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Liver, blood microdialysate and plasma pharmacokinetics of matrine following transdermal or intravenous administration

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Matrine is contained in several herbs used in traditional Chinese medicine, named *Sophora alopecuroides*, *Sophora flavescens* or *Sophora subprostrata*. *In vitro* and *in vivo* studies have focused on the treatment of chronic hepatitis or liver fibrosis using matrine. However, little is known about its liver pharmacokinetic profile. In this study pharmacokinetics of matrine in rat organs and tissues, such as liver, blood and skin were studied after intravenous (40 mg/kg) or transdermal administration (6 mg/cm^2, 5 cm^2). Samples were collected at timed intervals for measurement of matrine by a HPLC-UV method. The pharmacokinetic parameters were calculated by non-compartmental analysis using DAS 2.0. The $AUC_{(0\text{-}t)}$ values in the liver, blood microdialysates and plasma after intravenous administration were 395.91±74.48, 848.86±146.35 and 1304.07±305.92 min·mg/l, respectively. Following transdermal administration, the $AUC_{(0\text{-}t)}$ value in the liver, blood, plasma and skin microdialysates were 695.30±233.79, 1096.07±390.71, 2767.57±518.48 and 42735.77±27938.33 min·mg/l, respectively. Here, we show a promising delivery system for matrine that could replace traditional administration, and a better understanding of the transdermal pharmacokinetics of matrine, which may be helpful for further clinical and laboratory studies.

1. Introduction

Herbal medicines have been increasingly applied to treat various diseases and in the promotion of health in recent years. Matrine is the major active pharmaceutical ingredient of the dried roots of traditional Chinese herbs like *Sophora alopecuroides*, *Sophora flavescens* or *Sophora subprostrata*, which have been extensively used in China for the treatment of chronic hepatitis and liver fibrosis (Yuan et al. 2010; Jiang et al. 2015; Sabatino et al. 2015; Wu et al. 2016; Yang et al. 2016).Clinically, matrine is commonly administered *via* intravenous (*i.v.*) injection and oral capsules or tablets (Zhang et al. 2009). Oral administration leads to gastrointestinal reactions and low bioavailability. The absolute oral bioavailability of matrine was found to be only 20%, when compared with administration by injection (Ruan et al. 2010). Therefore, it is necessary to develop a new method of matrine administration. Compared with conventional pharmaceutical dosing regimens, transdermal administration offers an alternative pathway with many important advantages, including elimination of hepatic first-pass metabolism, enhancement of therapeutic efficacy, reduced side effects and improved patient compliance (Thiede et al. 2014; Tong et al. 2015; Gennari et al. 2016). Matrine is suitable for transdermal delivery, as it has a low molecular weight of 248.3, a melting point of 85 °C and a partition coefficient ($\log K_{oct/water}$) of 0.897. However, current transdermal administration studies have only reported the physicochemical properties, stability and skin penetration of matrine *in vitro*.

Several studies have been performed on the pharmacokinetics of matrine alone or as part of an herbal mixture following oral administration (Ruan et al. 2010; Yang et al. 2010; Tang et al. 2013; Wang et al. 2014). Almost all of these reports have only described matrine plasma concentration. However, it is essential to study the liver pharmacokinetics of matrine for further drug investigations. Wu et al. (2009) studied the tissue distribution of matrine and drug concentrations were determined by tissue (containing liver) homogenates, but little is known about the unbound liver pharmacokinetic profile of matrine. Microdialysis is a continuous sampling method suitable for *in vivo* pharmacokinetic measurements. This method is minimally invasive and provides samples of the unbound drug (only the unbound fraction is therapeutically active for drugs *in vivo*), which is an analytical advantage (Gao et al. 2014; Li et al. 2014a, b; Gottas et al. 2016; Joshi et al. 2016). This technology can be combined for multi-site synchronization of microdialysis experiments, and provides valuable information about matrine concentration changes in different parts for clinical applications.

