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Toxicokinetics of a single intraperitoneal and oral dose of prallethrin in mice

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ABSTRACT

The aim of this study was to determine the toxicokinetic profile of orally and intraperitoneally administered prallethrin, which is frequently used as an environmental health drug. For this purpose, prallethrin was administered to 42 female 2-3-month-old BALB/c mice, each weighing 35-40 grams, at a dose of 2 mg/kg bw by intraperitoneal and oral route. The mice were randomly assigned to two groups, each of 21 animals. While Group 1 was administered 2 mg/kg bw prallethrin in dimethyl sulfoxide by intraperitoneal route, Group 2 received a single oral dose of 2 mg/kg bw prallethrin in dimethyl sulfoxide. After the intraperitoneal and oral administration of prallethrin, intra-cardiac blood was drawn into heparinized tubes at certain periods. Plasma prallethrin concentrations were measured by gas chromatography using a micro-electron capture detector. The distribution profile was found to be consistent with the two-compartment open model. The plasma maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), half-life ($t_{1/2\beta}$), mean residence time (MRT), area under the curve ($AUC_{0\rightarrow\infty}$) and bioavailability (F) values for orally administered prallethrin were 3.66±0.78 ng/ml, 0.60±0.05 h, 10.20±1.24 h, 11.72±1.51 h, 15.19±4.43 ng/h.ml and 39.86%, respectively. For intraperitoneally administered prallethrin, the $t_{1/2\beta}$, MRT and $AUC_{0\rightarrow\infty}$ values were calculated as 7.46±0.54 h, 8.05±0.64 h and 38.10±5.80 ng/h.ml, respectively. The data obtained indicates that the oral bioavailability of prallethrin is lower than that of many other pyrethroids such as flumethrin and cypermethrin. Compared to some other pesticides in the same group, such as phenothrin, the half-life and mean *residence* time of prallethrin in the body are not short, when administered by both routes. The results obtained suggest that exposure to high doses of prallethrin may pose a risk of poisoning. In view of the toxicokinetic parameters determined, this study points out to the need for further studies to better understand the toxicity of prallethrin in mammals.

Key words: prallethrin; toxicokinetic; intraperitoneal; oral; mice

Introduction

Prallethrin is a structural derivative of natural pyrethrins. Pyrethrins are extracted from *Chrysanthemum cinerariaefolium* flowers and have a powerful effect against insects. Prallethrin (2-methyl-4-oxo-3-(2-propynyl) cyclopent-2-enyl (1RS)-cis) is the general name for the racemic

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mixture of 8 stereoisomers and is an insecticide included in the class of synthetic pyrethroids of a trans-chrysanthemic acid structure. Its molecular formula and molecular weight are $C_{19}H_{24}O_3$ and 300.40, respectively (EPA, 2003; CHANDRA et al., 2013), and its use is limited due to biodegradability. This compound is used as a mosquito repellent, similar to allethrin, a type I pyrethroid. Known to be particularly effective against mosquitoes, houseflies and cockroaches, prallethrin is also used in veterinary medicine for the treatment of domestic animals (MATSUNAGA et al., 1987; WHO, 2004; ARDHANARI et al., 2011; CHANDRA et al., 2013). Its mode of action is by contact, with a quick knockdown effect, and it affects the nervous system of insects. Pyrethroid neurotoxicity results from the ability of these compounds to change sodium, chloride and calcium channels in the nerves of mammals and insects. In case of dermal absorption, paraesthesia develops, but heals spontaneously within a few hours. Nausea, vomiting, abdominal pain, dizziness, headache, fatigue, palpitation, chest tightness and blurred vision are observed after oral administration. Coma, convulsions and pulmonary oedema are rare, but may occur in the event of severe poisoning. These symptoms are very similar to those associated with organophosphate poisoning, which require the use of atropine. Prallethrin can also cause hypersensitivity reactions, which can be fatal if the exposure occurs by inhalation (WHO, 2004; ARDHANARI et al., 2011).

In this study, the toxicokinetic profile of prallethrin was investigated in mice. This pesticide is used extensively. As is the case with other pyrethroids, its areas of use may place mammals under the risk of exposure. To our knowledge, to date, the toxicokinetics of prallethrin have not been studied. However, there are several detoxification/therapy studies, which can be referred to for cases of toxicity and intoxication (BHASKAR et al., 2010; MOSSA et al., 2013; SENTHILKUMARAN et al., 2014). As they provide data on absorption, tissue distribution, metabolism and elimination, toxicokinetic studies significantly contribute to evaluating the health risks of pyrethroids. In fact, when evaluating the toxicity of a compound, the absorption rate of the ingested amount of poison, in other words, the amount that passes into the systemic circulation, as well as the duration of the compound in the systemic circulation (elimination half-life) serve as important parameters. Toxicokinetic studies are also important in determining the mechanism of action of a toxic substance, severity of toxicity and treatment options. The present study was designed to collect toxicokinetic data for such scientific purposes, and the results obtained will serve as a reference for future research on prallethrin and other pyrethroids.

