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Tremor-Salivation Syndrome in Canine following Pyrethroid/Permethrin Intoxication

Sigal Klainbart[1], Yael Merbl[1], Efrat Kelmer[1], Olga Cuneah[2], Nir Edery[3] and Jakob A Shimshoni[2]*

[1]The Koret School of Veterinary Medicine, The Hebrew University of Jerusalem
[2]The Department of Toxicology, Kimron Veterinary Institute, Bet-Dagan
[3]The Department of Pathology, Kimron Veterinary Institute, Bet-Dagan

Abstract

A 17-month-old male King Charles cavalier was presented with acute onset of generalized body tremors, facial twitching and salivation after being exposed to 2 different classes of compounds of the pyrethrins/pyrethroids group as well as to imidacloprid. Bifenthrin toxicity was confirmed by gas chromatography mass spectrometry. Pyrethroid toxicosis in dogs is to the best of our knowledge rarely reported in the literature. The dog displayed neurological signs highly characteristic of Tremor-Salivation-syndrome associated with pyrethroid toxicosis. The plasma half-life of bifenthrin in dogs was 7.6 hr). Initial therapy consisted of diazepam, methocarbamol and IV fluids, followed by general anesthesia with isofluran and diazepam CRI. Supportive nursing care was provided as needed. Twenty-four hours post admission, the dogs was no longer under general anesthesia. Seventy two hours post admission the dog was discharged had no menace response, was alert and responsive when stimulated, ataxic while walking and showed normal eating behavior.

Introduction

Pyrethrins are naturally occurring cyclopropyl-ester phytotoxins possessing marked insecticidal properties and are mainly found in the flowers of certain *Chrysanthemum* species [1,2]. Pyrethrum is a mixture of 6 natural esters called pyrethrins. Naturally occurring pyrethrins are rapidly degraded by light, therefore, synthetic analogues known as pyrethroids, were developed to improve stability [1,2]. Pyrethroid use became widespread in the 90's and for decades was the most commonly used home and garden insecticides in the U.S [3,4]. Pyrethroids alter the normal function of the insect nervous system primarily by slowing the opening and closing of voltage- sensitive sodium channels resulting in hyperexitability state. This action on the nervous system leads to the adverse clinical signs seen in pyrethroid toxicosis [5-8]. Prior to 1970, little data was available on acute toxicity in mammals from pyrethrins and synthetic pyrethroids known at that time [8]. The discovery of various new pyrethroids with the potential for widespread use in agriculture, stimulated extensive research on pyrethroid toxicity [8]. The pyrethroids as class exhibit very low levels of systemic toxicity following dermal exposure as compared to the moderate toxicity observed due to oral exposure [1,4]. In mammals, two distinct toxic syndromes have been described [1,4]. The T-syndrome named after the prominent symptom of whole-body tremors, is induced by pyrethrins and non-cyano-pyrethroids (e.g., permethrin); and the CS-syndrome, characterized by choreoathetosis and salivation induced by deltamethrin and most other cyano-pyrethroids. Some pyrethroids produce both tremors and salivation and were therefore classified as intermediate TS-syndrome inducing agents [9,10]. Pyrethrins and pyrethroids are fat soluble compounds that undergo rapid metabolism and excretion after oral or dermal absorption in most mammals [1]. Following absorption, they are metabolized by hepatic microsomal esterases and oxidases. This is followed by rapid hepatic hydroxylation and conjugation into glucuronides, sulphates, or amino acids which are readily excreted into urine [11]. Cats, as oppose to other mammals appear to be particularly sensitive to the effects of pyrethroids, mainly permethrin, a class I pyrethroid insecticide commonly used in "spot on" pesticide preparations manufactured for flea control [12-19]. Deficiency of hepatic glucuronosyl transferase has been suggested as a potential explanation for their increased sensitivity [11,12]. Numerous reports have been published in the veterinary literature regarding permethrin toxicity in cats, however to the best of our knowledge, pyrethrin or pyrethroid toxicities are rarely reported in dogs [20,21]. This Case report describes acute pyrethroid toxicity in a king Charles cavalier dog.

