times were used in the calculation of these parameters.

TOLERABILITY ASSESSMENTS

Throughout the study, subjects were monitored by 2 investigators (Y.L. and Y.-M.L.). Tolerability was determined by clinical assessment; vital signs (ie, blood pressure, heart rate, breathing rate, body temperature) monitoring at baseline and at the end of the study, clinical laboratory tests (ie, hematology, blood biochemistry, hepatic function, renal function, urinalysis), 12-lead ECG measurements, and physical examinations were performed at baseline and after completion of the study. Adverse events (AEs) were assessed at the time of each blood draw using direct observation, spontaneous reporting, and nonspecific questioning. All AEs and serious AEs were recorded on the case-report form. All clinical laboratory tests were performed at the laboratory of Shanghai Xuhui Central Hospital, which is accredited by the National Center for Clinical Laboratories of China (which regularly tests and certifies laboratory testing facilities).

STATISTICAL ANALYSIS

A 2-tailed *t* test was used to compare the PK parameters (C_{max}, T_{max}, $t_{1/2}$, MRT, and AUC_{last}) between male and female subjects. $P < 0.05$ was considered to be statistically

significant. Descriptive data were reported as mean (SD). All statistical analyses were conducted using SPSS version 11.5 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 12 healthy Chinese subjects (6 males, 6 females; mean [SD] age, 25.2 [3.8] years; mean height, 165.7 [8.9] cm; mean body mass index, 21.6 [2.5] kg/m^2) were enrolled in the study. Baseline characteristics for the included participants are summarized in Table I.

PHARMACOKINETIC ANALYSIS

Mean plasma concentration–time profiles for LSB, RA, and LA after intravenous infusion of 100 and 200 mg of depside salts from *S miltiorrhiza* are shown in Figure 1. Mean values of the PK parameters for LSB, RA, and LA are summarized in Table II. Peak plasma concentrations of LSB, with mean concentrations of 4925 ng/mL at the 100-mg dose and 10,285 ng/mL at the 200-mg dose, were observed after ~0.7 hour during the 1-hour intravenous infusion with steady high plasma concentrations reached at 0.3 to 1 hour. There was a rapid decline in plasma concentrations immediately after the 1-hour infusion. The mean $t_{1/2}$ for LSB ranged from 2.3 to 2.9 hours. The mean C_{max} value for RA (308 ng/mL) was significantly lower than those for LA (674 ng/mL) and LSB (10,285 ng/mL) after administration of the 200-mg dose, and the $t_{1/2}$ for RA (0.58 h) was also significantly lower than those for LA (5.48 h) and LSB (2.87 h).

The overall pattern of the plasma concentration-time profiles for LSB, RA, and LA was not significantly different between all individuals in the 2 dose groups. Mean C_{max} and AUC_{last} values for LSB, RA, and LA were 1.77 to 2.30 times higher when the dose increased from 100 to 200 mg, whereas there were no significant increases in T_{max}, $t_{1/2}$, and MRT values for LSB, RA, and LA (Table II).

Table I. Baseline characteristics for included participants.* Data are mean (SD).

Variable	Male (n = 6)	Female (n = 6)	Total (N = 12)
Age, y	26.3 (3.8)	24.4 (3.5)	25.2 (3.8)
Height, cm	170.2 (5.4)	160.6 (5.6)	165.7 (8.9)
Weight, kg	64.2 (5.4)	52.3 (5.3)	58.2 (7.8)
BMI, kg/m^2	22.0 (2.5)	20.8 (2.3)	21.6 (2.5)
Body temperature, °C	36.8 (0.3)	36.5 (0.3)	36.7 (0.3)
Heart rate, beats/min	78.3 (11.5)	82.2 (12.3)	80.6 (10.4)
Respiration, breaths/min	16.3 (0.7)	16.5 (0.8)	16.4 (0.6)
SBP, mm Hg	116.6 (15.3)	116.1 (14.3)	116.4 (16.2)
DBP, mm Hg	76.8 (8.7)	74.5 (8.9)	75.4 (10.2)

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.
*There were no statistically significant differences observed between males and females.