Material and methods

Animals. A total of 42 female 2-3-month-old BALB/c mice, each weighing 35-40 g, were used in this study. The animals were physiologically healthy and not pregnant. Two groups, each of 21 mice, were established. Throughout the study period, the animals were housed at 20-22 ºC under a 12 h light/dark period. Mice pellet feed (17% crude protein, 10.5% crude fibre and 3.25% crude fat) and drinking water were given ad libitum. The first group was administered prallethrin (Sigma 32917 PESTANAL®, analytical standard) at a dose of 2 mg/kg.bw, in dimethyl sulfoxide as a vehicle, by intraperitoneal route. The second group received prallethrin at a dose of 2 mg/kg bw orally in the same vehicle. The administration dose was chosen considering the oral LD_{50} of prallethrin in rats, possible exposure risk during the use of prallethrin, possible oral pyrethroid dose that can be determined by the available method in blood for toxicokinetic evaluation, and the survival rate of animals. Following the administration of prallethrin, approx. 0.1 ml of blood (0.05-0.1 ml; drawn totally 14 times from each mouse heart) was collected at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24, 36 and 72 h under light ether anaesthesia. In view of the small amount of blood taken from the animals during sampling, as well as the sampling of each animal at 14 time points, the mice in groups 1 and 2 were divided into subgroups, each of 3 animals, such that equal volumes of blood were collected. During the blood collection periods indicated above, the blood of the 3 animals in each subgroup was pooled. Thus, in total, seven samples were obtained for each blood collection

period. Plasma was extracted by centrifuging the blood samples at 3000 rpm for 10 minutes, (Sigma 3K30). The plasmas were stored at -80 °C until analysis (Arctiko ULUF 550-2M). This study was approved by the Local Ethics Committee for Animal Experiments of Erciyes University (Decision No: 18-093).

Plasma prallethrin analysis. A modified version of the method described by YAVUZ et al. (2010) was used for the extraction of the samples. Accordingly, 0.5 ml of hexane/acetone (8:2, v/v) was added to 0.1 ml of plasma as indicated in the method and then was vortexed (Heidolph Reax ball) for 3 minutes. Following the centrifugation of the mixture at 3000 rpm in a refrigerated centrifuge at +4°C, 0.4 ml of the resulting supernatant was pipetted and evaporated under nitrogen (Miulab, NK200-IB). After being added 0.5 ml of hexane, the mixture was vortexed for 1 min and transferred to vials. Analyses were performed according to the methods described by MEKEBRI et al. (2008), WANG et al. (2009) and HUNTER et al. (2010) with some minor modifications. Accordingly, all plasma prallethrin analyses were performed using a capillary column (HP-5MS, 30 m long, 0.25 mm film thickness and 0.25 microns diameter), gas chromatograph coupled with a micro-electron capture detector (μECD) (Agilent 6890N), and an attached auto-sampler (Agilent 7683B). In the injection section, the injection mode was splitless. Using helium as the carrier gas and nitrogen as the auxiliary gas, the gas flow pattern was continuous and the gas flow rate was 60 ml/min. The injection port temperature, pressure, gas flow rate, gas discharge rate and sample volume loaded onto the device were 260 °C, 27 psi, 51.2 ml/min, 45.5 ml/min, and 5 μl, respectively. A μECD was selected for use and its temperature was set at 325 °C. The initial temperature of the oven was set at 70 °C for 2 minutes, and was later increased by 25 °C per minute up to 150 °C. In the second stage, the temperature was raised up to 200 °C by 3 °C per minute, and in the third stage, the temperature was increased by 8 °C per minute up to 280 °C. The total analysis time, column pressure, and column gas flow rate were 41.87 min, 27 psi, and 2.8 ml/min, respectively.

Quantity calculation and method validation. The prallethrin standard curve was generated using 11 different pesticide concentrations (0.1 ng/ml, 0.5 ng/ml, 1.0 ng/ml, 2.5 ng/ml, 5 ng/ml, 10 ng/ml, 25 ng/ml, 100 ng/ml, 250 ng/ml and 500 ng/ml). Prallethrin was added to the blank plasma, and the procedures applied for the extraction of the samples and plasma were followed. The same process was repeated for gas chromatography. While constructing the prallethrin standard curve for the determination of the plasma prallethrin levels, the detection limit (lowest plasma concentration) was used for the lower limit and the highest plasma concentration was used for the upper limit. The plasma prallethrin levels detected are presented in Table 1, Figs 1 and 2.

Table 1. Blood sampling time points and plasma prallethrin concentrations measured at these time points in mice administered with prallethrin at a dose of 2 mg/kg bw by intraperitoneal and oral route (arithmetic mean±standard error).

Blood sampling periods (h)	Intraperitoneal ng/ml	Oral ng/ml
0.083	41.51±4.89	1.65±0.25*
0.25	12.13±1.64	2.75±0.75*
0.50	7.19±1.47	3.25±0.81*
0.75	4.58±0.74	2.76±0.91

Table 1. Blood sampling time points and plasma prallethrin concentrations measured at these time points in mice administered with prallethrin at a dose of 2 mg/kg bw by intraperitoneal and oral route (arithmetic mean±standard error). (continued)

1	2.99±0.74	1.94±0.62
2	1.76±0.28	1.30±0.41
4	1.25±0.14	0.87±0.23
6	1.03±0.16	0.54±0.13*
8	0.82±0.18	0.41±0.10
12	0.57±0.16	0.33±0.07
18	0.34±0.04	0.26±0.10
24	0.29±0.02	ND
36	0.18±0.01	ND
72	ND	ND

*P<0.05. ND: Not determined.