Case Report

A 17-month-old male King Charles Cavalier weighing 7 kg was referred to the Hebrew University Veterinary Teaching Hospital (HUVTH), with a chief complaint of generalized tremors, ataxia, tachycardia and tachypnea. Forty-eight hours before clinical signs appeared, Biospotix® spray (geraniol essential oils) and Advantage spot on (100 mg/mL imidaclopride and 25 mg/mL moxidectin) were applied on the dog's skin. Furthermore, the owner's household was sprayed against insects using a commercial pyrethroid preparation (Admiral®c) 24 hours before clinical signs appeared. The dog was otherwise healthy, fully vaccinated, lived in an apartment and leash-walked. On the morning of admission, the dog presented to its referring veterinarian due to swaying, hypersalivating and vomiting. It did not fully respond to its owners, and progressed to a single seizure episode. Physical examination by the referring veterinarian revealed tachycardia (160 beats per minute), panting and tachypnea, generalized tremors, and four limb ataxia. At the clinic, the dog vomited once. The veterinarian suspected toxicosis, and therefore the dog was treated with a bolus of isotonic crystalloids (LRS, 120 mls IV),

***Corresponding author:** Jakob A Shimshoni, The Department of Toxicology, Kimron Veterinary Institute, Bet-Dagan, Israel, Tel: +972-3-9688911; Fax: +972-3-9681730; E-mail: jakobshimshoni@gmail.com

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metoclopramide (0.5 mg/kg SQ), diazepam (0.5 mg/kg IV), 3 activate charcoal tablets, and was referred to the HUVTH. On presentation, the dog was obtunded and non-ambulatory, with a rectal temperature of 38.8°C and panting. Engorged mucous membranes were also noted. Neurological examination revealed an absent bilaterally menace response, generalized body tremors as well as facial twitching were noted with four limb ataxia. Spinal reflexes, anal reflex, and tail muscle tone were intact. Abnormalities on CBC revealed a mild leukocytosis (WBC 17.15*109 cells/L [reference range (RR), 5.2-13.9*109 cells/L]); thrombocytopenia (70*109 cells/μL [RR, 143.3-400 *109 cells/μL]); and mean platelet volume of 29 fL [RR, 7.0-11.0fL]. Examination of the blood smear revealed neutrophilia (13.97*109 cells/L [RR, 3.9-8.0*109 cells/L]), platelet count was estimate was lower than normal, and platelets were estimated to be enlarged. The thrombocytopenia and elevated MPV are frequently observed for the aforementioned dog breed. Serum biochemistry profile was within the normal reference intervals. The dog was hospitalized in the intensive care unit and thoroughly washed with liquid detergent solution in warm water. An IV-catheter was placed in the cephalic vein, and the dog was treated with diazepam (0.5 mg/kg IV), methocarbamol (75 mg/kg slow IV), administered twice, 15 minutes apart. Since no improvement was seen and the dog exhibited ongoing severe tremors, anesthesia induction with propofol (1 mg/kg, IV) was performed and maintained with 100% oxygen and isoflurane (1 lit/min); followed by diazepam CRI (1 mg/kg/hr) and LRS (5 mls/kg/hr) administration. Nursing care included a forced warm air blanket, position changes, oropharyngeal antiseptics, suctioning of the ETT, and corneal lubrication. An indwelling urinary catheter was placed. Amoxicillin/clavulanic acid (15 mg/kg IV q12 h), and enrofloxacink (10 mg/kg slow IV, q24 h) were administrated due to owner's suspicion of vomiting and aspiration on the way to the hospital. Cultures obtained from broncho-alveolar lavage subsequently grew alpha hemolytic *Streptococcus spp*. and *Mycoplasma canis* susceptible to the above antibiotics. The dog was further anesthetized for 18 hours. Two attempts to waken the dog during this time were associated with severe tremors and twitching. Twenty-four hours post admission, the dogs was no longer under general anesthesia. While recovering, the dog vomited again, had mild tremors, twitching and meiosis and was assessed as stuporous. Methocarbamol (50 mg/kg slow IV) was re-administered as well as maropitant[l] (1 mg/kg SQq24hrs), while diazepam CRI was continued for an additional 24 hours. Sixty hours post admission there were almost no twitching signs and during awakening the dog displayed paddling in all 4 limbs, and while asleep there were no involuntary movements. During hospitalization vital signs and blood pressure were normal at all times. Seventy two hours post admission the dog was discharged to his owners care with continued antimicrobial treatment (amoxicillin/clavulanic acidm, 20 mg/kg, PO, q12hrs for 10 days). At discharge, it had no menace response but was alert and responsive when stimulated outside, ataxic while walking, and eating willingly. At a follow up 2 days, 1 week, and 1.5 months post discharge, the owners reported the dog completely recovered. During Hospitalization, whole blood was withdrawn each day (3 ml) for qualitative analysis of bifenthrin concentration. Bifenthrin was quantified in plasma according to the method published by Shimshoni et al. [22]. In brief, 1 mL of plasma was extracted with 4 mL acetonitrile and vortex mixed for 1 min with 500 mg $MgSO_4$ and 250 mg NaCl, Following centrifugation for 5 min at 4000 g, 4 mL of the organic layer was transferred to a clean test tube containing 50 mg Bondesil PSA and 50 mg $MgSO_4$ and vortex mixed for 1 min. Subsequently the sample was centrifuged for 5 min at 4000 g and the supernatant transferred to a clean tube and evaporated to dryness under a stream of N_2 at 40°C. The dried residual was reconstituted with 0.25 mL ethylacetate[o] and subjected to GC/MS analysis[p]. For quantitative analysis, standard stock solutions of bifenthrin[q] were prepared in methanol at a concentration range of 0.1-10 μg/mL. Calibration curves were performed utilizing blank plasma samples spiked with bifenthrin at concentration range of 0.01-5 μg/mL. The recovery of the analytical procedure was calculated with four replicates of 1 mL plasma spiked with 0.1 μg and 1 μg bifenthrin yielding a recovery of 75% and 80% respectively. Limits of detection (0.01 μg/mL) were calculated with blank samples as 3 times the signal to noise ratio and limit of quantization (0.03 μg/mL) as 10 times the signal to noise ratio. The quantitative analysis of bifenthrin was made on a model 7890A gas chromatograph[r] equipped with a single quadruple 5975C VL-MSD, nitrogen phosphorus detector and a J&W Megabore 5% phenyl-95% methyl silicone capillary column (0.25 μm* 15 m* 0.25 mm)[r]. The temperature program for identifying bifenthrin was as follows: injector temperature, 220°C; initial temperature, 80°C for 0 min; gradient of 17 °C/min until 180°C; gradient of 10°C until 250°C; gradient of 20°C until 300°C. The MS parameters were set as follows: source temperature, 230°C; transfer line, 230°C; positive ion monitoring; EI-MS (70 eV). Bifenthrin eluted with a retention time of 18.45 min. Figure 1 depicts bifenthrin plasma concentration (mg/L) versus time post hospital administration.

