VETERINARSKI ARHIV 91 (5), 547-558, 2021 DOI: 10.24099/vet.arhiv.1064

Toxicokinetic of phenothrin in rabbits

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KAYA, T., G. ERASLAN: Toxicokinetic of phenothrin in rabbits. Vet. arhiv 91, 547-558, 2021.

ABSTRACT

The toxicokinetics of single dose phenothrin were examined in rabbits. For this aim, a total of 14 New Zealand breed, 2 to 2.5 kg body weight, 6 month-old female rabbits were used. The animals were divided into two groups and each group had 7 animals. Phenothrin was administered intravenously to each animal in group 1, at a dose of 10 mg/kg b.w. and orally to each of the animals in group 2 at the same dose. Dimethyl sulfoxide was used as a solvent in application of phenothrin. Plasma phenothrin levels were measured by gas chromatography equipped with an ECD detector. Toxicokinetic evaluations were made according to the plasma phenothrin level-time curve. Phenothrin was found to be distributed according to the two-compartment open model. The values of elimination half-life ($t_{1/2\beta}$), mean residence time (MRT) and area under the curve ($AUC_{0\rightarrow\infty}$) after intravenous phenothrin administration were 2.57 ± 0.10 h, 2.79 ± 0.09 h and 6893.05 ± 261.26 ng/h/mL, respectively. On the other hand, the maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), $t_{1/2\beta}$, MRT and $AUC_{0\rightarrow\infty}$ after oral administration were 185.71 ± 8.21 ng/mL, 1.21 ± 0.20 h, 4.24 ± 0.39 h, 6.65 ± 0.54 h and 1054.04 ± 65.90 ng/h/mL, respectively. The oral bioavailability of phenothrin was calculated as 15.29%. Mean residence time was short and oral bioavailability was low. This may be one of the reasons why phenothrin is included in safe pesticides.

Key words: phenothrin; toxicokinetic; oral; intravenous; rabbit

Introduction

Phenothrin is a type I pyrethroid that affects the central and peripheral nervous system. Mammalian toxicity is generally lower than that of insects because at lower body temperatures it has a high toxic effect on sodium channels, but it is more toxic for aquatic organisms and bees, causing paralysis and death. The body temperature of insects and other invertebrates is about 10 degrees below that of mammals. Higher temperatures contribute to increased metabolic degradation of pyrethroid (KANEKO, 2010; JACKSON et al., 2011; GAD and PHAM, 2014). Phenothrin is a pesticide used in indoor environments against pests and formulated for use in greenhouses, the home, gardens and relaxation areas. It is selected for vector control in public health to control mosquitoes inside and outside, and is also preferred for combating insects and lice in grain storage facilities (COX, 2003; GAD and PHAM, 2014). The value of oral and dermal LD_{50} in rats is >5000 mg/kg b.w. (OĞUZ and AYDIN, 2001; JACKSON et al., 2011; ENSLEY, 2012; KAYA, 2014). The toxic effect of pyrethroids for animals depends on the types of physico-chemical properties, the amount

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ISSN 0372-5480
Printed in Croatia

taken, the route of exposure, and the its duration (BRADBURY and COATS, 1989; MERWE et al., 2012; GUPTA, 2016). The toxicokinetics of phenothrin in rabbits were investigated. In the study, the animals were given the same dose of oral and intravenous phenothrin once, and serial blood collection was performed at specific times. The toxicokinetic profile of phenothrin in rabbits was determined on the basis of the blood phenothrin concentration-time curve. Therefore, many other toxicokinetic parameters of the pesticide were evaluated, especially in terms of bioavailability, half-life and mean residence time in the body. The aim of this study was to evaluate the causes of the low toxicity of this pesticide, by examining its toxicokinetic profile in mammals. On the other hand, the data obtained will be determinative in approaching applications in the treatment of cases of poisoning that may occur from possible acute exposure at very high doses associated with species sensitivity. The toxicokinetics of some pyrethroids with low toxicity have been evaluated previously in different animal species (UEDA et al., 1975; WHITE et al., 1976; RIDLEN et al., 1984; SILVER and DAUTERMAN, 1989; TOMIGAHARA et al., 1996, 1997). However, studies on toxicokinetic evaluation of phenothrin are too limited and inadequate. There were no studies in which the parameters calculated were completely included and discussed. Therefore, in the present study, many parameters that reveal the status of absorption, distribution, metabolism and excretion of phenothrin were investigated simultaneously. These data are important in terms of guiding similar studies in the future.

Materials and methods

Instruments and chemicals. All chemicals and solvents used to analyse phenothrin were purchased from Merck and Sigma-Aldrich. The phenothrin analytical standard (Sigma 36193; PESTANAL®, analytical standard) was obtained from Sigma-Aldrich. The instrument used for all analysis was gas chromatography with a micro electron capture detector (μECD) (Agilent 6890N). The auto-sampler was attached to the gas chromatography device (Agilent 7683B). The gas chromatography column used was an Agilent J&W GC brand capillary column (HP-5MS, 30 m long, 0.25 mm film thickness and 0.25 mm diameter).

Animal. In the study, 14 New Zealand breed, 2-2.5 kg, 6 month old female rabbits were used. These animals were not pregnant, had similar physiological characteristics and were clinically healthy. The rabbits were divided into two equal groups of 7 animals each before the toxicokinetic trial. They were housed in special animal cages, and up to two animals were placed in each cage. Rabbit feed (17% crude protein, 10.5% crude cellulose, 3.25% crude oil) and water were available for the animals before and during the application. All animals were kept under the same conditions (22-24 ºC 12 hours light/dark) during the trial period.

Experimental design. The phenothrin analytic standard was dissolved in dimethylsulfoxide at a concentration of 10 mg/0.2 mL. Phenothrin was administered to both groups at a dose of 10 mg/kg b.w. The drug was administered once intravenously to the first group through the ear vein, and once to the second group through an oral catheter. Before and after intravenous and oral administration, blood samples were collected from the ear veins of the animals into heparinized tubes, at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 72 hours. Blood was centrifuged (3000 rpm for 10 minutes at +4 °C) and the plasma was transferred to eppendorf tubes. All the samples were stored in a freezer (at -80 °C) until analysis was performed. The reasons for choosing rabbits as experimental animals for the study were that they are laboratory animals and blood can be easily taken from the same animal at many times during toxicokinetic studies. In determining the dose applied, toxicokinetic studies performed previously with pyrethroid group insecticides (BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017), the exposure risk of living things (WHO, 1989; SANCHEZ-BAYO and GOKA, 2014), and the possibility of detecting phenothrin in the blood with the existing analysis methods during the blood draw time specified in the toxicokinetic study, were taken into consideration. The study was approved by Erciyes University Animal Experiments Local Ethics Committee (Decision No: 16-074).