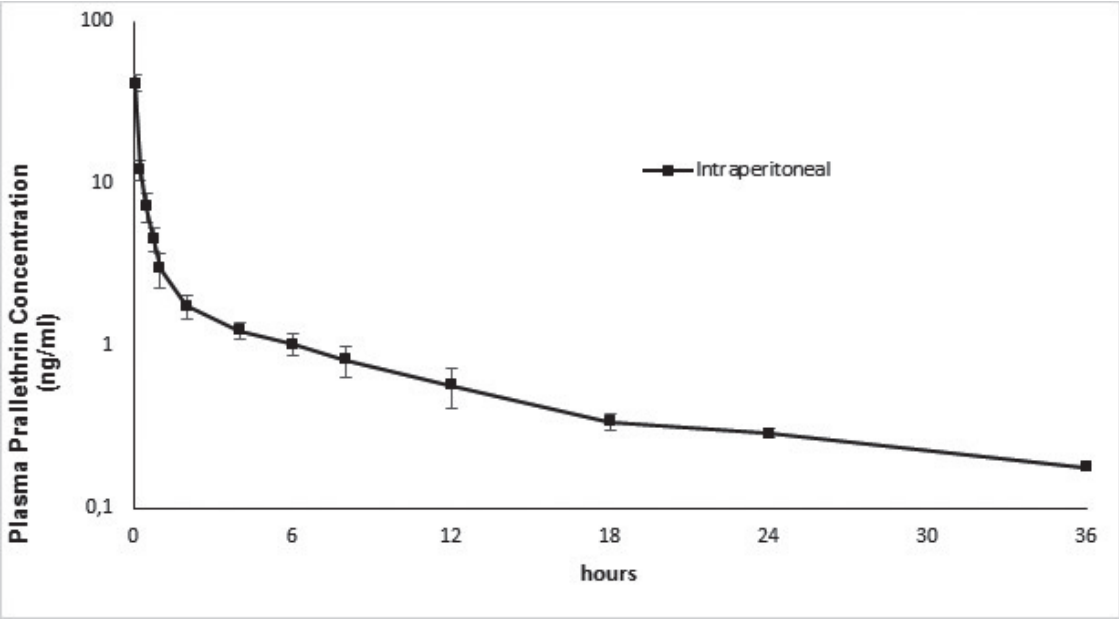

Fig 1. Semi-logarithmic plasma concentration-time curve (arithmetic mean±standard error) of prallethrin administered to mice at a dose of 2 mg/kg bw by intraperitoneal route (arithmetic mean±standard error).

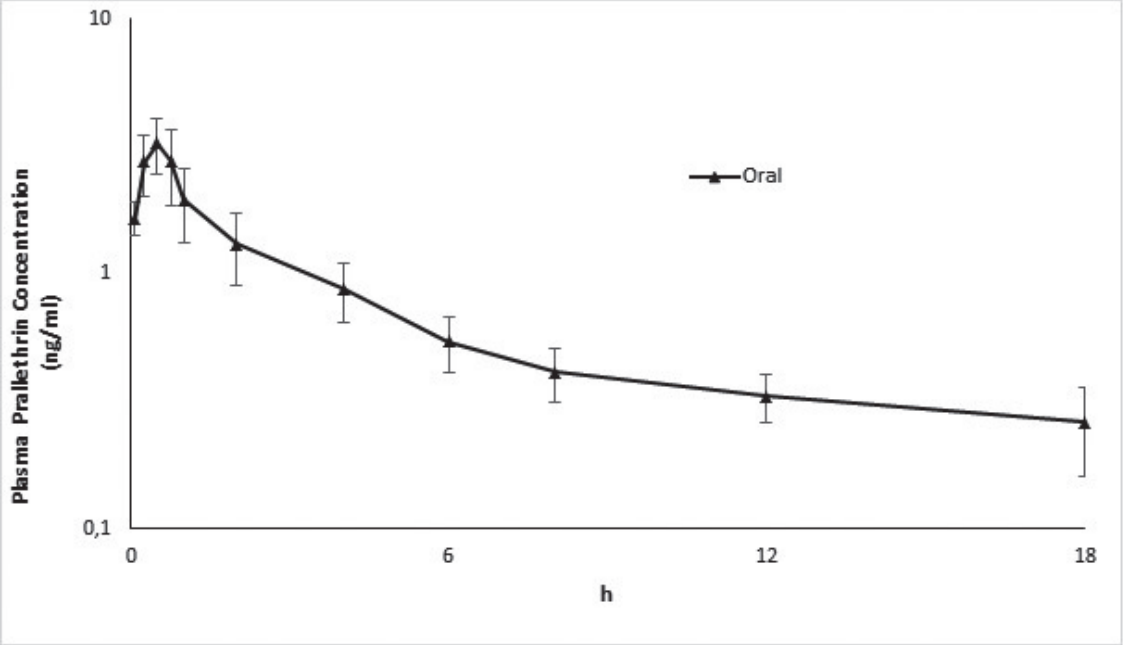

Fig 2. Semi-logarithmic plasma concentration-time curve (arithmetic mean±standard error) of prallethrin administered to mice at a dose of 2 mg/kg bw by oral route (arithmetic mean±standard error).

The recovery of the plasma prallethrin extraction method was determined based on the same concentrations used for the construction of the prallethrin standard curve. Prallethrin was added at the indicated levels to both blank plasma and the hexane/acetone extracts of blank plasma, and the procedure was performed in triplicate. Measurements were performed with the same device following the previously described procedures. The arithmetic means of the results were calculated for the calculation of the mean recoveries.

