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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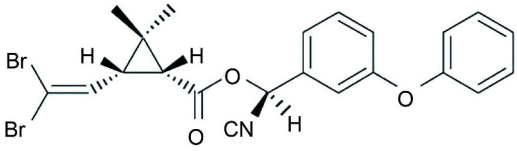

Figure 1. Chemical structure of DLM.

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