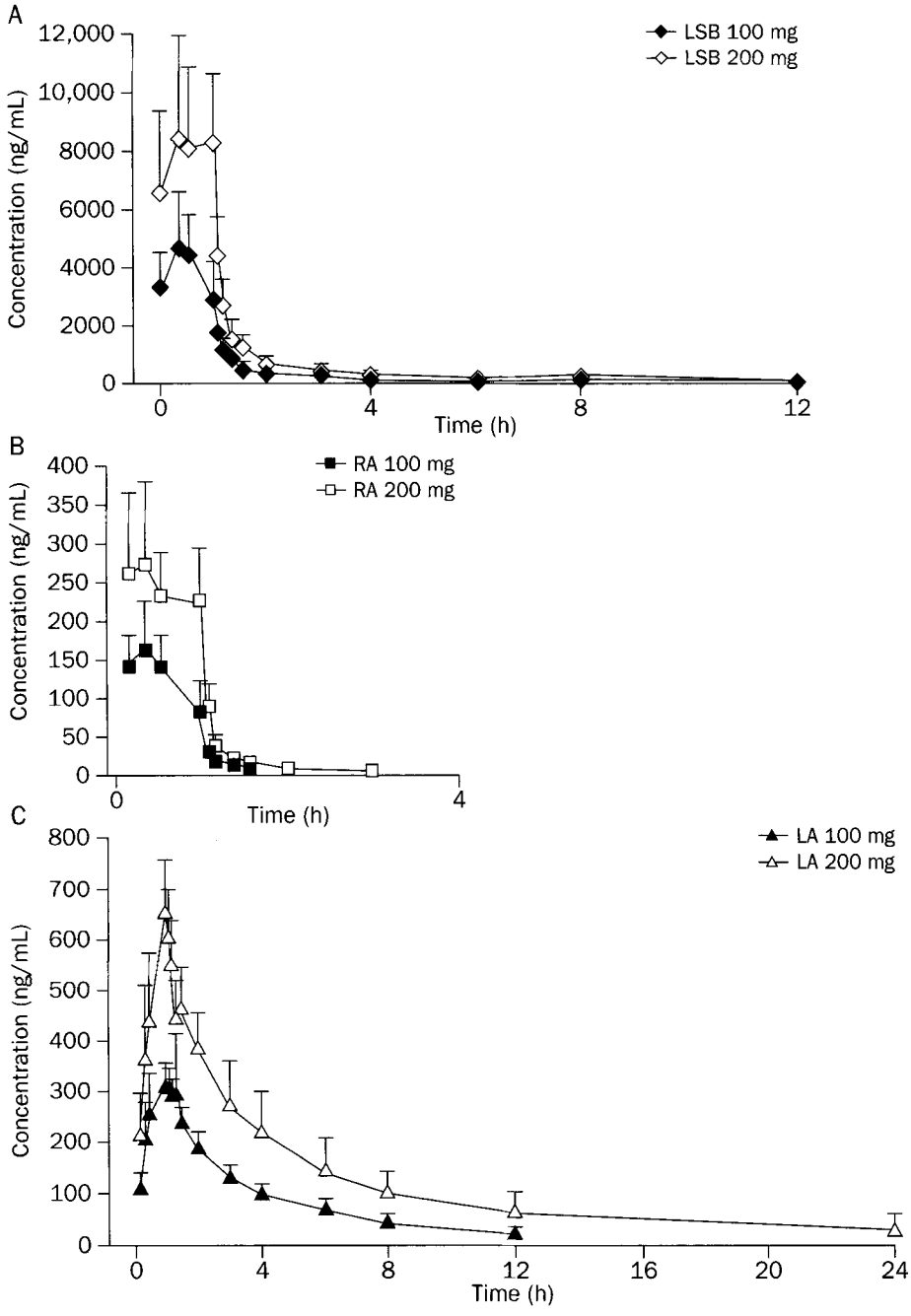

Figure 1. Mean plasma concentration–time profiles of (A) lithospermic acid B (LSB), (B) rosmarinic acid (RA), and (C) lithospermic acid (LA) after intravenous infusion of 100 or 200 mg of depside salts from *Salvia miltiorrhiza* in healthy individuals (N = 12).