The aim of this study was to characterize and compare the pharmacokinetics of unbound matrine in different tissues and organs of the rat (blood, liver and skin) using microdialysis, following transdermal and intravenous administration. This study may help to give more accurate pharmacokinetic parameters and better clarify the transdermal or intravenous administration process of matrine. This is the first report of the liver microdialysis of matrine.

2. Investigations and results

2.1. Validation of the analytical method

The HPLC method was able to rapidly and sensitively measuring matrine concentrations in microdialysate and plasma. The retention time was approximately 4.3 min for microdialysate or 5.5 min for plasma, and no interference was found from other endogenous compounds. The retention time was different microdialysate and plasma samples, as there was interference at 4.3 min in the plasma samples, meaning that appropriate adjustments to the mobile phase proportions were made.

To ensure the reliability of the assay, the analytical method was validated using blank Ringer's solution and plasma samples that were spiked with different matrine concentrations. The HPLC method showed good linearity throughout the concentration range of 0.10–25.00 µg/ml in Ringer's solution and over the range 0.32–81.80 µg/ml in plasma. The regression equations were Y = 11937.17X+232.26 (n=5, R^2=1.000) for samples in Ringer's solution and Y = 4751.17X+96.54 (n=5, R^2=1.000) for plasma samples. Intra-day and inter-day variability was determined, and all of the

R.S.Ds were less than 10.75%, with accuracy levels between 94.7-107.9%. The stability results indicated that matrine was stable during storage in both Ringer's solution and plasma.

2.2. Recovery of the probe

The results of probe recovery of matrine showed that recovery was not correlated with drug concentration (matrine: 2.5, 5.0, 10.0 μg/ml) and was inversely proportional to the perfusion velocity (1.0, 2.0, 3.0 μl/min). At the same flow rate, the recovery measured by *in vitro* positive dialysis was highly consistent with that measured by retrodialysis. *In vitro* recoveries from the concentric cannula probe and the linear probe were 41.57±0.92~81.67±0.96% and 44.69±1.24~82.99±1.26% at different perfusion velocities. Therefore, the recovery could be applied to the pharmacokinetic studies.

2.3. In vivo pharmacokinetic study of matrine

The concentration-time profiles and pharmacokinetic parameters of matrine in rat plasma and dialysates from liver, blood and skin following transdermal (6 mg/cm^2, 5 cm^2) or *i.v.* administration (40 mg/kg) are presented in Figs. 1-2 and Tables 1-2.

The pharmacokinetic results following *i.v.* administration of matrine showed that the AUC and C_{max} of matrine had the following trend: plasma > blood microdialysis > liver microdialysis. This was most likely due to the drug first entering the blood and then the liver, and the drug concentration from blood microdialysis identified the concentration of unbound drug, while the plasma concentration was made up of unbound and protein-bound matrine.

With regards to the pharmacokinetics of matrine transdermal administration, the AUC of matrine showed the following trend: subcutaneous microdialysis > plasma > blood microdialysis > liver microdialysis, and the C_{max} and AUC in the blood microdialysate were about 50% compared to those in plasma, suggesting that the concentration of unbound matrine was approximately 50% of the total plasma concentration. Compared with the pharmacokinetics of *i.v.* administered matrine (40 mg/kg), the transdermal patch group showed similar C_{max} in plasma and an MRT that was three times longer at different parts. The $AUC_{(0\text{-}t)s}$ of the patch was twice as large as those following *i.v.* injection, while the $AUC_{(0\text{-}360)s}$ of the patch was similar to those of *i.v.* administration.

