Retrospective Evaluation of Factors Associated with the Morbidity and Outcome of Permethrin Toxicosis in Cats

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ABSTRACT

Cats exposed to permethrins, which are present in ectoparasite control products intended for dogs, may develop signs of toxicity. This retrospective study describes the clinical course of permethrin toxicosis in cats, and examines if methocarbamol treatment had improved its morbidity and outcome. The study included 61cats diagnosed with permethrin toxicosis presented to the Hebrew University Veterinary Teaching Hospital. In most cases (89%), the owners have inadvertently applied anti-flea spot-on products designated for dogs to their cats, resulting in toxicosis-related clinical signs. These most common signs included tremors and twitching (90%), hypothermia (39%), seizures (30%), tachypnea (25%), abnormal mentation (18%), ataxia (16%), ptyalism (11%) and mydriasis (10%). Treatments included whole body bathing (85%), along with supportive care, sedatives and muscle relaxants. Some cats (5%) required general anesthesia. The median hospitalization period was one day (range, 1-9). The survival rate was 100%. Methocarbamol (50-330 mg/kg, slow IV PRN) was administered to 41 cats (67%), which had a shorter (P=0.032) hospitalization period (median, 1 day) compared to that of cats untreated with methocarbamol (2 days). Cats with seizures treated with methocarbamol had a shorter (P=0.08) hospitalization period compared to that of cats untreated with methocarbamol. In conclusion, permethrin toxicosis occurs in cats, mainly by inadvertent application of canine flea insecticide spot-ons. The overall prognosis of such cases, when treated intensively was excellent. Herein, methocarbamol treatment of cats with this toxicosis, in general, as well as particularly in those presenting seizures, decreased their morbidity, as reflected by a shorter hospitalization period.

Keywords: Pyrethroid; Methocarbamol; Feline; Poisoning; Seizures.

INTRODUCTION

Flea control poses a major challenge for companion animal owners (1). Permethrin is a synthetic pyrethroid substance, commonly included in flea-control products for companion animals. Pyrethroids act primarily on the nervous system, although their specific mechanism of activity in mammals is uncertain (2). With incoming action potentials, permethrin binds to and blocks sodium channels in their opened state. This leads to inhibition of conduction, preventing depolarization, resulting in repeated neuronal discharge. It appears that pyrethroid toxicosis in mammals results from disturbed function of sodium and chloride channels function rather than structural damage in excitable nerve and muscle cells (2).

Pyrethrins are naturally occurring compounds, including combinations of insecticidal esters (i.e., pyrethrins, cinerins and jasmolins), extracted from the flowers of *Chrysanthemum cinerariaefolium* and related plant species (1). The synthetic pyrethrin analogues are termed pyrethroids, which are modified to remain stable in sunlight, and are developed to broaden their pesticidal activity spectrum (3,4). Pyrethroids, including permethrin and flumethrin, are effective insecticides, and have a low toxicity index in most mammalian species,

including dogs (5). However, cats, show increased sensitivity to pyrethroids, mainly to permethrin, although its minimal lethal dose in cats has not been established (3). It is generally believed that the major contributing mechanism to its toxicity in cats is their deficiency or defect in hepatic glucuronyl transferase activity, responsible for detoxification of several compounds in mammals, and additionally, decreased hepatic ester hydrolysis rate (1, 3, 5). Insecticide products containing 45%-65% permethrin are intended for use in dogs only (6), while products suitable for cats contain concentrations <0.1% permethrin (1). Exposure to small amounts of concentrated permethrin can cause toxicosis in cats (1). Their exposure to permethrin-containing insecticides intended for use in dogs occurs typically by inadvertent application by their owners, but additionally, the risk of permethrin toxicosis in cats increases when cats are in close physical contact with dogs recently treated with such products, or when cats lick and groom these dogs (1). In addition, house-hold pest control is often performed with permethrin-containing insecticides, also posing risk of exposure (1, 7).

The severity of clinical signs of pyrethroid toxicosis in cats varies between individuals, ranging from no signs to severe toxicosis, and clinical signs appear within several hours of exposure, but might be delayed up to 72 hours (3). These range from hyperesthesia and mild focal tremors, muscle fasciculation and twitching, to generalized tremor and muscle fasciculation and ataxia, due the pyrethroid effect at the presynaptic nerve endings, and to seizures and convulsions. Ptyalism, mydriasis and hyperthermia are also common (3), while less common clinical signs include respiratory distress, vomiting, diarrhea, anorexia, temporary blindness, confusion and disorientation, head tilt, lethargy and death (1, 8). The London Centre of the Veterinary Poisons Information Service received an average of 50 inquiries annually between 1992 and 2000 regarding animal exposure to pyrethroids and pyrethrins, while between January to October of 1999, 98 feline and 17 canine permethrin exposure cases were recorded (2). In cats, the most common clinical signs of toxicosis observed included convulsions (33%), tremors (24%), twitching (22%) and ptyalism (21%) (2).