Table II. Pharmacokinetic parameters of lithospermic acid B (LSB), rosmarinic acid (RA), and lithospermic acid (LA) after intravenous infusion of 100 or 200 mg of depside salts from *Salvia miltiorrhiza* in healthy subjects (N = 12). Data are mean (SD).

Analytes	Sex	C_{max}, ng/mL	T_{max}, h	$t_{1/2}$, h	MRT, h	AUC_{last}, ng/mL/h
100-mg Dose						
LSB	Male	4042 (1404)	0.76 (0.29)	2.28 (1.17)	1.33 (0.83)	4170 (1431)
	Female	5986 (1901)	0.50 (0.29)	2.39 (0.65)	0.96 (0.14)	4977 (998)
	Total	4925 (1861)	0.64 (0.31)	2.33 (0.92)	1.16 (0.62)	4537 (1265)
RA	Male	156 (43)	0.57 (0.29)	0.16 (0.07)	0.57 (0.08)	127 (33)
	Female	191 (78)	0.37 (0.07)	0.29 (0.10)	0.52 (0.05)	131 (31)
	Total	174 (61)	0.47 (0.21)	0.23 (0.11)	0.54 (0.07)	129 (28)
LA	Male	324 (43)	1.01 (0.04)	3.78 (0.68)	4.88 (1.99)	1281 (453)
	Female	404 (136)	1.00 (0.31)	3.68 (0.38)	3.47 (0.13)	1166 (80)
	Total	361 (101)	1.01 (0.20)	3.74 (0.54)	4.24 (1.59)	1229 (330)
200-mg Dose						
LSB	Male	10,085 (1684)	0.69 (0.34)	2.97 (0.78)	1.17 (0.49)	9772 (1855)
	Female	10,485 (2879)	0.69 (0.34)	2.78 (1.12)	1.35 (0.72)	11,080 (3207)
	Total	10,285 (2259)	0.69 (0.33)	2.87 (0.93)	1.26 (0.59)	10,426 (2589)
RA	Male	338 (88)	0.61 (0.31)	0.46 (0.25)	0.64 (0.11)	283 (67)
	Female	278 (58)	0.47 (0.29)	0.70 (0.80)	0.68 (0.15)	237 (18)
	Total	308 (77)	0.54 (0.29)	0.58 (0.58)	0.66 (0.13)	260 (53)
LA	Male	647 (80)	0.82 (0.32)	6.25 (4.16)	5.42 (1.58)	2758 (958)
	Female	702 (88)	1.03 (0.07)	4.71 (0.95)	5.05 (0.49)	2826 (500)
	Total	674 (85)	0.92 (0.25)	5.48 (2.99)	5.24 (1.13)	2792 (729)

MRT = mean residence time; AUC_{last} = AUC from 0 to 24 hours.

Results of the *t* test (**Table III**) indicated that the values of primary PK parameters (C_{max}, T_{max}, $t_{1/2}$, MRT, and AUC_{last}) were not statistically different for male and female subjects in either dose group. With the exception of the $t_{1/2}$ in RA after a 100-mg dose ($P = 0.04$), all comparisons between males and females showed no significant differences.

METABOLISM AND URINARY EXCRETION

Metabolite plasma PK data were assessed after intravenous infusion of each dose level. Mean plasma concentration–time profiles for the metabolites M1, M2, and M3 after intravenous infusion at the 2 dose levels are shown in **Figure 2**. Pharmacokinetic parameters of M1, M2, and M3 in healthy subjects are summarized in **Table IV**. For the 200-mg dose, the mean C_{max} values for M1, M2, and M3 were 173, 168, and 106 ng/mL, respectively, and the AUC_{last} values were 162, 187, and 159 ng/mL/h.

The urinary excretion levels of LSB, RA, and LA during the 24 hours after intravenous administration are shown in **Table V** for both doses. The urinary excretion was 0.58% for LSB and 10.02% for LA. RA is a small-molecule analogue of LSB, and had urinary excretion of 25.21%. The concentrations of RA and LSB in the urine rapidly decreased during the 0- to 12-hour period after dosing. During the 12- to 24-hour period, RA and LSB were undetectable and LA was only 31.13 ng/mL in the urine.

