

Case Report

Bifenthrin Toxicity in a Dog

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Abstract

A 17-month-old male King Charles cavalier was presented with acute onset of generalized body tremors and facial twitching after being exposed to 2 different compounds of the pyrethrins/pyrethroids group and imidacloprid. Bifenthrin toxicity was confirmed by gas chromatography mass spectrometry. Initial therapy consisted of diazepam, metacarbamol and IV fluids, followed by general anesthesia with isofluran and diazepam CRI. Blood specimens were collected for following bifenthrin blood levels over time. Supportive nursing care was provided as needed. Twenty-four hours post admission, the dog 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. Pyrethroid toxicosis in dogs was to our best knowledge never been reported before. We describe the clinical signs, bifenthrin pharmacokinetics during hospitalization, and the successful treatment of bifenthrin toxicity in a young dog.

INTRODUCTION

Pyrethrins are naturally occurring cyclopropyl ester insecticides (pyrethrins I and II, cinerins I and II, and jasmolins I and II) highly prevalent in the flowers of *Tanacetum* (*Chrysanthemum cinerariaefolium*) and related species [1,2]. Naturally occurring pyrethrins are rapidly degraded by light, therefore, synthetic analogues known as pyrethroids, were developed to improve stability [3]. Pyrethroid use became widespread in the 1800's and for decades was the most commonly used home and garden insecticides in the U.S [3,4,5]. Pyrethroids alter the normal function of the insect nervous system primarily by slowing the opening and closing of voltage-sensitive sodium channels resulting in hyperexcitability. This action on the nervous system lead to the adverse clinical signs seen in pyrethroid toxicosis [6,7].

Prior to 1970, scarce data was available on acute toxicity in mammals from pyrethrins and pyrethroids known at that time [8]. The discovery of various new pyrethroids with the potential for widespread use in agriculture, stimulated extensive studies on pyrethroid toxicity both for academic research and for agriculture usage of insecticide products. In contrast to the moderate oral toxicity of most pyrethroids in rats, the pyrethroids exhibit very low levels of systemic toxicity following dermal exposure [9].

In mammals, two distinct toxic syndromes have been described: the T- syndrome named after the prominent symptom of whole-body tremors is induced by pyrethrins and noncyano-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 [10].

Pyrethrins and pyrethroids are fat soluble compounds that undergo rapid metabolism and excretion after oral or dermal absorption in most mammals. 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. Cats, as opposed to other mammals appear to be particularly sensitive to the effects of pyrethroids, most prominently permethrin, a class I pyrethroid insecticide commonly used in "spot on" pesticide preparations manufactured for flea control. Deficiency of hepatic glucuronosyl transferase has been suggested as a potential explanation for their increased sensitivity [7,12]. Numerous reports have been published in the veterinary literature regarding permethrin toxicity in cats [7,12-26]. but to our knowledge, pyrethrins or pyrethroid toxicity has not been reported yet in dogs. This Case report describes acute pyrethroid toxicity in a King Charles cavalier dog.

CASE REPORT

A 17-month-old intact 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 and Advantage spot on were

applied on the dog's skin. In addition, his household was sprayed using a commercial pyrethroid (Admiral®) 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 at 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 ml IV), 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 38.80 °C, panting, and a heart rate of 160 beats per minute. Engorged mucous membranes were noted. Neurological examination revealed an absent menace response bilaterally, generalized body tremors and 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 17.15×10^9 cells/L [reference range (RR), 5.2-13.9 $\times 10^9$ cells/L]); thrombocytopenia (70×10^9 cells/ μ L [RR, 143.3- 400 $\times 10^9$ cells/ μ L]); and mean platelet volume of 29 fL [RR, 7.0-11.0 fL]. Examination of the blood smear revealed neutrophilia (13.97×10^9 cells/L [RR, 3.9-8.0 $\times 10^9$ cells/L]), platelet count was estimate low than normal, and platelets were estimate to be enlarged. The thrombocytopenia and elevated MPV were attributed to its breed. Serum biochemistry profile^e was within reference intervals. An IV catheter was placed in the cephalic vein, and the dog was treated with diazepam^f (0.5 mg/kg IV). The dog was hospitalized in the intensive care unit and thoroughly washed with liquid detergent solution in warm water. Methocarbamol^g (75 mg/kg slow IV), was administered twice, 15 minutes apart. Since no improvement was seen and the dog exhibited ongoing severe tremors, anesthesia induction with propofol^h (1 mg/kg, IV) was performed, an endotracheal tube (ETT) was placed and anesthesia was maintained with 100% oxygen and isoflurane (1 lit/min). Diazepam CRI (1 mg/kg/hr) was initiated and LRS was administered at 5 ml/kg/hr. 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 acidⁱ (15 mg/kg IV q12h), and enrofloxacin^k (10 mg/kg slow IV, q24h) were administered due to owner's suspicion of vomiting and aspiration on the way to the hospital. Cultures obtained from broncho-alveolar lavage subsequently grew *Streptococcus spp.* alpha hemolytic and *Mycoplasma canis* susceptible to the above antibiotics. The dog was anesthetized for 18 hours. Two attempts to recover the dog during this time were associated with severe tremors and twitching. Twenty-four hours post admission, the dog was no longer under general anesthesia. While recovering, the dog vomited again, had fine tremors and twitching, miosis, and was assessed as stuporous. Methocarbamol (50 mg/kg slow IV) was re-administered and diazepam CRI was continued for an additional 24 hours. Maropitant^l (1 mg/kg SQ q24hrs) was added. Sixty hours post admission there were almost no twitching. While awake, the dog exhibited 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. A multidrug resistance protein 1 (MDR1) genotype test^m was negative. Seventy two hours post admission the dog was discharged to his owners care with continued antimicrobial treatment (amoxicillin/clavulanic acidⁿ, 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 follow up 2 days, 1 week, and 1.5 months post discharge, the owners reported the dog was back to normal. During Hospitalization, whole blood was withdrawn each day for bifenthrin level determination according to the method published by Shimshoni et al [29].