The method described by SHRIVASTAVA and GUPTA (2011) was used for determining the quantification limit (LOQ) and detection limit (LOD). According to this method, the definition limit is three times the noise peak area, and the measurement limit is ten times the noise peak area (ratio of signal to noise). Values for both parameters were obtained by comparing the prallethrin peak at hand and blank sample peak around the prallethrin retention time.

To determine the accuracy of the method, three different concentrations (5 ng/ml, 25 ng/ml and 100 ng/ml) of prallethrin were added to blank plasma. After the extraction method used in this study was performed, samples were loaded in the gas chromatograph, three times a day at the same time points for 5 days. The intra-day (within one day) and inter-day (between days) relative standard deviations (RSD%) of the results were calculated. To better understand the distribution profile of prallethrin, pharmacokinetic calculations were based on compartmental models. The plasma prallethrin concentration-time curve was evaluated according to correlation coefficients (r^2) and the Akaike Information Criteria (AIC) of the compartmental analysis (YAMAOKA et al., 1978). C_{max} and t_{max} values were determined from the plasma prallethrin concentration-time curve drawn after the oral administration of prallethrin. The PKCALC and GW-BASIC pharmacokinetic software, including the formulae/equations of SHUMAKER (1986) and WAGNER (1975), was used for all other toxicokinetic evaluations and calculations (A_1, A_2, A_3 mathematical coefficients; C_p^0, plasma prallethrin concentration at t_0; k_{ab}, first-order absorption rate constant of prallethrin for absorbable administration; $t_{1/2ab}$, half-life of absorption from the digestive tract in case of oral administration MAT, mean absorbtion time;

C_{max}, prallethrin peak plasma concentration; t_{max}, time to reach the maximum plasma prallethrin concentration; a, plasma prallethrin distribution rate constant; $t_{1/2a}$, plasma prallethrin distribution half-life; ß, plasma prallethrin elimination rate constant; $t_{1/2ß}$, prallethrin elimination half-life; V_1, central compartment distribution volume; V_2, peripheral compartment distribution volume; Vd_{ss}, apparent volume of distribution at steady state; Vd_{area}, volume of distribution according to area calculated; k_{12}, first order rate constant of the transition from the central compartment to the peripheral compartment; k_{21}, first order rate constant of the transition from the peripheral compartment to the central compartment; k_{10}, irreversible elimination rate constant of prallethrin; MRT, time required for the elimination of 63.2% of prallethrin from the body; Cl_T, prallethrin total plasma clearance; $AUC_{0\rightarrow8}$, area under the plasma prallethrin concentration-time (0 to t) curve; $AUC_{0\rightarrow\infty}$, area under the plasma prallethrin concentration-time (0 to ∞) curve; F, oral bioavailability).

Statistical calculations. The "SPSS 13.0 for Windows" statistical package program was used for statistical calculations. Values are expressed as the mean and the standard error of the mean. Student's t test was used to evaluate the statistical differences in the toxicokinetic parameters of orally and intraperitoneally administered prallethrin. Differences were considered significant only when $P<0.05$. Values are given as arithmetic mean and standard error. On the other hand, statistical comparisons could not be made for the two administration routes for parameters such as A_3, C_{p0}, k_{ab}, $t_{1/2ab}$, MAT, C_{max}, t_{max} and F, which were either not determined or could not be determined in this study.

Results

Validation data. The standard curve constructed for determining the plasma prallethrin levels was linear within the tested range (r^2: 0.9999). The equation of the standard curve was y=0.003x+0.002. All evaluations were based on this equation. Prallethrin recovery was determined as 82.01%. The quantification limit (LOD) of prallethrin was 0.04 ng/ml and the detection limit (LOQ) was 0.1 ng/ml. The intra-day precision was 5.26% on average and the inter-day precision was 6.34%.

Clinical findings. The group, which received oral prallethrin, displayed no clinical findings from the moment of administration until the end of the trial. On the other hand, during the first 3-5 minutes after intraperitoneal administration, there were tremors, hypersensitivity symptoms, incoordination, changes in the appearance of fur, and partial salivation, and these symptoms varied among the animals. Clinical findings peaked within the 10-15 minute period, then gradually weakened and disappeared after 25-30 minutes.

Toxicokinetic variables. Prallethrin showed a distribution consistent with the two-compartment open model, and calculations were made according to this model. Following the intraperitoneal administration of prallethrin, the drug levels determined in the blood samples taken at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 18, 24 and 36th hours were 41.51±4.89 ng/ml, 12.13±1.64 ng/ml, 7.19±1.47 ng/ml, 4.58±0.74 ng/ml, 2.99±0.74 ng/ml, 1.76±0.28 ng/ml, 1.25±0.14 ng/ml, 1.03±0.16 ng/ml, 0.82±0.18 ng/ml, 0.57±0.16 ng/ml, 0.34±0.04 ng/ml, 0.29±0.02 ng/ml and 0.18±0.01 ng/ml, respectively. At 72 h post-administration, the blood values were not determined. Prallethrin concentrations were determined as 1.65±0.25 ng/ml, 2.75±0.75 ng/ml, 3.25±0.81 ng/ml, 2.76±0.91 ng/ml, 1.94±0.62 ng/ml, 1.30±0.41 ng/ml, 0.87±0.23 ng/ml, 0.54±0.13 ng/ml, 0.41±0.10 ng/ml, 0.33±0.07 ng/ml and 0.26±0.10 ng/ml at 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12 and 18 h, respectively, following oral administration. Those at 24, 36 and 72 h post-administration could not be detected (Figs 1 and 2). The blood levels detected at 0.083, 0.25, 0.50 and 6 h displayed statistical differences (Table 1).