Plasma phenothrin analysis. Plasma phenothrin analysis was based on the method reported by YAVUZ et al. (2010). 0.5 mL of plasma was removed according to that method, and 2.5 mL of hexane/acetone (8:2, v/v) mixture was added. Then the tubes were vortexed for 3 minutes and placed in a refrigerated centrifuge and centrifuged for 10 minutes at 3000 rpm at +4 °C. 1.5 mL of the supernatant from the centrifuge tubes were transferred to another tube and evaporated under nitrogen gas. Subsequently, 1 mL of n-hexane was added to the tubes, vortexed and transferred into gas chromatography vials. Vials were placed in the auto-sampler for gas chromatography and measurements were performed. For measurement, the methods of HUNTER et al. (2010), MEKEBRI et al. (2008) and WANG et al. (2009) were used and some adaptations to the method were made. The type of detector used was μECD. The detector temperature was 325 °C. The carrier gas was helium, and nitrogen was used as the auxiliary gas. The sample volume applied to the port was 2 μL. The flow rate of the capillary column used was 2.8 mL/min. The gas chromatography temperature program was as follows: the initial temperature was 70 °C, the oven was kept at this temperature for two minutes; the temperature was then increased by 25 °C per minute to 150 °C; it was subsequently raised to 200 °C with an increase of 3 °C per minute. Finally, it was increased to 280 °C with an increase of 8 °C per minute. The total analysis time was 41.87 minutes. The injection port and μECD temperature were maintained at 260 °C and 325 °C, respectively. The retention time of phenothrin is 29.894 min.

Preparation of standard curve. Before starting the experiment, plasma extracted from the blood of animals in the groups was used to prepare the standard curve. Phenothrin was added to the plasma in the specified amounts so that ranged from 10 ng/mL plasma-20000 ng/mL plasma in 11 different concentrations, and was slowly vortexed for a short time, followed by being kept at room temperature for 30 minutes. Then, the same procedure as described in the method was performed and it was placed in the gas chromatograph and analyzed. Analyses were repeated three times for each concentration point, and the arithmetic mean of the obtained data was taken. n-hexane was used as the solvent in the preparation of the phenothrin stock and other diluted solutions.

Method validation. For method recovery, in the preparation of the stock and other diluted solutions of phenothrin, n-hexane was used as the solvent. In concentrations where the standard curve was prepared (11 different concentrations in the range from 10 ng/mL plasma to 20000 ng/mL plasma), phenothrin was added to blank plasma. Following the addition of phenothrin to blank plasma, the samples were vortexed and kept at room temperature for thirty minutes. Subsequently, extraction was carried out and analyzed by gas chromatography. The peak areas obtained were compared to the standard peak areas prepared after the similar procedures indicated in the method, by adding phenothrin at the same concentration following blank plasma extraction (with 2.5 mL of hexane/acetone). The process was repeated three times for each concentration and the recovery rates were determined and their arithmetic means calculated. To determine the limit of detection (LOD) and the limit of quantification (LOQ), the sample/noise peak ratio was taken into consideration (SHRIVASTAVA and GUPTA, 2011). According to this method, the phenothrin peak/noise peak ratio was 3:1 for determination of the limit of detection, and 10:1 for evaluation of the limit of quantification. For precision determination, phenothrin was added at a certain concentration to the blank plasma obtained from all animals in the groups before starting the experiment, followed by extraction. The extract obtained was subjected to the same steps as the sample procedure, and then applied to the gas chromatograph for in-day and inter-day analysis in specific time periods. Thus, relative standard deviations (RSD%) of peak areas obtained during the in-day and inter-day analyses were calculated.

Toxicokinetic calculations. Correlation coefficients (r^2) and compliance with Akaike Information Criterion (AIC) were determined for different compartmental models, based on the plasma phenothrin concentration-time curve (YAMAOKA et al., 1978). According to the data obtained, the most appropriate compartmental distribution model was found for the toxicokinetic calculations. C_{max} and t_{max} values were calculated by considering the phenothrin plasma concentration-time curve of each animal. PKCALC and GW-BASIC pharmacokinetic

programs, including the formulas/equations of SHUMAKER (1986) and WAGNER (1975), were used for evaluations and calculations of other toxicokinetic parameters (A_1, A_2, A_3 mathematical coefficients; C_p^0, plasma phenothrin concentration at t_0; k_{ab}, first-order absorption rate constant of phenothrin in absorbable administration; $t_{1/2ab}$, the half-life of absorption from the digestive tract in the case of oral administration; C_{max}, phenothrin plasma peak concentration; t_{max}, the time at which the plasma phenothrin maximum concentration reaches; α, plasma phenothrin distribution rate constant; $t_{1/2\alpha}$, plasma phenothrin distribution half-life; β, plasma phenothrin elimination rate constant; $t_{1/2\beta}$, phenothrin elimination half-life; V_1, central compartment distribution volume; V_2, the peripheral compartment distribution volume; Vd_{ss}, apparent volume of distribution at steady state; Vd_{area}, volume of distribution according to area calculated; k_{12}, the first order rate constant of the transition from the central compartment to the peripheral compartment; k_{21}, the first order rate constant of the transition from the peripheral compartment to the central compartment; k_{10}, the irreversible elimination rate constant of phenothrin; MRT, the time required for elimination 63.2% of phenothrin from the body; Cl_T, phenothrin total plasma clearance; $AUC_{0\rightarrow8}$, area under the curve plasma phenothrin concentration-time 0 to t; $AUC_{0\rightarrow\infty,}$ area under the curve plasma phenothrin concentration-time 0 to ∞; F, oral bioavailability).

Statistical calculation. The evaluation of the data obtained from the study was carried out in the SPSS 13.0 for Windows statistical package program. All data are presented as arithmetic mean and standard error. The Student t test was used to determine the difference between the two groups on the basis of $P<0.05$.

Results

Method findings. Plasma phenothrin standard curve in the following calculations showed linearity in the range specified concentrations (r^2: 0.9999). In the study, the average recovery of the extraction method for phenothrin was found to be 75.63%. According to the methods and conditions specified in the gas chromatography device for phenothrin, the detection limit (LOD) is 4 ng/mL and the quantification limit (LOQ) is 10 ng/mL. The average in-day and inter-day accuracy of the method is 3.58% and 5.23%, respectively.

Clinical findings. All of the animals used in the toxicokinetic study survived. In other words, no animals had died by the end of the study. During intravenous administration, some central nervous system symptoms, such as restlessness, tremor and increased salivation, were observed during the first 15 minutes following administration. However, these symptoms were not observed later, that is, they quickly disappeared. No signs of toxicity were detected in any animals of the oral administration group.