3. Discussion

Several studies have investigated matrine pharmacokinetics in rats following *i.v.* administration. Ruan et al. (2010) showed that after the *i.v.* administration of 20 mg/kg matrine in conscious wistar rats, the $AUC_{(0\text{-}t)}$ in plasma was 3048.0 min· mg/l and $t_{1/2}$ was 287.4 min. Yang et al. (2010) showed that after *i.v.* administration of 2 mg/kg matrine in anaesthetized SD rats, the $AUC_{(0\text{-}t)}$ in plasma was 108.6 min· mg/l and $t_{1/2}$ was 142.0 min, while Wu et al. (2009) showed that *i.v.* administration of 15 mg/kg matrine to anaesthetized SD rats, resulted in an $AUC_{(0\text{-}t)}$ in plasma of 184.8 min· mg/l and $t_{1/2}$ of 152.4 min. In our study, *i.v.* administration of matrine to anaesthetized SD rats resulted in an $AUC_{(0\text{-}t)}$ in plasma of 1304.1 min· mg/l and $t_{1/2}$ of 132.8 min. In the above studies, there was no difference in $t_{1/2}$ in SD rats. There were some differences in the AUC, which may have been due to different doses, sampling methods, species and status of the rats. In the three studies mentioned above, *i.v.* administration was performed through the tail vein, and venous blood samples were collected from eye sockets vein, tail vein, and or femoral artery. In our study, *i.v.* administration was performed through the femoral vein and venous blood samples were collected from the tail vein.

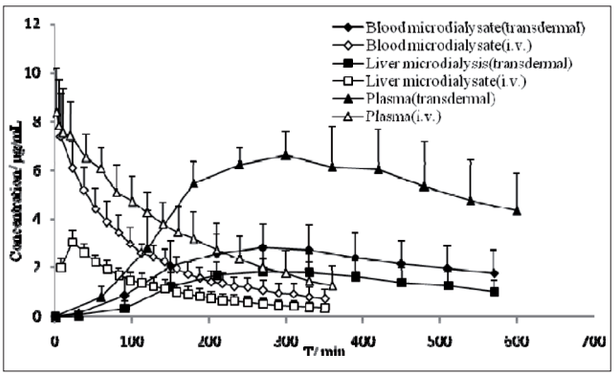

Fig. 1: Concentration versus time profiles of matrine in rat plasma, blood and liver microdialysates after *i.v.* administration (40 mg/kg) or transdermal administration (6 mg/cm^2, 5 cm^2) in rats (mean±SD, *n*=6).

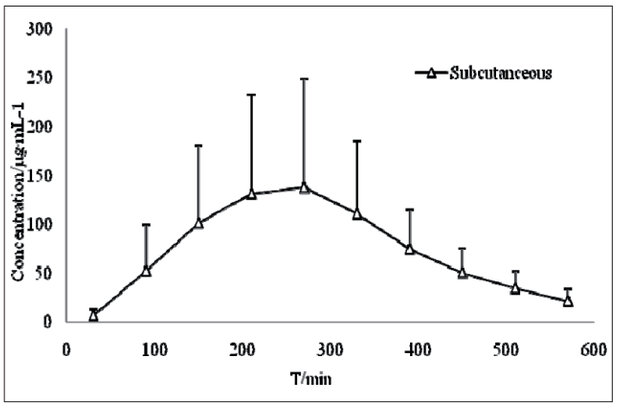

Fig. 2: Concentration versus time profiles of matrine in rat skin microdialysates after transdermal administration (6 mg/cm^2, 5 cm^2) in rats (mean±SD, *n*=6).