Following the intraperitoneal administration of prallethrin, the A_1 and A_2 values were 79.95±10.08 ng/ml and 2.64±0.36 ng/ml, respectively. $t_{1/2\alpha}$ was 0.082±0.004 h and the α value was 8.54±0.65 h^{-1}. $t_{1/2\beta}$ was 7.46±0.54 h. The β value was 0.097±0.010 h^{-1}. $C_p{}^0$ was 82.60±10.35 ng/ml. V_1 was 27.37±4.30 mL/kg. V_2, Vd_{ss} and Vd_{area} were 427.24±40.23 mL/kg, 454.62±43.24 mL/kg and 16.22±2.86 mL/kg, respectively. k_{12}, k_{21} and k_{10} were 6.04±0.55 h^{-1}, 0.37±0.02 h^{-1} and 2.22±0.15 h^{-1}, respectively. MRT was 8.05±0.64 h. The total clearance (Cl_T) was 60.55±9.78 mL/h/kg. The area under the

curve ($AUC_{0\rightarrow36}$ and $AUC_{0\rightarrow\infty}$) was calculated as 29.16±4.61 ng/h/L and 38.10±5.80 ng/h/L (Table 2).

Following the oral administration of prallethrin, the A_1, A_2 and A_3 values were 5.44±1.63 ng/ml, 0.76±0.14 ng/ml and -6.35±1.93 ng/ml, respectively. $t_{1/2ab}$ was 0.13±0.02 h. The k_{ab} value was determined as 5.66±0.78 h^{-1}. The $t_{1/2\alpha}$ value was 0.86±0.21 h, and the α value was 1.42±0.50 h^{-1}. While the $t_{1/2\beta}$ value was 10.20±1.24 h, the $_{\beta}$ value was 0.073±0.007 h^{-1}. MAT was 3.67 h. While the C_{max} was 3.66±0.78 ng/ml, the t_{max} value was found to be 0.60±0.05 h. The V_1 value was calculated as 192.63±29.14 mL/kg. V_2, Vd_{ss} and Vd_{area} were 415.44±91.90 mL/kg, 7239.66±1894.93 mL/kg and 966.02±117.9 mL/kg, respectively. k_{12}, k_{21} and k_{10} were 0.90±0.40 h^{-1}, 0.28±0.06 h^{-1} and 0.31±0.04 h^{-1}, respectively. MRT was 11.72±1.51 h. The total clearance (Cl_T) was 69.02±10.51 mL/h/kg. The area under the curve ($AUC_{0\rightarrow8}$ and $AUC_{0\rightarrow\infty}$) was 11.25±3.16 ng/h/ml and 15.19±4.43 ng/h/ml. The bioavailability (F) of prallethrin was 39.86%. Of the toxicokinetic parameters examined, only A_1, A_2, α, $t_{1/2\alpha}$, V_1, Vd_{ss}, Vd_{area}, k_{12}, k_{10}, MRT, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ differed between the groups (Table 2).

Table 2. Some toxicokinetic variables of prallethrin administered to mice at a dose of 2 mg/kg bw by intraperitoneal and oral route (arithmetic mean±standard error).

Parameters[a]	Intraperitoneal	Oral
A_1 (ng/ml)	79.95±10.08	5.44±1.63*
A_2 (ng/ml)	2.64±0.36	0.76±0.14*
A_3 (ng/ml)	-	-6.35±1.93
C_p^0 (ng/ml)	82.60±10.35	-
k_{ab} (h^{-1})	-	5.66±0.78
$t_{1/2ab}$ (h)	-	0.13±0.02
MAT (h)	-	3.67
C_{max} (ng/ml)	-	3.66±0.78
t_{max} (h)	-	0.60±0.05
α (h^{-1})	8.54±0.65	1.42±0.50*
$t_{1/2\alpha}$ (h)	0.082±0.004	0.86±0.21*
β (h^{-1})	0.097±0.010	0.073±0.007
$t_{1/2\beta}$ (h)	7.46±0.54	10.20±1.24
V_1 (mL/kg)	27.37±4.30	192.63±29.14*
V_2 (mL/kg)	427.24±40.23	415.44±91.90
Vd_{ss} (mL/kg)	454.62±43.24	7239.66±1894.93*
Vd_{area} (mL/kg)	16.22±2.86	966.02±117.91*
k_{12} (h^{-1})	6.04±0.55	0.90±0.40*
k_{21} (h^{-1})	0.37±0.02	0.28±0.06
k_{10} (h^{-1})	2.22±0.15	0.31±0.04*
MRT (h)	8.05±0.64	11.72±1.51*
Cl_T (mL/h/kg)	60.55±9.78	69.02±10.51
$AUC_{0\rightarrow t}$ (ng/h.ml)	29.16±4.61	11.25±3.16*
$AUC_{0\rightarrow\infty}$ (ng/h.ml)	38.10±5.80	15.19±4.43*
F (%)	-	39.86