Toxicokinetic parameters. Within the scope of the study, distribution patterns were examined on the basis of the plasma phenothrin concentration-time curve and it was concluded that phenothrin follows a distribution profile that is more compatible with the two-compartment open model. After the intravenous administration of phenothrin, as a result of direct observation of the plasma concentration-time curve prepared from blood taken during the planned periods of the study and also the analyses/calculations, it was understood that the this pesticide showed rapid transfer from plasma to other biological compartments. Meanwhile, it entered the excretion period in the ongoing process. The same was true for oral administration. However, in oral administration, the slope of both distribution and excretion period was lower for both phases. Plasma phenothrin concentrations at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6 and 8 hours of intravenous administration were observed as 8549.85 ± 535.49 ng/mL, 3178.14 ± 286.57 ng/mL, 1810.28 ± 153.33 ng/mL, 1274.42 ± 87.84 ng/mL, 842.71 ± 57.21 ng/mL, 593.57 ± 17.07 ng/mL, 425.14 ± 11.00 ng/mL, 299.57 ± 9.37 ng/mL and 166.71 ± 12.51 ng/mL, respectively, while with oral administration they were 49.57 ± 5.83 ng/mL, 83.57 ± 8.14 ng/mL, 135.14 ± 19.13 ng/mL, 159.71 ± 11.85 ng/mL, 144.42 ± 7.53 ng/mL, 98.71 ± 3.54 ng/mL, 70.00 ± 3.20 ng/mL, and 48.00 ± 3.85 ng/mL for 0.25, 0.5, 0.75, 1, 2, 4, 6 and 8 hours, respectively. When the two administration routes were compared, a significant difference was found between the two groups for the periods in which phenothrin was detected. In other blood collection periods (12, 18, 24, 36 and 72th hours), plasma phenothrin amounts were undetectable/below detectable limits (Table 1 and Fig 1).

Table 1. Blood collection periods and plasma phenothrin levels (ng/mL) of phenothrin administered intravenously and orally to rabbits at a dose of 10 mg/kg b.w. in the toxicokinetic study (arithmetic mean ± standard error)

Blood Collection Intervals (h)	Intravenous (ng/mL)	Oral (ng/mL)
0.083	8549.85 ± 535.49	-
0.25	3178.14 ± 286.57	49.57 ± 5.83*
0.50	1810.28 ± 153.33	83.57 ± 8.14*
0.75	1274.42 ± 87.84	135.14 ± 19.13*
1	842.71 ± 57.21	159.71 ± 11.85*
2	593.57 ± 17.07	144.42 ± 7.53*
4	425.14 ± 11.00	98.71 ± 3.54*
6	299.57 ± 9.37	70.00 ± 3.20*
8	166.71 ± 12.51	48.00 ± 3.85*
12	-	-
18	-	-
24	-	-
36	-	-
72	-	-

* P<0.05

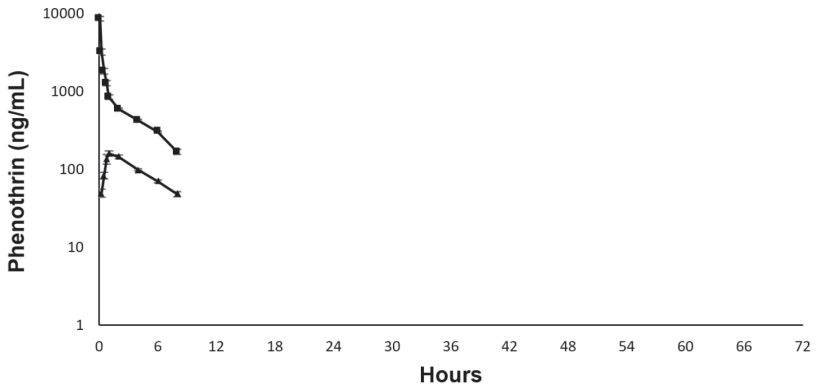

Fig. 1. Phenothrin semi-logarithmic plasma concentration-time curve (arithmetic mean ± standard error) of phenothrin given to rabbits intravenously and orally at a dose of 10 mg/kg b.w. in the toxicokinetic study.

Following oral administration of phenothrin, the $t_{1/2ab}$ value was 0.47 ± 0.03 hours. The k_{ab} value was 1.49 ± 0.10 hours^{-1}. C_{max} was 185.71 ± 8.21 ng/mL. C_{max} reached 1.21 ± 0.20 hours (t_{max}). The C_p^0 value of phenothrin was 15816.59 ± 1226.93 ng/mL. After intravenous administration, the $t_{1/2\alpha}$ value was 0.08 ± 0.005 hours. This value was 1.26 ± 0.22 hours following oral administration. After intravenous and oral administration, α was 8.33 ± 0.68 hours^{-1} and 0.62 ± 0.07 hours^{-1}, respectively. $t_{1/2\beta}$ values were 2.57 ± 0.10 hours in the intravenous group and in contrast 4.24 ± 0.39 hours in the oral group. β was also consistent with these values (intravenous: 0.27 ± 0.011 hour^{-1} and oral: 0.17 ± 0.015 hour^{-1}). V_1 values for intravenous and oral administration were 655.17 ± 50.00 mL/kg and 7606.54 ± 524.37 mL/kg, respectively. For intravenous and oral intake; V_2, V_{dss} and Vd_{area} values were: 3439.46 ± 232.59 mL/kg, 4094.64 ± 245.18 mL/kg and 5448.87 ± 313.41 mL/kg; 876.87 ± 308.41 mL/kg, 9556.01 ± 355.26 mL/kg and 8878.16 ± 822.56 mL/kg, respectively. The values of k_{12}, k_{21} and k_{10} were 5.30 ± 0.52 hours^{-1}, 0.99 ± 0.07 hours^{-1}, 2.30 ± 0.18 hours^{-1} and 0.05 ± 0.01 hours^{-1}, 0.54 ± 0.06 hours^{-1}, 0.19 ± 0.01 hours^{-1} were calculated for intravenous and oral administration, respectively. The MRT value of the pesticide was 2.79 ± 0.09 hours and 6.65 ± 0.54 hours for intravenous and oral intake, respectively. Total

plasma clearance (Cl_T) was 1463.68 ± 57.10 mL/h/kg and 1473.29 ± 84.76 mL/h/kg in the intravenous and oral phenothrin groups. The area under the curve ($AUC_{0 \rightarrow 8}$ and $AUC_{0 \rightarrow \infty}$) was 5180.92 ± 185.17 ng/h/mL and 6893.05 ± 261.26 ng/h/mL for intravenous administration and was 762.77 ± 24.98 ng/h/mL and 1054.04 ± 65.90 ng/h/mL for oral administration, respectively. Oral bioavailability (F) of phenothrin was 15.29%. The data for other variables not expressed are given in Table 2. Of the toxicokinetic parameters considered, there was no significant difference between the groups in terms of Cl_T (Table 2).

Table 2. Some toxicokinetic variables (arithmetic mean ± standard error) of phenothrin administered intravenously and orally to rabbits at a dose of 10 mg/kg b.w.