TOLERABILITY

The 2 doses of depside salts from *S miltiorrhiza* appeared to be well tolerated in the population investigated. No AEs were reported by the subjects or found by the investigators in the analysis of vital signs, 12-lead ECG measurements, physical examinations, or clinical laboratory tests.

Table III. Group difference of pharmacokinetic parameters between male and female subjects after administration of 100- or 200-mg doses (N = 12). Data are *P* values.

Analyte	C_{max}	T_{max}	$t_{1/2}$	MRT	AUC_{last}
100-mg Dose					
LSB	0.10	0.17	0.85	0.32	0.30
RA	0.40	0.15	0.04	0.21	0.84
LA	0.27	0.93	0.78	0.14	0.57
200-mg Dose					
LSB	0.78	1.00	0.74	0.63	0.41
RA	0.19	0.44	0.50	0.64	0.16
LA	0.29	0.17	0.41	0.60	0.88

MRT = mean residence time; AUC_{last} = AUC from 0 to 24 hours; LSB = lithospermic acid B; RA = rosmarinic acid; LA = lithospermic acid.

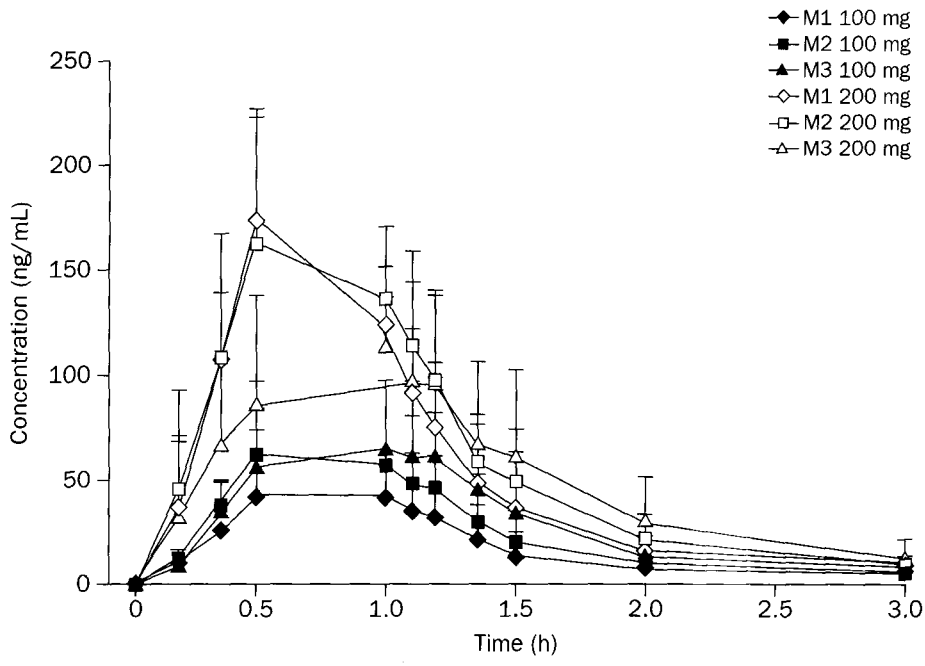

Figure 2. Mean plasma concentration–time profiles of metabolites M1, M2, and M3 after intravenous infusion of 100 or 200 mg of depside salts from *Salvia miltiorrhiza* in healthy individuals (N = 12).

Table IV. Pharmacokinetic parameters of metabolites M1, M2, and M3 after intravenous infusion of 100 or 200 mg of depside salts from *Salvia miltiorrhiza* in healthy subjects (N = 12). Data are mean (SD).

Metabolite	C_{max}, ng/mL	T_{max}, h	$t_{1/2}$, h	MRT, h	AUC_{last}, ng/mL/h
100-mg Dose					
M1	49 (33)	0.70 (0.27)	0.49 (0.11)	1.06 (0.15)	56 (38)
M2	66 (34)	0.70 (0.27)	0.61 (0.45)	1.04 (0.08)	77 (45)
M3	74 (39)	0.93 (0.25)	0.63 (0.19)	1.13 (0.14)	93 (53)
200-mg Dose					
M1	173 (51)	0.63 (0.25)	0.52 (0.21)	0.98 (0.12)	162 (59)
M2	168 (62)	0.75 (0.29)	0.52 (0.19)	1.01 (0.08)	187 (79)
M3	106 (52)	1.04 (0.08)	0.60 (0.14)	1.17 (0.05)	159 (90)

MRT = mean residence time; AUC_{last} = AUC from 0 to 24 hours.

