Original Article

Application of Gas Chromatography-mass Spectrometry in Analyzing Pharmacokinetics and Distribution of Deltamethrin in Miniature Pig Tissues*

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Abstract

Objective To characterize the pharmacokinetics and distribution profiles of deltamethrin in miniature pig tissues by gas chromatography-mass spectrometry (GC-MS).

Methods Pharmacokinetics and distribution of deltamethrin in blood and tissues of 30 miniature pigs were studied by GC-MS after oral administration of deltamethrin (5 mg/kg bw). Data were processed by 3P97 software.

Results The serum deltamethrin level was significantly lower in tissues than in blood of miniature pigs. The $AUC_{0\text{-}72\ h}$, C_{max}, of deltamethrin were 555.330±316.987 ng h/mL and 17.861±11.129 ng/mL, respectively. The T_{max}, of deltamethrin was 6.004±3.131 h.

Conclusion The metabolism of deltamethrin in miniature pigs is fit for a one-compartment model with a weighting function of $1/C^2$. Deltamethrin is rapidly hydrolyzed and accumulated in miniature pig tissues.

Key words: Deltamethrin; Miniature pig; Pharmacokinetics; Tissue distribution; GC-MS

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INTRODUCTION

Pyrethroids representing an increasing proportion of pesticide sale around the world, especially in the United States[1] are extensively used in agriculture, forestry and public health due to their insecticidal potency, slow pest resistance, and relatively low acute toxicity[2-4]. Traditionally, pyrethroids are divided into type I and type II according to their structures and toxicological actions. Compared to type I, type II contains an additional cyano group. Deltamethrin (DLM), a commonly used type II pyrethroid (Figure 1), is available as a single isomer[5]. DLM, with a low persistence and high effectiveness, is widely used in agriculture[6]. DLM, as one of the most potent neurotoxicants of pyrethroids[7], induces neurotoxicity by slowing down the opening and closing of voltage-gated sodium channels[8], voltage-gated calcium channels[9], and/or both sodium and calcium channels[10]. Human exposure to DLM via dermal contact and ingestion may cause acute poisoning with symptoms of rashes, blistering, sore throat, nausea, abdominal pain, or even loss of

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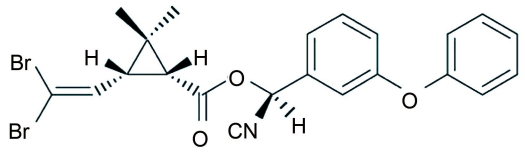

Figure 1. Chemical structure of DLM.

consciousness[11]. It is thus important to study its absorption, distribution, and metabolism in mammalian species, in order to assess its risk to health.

Previous studies have been mainly focused on the determination, toxicity and metabolism of DLM in different animals. Galetin et al.[12] reported that the absorption and distribution of pyrethroids in humans are similar to the findings in other mammalian species. Pigs, which are more similar to humans[13-15], are more suitable than other mammalian species for studying the metabolism and distribution of DLM. Thus, the absorption and distribution manners of DLM in pig tissues may be more helpful for corresponding studies in humans.

Pharmacokinetics (PK) is a comprehensive study with concurrent absorption, distribution, metabolism, and elimination of DLM by determining the target organ dose of toxic moiety over time, and in turn the magnitude and duration of toxicity[16-17]. Mirfazaelian et al.[18], Kim et al.[5] and Tornero-Velez et al.[19] revealed that adipose tissue, skin, and skeletal muscle are the major depots for DLM, and the T_{max} is relatively long. Godin et al.[20-21] showed that liver is the primary metabolic organ for clearing DLM.

Until now, no report is available on PK, distribution and disposition of DLM in pig tissues. In the present study, miniature pigs were used as an animal model to assess PK, absorption and distribution of DLM in pig tissues. Furthermore, DLM in blood and tissues of miniature pigs were quantified by gas chromatography-mass spectrometry (GC-MS). The results are critical for the assessment of risk in humans exposed to DLM.

MATERIALS AND METHODS

Chemicals and Materials

The standard DLM and *d_6-trans*-cypermethrin with its purity higher than 98% were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). DLM of industrial grade with a purity of 80.83% was provided by Spark Technical Research Institution of Baoding (Hebei, China). Acetone, cyclohexane, and ethyl acetate of chromatographic grade were purchased from Fisher Company (Fisher Scientific, Fairlawn, NJ, USA). Petroleum ether and hexane of chromatographic grade were purchased from J. T. Baker Company (Phillipsburg, NJ, USA). Florisil solid phase extraction cartridges (2 mg, 12 mL, 20/PK) were purchased from Agilent Technologies (Palo Alto, CA, USA). Guaranteed reagents of anhydrous magnesium sulfate and sodium chloride were purchased from Chemical Reagent Company in Beijing. Water was produced in the Milli-Q ultra-pure water system.