Parameters[¥]	Intravenous	Oral
A_1 (ng/mL)	14413.62 ± 1257.14	61.77 ± 13.94*
A_2 (ng/mL)	1402.96 ± 96.75	191.91 ± 11.73*
A_3 (ng/mL)	-	-276.057 ± 16.95
C_p^0 (ng/mL)	15816.59 ± 1226.93	-
k_{ab} (h^{-1})	-	1.49 ± 0.10
$t_{1/2ab}$ (h)	-	0.47 ± 0.03
C_{max} (ng/mL)	-	185.71 ± 8.21
t_{max} (h)	-	1.21 ± 0.20
α (h^{-1})	8.33 ± 0.68	0.62 ± 0.07*
$t_{1/2\alpha}$ (h)	0.08 ± 0.005	1.26 ± 0.22*
β (h^{-1})	0.27 ± 0.011	0.17 ± 0.015*
$t_{1/2\beta}$ (h)	2.57 ± 0.10	4.24 ± 0.39*
V_1 (mL/kg)	655.17 ± 50.00	7606.54 ± 524.37*
V_2 (mL/kg)	3439.46 ± 232.59	876.87 ± 308.41*
Vd_{ss} (mL/kg)	4094.64 ± 245.18	9556.01 ± 355.26*
Vd_{area} (mL/kg)	5448.87 ± 313.41	8878.16 ± 822.56*
k_{12} (h^{-1})	5.30 ± 0.52	0.05 ± 0.01*
k_{21} (h^{-1})	0.99 ± 0.07	0.54 ± 0.06*
k_{10} (h^{-1})	2.30 ± 0.18	0.19 ± 0.01*
MRT (h)	2.79 ± 0.09	6.65 ± 0.54*
Cl_T (mL/h/kg)	1463.68 ± 57.10	1473.29 ± 84.76
$AUC_{0 \rightarrow 8}$ (ng/h/mL)	5180.92 ± 185.17	762.77 ± 24.98*
AUC0→∞ (ng/h/mL)	6893.05 ± 261.26	1054.04 ± 65.90*
F (%)	-	15.29

[¥]. A_1, A_2, A_3 mathematical coefficients; C_p^0, plasma phenothrin concentration at t_0; k_{ab}, first-order absorption rate constant of phenothrin in absorbable administration; $t_{1/2ab}$, the half-life of absorption from the digestive tract in the case of oral administration; C_{max}, phenothrin plasma peak concentration; t_{max}, the time at which the plasma phenothrin maximum concentration reaches; α, plasma phenothrin distribution rate constant; $t_{1/2\alpha}$, plasma phenothrin distribution half-life; β, plasma phenothrin elimination rate constant; $t_{1/2\beta}$, phenothrin elimination half-life; V_1, central compartment distribution volume; V_2, the peripheral compartment distribution volume; Vd_{ss}, apparent volume of distribution at steady state; Vd_{area}, volume of distribution according to area calculated; k_{12}, the first order rate constant of the transition from the central compartment to the peripheral compartment; k_{21}, the first order rate constant of the transition from the peripheral compartment to the central compartment; k_{10}, the irreversible elimination rate constant of phenothrin; MRT, the time required for elimination 63.2% of phenothrin from the body; Cl_T, phenothrin total plasma clearance; $AUC_{0 \rightarrow 8}$, area under the curve plasma phenothrin concentration-time 0 to t; $AUC_{0 \rightarrow \infty}$, area under the curve plasma phenothrin concentration-time 0 to ∞; F, bioavailability. *. $P<0.05$.

Discussion

Method findings. The quantification limit (10 ng phenothrin/mL plasma) was used as the lower limit in order to establish the calibration curve for the measurement of samples taken during the toxicokinetic study; following gas chromatography analysis of the samples taken during the study, the maximum peak area obtained was taken into account in determining the upper limit of the calibration curve. In the specified ranges (10 ng phenothrin/mL plasma-20000 ng phenothrin/mL plasma), the standard curve was found to have a linear character and at the same time a high value of r^2 (0.9999). When previous studies with other pyrethroids were evaluated (YAN et al., 2010; BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017; NARDELLI et al., 2018), the current study values were found to be close to previous study data. The recovery value of the method followed for sample extraction was 75.63% for phenothrin. This rate is similar to those in former studies conducted for this purpose (CHERSTNIAKOVA et al., 2006; SINGH et al., 2016; NARDELLI et al., 2018). The limit of detection (LOD) of the method used for phenothrin analysis was 4 ng/mL, and the limit of quantification (LOQ) was 10 ng/mL. The calculated values were found to be higher than those of previous studies (YAN et al., 2010; LIN et al., 2011; GÖGEBAKAN and ERASLAN, 2015). It is understood that the in-day and inter-day precision values of the method used are within the acceptable limits. These results are similar to those found in previous studies with other pyrethroids (HIRAHARA et al., 1997; JIANG et al., 2004; MUDIAM et al., 2012; OUATTARA et al., 2013).

Toxicokinetic variable. As mentioned earlier, to select the applied dose, we considered both toxicokinetic studies carried out with pyrethroid insecticides in different experimental animals and the detection limit of the amount of phenothin in the blood samples collected during the toxicokinetic study, using the present methods and devices. In this context, phenothrin is already included as a non-toxic/safe substance (oral rat LD_{50}>5000 mg/kg b.w.) by the World Health Organization (WHO) (WHO, 1989; KAYA, 2014). However, previous studies have reported some dose-related effects, such as genotoxic (NAGY et al., 2014), oxidative damage in DNA (ATMACA and AKSOY, 2015), liver (NAGY et al., 2014; ATMACA and AKSOY, 2015), kidneys (ATMACA and AKSOY, 2015), lungs (ATMACA and AKSOY, 2015), spleen (ATMACA and AKSOY, 2015), brain, genital organs and other systems, and blood formed elements (U.S. EPA, 1989a,b 1995; NATIONAL RESEARCH COUNCIL, 1999; YAMADA et al. 2003; HASSAN, 2017). However, when compared with other pyrethroid group pesticides in general, the role of the potential toxicokinetic profile as a justification for the high oral LD_{50} value of this pesticide should not be overlooked. No detailed studies on the toxicokinetics of phenothrin have been found. The studies performed are especially on the metabolism of the compound in cases of dermal and oral exposure (MIYAMOTO et al., 1974; KANEKO et al., 1981; IZUMI et al., 1984). In this study, the toxicokinetic properties of the pesticide were investigated in detail. Phenothrin exhibited a distribution profile compatible with the two-compartment open model in rabbits. This distribution model was observed in studies conducted with pesticides from the pyrethroid group in different experimental animals (SILVER et al., 1989; ANADÓN et al., 1991, 1996; BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017).

Clinical symptoms (restlessness, tremors, and increased salivation) were only observed in the first 15 minutes in the intravenous group, partially overlapping with toxicokinetic studies performed with other pyrethroids, but these symptoms were less pronounced than in other studies (ANADÓN et al., 1996; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017).