It is important to quantify drug concentrations at different body sites, especially in certain organs, such as the liver. The $AUC_{liver/blood}$ or $AUC_{liver/plasma}$ is used to describe the drug distribution to the liver after administration. Some studies have investigated liver homogenates following intravenous administration of matrine in SD rats (Wu, et al. 2009). However, the unbound drug concentration is related to pharmacological effects, therefore, tissue homogenates do not reflect the real drug concentration that has a pharmacological effect. In our study, the $AUC_{liver/blood}$ of unbound matrine in liver compared to blood was 47.49±9.80 % following *i.v.* administration, and the value increased to 67.32±19.62 % after transdermal administration, however, there was no significant difference between the two groups (P> 0.05). $AUC_{liver/plasma}$ (unbound matrine in liver compared to total matrine concentration in plasma) and $AUC_{blood/}AUC_{plasma}$ (unbound matrine in blood compared to total matrine concentration in plasma) also showed no significant difference between *i.v.* and transdermal administration. This result showed that the distribution of matrine after transdermal administration was similar to that following *i.v.* administration. Unbound drug in the liver and blood was collected in our study by microdialysis, and the results showed that the drug concentration in the liver was lower than in blood or plasma, as protein-bound drug cannot permeate the microdialysis membrane only allowing any unbound drug to be measured. Since microdialysis can be used to measure the concentration of unbound drug in the blood, the bound concentration of matrine in the plasma in our study could be calculated as 33% (=1-$AUC_{blood\ /plasma}$). Using ultrafiltration, it has been reported that the *in vitro* plasma protein binding of matrine is about 10% (Tang, et al. 2013). These conflicting data may be caused by different methods: *in vitro* vs *in vivo* and ultrafiltration *vs* microdialysis.

The pharmacokinetic profile of matrine following transdermal administration indicated that the $MRT_{(0\text{-}t)}$ of matrine in rats increased significantly after transdermal administration. The AUCs from different organs and tissues following transdermal administration were higher than those after *i.v.* administration. One possible reason for this is that the transdermal administration dosage was approximately 30 mg (i.e. 6 mg/cm^2 x 5 cm^2) for one rat, while the *i.v.* dose was approximately 12 mg (40 mg/kg). C_{max} of two administration routes were similar (P> 0.05), indicating that the 5 cm^2 patch group achieved similar effects to those seen in the *i.v.* administration group and that transdermal administration plays a role in long and slow

Table 1: Non-compartmental pharmacokinetic parameters of matrine in rat plasma, blood and liver microdialysates following *i.v.* administration (40 mg/kg) in rats (mean±SD, *n*=6)

Parameter	Liver microdialysate	Blood microdialysate	Plasma
$AUC_{(0-t)}$ (min· mg/l)	395.91±74.48**	848.86±146.35	1304.07±305.92*
$AUC_{(0-\infty)}$ (min· mg/l)	483.50±114.86**	1072.00±336.21	1600.14±571.15**
$MRT_{(0-t)}$ (min)	111.20±16.19	107.203±18.26	123.46±18.87*
$T_{1/2}$(min)	161.91±112.82	165.96±126.50	132.77±72.24
T_{max} (min)	22.50±0.00**	10.00±6.12	5.50±7.20**
CL_z /F (l/min/kg)	0.09±0.02**	0.04±0.01	0.03±0.01**
Vz /F (l/kg)	18.96±12.64	8.22±3.42	4.64±1.23
c_{max}(mg/l)	3.01±0.51**	7.38±1.74	8.62±1.49
$AUC_{liver/blood}$(%)	47.49±9.80		
$AUC_{liver/plasma}$(%)	31.14±5.76		
$AUC_{blood/plasma}$(%)	67.34±13.23		

* $P<0.05$ compared with blood microdialysate.
** $P<0.01$ compared with blood microdialysate.

Table 2: Non-compartmental pharmacokinetic parameters of matrine in rat plasma, blood , liver and skin microdialysates following transdermal administration (6 mg/cm², 5 cm²) in rats (mean±SD, *n*=6)

Parameter	Liver microdialysate	Blood microdialysate	Plasma	Subcutaneous microdialysate
$AUC_{(0-t)}$ (min· mg/l)	695.30±233.79*	1096.07±390.71	2767.57±518.48**	42735.77±27938.33*
$AUC_{(0-360)}$ (min· mg/l)	357.74±109.63*	576.27±204.57	1489.62±219.11**	
$MRT_{(0-t)}$ (min)	326.41±26.65	322.33±25.58	344.29±22.00	289.87±30.89
T_{max} (min)	270.00±75.90	280.00±70.14	340.00±72.66	240.00±82.70
C_{max}(mg/l)	1.97±0.65*	3.05±1.08	6.98±1.37**	141.43±108.25*
$AUC_{liver/blood}$(%)	67.32±19.62			
$AUC_{liver/plasma}$(%)	25.09±6.98			
$AUC_{blood/plasma}$(%)	40.20±14.97			