Experimental Design of Miniature Pigs

Thirty miniature pigs weighing 20-25 kg were purchased from Beijing Institute of Animal Husbandry and Veterinary Institute, Chinese Academy of Agricultural Sciences. The miniature pigs were acclimated to standard housing and environmental conditions for 1 week prior to the study.

Eighteen miniature pigs were divided into 6 experimental groups (3 in each) and another 3 pigs served as control. The animals in experimental groups were administered orally with DLM (5 mg/kg bw) dissolved in vegetable oil, and those in the control group were given orally vegetable oil. Distribution of DLM in their tissues were detected (Figure 2).

All animals were used in accordance with the Guidelines for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996). All procedures were approved by the Animal Care Review Committee, China Agricultural University.

Sample Collection

Blood samples (10 mL) were taken from jugular vein at 0, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 72 h, respectively, after DLM treatment. Pigs were sacrificed at 3, 6, 12, 24, 36, and 72 h, respectively, after oral DLM. Heart, liver, spleen, lung, kidney, brain, muscle, and fat tissues were collected, homogenized and stored at -80 °C.

Pretreatment of Blood Samples

Five mL blood was placed into a polypropylene centrifuge tube and 100 μL *d_6-trans*-cypermethrin solution (1.0 mg/L), into which 30 mL acetone: petroleum ether (1:1, v/v) solution, 1 g sodium chloride, 4 g anhydrous magnesium sulfate were added. The mixture was extracted by ultrasonication

for 30 min and centrifuged at 10 000 rpm for 5 min. The supernatant was transferred and dried at 38 °C. The residues were reconstituted by 5 mL hexane, and concentrated to 1 mL under a gentle stream of nitrogen at 40 °C for further solid-phase extraction (SPE) purification. The Florisil cartridge was conditioned with 5 mL hexane, and the extract was then applied onto the cartridge. The loading fraction and fractions eluted by 9 mL hexane: acetone (95:5, v/v) solution were collected and dried. The residues were redissolved in 1.0 mL hexane for GC-MS analysis.

Pretreatment of Tissue Samples

Homogenized tissue samples (1.00 g for fat, 5.00 g for the others) containing 100 μL internal standard (1.0 mg/L d_6-*trans*-cypermethrin), 30 mL solution of acetone: petroleum ether (1:1, v/v), 2 g sodium chloride and 8 g anhydrous magnesium sulfate were subjected to ultrasonic extraction for 30 min. After centrifugation at 10 000 rpm for 5 min, the supernatants were transferred and the residues were extracted for one more time. The two supernatants were combined and dried. The residues were reconstituted by 10 mL cyclohexane: ethyl acetate (1:1, v/v) and purified by gel permeation chromatography (GPC) on the column of CO785 (25×250 mm, Accuprep MPSTM, J2 Scientific, Columbia, USA) at the mobile phase of cyclohexane: ethyl acetate (1:1, v/v) at a flow rate of 4.7 ml/min. The fractions at 8-14 min were collected and dried. The residues were reconstituted by 0.5 mL hexane for GC-MS analysis.

GC-MS Analysis

GC-MS analysis was carried out with a Varian 450 gas chromatograph plus Varian 320 mass spectrometer in negative chemical ionization (NCI) mode. Separations were achieved on a VF5-MS capillary column (30 m×0.25 mm i.d.×0.25 μm, Varian, Las Vegas, NV, USA). Selected ion monitoring (SIM) was chosen to increase its sensitivity. Samples were introduced in split-injection mode (20:1) at 260 °C and the oven temperature was ramped from 80 to 290 °C at 15 °C/min, held at 290 for 10 min and then raised to a final temperature of 300 °C at a rate of 20 °C/min and held for 5 min. High purity helium (>99.999%) was used as the carrier gas with the column flow of 1.0 ml/min. The temperatures of the ion source and manifold were 250 °C and 40 °C, respectively. The electron energy was 70 eV and electron multiplier was 1000 V. The monitored SIM ions were m/z 79, 81, 137, 297 for DLM, and m/z 177, 179, 213, 215 for d_6-*trans*-cypermethrin. Quantitative ions were selected at m/z 79 for DLM, at m/z 213 for d_6-*trans*-cypermethrin. The chromatogram is shown in Figure 3.