Toxicokinetic examinations are studies examining the absorption, distribution, metabolism and excretion of the compound simultaneously (BAGGOT, 1982; SMITH et al., 1990; MERWE et al., 2012; GUPTA, 2016). Many parameters were examined in the study to evaluate these processes following intravenous and oral phenothrin

administration in rabbits. When the values of k_{ab}, $t_{1/2ab}$, $AUC_{0\rightarrow8}$ and $AUC_{0\rightarrow\infty}$ values which are among the parameters expressing the absorption and absorption rate from the variables including absorption stage of phenothrin (BAGGOT, 1982; SMITH et al., 1990; KAYA, 2006; MERWE et al., 2012; GUPTA, 2016) were observed, $t_{1/2ab}$ value was found to be 0.47 ± 0.03 hours, and k_{ab} value was found to be 1.49 ± 0.10 hours^{-1} following oral administration. When the area under the curves are compared to between the intravenous group ($AUC_{0\rightarrow\infty}$: 6893.05 ± 261.26 ng/h/mL) and oral group ($AUC_{0\rightarrow\infty}$: 1054.04 ± 65.90 ng/h/mL), $AUC_{0\rightarrow\infty}$ values indicate that the oral bioavailability (15.29%) of phenothrin is very low. Low systemic bioavailability is dependent not only on absorption but also on high first pass effect. These data were lower than the studies performed with several pyrethroids for different experimental animals (BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017). However, it is close to that of permethrin in poultry (GÖGEBAKAN and ERASLAN, 2015). In this effect, it should be kept in mind that metabolism may be important in the gastrointestinal lumen associated with the microbial flora of the digestive system, which is due to the physicochemical properties. Pyrethroid group insecticides are also metabolized by this pathway (MIYAMOTO, 1976; SODERLUND and CASIDA, 1977; CROW et al., 2007; ANADÓN et al., 2009). C_{max} and t_{max} are among the parameters that can be indicative of absorption rate (SHEN, 2008; MERWE et al., 2012; GUPTA, 2016). The time to reach t_{max} is not long, but C_{max} is very low considering the given dose. These findings support the above considerations. The results obtained were similar in terms of t_{max}, near to some studies performed with different pyrethroids in some experimental animals (ANADÓN et al., 1996; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017) and different (ANADÓN et al., 2006; BAŞÇİ and ERASLAN, 2015; GAMMON et al., 2015) from others. C_{max} and AUC values were lower than those of flumethrin (BAŞÇİ and ERASLAN, 2015) and permethrin (GÖGEBAKAN and ERASLAN, 2015) in broiler and rabbits at the same dose.

The $t_{1/2\alpha}$ from the parameters indicating the distribution of phenothrin in the biological system (KAYA, 2014; MERWE et al., 2012; GUPTA, 2016) was 0.08 ± 0.005 hours after intravenous administration and 1.26 ± 0.22 hours following the oral administered group. α are 8.33 ± 0.68 hours^{-1} for intravenous applications and 0.62 ± 0.07 hours^{-1} for oral applications. Mentioned distribution after intravenous administration can be explained by the transport of the phenothrin directly into the systemic circulation followed by the passage of highly vascularized tissues/organs and rapid dissolution in the lipophilic medium (GAUGHAN et al., 1978; HUNT et al., 1979; ANADÓN et al., 1991, 1996, 2006; KIM et al., 2008; ALONSO et al., 2015; CHANG et al., 2016; HUGHES et al., 2016; WILLEMIN et al., 2016; AMARANENI et al., 2017). In the case of oral administration, the distribution period is longer due to the presence of a gastro-intestinal tract barrier. For blood flow rate play an important role among the factors affecting the distribution profile of the drug (BAGGOT, 1982; RIVIERE, 2009; MERWE et al., 2012; GUPTA, 2016).

V_1 and V_2 include variables that reveal the central compartment distribution volume/peripheral compartment distribution volume (BAGGOT, 1982; SHEN, 2008; MERWE et al., 2012). The V_1 value was 655.17 ± 50.00 mL/kg and 7606.54 ± 524.37 mL/kg for intravenous and oral administration, while the V_2 value was 3439.46 ± 232.59 mL/kg and 876.87 ± 308.41 mL/kg is responsible for the physico-chemical structure and rather lipophilic character of the phenothrin. Similar findings have been found in other studies performed with pyrethroids (BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017). The transport rates between compartments (central/peripheral compartment) of phenothrin (k_{12} and k_{21}), V_{dss} and Vd_{area} also show this. These changes have been detected in studies previously conducted with some pyrethroids in experimental animals (ANADÓN et al., 1991, 1996, 2006; BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017).

The $t_{1/2\beta}$ value (KAYA, 2006; SHEN, 2008), one of the variables expressing the mean residence time (indirectly its metabolism and excretion), was

2.57 ± 0.10 hours in the intravenous group and 4.24 ± 0.39 hours in the oral administration group. That is, the half-life is longer in the oral administered group. MRT value (SHEN, 2008; MERWE et al., 2012) which was also similar was 2.79 ± 0.09 hours for intravenous administration and 6.65 ± 0.54 hours for oral intake. When the toxicokinetic studies performed in experimental animals with other pyrethroids are reviewed (ANADÓN et al., 1991, 1996, 2006; BAŞÇİ and ERASLAN, 2015; HÜYÜK and ERASLAN, 2017; ERASLAN et al., 2017), it can be understood that this time is quite short in phenothrin its metabolism/excretion occurs rapidly. Significant differences in $t_{1/2\beta}$ and MRT can be explained by the gradual absorption from the gastro-intestinal barrier for the oral group. This fact has also been reported in former studies planned with other pyrethroids using various animal species (ANADÓN et al., 1991, 1996; KIM et al., 2008; BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017). Likewise, when the plasma phenothrin level-time curve is evaluated, the plasma phenothrin concentration is within measurable limits only up to 8 hours in the intravenous (166.71 ± 12.51 ng/mL) and oral (48.00 ± 3.85 ng/mL) group. This means that the metabolism of phenothrin is very fast. The Cl_T value (BAGGOT, 1982; GUPTA, 2016), one of the variables indicating the excretion rate of phenothrin, was quite rapid for both groups (intravenous: 1463.68 ± 57.10 mL/h/kg; oral: 1473.29 ± 84.76 mL/h/kg). There is no difference between groups in terms of total plasma clearance. This was similar in other studies (ANADÓN et al., 1991, 1996, 2006). Phenothrin total plasma clearance is faster than previous studies done with other pyrethroids (ANADÓN et al., 1996; BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017). Changes in k_{10} (intravenous: 2.30 ± 0.18 $hours^{-1}$ and oral: 0.19 ± 0.01 $hours^{-1}$) were also consistent with total plasma clearance values. Other studies have also similar results (ANADÓN et al., 1996; 2006; BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017).

Conclusions

Absorption of phenothrin from the application site is not complete. This primarily indicates that the gastrointestinal lumen has a high chemical destructive capacity before the absorption stage associated with the digestive tract flora. On the other hand, high exposure to the first-pass effect in terms of systemic bioavailability (the first and both may have the same result) also produces the same result. The drug half-life and mean residence time are not long. Clinical findings are superficial and short-term. There was no evidence of poisoning directly related to the bioavailability of phenothrin after oral administration. The reasons why phenothrin is considered to be a safe pesticide are likely, high digestive disruption after oral exposure and/or high exposure to first pass effect during the transition to systemic circulation from gastro-intestinal tract. All of these can also be a cause of low bioavailability. Furthermore, it is also important that this pesticide is rapidly metabolized. These results also shed light on the evaluation of treatment options in cases of poisoning associated with high dose species sensitivity.