[a]. A_1, A_2, A_3 mathematical coefficients; C_p^0, plasma prallethrin concentration at t_0; k_{ab}, first-order absorption rate constant of prallethrin for absorbable administration; $t_{1/2ab}$, half-life of absorption from the digestive tract in case of oral MAT, mean absorbtion time; administration; C_{max}, prallethrin peak plasma concentration; t_{max}, time to reach the maximum plasma prallethrin concentration; α, plasma prallethrin distribution rate constant; $t_{1/2\alpha}$, plasma prallethrin distribution half-life; ß, plasma prallethrin elimination rate constant; $t_{1/2ß}$, prallethrin elimination half-life; V_1, central compartment distribution volume; V_2, peripheral compartment distribution volume; Vd_{ss}, apparent volume of distribution at steady state; Vd_{area}, volume of distribution according to area calculated; k_{12}, first order rate constant of the transition from the central compartment to the peripheral compartment; k_{21}, first order rate constant of the transition from the peripheral compartment to the central compartment; k_{10}, irreversible elimination rate constant of prallethrin; MRT, time required for the elimination of 63.2% of prallethrin from the body; Cl_T, prallethrin total plasma clearance; $AUC_{0\rightarrow8}$, area under the plasma prallethrin concentration-time (0 to t) curve; $AUC_{0\rightarrow\infty}$, area under the plasma prallethrin concentration-time (0 to ∞) curve; F, oral bioavailability; *P<0.05: Statistically significant; (-): Incalculable pharmacokinetic parameters due to the route of administration.

Discussion

Validation data. The calibration curve was linear over the concentration range evaluated in the study. Given the correlation coefficient (r^2 value) of the standard curve having been calculated as 0.9999, the equation of the curve was found to be safe for calculating prallethrin levels. Similar results have been reported in previous studies on pesticides (GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017). The recovery rate was determined to be 82.01%, which was considered sufficient for the toxicokinetic/pharmacokinetic study of a pyrethroid. This rate was higher than that reported in several previous studies (KAYA and ERASLAN, 2021) and was lower than that reported in some others (GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017). On the other hand, under the analysis conditions of the present study, for prallethrin, the quantification limit (LOD) was 0.04 ng/ml and the detection limit (LOQ) was 0.1 ng/ml. These values are lower than those reported in previous toxicokinetic studies performed with the same method/analysis conditions (BAŞÇİ AND ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021). In addition, the precision of the method (intra-day and inter-day reproducibility values) was within the accepted variable limits. Similar results were achieved in previous studies (PÉREZ et al., 2010; GÖGEBAKAN and ERASLAN, 2015; SINGH et al., 2016; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021).

Toxicokinetic variables. The dose administered in the present study was 2 mg/kg body weight, and was selected in view of the doses used in previous studies on pyrethroid insecticides (BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017). Furthermore, the LD_{50} of prallethrin (SEKİ et al., 1987; WHO, 2019), the conditions required for determining the concentration of the given dose in blood during the study using the current analysis method as stated in the material-method section, and the survival status of the mice included in the trial during the toxicokinetic study period were also taken into account.

Which compartment model the distribution pattern was consistent with was determined in view of the plasma prallethrin concentration-time curve, the correlation coefficients (r^2) of the compartmental analysis performed for each compartment in the pharmacokinetic program, as well as the Akaike Information Criteria (AIC). Accordingly, the distribution of prallethrin in mice was considered to be best described with the two-compartment open model. Time-dependent plasma concentrations of the pesticide after intraperitoneal and oral administration demonstrated a firstly rapid and then slower decrease in blood concentrations. These results were reached both visually and by pharmacokinetic calculations. According to the two-compartment open model, the pesticide first tends to pass into highly vascularized tissues/organs, and then diffuses into less vascularized compartments (LANCASTER, 1980; RIVIERE, 1997; KAYA, 2006, 2014; AHMED, 2015; GUPTA, 2016). Similar distribution profiles have been reported in previous studies on other pyrethroids, such as permethrin, deltamethrin, lambda-cyhalothrin, flumethrin, cypermethrin and phenothrin (ANADÓN et al., 1991, 1996, 2006; BAŞÇİ and ERASLAN, 2015; GÖGEBAKAN and ERASLAN, 2015; ERASLAN et al., 2017; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021).

The clinical symptoms observed in the present study were very severe, and the findings were related to the administration route. The blood concentration of the pesticide and the symptoms of intoxication were found to be correlated. Accordingly, no symptoms having been observed after oral administration until the end of the trial were attributed to the blood concentrations being far below the levels capable of causing acute effects. On the other hand, during the 30 min period after intraperitoneal administration, the symptoms observed in association with the very high blood concentrations of the pesticide included hypersensitivity, tremors, changes in the

appearance of the hair and incoordination. The severity of the symptoms observed within the first 15 minutes post-administration were also related to the blood concentration of prallethrin. Similar findings have been reported in previous studies on pyrethroids (ANADÓN et al., 1996; ERASLAN et al., 2017, HÜYÜK and ERASLAN, 2017).