Calibration Curves and Quality Control

The internal standard calibration by d_6-*trans*-cypermethrin was used for the quantitative analysis. The calibration series were constructed in hexane with a known amount of DLM. The calibration series were 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, and 5 mg/L, with 0.1 mg/L of d_6-*trans*-cypermethrin.

The quality control (QC) samples were made by blank samples with a spiked known amount of DLM. The QC samples were pretreated as the blood or tissue samples and performed at a low spiked level (0.01 mg/kg for tissues, and 0.01 mg/L for blood, LQC), a medium spiked level (0.02 mg/kg or mg/L, MQC) and a high spiked level (0.20 mg/kg or mg/L, HQC). The recovery of QC samples should be in the

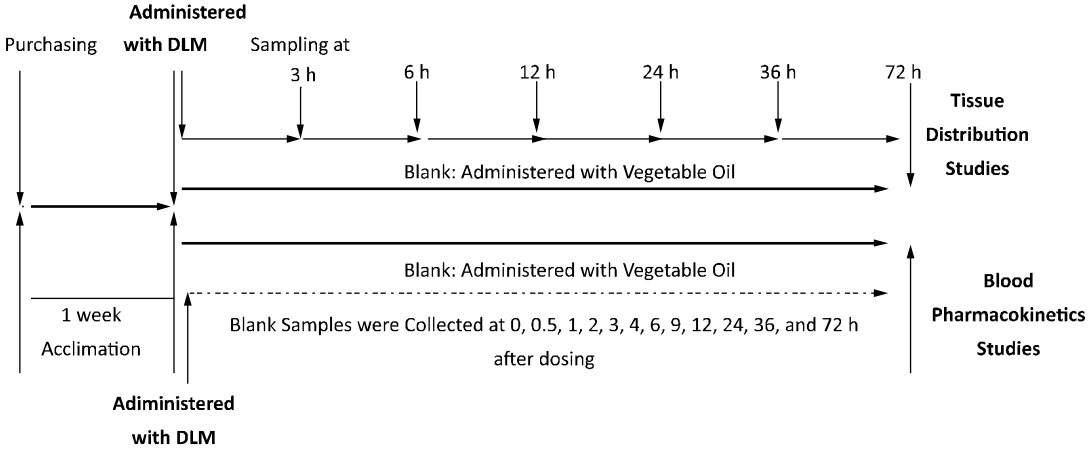

Figure 2. Distribution of DLM in pig tissues.

range of 60%-120% with a relative standard deviation (RSD) less than 20%.

Data Analysis

Data were analyzed using the 3P97 PK software (Chinese Mathematics & Pharmacological society) in a one-compartment model, and a weighting function of $1/C^2$ for data fitting and parameter estimation. PK parameters of blood and tissue were calculated, including absorption half-time ($T_{1/2(Ka)}$), elimination half-life ($T_{1/2(Ke)}$), time for maximal concentration (T_{max}), maximal concentration (C_{max}), mean retention time (MRT), area under AUC, total body clearance as a function of bioavailability (Cl/F) and volume of distribution (V/F).

RESULTS

Selectivity and Stability

As shown in Figure 4, good selectivity was obtained, and no Interference peaks to DLM or internal standard in different matrices were found.

Analyte stability of freeze-thaws, long-term and short-term in different matrices, was tested using LQCs and HQCs. The frozen and thawed samples were tested for long-term and short-term stability. The results showed that the stability of freeze-thaws was acceptable with a deviation less than 5%. The extracts from blood and tissue samples were stable at least for 2 weeks at -20 °C.

Matrix Effect

DLM standards in solvent and matrix extracts were injected into GC-MS to evaluate the matrix effect. The results showed that response of DLM in different tissues and blood samples neither increased nor decreased compared with that in solvent. Therefore, the calibration curve plotted was preferred.

Linearity and Limit of Detection

The standard calibration curves were linear over a range of 0.001-5 mg/L with the correlation coefficient higher than 0.999. The GC-MS chromatograms of different blank matrix and tissue samples are shown in Figure 4.

Limit of detection (LOD) and limit of quantitation (LOQ) were determined as the analyte concentrations. The LOD and LOQ for DLM were 0.1 and 0.3 μg/L for blood sample and 0.1 and 0.3 μg/kg for tissue sample.