Permethrin toxicosis in cats is diagnosed based on a history of recent exposure, along with the typical clinical signs. Routine laboratory tests in such cases show non-specific abnormalities, although serum muscle enzyme activity might increase due to tremor and seizures (2).

Treatment of permethrin toxicosis consists of muscle tremor and seizure control, along with supportive care, including intravenous (IV) fluids to combat hyperthermia and dehydration secondary to the increased muscle activity and protect the kidneys from injury secondary to seizure-induced muscle injury myoglobin breakdown products (1,2). Whole body bathing is indicated in cases of dermal exposure (2). In severe cases, general anesthesia and positive pressure ventilation (PPV) are needed (8). In addition, treatment with intravenous lipid emulsions has been reported for this toxicosis with promising results (9,10).

Methocarbamol, a centrally acting muscle relaxant, was used successfully by IV constant rate infusion (CRI) to treat three cats with permethrin toxicosis, and was anecdotally mentioned in a report of such cases in Australia, UK and USA (1, 3, 6).

This retrospective study describes the clinical course of permethrin toxicosis in a relatively large cohort of cats, and examined factors associated with their morbidity and mortality, including the impact of methocarbamol therapy on the outcome.

MATERIALS AND METHODS

The medical records of cats admitted to the Hebrew university Veterinary Teaching Hospital (HUVTH) between 2007 and 2018 were retrospectively investigated for cases of permethrin or pyrethroid toxicosis in cats, requiring hospitalization, which had complete records. The search was done using two methods; 1) Prior to implementation of the computerized medical record system (years 2007 to 2016), the hospital's computerized discharge summaries were searched for several relevant keywords (e.g., pyrethroid, pyrethrin, permethrin and methocarbamol) and commercial names of permethrin- or other pyrethroid-containing insecticides available in Israel (e.g., Advantix, Duowin, as well as Soltif, which contains flumethrin). Using this method, toxicosis cases of cats that had died or were euthanized during this period were not identified. As of year 2017, the computerized medical record system having been fully integrated by the HUVTH, and from that time onward an electronic search was carried out according to the diagnosis, and hence, all cases, whether discharged alive or those that died or were euthanized during hospitalization were identified. Cats were included if their owners reported exposure to a pyrethroid-

containing product, and if they showed the typical clinical signs of pyrethroid toxicosis.

Data collected from the medical records included the signalment, details of the product that had induced the toxicosis (i.e., commercial name, active insecticides and dose route of exposure), time-periods from exposure to onset of clinical signs and to presentation to the HUVTH. The historical and presenting clinical signs upon admission to the HUVTH, the administered treatment, occurrence of complications, the length of hospitalization and the outcome (i.e., discharged alive, died or euthanized) were saved.

Statistical analysis

The distribution pattern of continuous variables was examined using the Shapiro-Wilk's test. Continues variables were compared between two groups using the Student's *t*-test (for normally distributed data) and the non-parametric Mann-Whitney test (for non-normally distributed data). Categorical variables were compared between two groups by the Fisher's exact test or chi-square test. Two-way ANOVA was used to examine the associations between two independent categorical variables and dependent quantitative variables (i.e., methocarbamol treatment or presence of seizures, and the length of hospitalization). Eta^2 was used to evaluate the effect of group size on the ANOVA results. All tests were 2-tailed, and in all, $P<0.05$ was considered significant.

RESULTS

The search of years 2007-2016 (prior to full integration of the computerized system in the HUVTH) identified 147 pyrethroid toxicosis cases in cats, of which only 81 medical records (55.1%) were available. Unfortunately, during preparation to collect the data from these medical records, 40 records that had been retrieved, were accidently lost during renovations in the HUVTH. Therefore, the study finally included the remaining 41 cases, as well 20 additional cases, identified through the computerized record system. Thus, the study included 61 cats; 25 females (41%; 17 neutered) and 36 males (59%; 31 neutered). Most were domestic shorthair cats (47; 77%), while 14 were pure-bred, including Persian (5; 8%), Maine Coon (4; 7%), Siamese (3; 5%) and British shorthair (2; 3%). The median age was 2 years (range, 0.3-13.0 years). The median body weight was 4.2 kg (range, 1.0-7.4 kg).