For intraperitoneally administered prallethrin, the $t_{1/2\alpha}$ value, indicating distribution half-life (SHEN, 2008; GRECH et al., 2017; TURFUS et al., 2017), was 0.082±0.004 h and the α value was 8.54±0.65 h^{-1}. These data suggest that the pesticide rapidly passes into highly vascularized tissues/ organs. The highly lipophilic structure of the pesticide (MARONI et al., 2000; MARGARITI et al., 2007; HOUSSET et al., 2009; MAUND et al., 2012; MERWE et al., 2012; MIKATA et al., 2012; LIU et al., 2017) is also a significant determinant in this distribution. In addition, V_1 and V_2 (KAYA, 2006; 2014), which demonstrate the distribution profile of prallethrin, having been determined as 27.37±4.30 mL/kg and 427.24±40.23 mL/kg, respectively (V_2 being greater than V_1), points out to a tendency of transition from highly vascularized compartments (perfused central compartment) to less vascularized lipophilic compartments (peripheral compartment). The mean time of residence in the body (MRT: 8.05±0.64 h) further supports this assessment. Furthermore, k_{12} (6.04±0.55 h^{-1}) being greater than k_{21} (0.37±0.02 h^{-1}) also indicates that diffusion from the central compartment to the peripheral compartment was faster than the return. The Vd_{ss} and Vd_{area} parameters further support this opinion. Similar results have been reported in previous studies (ANADÓN et al., 2006; ERASLAN et al., 2017). There may be two reasons why the $t_{1/2\beta}$ and MRT values representing (KAYA, 2006, 2014; SHEN, 2008) the primary half-life and mean residence time/excretion of prallethrin were 7.46±0.54 h and 8.05±0.64 h, respectively. Firstly, due to the physico-chemical properties of the pesticide (being lipophilic), accumulation in peripheral tissues with high fat content and slow return from compartments could have been effective. Secondly, it should be noted that the metabolism of prallethrin is very rapid in the liver and other biotransformation organs. The $t_{1/2\beta}$ and MRT values determined in the present study are similar to those reported in several previous toxicokinetic studies (ANADÓN et al., 2006; ERASLAN et al., 2017), shorter than those reported in some other studies (ANADÓN et al., 1996; BAŞÇİ and ERASLAN, 2015; RODRÍGUEZ et al., 2018) and longer than those indicated in other research (GÖGEBAKAN and ERASLAN, 2015; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021).

Cl_T and k_{10} having been determined as 60.55±9.78 mL/h/kg and 2.22±0.15h^{-1}, respectively, further supports these results. When compared to those reported in previous studies (ANADÓN et al., 1991, 1996; ERASLAN et al., 2017; RODRÍGUEZ et al., 2018; KAYA and ERASLAN, 2021), these values are lower. The variables that define the absorption process/rate of absorption of orally administered prallethrin, including k_{ab}, $t_{1/2ab}$, MAT, $AUC_{0\rightarrow8}$, $AUC_{0\rightarrow\infty}$, C_{max} and t_{max}, were 5.66±0.78 h^{-1}, 0.13±0.02, 3.67 h, 11.25±3.16 ng/h.ml, 15.19±4.43 ng/h.ml, 3.66±0.78 ng/ml and 0.60±0.05 h, respectively. These values suggest that absorption was slow and the mean absorption time was short according to cypermethrin (ERASLAN et al., 2017), flumethrin (BAŞÇİ AND ERASLAN, 2015) and permethrin (GÖGEBAKAN AND ERASLAN, 2015). Compared to intravenous $AUC_{0\rightarrow\infty}$, bioavailability was low (39.86%), meaning that absorption was limited. However, factors affecting the systemic bioavailability of orally administered prallethrin are not limited to the rate of passage from the intestinal lumen to other body parts, and also include metabolism by the intestinal microbial flora and the first-pass effect in the liver. These values are greater/longer/larger than those reported in some previous studies (GÖGEBAKAN and ERASLAN, 2015; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021) and less/ shorter/narrower than those indicated in some other studies (ANADÓN et al., 1991, 1996, 2006). The bioavailability calculated in the present study is lower than that reported in several previous studies on pyrethroid insecticides (ANADÓN et al., 1991, 2006; RODRÍGUEZ et al., 2018) and higher than that indicated in some other studies (ANADÓN et al., 1996; GÖGEBAKAN and ERASLAN, 2015;

HÜYÜK and ERASLAN, 2017). In the present study, the t_{max} was short, and the C_{max} was very low. This was also observed for k_{ab} and $t_{1/2ab}$. These values are shorter/lower than those reported in other studies (GAMMON et al., 2015; RODRIGUEZ et al., 2018). $t_{1/2\alpha}$ (HOLZ and FAHR, 2001; KAYA, 2006), as an indicator of the distribution profile of prallethin, being 0.86±0.21 h, and the α value being 1.42±0.50 h^{-1}, both suggest that the distribution half-life of orally administered prallethrin is relatively longer than that of intravenously administered prallethrin. Contributing factors may include the bioavailability of the pesticide and the rate of blood flow in the intestinal lumen (DEGEORGE, 1995; DIXIT et al., 2003; MERWE et al., 2012; GUPTA, 2016; BUXTON, 2018;). V_1 and V_2 having been calculated as 192.63±29.14 mL/kg and 415.44±91.90 mL/kg, respectively, suggests that the pesticide has a large-scale distribution in the peripheral compartment (especially in lipophilic regions). Other parameters (k_{12}, k_{21}, Vd_{ss}, Vd_{area}) further support this result. Similar results have been obtained in previous studies (ANADÓN et al., 1996, 2006; BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017; KAYA and ERASLAN, 2021). $t_{1/2\beta}$ and MRT (GUPTA, 2016; MERWE et al., 2012), which define the half-life and mean residence time of intravenously administered prallethrin, were found to be 10.20±1.24 h and 11.72±1.51 h, respectively, and were longer. These results show that the pesticide continues to be absorbed from the digestive tract and enters the intestinal-liver circulation at a high rate even during the excretion phase. Both similar (ANADÓN et al., 2006; ERASLAN et al., 2017; RODRÍGUEZ et al., 2018) and different (ANADÓN et al., 1991, 1996; BAŞÇİ and ERASLAN, 2015) results have been reported in previous studies. Cl_T and k_{10} (BAGGOT, 1982; GUPTA, 2016), which are indicators of pesticide metabolism, were 69.02±10.51 mL/h/kg and 0.31±0.04 h^{-1}. Cl_T did not differ between the two routes of administration. Similar results have been reported in previous studies (ANADÓN et al., 1991, 1996, 2006; ERASLAN et al., 2017; RODRÍGUEZ et al., 2018; KAYA and ERASLAN, 2021). In the present study, prallethrin clearance was found to be slower than that reported for some other pyrethroids (ANADÓN et al., 1991, 1996, 2006; ERASLAN et al., 2017; RODRÍGUEZ et al., 2018; HÜYÜK and ERASLAN, 2017; KAYA and ERASLAN, 2021). The changes observed in k_{10} are compatible with the clearance values. Similar results have been reported for the k_{10} value in previous research (ANADÓN et al., 1996, 2006; BAŞÇİ and ERASLAN, 2015; ERASLAN et al., 2017; RODRÍGUEZ et al., 2018; KAYA and ERASLAN, 2021).