Recovery Studies

The accuracy and precision of the method were expressed as the results of inter- and intra-day reproducibility. LQCs, MQCs, and HQCs of 6 replicates were analyzed according to the procedure as previously described. As shown in Table 1, the intra-and inter-day recoveries of DLM were 88.8%-113.1% at the concentrations of 0.01, 0.02, and 0.20 mg/L with the coefficient of variation <10.9%,

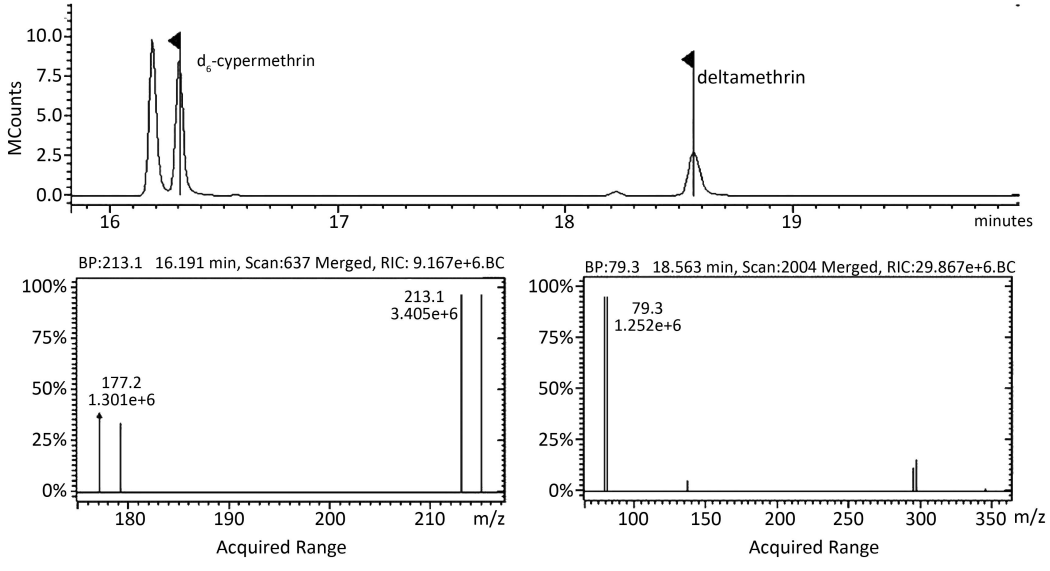

Figure 3. Chromatogram of DLM standard and *d_6-trans*-cypermethrin (0.02 mg/L).

which demonstrated a good precision and accuracy for the current method.

PK of DLM in Miniature Pig Blood Sample

The average concentration of DLM in blood sample at 12 different time points was fit for the one-compartment model with a weighting function of $1/C^2$. The mean blood concentration-time curve for DLM is shown in Figure 5. Oral DLM could be detected in blood sample at 30 min, the serum level of DLM increased rapidly and reached its peak (17.86 ng/mL) at 6 h, and then decreased slowly until 72 h with no DLM detected.

The blood PK parameters are summarized in Table 2. After oral DLM, its enterohepatic circulation was demonstrated. The $T_{1/2(Ka)}$ and $T_{1/2(Ke)}$ were 2.68 h and 20 h, respectively. The T_{max} for DLM was characterized by its peak at 6.00 h, and the $AUC_{0\text{-}72\ h}$ was 555.33±316.99 ng h/mL. Meanwhile, the MRT was 14.92 h, indicating that DLM was slowly eliminated at a rate of 0.011 ml/h.

Concentrations and PK Parameters of DLM in Miniature Pig Tissue Samples

The concentrations of DLM in different tissue samples are shown in Table 3. In general, the DLM residue level was low in different tissue samples except that (1.98 mg/kg) in fat tissue sample. The data analyzed by 3P97 software for the model predictions and time curves are shown in Figure 6. The curves could clearly show the absorption, distribution and elimination of DLM in different tissue samples. The elimination tendency of DLM was similar in all tissue samples except in liver tissue sample.