Acknowledgements

This research (project code: TYL-2017-7190) was supported by the Research Fund of Erciyes University. Study is Master of Science Thesis of Tarık Kaya.

References

ALONSO, M. B., M. L. FEO, C. CORCELLAS, P. GAGO-FERRERO, C. P. BERTOZZI, J. MARIGO, L. FLACH, A. C. O. MEIRELLES, V. L. CARVALHO, A. F. AZEVEDO, J. P. M. TORRES, J. LAILSON-BRITO, O. MALM, M. S. DIAZ-CRUZ, E. ELJARRAT, D. BARCELÓ (2015): Toxic heritage: Maternal transfer of pyrethroid insecticides and sunscreen agents in dolphins from Brazil. Environ. Pollut. 207, 391-402.

AMARANENI, M., J. PANG, J. V. BRUCKNER, S. MURALIDHARA, T. B. MORTUZA, D. GULLICK, S. HOOSHFAR, C. A. WHITE, B. S. CUMMINGS (2017): Influence of maturation on in vivo tissue to plasma partition coefficients for cis- and trans-permethrin. J. Pharm. Sci. 106, 2144-2151.

ANADÓN, A, M. R. MARTINEZ-LARRAÑAGA, M. J. DIAZ, P. BRINGAS (1991): Toxicokinetics of permethrin in the rat. Toxicol. Appl. Pharmacol. 110, 1-8.

ANADÓN, A., M. MARTÍNEZ, M. A. MARTÍNEZ, M. J. DÍAZ, M. R. MARTÍNEZ-LARRAÑAGA (2006):

Toxicokinetics of lambda-cyhalothrin in rats. Toxicol. Lett. 165, 47-56.

ANADÓN, A., M. R. MARTÍNEZ-LARRAÑAGA, M. A. MARTÍNEZ (2009): Use and abuse of pyrethrins and synthetic pyrethroids in veterinary medicine. Vet. J. 182, 7-20.

ANADÓN, A., M. R. MARTINEZ-LARRAÑAGA, M. L. FERNANDEZ-CRUZ, M. J, DIAZ, M. C. FERNANDEZ, M. A. MARTINEZ (1996): Toxicokinetics of deltamethrin and its 4'-HO-metabolite in the rat. Toxicol. Appl. Pharmacol. 141, 8-16.

ATMACA, E., A. AKSOY (2015): d-Phenothrin induced oxidative DNA damage in rat liver and kidney determined by HPLC-ECD/DAD. Environ. Toxicol. 30, 607-613.

BAGGOT, J. D. (1982): Clinical pharmacokinetic in veterinary medicine. Clin. Pharmacokinet. 22, 254-273.

BAŞÇİ, Z., G. ERASLAN (2015): Toxicokinetic of flumethrin in rabbits. Drug. Chem. Toxicol. 38, 92-97.

BRADBURY, S. P., J. R. COATS (1989): Comparative toxicology of the pyrethroid insecticides. Rev. Environ. Contam. Toxicol. 108, 133-177.

CHANG, J., J. LI, H. WANG, Y. WANG, B. GUO, J. YIN, W. HAO, W. LI, J. LI, P. XU (2016): Tissue distribution, metabolism and hepatic tissue injury in Chinese lizards (*Eremias argus*) after a single oral administration of lambda-cyhalothrin. Environ. Pollut. 218, 965-972.

CHERSTNIAKOVA, S. A., G. E. GARCIA, J. STRONG, D. BI, J. WEITZ, M. J. ROY, L. R. CANTILENA (2006): Rapid determination of N,N-diethyl-m-toluamide and permethrin in human plasma by gas chromatography-mass spectrometry and pyridostigmine bromide by high-performance liquid chromatography. J. Anal. Toxicol. 30, 21-26.

COX, C. (2003): Sumithrin (d-phenothrin). J. Pesticide Reform. 23, 10-14.

CROW, J. A., A. BORAZJANI, P. M. POTTER, M.K. ROSS (2007): Hydrolysis of pyrethroids by human and rat tissues: examination of intestinal, liver and serum carboxylesterases. Toxicol. Appl. Pharmacol. 221, 1-12.

ENSLEY, S. M. (2012): Pyrethrins and Pyretroids. In: Veterinary Toxicology, Basic and Clinical Principles. 2nd ed. (Gupta, R. C., Ed.), San Diego, Academic Press, pp. 591-595.

ERASLAN, G., M. Y. TEKELI, M. KARABACAK (2017): Toxicokinetic of cypermethrin in broiler chickens. Frensen. Environ. Bull. 26, 4704-4710.

GAD, S. C., T. PHAM (2014): Phenothrin. In: Encyclopedia of Toxicolog. (Wexler, P., Ed.), New York, Academic Press, pp. 884-886.

DOI: 10.1016/b978-0-12-386454-3.01198-2

GAMMON, D., Z. LIU, A. CHANDRASEKARAN, S. ELNAGGAR (2015): The pharmacokinetic properties of bifenthrin in the rat following multiple routes of exposure. Pest. Manag. Sci. 71, 835-841.

GAUGHAN, L. C., M. E. ACKERMAN, T. UNAI, J. E. CASIDA (1978): Distribution and metabolism of trans- and cis-permethrin in lactating Jersey cows. J. Agric. Food. Chem. 26, 613-618.

GÖGEBAKAN, T., G. ERASLAN (2015): Single-dose toxicokinetics of permethrin in broiler chickens. Br. Poult. Sci. 56, 605-611.

GRAY, A. J., T. A. CONNORS, H. HOELLINGER, N. M. NAM (1976): The relationship between the pharmacokinetics of intravenous cismethrin and bioresmethrin and their mammalian toxicity. Pestic. Biochem. Physiol. 6, 491-500.

GUPTA, P. K. (2016): Principles and Basic Concept of Toxicokinetic, In: Fundamentals of Toxicology: Essential Concepts and Applications, New York, Academic Press, pp. 87-107.

HASSAN, S. L. (2017): Toxicopathological changes in internal organs of albino mice after treatment with sumithrin. Adv. Anim. Vet. Sci. 5, 167-173.

HIRAHARA, Y., Y. TSUMURA, Y. NAKAMURA, Y. TONOGAI, T. SHIBATA (1997): Analysis of phenothrin and its metabolite 3-phenoxybenzoic acid (PBA) in agricultural products by GC and lon-Trap GC/MS. J. Food. Prot. 60, 305-308.

HUGHES, M. F., D. G. ROSS, B. C. EDWARDS, M. J. DEVITO, J. M. STARR (2016): Tissue time course and bioavailability of the pyrethroid insecticide bifenthrin in the Long-Evans rat. Xenobiotica. 46, 430-438.