Discussion

The broad-spectrum antiparasitic and insecticidal activity of pyrethrins and pyrethroids has revolutionized pest control in veterinary medicine. Effectiveness, low cost, the conception of "natural" compounds and low levels of systemic toxicity following dermal exposure had made those compounds the most commonly used home and garden insecticides in the U.S [1,3]. In the last decade, many reports describing permethrin toxicity in cats emerged, whereas canine intoxications were seldom reported in the literature [12-21]. The dog presented in this case was exposed to 2 different pyrethrins/pyrethroids compound calsses, namely Admiral®, consisting of 7.9% bifenthrin and Biospotix®, an insecticide containing 0.2% pyrethrum. Furthermore, Advantage® spot on (10% imidacloprid) was applied. The clinical signs observed were highly characteristic of pyrethroid intoxication. Consequently, the dog was treated with an anti-convulsant (diazepam), tremor control and supportive care, eventually leading to a full recovery. Diagnosis of pyrethrin toxicosis is generally based on history of exposure and typical clinical signs, which commonly include hyperexcitability, generalized tremors and seizures [12-21]. The dog in this case exhibited clinical signs consistent with the TS-syndrome, most likely explained by concomitant exposure to pyrethrum and bifenthrin. Moreover, since pyrethroids and imidacloprid are metabolized via the liver by a conjugation pathway, we suspect this pathway was "overwhelmed" by