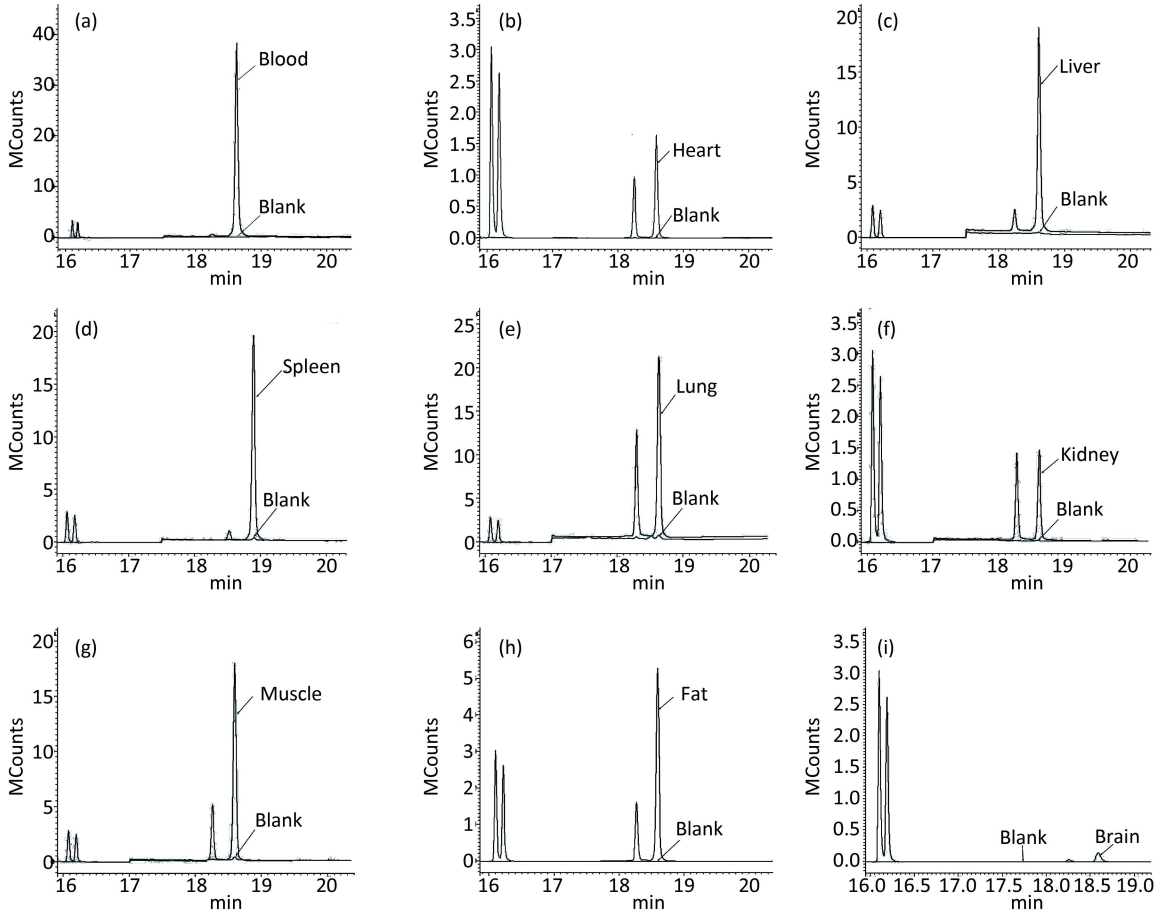

Figure 4. Chromatograms of DLM in blood (a), heart (b), liver (c), spleen (d), lung (e), kidney (f), muscle (g), fat (h), brain (i) and their blank matrix samples.

Table 1. Method Validation in Different Matrices

Tissue Type	Spiked (mg/kg)	Calibration Curve	*r*	Intra-day (*n*=6)		Inter-day (*n*=6)	
				Accuracy (%)	Precision (RSD%)	Accuracy (%)	Precision (RSD%)
Blood	0.01	Y=0.4688X-0.0534	0.9992	108.9	4.7	90.1	6.9
	0.02			109.5	3.3	88.8	6.4
	0.20			113.1	9.7	96.1	9.0
Heart	0.01	Y=0.8256X-0.0108	0.9996	92.6	5.1	95.1	6.8
	0.02			98.3	4.6	97.5	4.9
	0.20			105.9	6.3	102.7	7.2
Liver	0.01	Y=0.4829X-0.08223	0.9994	92.4	5.9	97.3	6.5
	0.02			90.0	4.5	95.3	7.4
	0.20			91.8	7.8	99.5	10.9
Spleen	0.01	Y=0.4752X+0.0023	0.9997	94.6	3.8	95.2	5.7
	0.02			94.0	4.1	97.4	5.2
	0.20			96.2	3.6	96.8	4.9
Lung	0.01	Y=0.4691X-0.0094	0.9996	95.8	2.7	97.2	3.6
	0.02			94.2	3.5	96.8	2.6
	0.20			96.9	3.8	98.4	2.3
Kidney	0.01	Y=0.5012X-0.0035	0.9998	99.9	4.9	101.2	7.9
	0.02			102.4	5.1	98.6	5.8
	0.20			102.9	5.4	101.7	6.3
Muscle	0.01	Y=0.4940X+0.0028	0.9997	101.3	3.2	102.5	4.0
	0.02			98.7	4.3	99.1	4.9
	0.20			100.5	5.1	99.7	5.3
Fat	0.01	Y=0.5349X-0.0389	0.9993	109.4	7.9	108.3	7.4
	0.02			107.2	6.5	104.9	8.7
	0.20			100.8	5.9	103.1	4.5
Brain	0.01	Y=0.2946X-0.0134	0.9994	101.6	4.9	100.9	5.8
	0.02			100.4	3.8	102.5	4.6
	0.20			100.7	3.5	101.6	4.1