HUNT, L. M., B. N. GILBERT, C. A. LEMEILLEUR (1979). Distribution and depletion of radioactivity in hens treated dermally with 14C-labeled permethrin. Poult. Sci. 58, 1197-1201.

HUNTER, R. E., A. M. RIEDERER, P. B. RYAN (2010): Method for the determination of organophosphorus and pyrethroid pesticides in food via gas chromatography with electron-capture detection. J. Agric. Food Chem. 58, 1396-1402.

HÜYÜK, R., G. ERASLAN (2017): Toxicokinetics of the broad-spectrum pyrethroid insecticide deltamethrin in broiler chickens. Br. Poult. Sci. 58, 95-99.

IZUMI, T., H. KANEKO, M. MATSUO, J. MIYAMATO (1984): Comparative metabolism of the six stereoisomers of phenothrin in rats and mice. J. Pesticide. Sci. 9, 259-267.

JACKSON, D., B. LUUKINEN, J. GERVAIS, K. BUHL, D. STONE (2011): d-Phenothrin: Technical Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services, http://npic.orst.edu/factsheets/archive/dphentech.html.

JIANG, W., R. T. KON, R. A. OTHOUDT, R. A. LEAVITT, S. KUMAR, L. D. GEISSEL, E. A. GOMAA (2004): Method development, validation, and analysis of bifenthrin residues in fresh and dry cilantro foliages and cilantro seeds using GC-ECD. Bull. Environ. Contam. Toxicol. 73, 9-16.

KANEKO, H. (2010): Pyrethroid Chemistry and Metabolism (Chapter 76), In: Hayes' Handbook of Pesticide Toxicology. pp. 1635-1663.

KANEKO, H., H. OHKAWA, J. MIYAMOTO (1981): Absorption and metabolism of dermally applied phenothrin in rats. J. Pesticide. Sci. 6, 169-182.

KAYA, S. (2006): Pharmacocinetic. In: Veterinary Pharmacology. (Kaya, S., Ed.). Medisan Press, Vol. 1, 4th ed. Ankara, pp. 21-88 (in Turkish).

KAYA, S. (2014): Pesticides. In: Veterinary Toxicology. (Kaya, S., Ed.) Medisan Press, Ankara, pp. 301-392 (in Turkish).

KIM, K. B., S. S. ANAND, H. J. KIM, C. A. WHITE, J. V. BRUCKNER (2008): Toxicokinetics and tissue distribution of deltamethrin in adult Sprague-Dawley rats. Toxicol. Sci. 101, 197-205.

LIN, C. H., C. T. YAN, P. V. KUMAR, H. P. LI, J. F. JEN (2011): Determination of pyrethroid metabolites in human urine using liquid phase microextraction coupled in-syringe derivatization followed by gas chromatography/electron capture detection. Anal. Bioanal. Chem. 401, 927-937.

MEKEBRI, A., D. B. CRANE, G. J. BLONDINA, D. R. OROS, J. L. ROCCA (2008): Extraction and analysis methods for the determination of pyrethroid insecticides in surface water, sediments and biological tissues at environmentally relevant concentrations. Bull. Environ. Contam. Toxicol. 80, 455-460.

MERWE, D. V. M., R. GEHRING, J. L. BUUR (2012): Toxicokinetic. In: Veterinary Toxicology, 2nd ed., (Gupta, R. C., Ed.). Academic Press, USA, pp. 37-47.

MIYAMOTO, J. (1976): Degradation, metabolism and toxicity of synthetic pyrethroids. Environ. Health. Perspect. 14, 15-28.

MIYAMOTO, J., T. SUZUKI, C. NAKAE (1974): Metabolism of phenothrin or 3-phenoxybenzyl d-trans-chrysanthemumate in mammals. Pestic. Biochem. Phys. 4, 438-450.

MUDIAM, M. K. R., R. JAIN, S. K. MAURYA, H. A. KHAN, S. BANDYOPADHYAY, R. C. MURTHY (2012): Low density solvent based dispersive liquid-liquid microextraction with gas chromatography-electron capture detection for the determination of cypermethrin in tissues and blood of cypermethrin treated rats. J. Chromatogr. B. Analyt. Technol. Biomed. Life. Sci. 895-896, 65-70.

NAGY, K., G. RÁCZ, T. MATSUMOTO, R. ÁDÁNY, B. ÁDÁM (2014): Evaluation of the genotoxicity of the pyrethroid insecticide phenothrin. Mutat. Res. Genet. Toxicol. Environ. Mutagen. 770, 1-5.

NARDELLI, V., F. CASAMASSIMA, G. GESUALDO, D. LI, W. M. V. MARCHESIELLO, D. NARDIELLO, M. QUINTO (2018): Sensitive screening method for determination of pyrethroids in chicken eggs and various meat samples by gas chromatography and electron capture detection. J. Agric. Food Chem. 66, 10267-10273.

NATIONAL RESEARCH COUNCIL (1999): Commission on the Life Sciences. Board on Environmental Studies and Toxicology. Committee on Hormonally Active Agents in the Environment. Hormonally active agents in the environment. Washington, D.C. National Academy Press, p. 10.

OĞUZ, H., H. AYDIN (2001): The use of pyrethroid insecticides in veterinary medicine and their importance in public health enviromental sanitation. Veterinarium 12, 39-46 (in Turkish).

OUATTARA, J. P. N., O. PIGEON, P. SPANOGHE (2013): Validation of a multi-residue method to determine deltamethrin and alpha-cypermethrin in mosquito nets by gas chromatography with electron capture detection (GC-μECD). Parasit. Vectors 6, 77,

DOI: 10.1186/1756-3305-6-77

RIDLEN, L. R., R. J. CHRISTOPHER, G. W. IVIE, R. C. BEIER, B. J. CAMP (1984): Distribution and metabolism of cis- and trans-resmethrin in lactating Jersey cows. J. Agric. Food. Chem. 32, 1211-1217.

RIVIERE, J. E. (2009): Pharmacokinetic, In: Veterinary Pharmacology and Threpeutics. (Riviere, J. E., M. G. Papich, Eds). 9th ed, USA: Wiley-Blackwell, pp. 47-73.

SANCHEZ-BAYO, F., K. GOKA (2014): Pesticide residues and bees-A risk assessment. PLoS One. 9, e94482,

DOI: 10.1371/journal.pone.0094482

SHEN, D. D. (2008): Toxicokinetics. Casarett and Doull's Toxicology, The Basic Science of Poisons, 7th ed., (Klaassen, C. D., Ed.), pp. 305-325.

SHRIVASTAVA, A., V. B. GUPTA (2011): Methods for the determination of limit of detection and limit of quantitation of the analytical methods. Chron. Yong. Sci. 2, 21-25.

SHUMAKER, R. C. (1986): PKCALC a Basic interactive computer program for statistical and pharmacokinetic analysis of data. Drug. Metabol. Rev. 17, 331-348.