* $P<0.05$ compared with blood microdialysate.
** $P<0.01$ compared with blood microdialysate.

controlled release of matrine. After 360 min, AUCs following transdermal administration were similar to those after *i.v.* administration ($P>$ 0.05), while the $AUCs_{(0-t)}$ of the transdermal administration group were twice as large as those of the *i.v.* group, where the drug concentration-time curve was not yet complete after 10 h. After transdermal administration, the drug concentration in the skin was very high, which suggested that the skin of rats may have a drug storage effect. However, the variation was very large, which may be caused by individual differences in rat skin. The standard deviation in rat plasma, blood and liver microdialysate samples was much smaller. The results indicated matrine rapidly permeates the skin and then slowly moves into the blood stream or other tissues.

In vitro probe recovery of matrine had been previously studied and was used here due to its convenience and rationality. It is generally understood that the real microdialysate concentration is calculated as $C_{real}=C/R_{dial}$ (C is microdialysate concentration, R_{dial} is the recovery). Therefore, the *in vitro* probe recovery was used as $R_{dial.}$ Sampling time points were short for *i.v.* administration, which meant that the perfusion velocity was set at 2 µl/min, while slow changes in concentration occurred following transdermal administration, and the perfusion velocity for transdermal administration was set at 1 µl/min, where the recovery of the probe may have been higher. In conclusion, the present study showed that it was feasible to simultaneously sampling matrine from liver, blood and skin using three microdialysis probes. Transdermal administration is a promising drug delivery route for matrine compared with *i.v.* administration. The drug concentration-time curve was not complete up to 10 h after matrine administration. There is also a need for further studies in awake animals, as sampling time is limited when animals are under anaesthesia.

4. Experimental

4.1. Chemicals

A matrine standard was obtained from National Institutes for Food and Drug Control (Beijing, China). Matrine (>= 98%) was purchased from Xi'an Sino-herb Bio-technology Co. (Xi'an, China). Laurocapram was provided by Xinxiang Gaojin Pharmaceutical Co. (He'nan, China). Peppermint oil was obtained from Hengcheng Natural Perfume Oil Refinery (Jiangxi, China). Polyacrylate pressure-sensitive adhesive was obtained from National Starch & Chemical Company (Bridgewater, USA). HPLC-grade acetonitrile was obtained from Tedia Co. (Fairfield, USA). Ringer's solution (144 mmol/l Na^+, 1.5 mmol/l Ca^{2+}, 4.0 mmol/l K^+ and 2.3 mmol/l Mg^{2+}) was prepared in ultra pure deionized water and filtered through a 0.45-µm nylon filter membrane before use. All other reagents were of analytical grade and commercially available.

4.2. Animals

Male Sprague-Dawley rats (290-310 g) were obtained from Zhejiang Laboratory Animal Center (Hangzhou, China). Animals were kept in a climate controlled room with temperature maintained at 20 °C and a light-dark cycle of each 12 h, and were acclimatized for at least one week before use. Water and standard laboratory food were available *ad libitum* until 12 h before the experiments, at which time only water was given. All experiments were performed according to the guidelines for the care and use of animals as established by Zhejiang Academy of Medical Sciences. Zhejiang Academy of Medical Sciences ethics/use committee approved all animal experiments.

4.3. Preparation of patch

A transdermal adhesive patch was formulated to determine the optimum combination of permeation enhancer, pressure-sensitive adhesive, and solvent. Briefly, matrine was dissolved in ethyl acetate in a glass bottle and then laurocapram (12%, w/w), peppermint oil (16%, w/w), polyacrylate pressure-sensitive adhesive were added successively, with stirring until they were uniformly mixed. The resulting solution was poured on circular aluminum foil placed in glass plate, and the area and thickness were determined by spreading. The patch was then molded at room temperature in a dust-free environment and dried at 60 °C in an oven for 30 min. A backing film, made of aluminum was applied with the help of adhesive and a release liner was applied on other side of the film to complete the transdermal patch (6 mg/cm²).