DISCUSSION

The broad-spectrum antiparasitic activity of pyrethrins and pyrethroids has revolutionized parasitic control in veterinary medicine. Effectiveness, low cost, the conception of a "natural" compound, 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 [3,4,5]. In the last decade, reports describing permethrin toxicity in cats frequently emerged, whereas toxicity case reports in dogs are lacking [7,12-26]. To the best of our knowledge this is the first report describing pyrethroid toxicity in a dog.

The dog presented in this case was exposed to 2 different compound of the pyrethrins/pyrethroids group, namely Admiral[®], an insecticide comprised of 7.9 % bifenthrin and 1 % condensed naphthalene sulfonate and Biospotix[®], an insecticide comprised of natural pyrethrum 0.2 %, geraniol 0.5 % (v/v) (containing termézetespiretingeránium, lavender essential oils, citronella, aqua exipient, and alcohol qsp.) Concomitantly, Advantage[®] spot on (10% imidacloprid, 0.1% butylhydroxytoluene, benzyl alcohol) was applied. The dog was treated with an anti-convulsing agent (diazepam) while supportive care together with tremor controlling means, lead eventually 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 [13]. The dog exhibited clinical signs compatible with pyrethrin toxicity (swaying, hypersalivation, seizures, tremors, twitching of the facial muscles, four limb ataxia and paddling) consistent with the TS-syndrome. The dog's exposure to bifenthrin could not be quantitatively determined, since the dog was potentially exposed via the oral and dermal route to an unknown bifenthrin dosage. Since pyrethroids and imidacloprid are metabolized via the liver by a conjugation pathway, we suspect this pathway was "overwhelmed" by the amount of compounds to be metabolized, resulting in enhanced toxicity. Blood was withdrawn daily from the dog for determination of bifenthrin plasma levels, enabling to determine its plasma half-life. There is very little data in the literature regarding bifenthrin blood levels in toxicosis. In one report [27] rats were exposed to bifenthrin, reporting a 20% and 80% decrease in motor function (a parameter of neurological toxicity), observed at a plasma concentrations of 40 μ g/L, and 269 μ g/L, respectively, at 4 hr post exposure. Plasma concentrations inducing 20% and 80% reduction of motor activity at 7hr post exposure were 16.6 and 117 μ g/L

concentration vs. time Curve

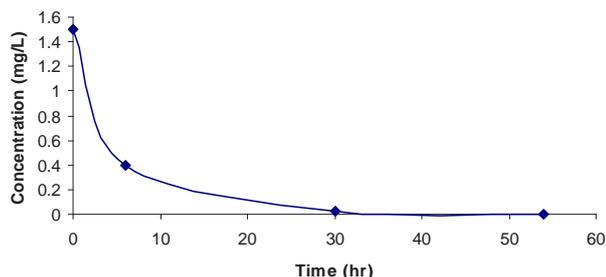


Figure 1 Plasma concentration vs. time curve following extravascular exposure to bifenthrin.

respectively. In the present study, the dog was admitted 24-30hr post bifenthrin exposure, displaying a peak blood level of 150 µg/L; hence a much higher initial plasma concentration as compared to the toxic levels reported in the aforementioned study in rats. Pyrethroids are reportedly eliminated in the first 12-24hr after absorption.²⁸ In the present case study, bifenthrin plasma levels dropped dramatically over a time period of 30 hr with a half-life of 7.6 hr (Figure 1). Several studies suggest that toxicity from pyrethroids occurs when central nervous system pyrethroid concentrations exceed threshold quantities [27]. Since the clinical signs persisted long after the elimination of bifenthrin from the plasma compartment, cerebrospinal fluid levels might present a better predictor of bifenthrin toxicity [27]. In conclusion, this is the first report of pyrethroid toxicity in a dog that was exposed to 2 types of pyrethroids and imidacloprid. The dog exhibited classic neurological signs of pyrethroid toxicity and was fully recovered following symptomatic and supportive care.

FOOTNOTES

- 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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