SILVER, I. S., W. C. DAUTERMAN (1989): The pharmacokinetics and metabolism of (1R, cis)- and (1R, trans)-tetramethrin in rats. Xenobiotica 19, 301-314.

SINGH, S. P., N. DWIVEDI, K. S. RAJU, I. TANEJA, M. WAHAJUDDIN (2016): Validation of a rapid and sensitive UPLC-MS-MS method coupled with protein precipitation for the simultaneous determination of seven pyrethroids in 100 μL of rat plasma by using ammonium adduct as precursor ion. J. Anal. Toxicol. 40, 213-221.

SMITH, D. A., M. J. HUMPHREY, C. CHARUEL (1990): Design of toxicokinetic studies. Xenobiotica. 20, 1187-1199.

SODERLUND, D. M., J. E. CASIDA (1977): Effects of pyrethroid structure on rates of hydrolysis and oxidation by mouse liver microsomal enzymes. Pestic. Biochem. Physiol. 7, 391-401.

TOMIGAHARA, Y., M. ONOGI, K. SAITO, H. KANEKO, I. NAKATSUKA, S. YAMANE (1997): Metabolism of tetramethrin isomers in rat: IV. Tissues responsible for formation of reduced and hydrated metabolites. Xenobiotica 27, 961-971.

TOMIGAHARA, Y., M. ONOGI, M. MIKI, K. YANAGI, K. SHIBA, H. KANEKO, I. NAKATSUKA, H. YAMADA (1996): Metabolism of tetramethrin isomers in rat. III. Stereochemistry of reduced metabolites. Xenobiotica 26, 201-210.

U.S. EPA (1989a): Office of Pesticides and Toxic Substances. Sumithrin (d-phenothrin)-review of toxicity studies submitted by Sumitomo Chemical Company in support of EAP#1H45283 and EPA Registration No. 10308-6. Memo from E.R. Budd, Health Effects Div. to J.M. Tavano, Registration Div. Washington, D.C., Mar. 16. See attached Data Evaluation Report for MRID No. 402764-01-02.

U.S. EPA (1989b): Office of Pesticides and Toxic Substances. Sumithirin (d-phenothrin-review of rat reproduction study. Memo from W. Dykstra, Health Effects Div. to J. Tavano, Registration Div. Washington, D.C., Jul. 27.

U.S. EPA (1995): Office of prevention, pesticides, and toxic substances. d-phenothrin (sumithrin)-submission of a 90-day inhalation toxicity study in rats. (EPA ID 06905). Washington, DC, June 13.

UEDA, K., L. C. GAUGHAN, J. E. CASIDA (1975): Metabolism of (+)-trans- and (+)-cis-resmethrin in rats. J. Agric. Food. Chem. 23, 106-115.

WAGNER, J. G. (1975): Fundamentals of clinical pharmacokinetics, 1st ed. Drug Intelligence Pub. Inc, Hamilton Press, IL, USA, pp. 57-128.

WANG, D., D. P. WESTON, M. J. LYDY (2009): Method development for the analysis of organophosphate and pyrethroid insecticides at low parts per trillion levels in water. Talanta. 78, 1345-1351.

WHO (1989): d-phenothrin: Health and Safety Guide. PCS International programme on chemical safety health and safety guide no: 32, United Nations Environment Programme Internatıonal Labour Organisation, Geneva.

WILLEMIN, M. E., S. DESMOTS, R. LE GRAND, F. LESTREMAU, F. A. ZEMAN, E. LECLERC, C. MOESCH, C. BROCHOT (2016): PBPK modelling of the cis- and trans-permethrin isomers and their major urinary metabolites in rats. Toxicol. Appl. Pharmacol. 294, 65-77.

YAMADA, T., S. UEDA, K. YOSHIOKA, S. KAWAMURA, T. SEKI, Y. OKUNO, N. MIKAMI (2003): Lack of estrogenic or (anti-) androgenic effects of d-phenothrin in the uterotrophic and Hershberger assays. Toxicology 186, 227-239.

YAMAOKA, K., T. NAKAGAWA, T. UNO (1978): Application of Akaike's information criterion (AIC) in the evaluation of linear pharmacokinetic equations. J. Pharmacokinet. Biopharm. 6, 165-175.

YAN, H., F. QIAO, M. TIAN, K. H. ROW (2010): Simultaneous determination of nine pyrethroids in indoor insecticide products by capillary gas chromatography. J. Pharm. Biomed. Anal. 51, 774-777.

YAVUZ, O., A. AKSOY, Y. K. DAS, E. ATMACA (2010): Evaluation of liquid-liquid and different solid phase extraction cartridges for determination of selected synthetic pyrethroid insecticides in whole blood. Asian. J. Chem. 22, 4026-4032.

Received: 23 April 2020
Accepted: 30 June 2020

KAYA, T., G. ERASLAN: Toksikokinetika fenotrina u kunića. Vet. arhiv 91, 547-558, 2021.

SAŽETAK

U ovom je radu istraživana toksikokinetika pojedinačne doze fenotrina u kunića. U tu je svrhu korišteno ukupno 14 ženki kunića novozelandske pasmine, tjelesne mase 2 – 2,5 kg i starosti 6 mjeseci. Životinje su podijeljene u dvije skupine po sedam jedinki. U skupini 1 fenotrin je primijenjen intravenski u dozi od 10 mg/kg tjelesne mase, dok je u skupini 2 u istoj dozi primijenjen oralno. Dimetil-sulfoksid upotrijebljen je kao nosač fenotrina. Razine fenotrina u plazmi mjerene su plinskom kromatografijom upotpunjenom ECD detektorom. Toksikokinetika je procijenjena prema vremenskoj krivulji fenotrina u plazmi. Fenotrin je raspodijeljen prema modelu s dva odjeljka. Vrijeme poluraspada ($t_{1/2\beta}$) bilo je 2,57 ± 0,10 h, prosječno vrijeme zadržavanja (MRT) 2,79 ± 0,09 h, a područje ispod krivulje ($AUC_{0\rightarrow\infty}$) nakon intravenske primjene fenotrina 6893,05 ± 261,26 ng/h/mL. S druge strane, nakon oralne primjene maksimalna koncentracija u plazmi (C_{max}) bila je 185,71 ± 8,21 ng/mL, vrijeme postizanja maksimalne koncentracije C_{max} (t_{max}) 1,21 ± 0,20 h, $t_{1/2\beta}$ 4,24 ± 0,39 h, MRT 6,65 ± 0,54 h i $AUC_{0\rightarrow\infty}$ 1054,04 ± 65,90 ng/h/mL. Oralna biodostupnost fenotrina bila je 15,29 %. Prosječno vrijeme zadržavanja bilo je kratko, a oralna biodostupnost niska. To bi mogao biti jedan od razloga zbog čega se fenotrin upotrebljava kao siguran pesticid.

Ključne riječi: fenotrin; toksikokinetika; oralna primjena; intravenska primjena; kunić