4.4. Animal experiments

Recovery of the probe (R_{dial}) was carried out using an *in vitro* method (Wang et al. 2008; Deshmukh et al. 2015; Langkilde et al. 2015). Individual microdialysis probes were placed in a beaker containing a stirred matrine standard solution at different concentrations at 37 °C and perfused with drug free Ringer's solution at different flow-rates. After an equilibration period of 30 min samples were collected in 5 x 30 µl aliquots. Matrine concentrations in the dialysate (C_{dial}) or standard solution (C_{Stand}) were determined by HPLC. R_{dial} was calculated as $R_{dial} = C_{dial}/C_{Stand}$.

Before surgery, the rats were anesthetized with an intraperitoneal dose of 20% (w/v) urethane (1.25 g/kg) and were placed on a 37 °C heating pad. Throughout the experiment, all animals were kept under anaesthesia. The skin of the right jugular region was shaved and a flexible concentric cannula probe (CMA 20 Elite, 10 mm, CMA, Sweden) was inserted into the jugular vein. A liver linear probe (CMA 30 Linear MD Probe, 10 mm, CMA, Sweden) was positioned the median lobe of the liver. The lobe was carefully replaced and the upper abdomen was superficially closed (Tsai 2002; Lu et al. 2014). The skin of the hypogastrium was shaved and a concentric probe (CMA 20 MD Elite Probe, 10 mm, CMA, Sweden) inserted subcutaneously. After implantation, the inlet tube of the probe was connected to a microinjection pump (MD-1001) and Ringer's solution was pumped through the microdialysis probe.

To determine matrine concentrations following *i.v.* injection into the femoral vein in rats, microdialysis probes were inserted into both the jugular vein and liver as described above. The probes were perfused with Ringer's solution at a flow–rate of 2.0 µl/min. After an equilibration period of 60 min, matrine (40 mg/kg) was then administered intravenously. Liver and blood dialysate samples were collected at 15 min intervals from 0 to 240 min and then at 20 min intervals from 240 min to 360 min after dosing. At 0, 2, 5, 10, 20, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450 min, 0.1 ml blood samples were taken from the tail vein and placed in a heparinized polyethylene (PE) conical tube, then centrifuged at 10,000 rpm for 6 min. From each sample, 40 µl of plasma was recovered.

To determine matrine concentrations following transdermal administration in rats, microdialysis probes were inserted into three sites (jugular vein, liver and skin) as described above. The probes were perfused with Ringer's solution at a flow rate of 1.0 µl/min. After a recovery period of 60 min, a patch containing 6 mg/cm^2 matrine was applied at the hypogastrium skin (5 cm^2) where the skin probe was implanted. Dialysates were collected at 60 min intervals for up to 600 min after dosing. Blood samples were collected in heparinized polyethylene (PE) conical tubes at 60 min intervals for up to 600 min, as described above. All samples were stored at -20 °C and assayed within one month.

4.5. Analytical procedures

The HPLC system contained LC-20AT pump, SPD-20A UV detector and N2000 chromatographic workstation (Intelligent Information Engineer Ltd., Zhejiang University). A Diamonsil C18 column (4.6 mm×150 mm, 5 µm, Dikma) was used for analysis with a mobile phase of 0.1% phosphoric acid (triethylamine to adjust pH value to 7.6-7.7) and acetonitrile (65:35,V/V) at a flow- rate of 1.0 ml/min for the analysis of matrine microdialysis samples. For matrine plasma samples, the mobile phase consisted of 70:30 0.1% phosphoric acid:acetonitrile. UV detection was performed at 220 nm and the temperature of column oven was maintained at 35 °C.