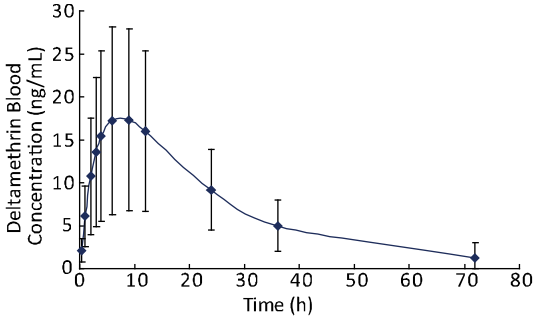

Figure 5. Blood concentration-time profiles of oral DLM (5 mg/kg bw) in miniature pigs (*n*=6, mean±SD).

Table 2. PK Parameters of Oral DLM in Blood Sample (mean±SD, *n*=6)

Parameters	Unit	Value
$T_{1/2(Ka)}$	h	2.680±1.919
$T_{1/2(Ke)}$	h	20.169±16.546
T_{max}	h	6.004±3.131
C (max)	μg/L	17.861±11.129
$AUC_{0\text{-}72\ h}$	μg h/L	555.330±316.987
MRT	h	14.929±7.560
Cl/F (s)	L/(h kg)	0.011±0.006
V/F (c)	L/kg	0.339±0.397

Table 3. Concentration of Oral DLM in Different Tissue Samples at Different Time Points (*n*=3, mg/kg)

Time	Heart	Liver	Spleen	Lung	Kidney	Brain	Fat	Muscle
3 h	0.138	0.021	0.011	0.204	0.056	0.015	0.418	0.035
6 h	0.170	0.009	0.015	0.125	0.032	0.019	0.720	0.056
12 h	0.383	0.032	0.024	0.108	0.121	0.023	1.984	0.093
24 h	0.130	0.0003	0.004	0.043	0.042	0.004	0.719	0.018
36 h	0.021	0.002	0.017	0.013	0.020	0.002	0.134	0.021
72 h	0.015	0.002	0.005	0.002	0.008	ND*	0.141	0.013

Note. * not detected.