Table V. The urinary excretion of lithospermic acid B (LSB), rosmarinic acid (RA), and lithospermic acid (LA) during 24 hours after intravenous administration of 100 or 200 mg of depside salts from *Salvia miltiorrhiza* in healthy subjects (N = 12). Data are mean (SD).

	Excretion Amount, mg		Excretion Recovery, %	
Component	100 mg	200 mg	100 mg	200 mg
LSB	0.51 (0.37)	0.67 (0.31)	0.58 (0.42)	0.38 (0.18)
RA	1.13 (0.93)	1.81 (0.95)	25.21 (20.61)	20.11 (10.50)
LA	0.09 (0.07)	0.11 (0.06)	10.02 (7.72)	6.34 (3.20)

DISCUSSION

A previous study indicated that LSB, RA, and LA are rapidly eliminated from the serum and distributed widely after intravenous administration of depside salts from *S miltiorrhiza* in rats.[2] In clinical practice, 1-hour intravenous infusion is used to obtain steady high plasma concentrations and prolong the $t_{1/2}$ of LSB, RA, and LA. In this study, steady high plasma concentrations were obtained during the 1-hour intravenous infusion, followed by a rapid decline in plasma concentrations immediately after the infusion. When the dose of depside salts from *S miltiorrhiza* was increased from 100 to 200 mg, the elimination $t_{1/2}$ was also increased from 2.33 to 2.87 hours for LSB, from 0.23 to 0.58 hour for RA, and from 3.74 to 5.48 hours for LA; however, the differences were not statistically significant.

RA was eliminated more rapidly than LSB and LA, with the plasma concentration decreasing to less than the lower limit of quantitation within 3 hours of dosing. The AUC_{last} value of LSB was much greater than those of RA and LA, which is in agreement with the high amount of LSB (87.7%) in depside salts from *S miltiorrhiza*. Although only 0.9%, the AUC_{last} value for LA was ~20% of the total AUC value. This may be owing to the long $t_{1/2}$ of LA.

Based on the PK parameters (C_{max}, T_{max}, $t_{1/2}$, MRT, AUC_{last}) between the sexes investigated in the present study, no significant difference was found between men and women; however, there was a significance ($P = 0.04$) observed in the $t_{1/2}$ for RA at the 100-mg dose that may not be clinically significant.

Comparison of LSB and the metabolite PK parameters for both groups suggested that the C_{max} and AUC values of the metabolites were much lower than those of the parent drug LSB. These results are not statistically different from those found in rats, because LSB is methylated rapidly in liver and most of the metabolites (M1, M2, and M3) were excreted directly into bile and finally into feces.[2] The low urinary excretion of LSB (0.58%) also indicated that renal secretion is not the main excretion pathway.

LIMITATIONS

The study was conducted in a small population of healthy Chinese adult subjects with a single dose administered. The PK characteristics of depside salts from *S miltiorrhiza*

might differ in other populations. As the study was designed without a sample-size analysis performed a priori, there is a possibility of a Type II error when no statistically significant differences between the sexes are found. Because there was no correction for multiple comparisons, there is a possibility of false-positive findings.

CONCLUSIONS

In this study of healthy Chinese adult male and female volunteers, there were no significant differences observed in the PK parameters of LSB and LA after a single intravenous infusion of depside salts from *S miltiorrhiza* at a dose of 100 or 200 mg. Both doses were generally well tolerated in this population.

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Drs. Jia and Lu contributed equally to this study. The authors have indicated that they have no conflicts of interest regarding the content of this article.

Dr. Wang and Mr. Yu designed the study. Mr. Jia and Dr. X.-C. Li prepared the manuscript. Dr. Lu, Mr. G.-Y. Liu, and Dr. S.-J. Li analyzed the data. Drs. Y. Liu and Y.-M. Liu collected the data. Green Valley Co. Ltd. sponsored the study by providing the study drug.

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