Conclusions

In result, the systemic bioavailability of orally administered prallethrin in female BALB/c mice is low, compared to that of some other pyrethroids, such as flumethrin and cypermethrin. On the other hand, the half-life and residence time in the body are moderate similar to cypermethrin. Based on the data obtained in this study; the distribution of prallethrin in the body is limited for both intraperitoneal and oral administration, the pesticide does not pass into adipose tissue at a high rate, is metabolized moderately in biotransformation structures/organs, and compared to some other pyrethroids such as permethrin and phenothrin, is not rapidly excreted by excretion organs. Ultimately, the first-pass effect and entero-hepatic cycle are determining factors in the metabolism/degradation of the pesticide. Intestinal microflora (activity of drug-degrading enzymes) and the physicochemical structure of prallethrin are also influential on bioavailability. In this context, the LD_{50} value and bioavailability may be correlated. The residue potential of prallethrin is considered to be low. In cases of poisoning, especially in the event of acute high-dose exposure, traditional treatment options are chosen, such as symptomatic interventions and applications to reduce/limit absorption, increase microsomal enzyme activity and accelerate metabolism/excretion with barbiturates. The present study not only provides significant input on the toxic mechanism of prallethrin, its toxicity in case of exposure, and precautions to be taken for its safe use, but also provides insight into the preparation of treatment protocols for cases of poisoning and constitutes a reference for future studies.

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SAŽETAK

Cilj je ovog istraživanja bio odrediti toksikokinetički profil oralne i intraperitonealne primjene praletrina, lijeka koji se često upotrebljava jer nije štetan za okoliš. S tom je svrhom praletrin primijenjen u 42 ženke BALB/c miševa stare 2 – 3 mjeseca, tjelesne mase 35 – 40 grams, u dozi od 2 mg/kg intraperitonealno i oralno. Miševi su nasumično podijeljeni u dvije skupine sa po 21 jedinkom u svakoj skupini. Dok je u skupini 1 praletrin primijenjen u dozi od 2 mg/kg u dimetil-sulfoksidu intraperitonealno, životinje u skupini 2 primile su pojedinačnu dozu od 2 mg/kg praletrina u dimetil-sulfoksidu oralno. Nakon intraperitonealne i oralne primjene praletrina, intrakardijalna krv uzeta je u heparinizirane epruvete u određenim intervalima. Koncentracije plazmatskog praletrina izmjerene su plinskom kromatografijom upotrebom mikroelektronskog detektora. Za oralno primijenjen praletrin maksimalna koncentracija u plazmi (C_{max}) bila je 3,66 ± 0,78 ng/mL, vrijeme do postizanja maksimalne koncentracije (t_{max}) 0,60 ± 0,05 h, poluvijek ($t_{1/2\beta}$) 10.20±1.24 h, srednje vrijeme zadržavanja (MRT) 11,72 ± 1,51 h, površina ispod krivulje ($AUC_{0\rightarrow\infty}$) 15,19 ± 4,43 ng/h.mL i bioraspoloživost (F) 39,86 %. Za intraperitonealno primijenjen praletrin vrijednost $t_{1/2\beta}$ bila je 7,46 ± 0,54 h, MRT-a 8,05 ± 0,64 h i $AUC_{0\rightarrow\infty}$ 38,10 ± 5,80 ng/h.mL. Rezultati pokazuju da je oralna bioraspoloživost praletrina manja nego kod mnogih drugih piretroida, poput flumetrina i cipermetrina. U usporedbi s drugim pesticidima u istoj skupini, poput fenotrina, poluvijek i srednje vrijeme zadržavanja praletrina u organizmu nisu kratki ako se primjenjuju na oba načina. Rezultati također pokazuju i da je izloženost visokim dozama praletrina rizična zbog mogućeg otrovanja. S obzirom na ustanovljene toksikokinetičke pokazatelje, ovaj rad pokazuje da su potrebna daljnja istraživanja radi boljeg razumijevanja toksičnosti praletrina u sisavaca.

Ključne riječi: praletrin; toksikokinetika; intraperitonealna primjena; oralna primjena; miševi