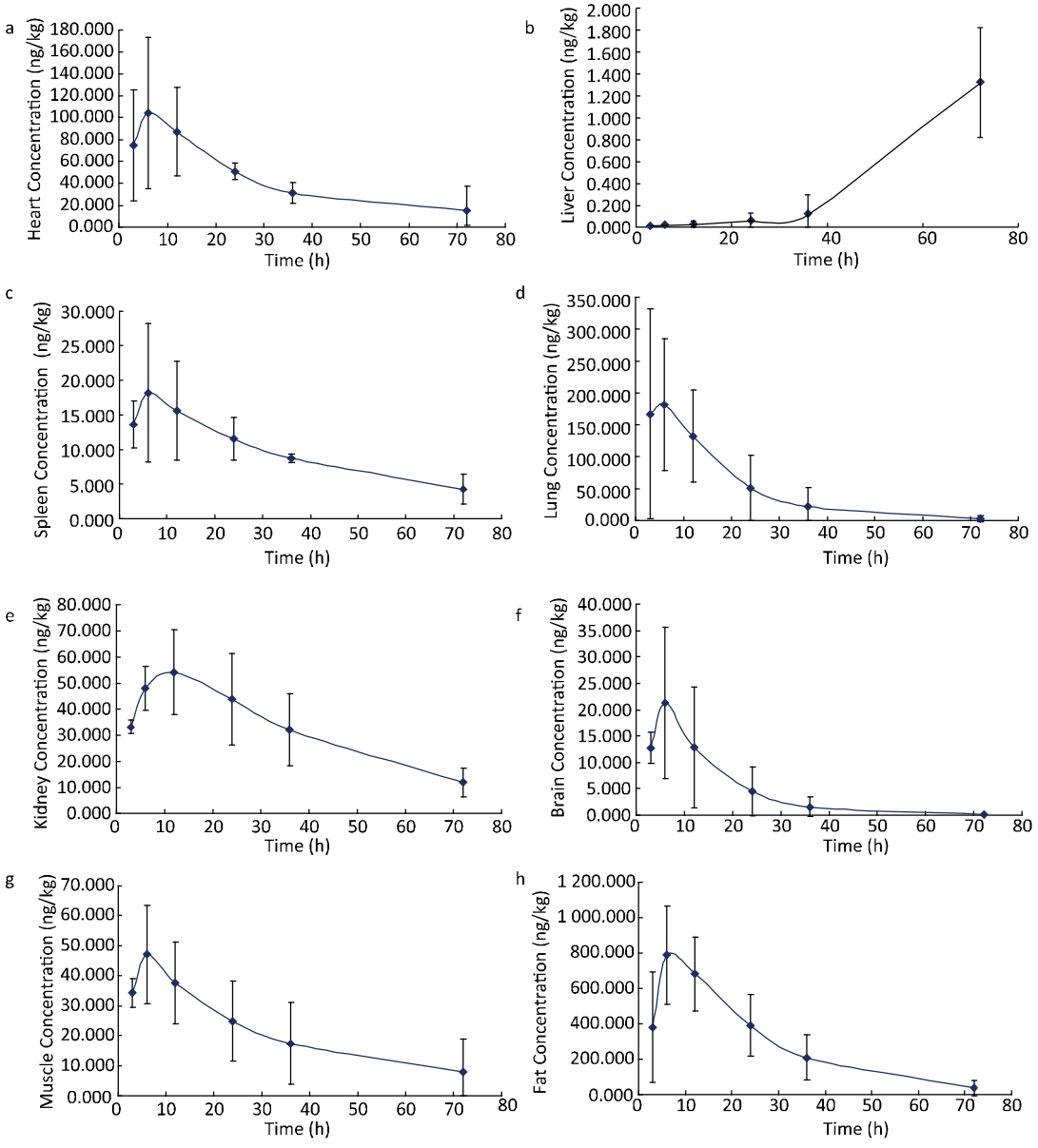

Figure 6. Model predictions and time course concentration data of DLM in heart (a), liver (b), spleen (c), lung (d), kidney (e), brain (f), muscle (g), fat (h) tissue samples from miniature pigs after oral administration (*n*=3, mean±SD).

The calculated PK parameters of DLM in different tissue samples are listed in Table 4. The $T_{1/2(Ka)}$ was 0.387-4.772 h, and the $T_{1/2(Ke)}$ was >7 h, indicating that the DLM was slowly eliminated in tissues. The C_{max} was 0.01-1.23 mg/kg, and the T_{max} was 1.997-11.390 h. The $AUC_{0\text{-}72\ h}$ was higher in fat and heart tissue samples than in liver and brain tissue samples. Similar trends were found for Cl/F(s) and V/F(c).

DISCUSSION

Few studies are available on pharmacokinetics and distribution of DLM in experimental animals. In the present study, the pharmacokinetics, absorption, distribution, and metabolism of DLM in miniature pigs were described. Since their dietary habit, digestion mode, hematological and hematochemical constants, and viscera weights are more similar to humans[13-15], the absorption and distribution of DLM in miniature pigs may be more helpful for corresponding studies in humans.

Furthermore, a GC-MS-SIM method was developed for the determination of DLM in blood and tissue samples from miniature pigs with two different novel cleanup procedures. Kim et al.[22] analyzed DLM in plasma, liver, kidney, and brain tissue samples by HPLC with the LOD of 10 μg/L. The LOD was lower in the present study than in previous studies (0.1 μg/L *vs* 1 μg/L and 5 μg/L)[23-24].

The 3P97 software is widely applied in calculating the pharmacokinetic parameters and $AUC_{0\text{-}t}$ in different tissues[25-26]. The pharmacokinetic parameters in the present study were different from those in previous studies[22,27]. The C_{max} of 0.95 μg/mL plasma and 0.21 μg/g brain in adult rats was 1 and 2 h, respectively, after oral administration of 10 mg/kg DLM[22], which corresponded with the results of 17.861 μg/L blood and 0.025 μg/g brain in miniature pigs after oral administration of 5 mg/kg DLM in the present study. It was reported that DLM could be detected at 8.3 h in plasma of adult SD rats administered orally with 20 mg/kg[28]. These differences could be ascribed to the different animal species and dosages. The DLM residue level was low in different tissues of pigs, which is consistent with the reported level[29].