Drug concentration was determined by HPLC. Microdialysates (liver, blood and skin) were analyzed directly, but plasma samples required the precipitation of proteins prior to injection onto the HPLC. To precipitate proteins, 60 µl acetonitrile was added to 40 µl plasma sample and the mixture was vortexed for 2 min before centrifugation at 10,000 rpm for 6 min. The supernatant was transferred to another PE tube and analyzed by HPLC. Standard solutions of matrine (100.0 and 818.0 µg/ml) were prepared in methanol. Calibration standards were prepared by serial dilution of the standards with Ringer's solution to give concentrations of 0.10, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.50, 25.00 µg/ml and with blank plasma to give concentrations of 0.32, 0.64, 1.28, 2.56, 5.11, 10.23, 20.45, 40.90, 81.80 µg/ml. QC samples were prepared in a similar manner at concentrations of 0.20, 1.56 and 25.00 µg/ml in Ringer's solution and 0.64, 5.11 and 81.80 µg/ml in plasma. Linearity was assessed by analyzing nine standards with concentrations over the range of 0.10–25.00 µg/ml in Ringer's solution and over the range of 0.32–81.80 µg/ml in plasma. Intra-day precision and accuracy were determined by assaying five replicates of the QC samples in a single day, while inter-day precision and accuracy were estimated by analyzing triplicate QC samples over five consecutive days. Stability was evaluated by analyzing QC samples under two conditions, i.e. freeze-thaw for three cycles at -20 ˚C for a month, or room temperature for 12 h.

4.6. Data analysis

DAS 2.0 pharmacokinetic software (Mathematical Pharmacology Professional Committee of China, Shanghai, China) was used to calculate the pharmacokinetic parameters. The apparent clearance (CLz/F) and apparent volume of distribution (Vz/F) were calculated as CLz/F=Dose/AUC and Vz/F=CLz/F/Zeta, respectively. Zeta was used as the parameter of the non-compartmental model, which was calculated from the slope of the last points belonging to the elimination phase of the concentration versus time curve. All data were expressed as mean±SD values. The student's t-test was used to determine statistical differences and a value of $P<0.05$ was considered statistically significant.

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Conflicts of interest: None declared.

References

Deshmukh G, Sun K, Liederer BM, Ding X, Liu X (2015) Use of cassette dosing to enhance the throughput of rat brain microdialysis studies. Drug Metab Dispos 43: 1123-1128.

Gao Q, Zhao Y, Yu J, Yang T, Ding P (2014) Microdialysis as a tool to determine the skin concentration of mometason furoate in rats. Pharmazie 69: 787-791.

Gennari CG, Selmin F, Ortenzi MA, Franze S, Musazzi UM, Casiraghi A, Minghetti P, Cilurzo F (2016) In situ film forming fibroin gel intended for cutaneous administration. Int J Pharm 511: 296-302.

Gottas A, Arnestad M, Halvorsen PS, Bachs LC, Hoiseth G (2016) Pharmacokinetics of heroin and its metabolites in vitreous humor and blood in a living pig model. Forensic Toxicol 34: 277-285.

Jiang M, Wang L, Jiang W, Huang S (2015) Simultaneous determination of 14-thienyl methylene matrine and matrine in rat plasma by high-performance liquid chromatography-tandem mass spectrometry and its application in a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci 974:126-130.

Joshi A, Patel H, Joshi A, Stagni G (2016) Pharmacokinetic applications of cutaneous microdialysis: Continuous+intermittent vs continuous-only sampling. J Pharmacol Toxicol Methods 83: 16-20.

Li J, Mao C, Li L, Ji D, Yin F, Lang Y, Lu T, Xiao Y, Li L (2014) Pharmacokinetics and liver distribution study of unbound curdione and curcumol in rats by microdialysis coupled with rapid resolution liquid chromatography (RRLC) and tandem mass spectrometry. J Pharm Biomed Anal 95: 146-150.

Li SS, Song ZH, Xiong LQ, Zhang Q, Liu Q, Li GF (2014) The percutaneous permeability and absorption of dexamethasone esters in diabetic rats: a preliminary study. Drug Deliv 21: 17-25.