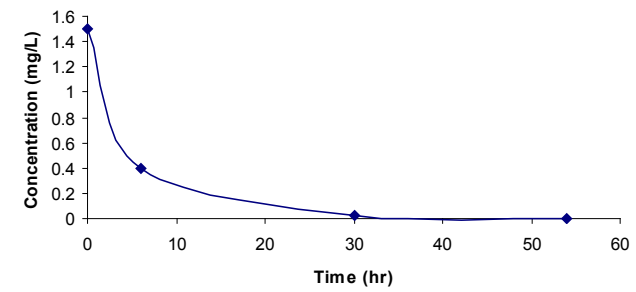

Figure 1: Plasma concentration vs time curve of bifenthrin.

the amount of compounds to be metabolized, resulting in enhanced toxicity leading to the observed clinical signs. Blood samples were withdrawn daily from the dog, in order to monitor the pyrethroid and permethrin plasma levels, however only bifenthrin could be detected and quantified over a time period of 54 hr from the time of hospital admission. Due to the 4 times shorter half life of bifenthrin as compared to permethrin in rats, it is not surprising that permethrin could not be determined in the present plasma samples [23]. Due to the scarce reports of canine intoxication with bifenthrin, the present case study reveals for the first time bifenthrin plasma elimination course, yielding a half-life of 7.6 hr (Figure 1). Few studies in rats were conducted in order to elucidate the correlation between bifenthrin plasma levels and neurotoxicity [4,23]. At plasma levels of 40 µg/L and 269 µg/L a 20% and 80% decrease in motor function (a parameter of neurological toxicity) was observed at 4 hr post drug exposure respectively. A 20% and 80% reduction of motor activity at 7 hr post drug exposure was observed at plasma concentrations of 16.6 µg/L and 117 µg/L respectively. The maximal plasma concentration determined in the present study (150 µg/L) 24-30 hr post bifenthrin exposure exceeded the toxic levels reported in the rats, explaining the severe clinical signs observed in the present case study. Pyrethroids are reportedly eliminated in the first 12-24 hrs after absorption [4,23]. Furthermore, since the relationship between neurotoxicity and bifenthrin plasma levels could be described by a counterclockwise hysteresis curve, CSF concentrations might serve as a better predictor of bifenthrin toxicity than plasma levels [23]. This may explain why in the present case study, clinical signs persisted 72 hrs post-admission, despite declining bifenthrin blood levels during hospitalization (Figure 1).

In conclusion, this study provides detailed description of severe canine bifenthrin toxicity and the successful treatment thereof leading eventually to the full recovery of the dog. Furthermore, bifenthrin half life in canine was determined for the first time following extravascular exposure to toxic bifenthrin dosage. The dog displayed neurological signs highly characteristic of TS-syndrome associated with pyrethroid toxicosis.

Foot Notes

a. Biogance laboratories, Angers, St Leonard, France.

b. Bayer Animal Health, Germany.

c. Makhteshim-Agan Industries Ltd, Beer Sheva, Israel.

d. Impedance analyzers Abacus or Arcus, Diatron, Wien, Austria.

e. Cobas-Mira, Roche, Mannheim, Germany, at 37°C.

f. Assival, Teva industries, Petach-Tikva, 49131, Israel.

g. Ortoton, Merckle Recordati GmbH, Ulm, Germany.

h. Diprofol, Taro Pharmaceutical, Yakum, Israel.

i. Hartmann's solution, Cure Medical, Emek Hefer, Israel.

j. Augmentin, SmithKline Beecham PLC, Brentford, UK.

k. Baytril, Bayer Healthcare, Leverkusen, Germany.

l. Cerenia, Pfizer PGM, Kent, NJ, USA.

m. Augmentin, SmithKline Beecham PLC, Brentford, UK.

n. Karnieli Ltd. Veterinary Division, Q. Tivon, Israel.

o. Sigma-Aldrich Ltd. Park Rabin Rehovot, Israel.

p. Model 7890A gas chromatograph, Agilent Technologies, Santa Clara, USA.

q. Supelco analytical, Sigma-Aldrich., Park Rabin Rehovot, Israel

r. Agilent Technologies, Santa Clara, USA.

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