Little information is available on the location of absorption of pyrethroids in humans and other experimental models except for SD rats. It was presumed that pyrethroids crossed the intestinal cells due to the large exposed surface area and passed into the enterohepatic circulation by diffusing across lipid membranes[30]. Generally, DLM are rapidly absorbed by combing lipid membranes of red blood cells after oral administration, and reach different tissues/organs with circulation by diffusion[31]. The absorption, elimination and metabolic rate, and distribution pattern are rather different in different tissues. In the present study, DLM were accumulated in fat, heart and muscle tissues, rapidly eliminated in liver and hardly detected in liver at the last time phase. Liver is the major metabolic organ for detoxifying pesticides[32-33], which can explain the rapid elimination of DLM in liver. Our results are consistent with the reported findings[20,34]. In this study, DLM were absorbed slowly. The T_{max} was 6 h and the bioavailability of DLM was much lower than that in previous studies[18,27]. It might be anticipated that oil can act as a reservoir in the gut to delay the absorption of DLM[35].

Table 4. Pharmacokinetic Parameters of Oral DLM in Tissue Samples from 6 Miniature Pigs (mean±SD)

Parameters	Unit	Heart	Liver	Spleen	Lung	Kidney	Brain	Muscle	Fat*
$T_{1/2(Ka)}$	h	4.772±2.005	1.756±0.973	2.121±0.326	5.210±0.241	4.611±1.355	0.387±0.109	0.459±0.054	3.870±0.338
$T_{1/2(Ke)}$	h	7.089±3.082	10.821±4.812	39.613±14.501	11.530±1.026	15.196±4.792	12.337±4.762	20.045±2.311	11.013±0.546
T_{max}	h	8.337±4.243	5.499±2.591	9.465±2.231	9.322±0.798	11.390±4.293	1.997±0.638	2.560±0.240	9.003±0.546
$C_{(max)}$	mg/kg	0.282±0.140	0.013±0.004	0.016±0.0113	0.174±0.0395	0.065±0.003	0.025±0.007	0.061±0.002	1.233±0.250
$AUC_{0\text{-}72\ h}$	mg h/kg	6.519±3.251	0.289±0.128	1.083±0.247	3.741±0.879	2.404±0.984	0.502±0.104	1.943±0.319	34.537±1.380
Cl/F(s)	L/(h kg)	0.767±0.159	17.295±6.924	4.618±2.869	1.337±0.450	2.080±0.863	9.964±2.310	2.574±0.914	0.145±0.0176
V/F(c)	L/kg	7.844±2.984	170.014±62.652	263.928±96.575	22.705±3.414	45.600±10.078	177.353±40.816	74.424±16.487	2.300±0.132

Note. * The model fits for the one-compartment model with a weighting function of $1/C^2$ while the others with a weighting function of 1.

DLM are widely and rapidly distributed in fat, brain and skeletal muscle[5,19]. It was reported that DLM concentration was higher in central nervous system than in plasma after oral administration[36]. In this study, the highest DLM residue level (1.23 mg/kg) was observed in fat tissue sample, and the Tmax was approximately 9 h after initial exposure. Akhtar et al.[37] reported that permethrin and/or its metabolites were detected in fat tissue from cows on day 9 after oral dosing, suggesting that DLM was mainly stored in fat tissue. Meanwhile, the peak concentration of DLM was 0.03 mg/kg in brain tissue sample from miniature pigs at 2 h after oral administration (Figure 6 h) and then rapidly declined, indicating that the metabolic process of DLM in the brain was not mediated by metabolism. The results are in accordance with the previous findings[21,38]. Sathanandam et al.[39] displayed that DLM was rapidly distributed in nerve tissues with a distribution half-time of 2.1 h in rats after giving single oral dose, showing that DLM might accumulate in brain due to its relatively high blood flow and lipid content.

In conclusion, a sensitive GC-MS method has been established for the quantification of DLM in blood and tissues. The current method shows a good linearity within the range of 0.001-5 mg/L, and can yield a good precision and accuracy. The pharmacokinetic parameters of oral DLM (5 mg/kg bw) in miniature pigs suggest that metabolism of DLM in miniature pigs follows a one-compartment model with a weighting function of $1/C^2$ and that DLM is rapidly hydrolyzed in liver tissue, and mainly accumulated in fat, heart, and muscle tissues.

CONFLICT OF INTEREST

No author has any financial/conflict interest to disclose.

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