Lu CM, Hou ML, Lin LC, Tsai TH (2014) Development of a microdialysis system to monitor lamivudine in blood and liver for the pharmacokinetic application in herbal drug interaction and the gene expression in rats. J Pharm Biomed Anal 96: 231-240.

Ruan J, Liu J, Zhu D, Gong T, Yang F, Hao X, Zhang Z (2010) Preparation and evaluation of self-nanoemulsified drug delivery systems (SNEDDSs) of matrine based on drug-phospholipid complex technique. Int J Pharm 386: 282-290.

Sabatino L, Scarangella M, Lazzaro F, Scordino M, Picariello G, Leotta C, Traulo P, Gagliano G (2015) Matrine and oxymatrine in corroborant plant extracts and fertilizers: HPLC/MS-MS method development and single-laboratory validation. J Environ Sci Health B 50: 862-870.

Tang L, Dong LN, Peng XJ, Li Y, Shi J, Zhou FY, Liu ZQ (2013) Pharmacokinetic characterization of oxymatrine and matrine in rats after oral administration of radix Sophorae tonkinensis extract and oxymatrine by sensitive and robust UPLC-MS/MS method. J Pharm Biomed Anal 83: 179-185.

Thiede AJ, Garcia KD, Stolarik DF, Ma J, Jenkins GJ, Nunamaker EA (2014) Pharmacokinetics of sustained-release and transdermal buprenorphine in Göttingen minipigs (Sus scrofa domestica). J Am Assoc Lab Anim Sci 53: 692-699.

Tong Y, Pan H, Sun C, Xin X, Ding L, Ma P (2015) Simultaneous determination of tazarotene and its active metabolite tazarotenic acid in minipig plasma by LC-MS/MS and its application in pharmacokinetic study after topical administration of tazarotene gel. J Chromatogr B Analyt Technol Biomed Life Sci 978-979: 173-178.

Tsai TH (2002) Determination of naringin in rat blood, brain, liver, and bile using microdialysis and its interaction with cyclosporin a, a p-glycoprotein modulator. J Agric Food Chem 50: 6669-6674.

Wang Q, Chen G, Zeng S (2008) Distribution and metabolism of gastrodin in rat brain. J Pharm Biomed Anal 46: 399-404.

Wang Q, Shi L, Tang X, Wang Q, Dang X, Zhang Y (2014) Pharmacokinetic study of multiple active constituents from Kushen-Gancao Decoction after oral administration in rat by HPLC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 965: 19-26.

Wu C, Sun X, Feng C, Liu X, Wang H, Feng F, Zhang J (2016) Proton-coupled organic cation antiporter contributes to the hepatic uptake of matrine. J Pharm Sci 105: 1301-1306.

Wu W, Huang J, Liu S, Li X, Cai Y (2009) Study on pharmacokinetics and tissue distribution of stealth matrine liposomes in rats. Zhongguo Zhong Yao Za Zhi 34: 751-755.

Yang Z, Gao S, Yin T, Kulkarni KH, Teng Y, You M, Hu M (2010) Biopharmaceutical and pharmacokinetic characterization of matrine as determined by a sensitive and robust UPLC-MS/MS method. J Pharm Biomed Anal 51: 1120-1127.

Yang Z, Wang L, Wang X (2016) Matrine induces the hepatic differentiation of WB-F344 rat hepatic progenitor cells and inhibits Jagged 1/HES1 signaling. Mol Med Rep 14: 3841-3847.

Yuan F, Chen J, Wu WJ, Chen SZ, Wang XD, Su Z, Huang M (2010) Effects of matrine and oxymatrine on catalytic activity of cytochrome p450s in rats. Basic Clin Pharmacol Toxicol 107: 906-913.

Zhang XL, Xu HR, Chen WL, Chu NN, Li XN, Liu GY, Yu C (2009) Matrine determination and pharmacokinetics in human plasma using LC/MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 877: 3253-3256.