The mode and exposure route (n=54) included direct exposure by owners (41 cats; 76%), spot-on products (39 cats), collar and spray (1 each), while indirect environmental exposure was recorded in 13 cats, including home pest control products (5 cats), grooming a dog recently treated a permethrin-containing insecticide (Duowin, Virbac, Carros, France; 1 cat) and licking pest control products (7 cats). In the remaining seven cats, the medical record mentioned an exposure to permethrin, however the route of exposure was not recorded. All seven cats showed typical clinical signs.

The permethrin/pyrethroid-containing product brands (n=44) included Advantix (K9 Advantix; Bayer HealthCare, Kansas City, KA; 27 cats; 61%), Activyl tick plus (Virbac Limited, Suffolk, UK; 6 cats; 14%), Duowin contact (Virbac, Carros, France; 4 cats; 9%), Soltif (Solano, Beit Shean, Israel) and Vectra 3D (Ceva Santé Animale, Libourne, France (2 each; 5%), Hartz (Hartz Pest Control, Huston, TX), Killer (Rimi, Petach-Tikva, Israel) and Shoham (Rimi, Petach-Tikva, Israel; 1 each; 2%).

The permethrin concentration applied was recorded in nine cases, all treated with Advantix, including ampoules for dogs weighing 4-10 kg, containing 0.5 g permethrin (4 cats), for dogs weighing 10-20 kg, containing 1.25 g permethrin (3 cats) and for dogs weighing >25 kg, containing 2 g permethrin (2 cats). Nevertheless, the exact amount applied from each ampoule was unknown.

The median lag of time from exposure to onset of clinical signs (n=43) was eight hours (range, 0 to 24 hours). The onset of clinical signs was >24 hours from the exposure in six cats (14%), while in two cats (4%), signs appeared immediately post-exposure. In 24 cats (56%) the clinical signs lasted <12 hours.

The recorded clinical signs included generalized tremor and twitching (55 cats; 90%), hypothermia (24; 39%), seizures (18; 30%), tachypnea (15; 25%), abnormal mentation (13; 21%), ataxia (10; 16%), ptyalism (7; 11%), mydriasis (6; 10%), dehydration (4 cats; 7%), tachycardia, anorexia, and nasal discharge (3 cats each; 5%); hyperesthesia (2; 3%), vomiting, local alopecia on the spot-on application site, anxiety, third eyelid prolapse and obsessive nasal itching (1 cat each; 2%).

Whole body bath with shampoo or liquid soap was done in 52 cats (85%). Other treatments included intra-rectal diazepam (Assival, Teva Pharmaceutical Industries, Petach-Tikva, Israel; 9 cats; 15%), IV propofol (Lipuro, German Health Alliance, Berlin, Germany; 12 cats; 20%), IV midazolam

(Rafa pharmaceuticals, Jerusalem, Israel; 21 cats; 34%), IV or IM phenobarbital (Luminal, Desitin Pharma spol.s.r.o., Praha, Czech Republic; 12 cats; 20%), general isoflurane anesthesia for 24 hours (Isoflurane, Baxter, Deerfield, IL; 3 cats; 5%), IV mannitol (Osmitrol, Baxter, Deerfield, IL; 10 cats; 16%) and IV methocarbamol (Ortoton GmbH, Ibbenbüren, Germany; 39 cats; 64%).

The survival rate of this cohort was 100%. The median hospitalization period was 1 day (range, 0-9). The hospitalization period was significantly (P=0.038) shorter in methocarbamol-treated cats (median, 1 day; range 0-4) compared to those untreated with the drug (median, 2 days; range, 1-9). Whole body bath treatment did not decrease the occurrence of seizures (P=0.235), muscle tremor or twitching (P=0.637) at presentation, nor did it decrease the length of hospitalization (P=0.727).

Among the cats presented with seizures and treated with methocarbamol (n=14), the hospitalization period was shorter compared to that of those untreated with methocarbamol (n=4), although this did not reach statistical significance (P=0.08). Among the cats that presented with muscle tremor, and treated with methocarbamol (n=37), the length of hospitalization (median, 1 day; range 0-4) was significantly (P=0.031) shorter compared to those untreated with methocarbamol (n=18; median, 2 days; range, 1-9).

There was a strong (Eta^2=0.184) and significant (P=0.001) interaction between methocarbamol treatment and presence of seizures (as independent categorical variables) with the length of hospitalization time (as the dependent variable). The hospitalization period was significantly (P=0.001) shorter in cats presented with seizures and treated with methocarbamol (median, 1 days; range, 0-3) compared to cats with seizures and untreated with methocarbamol (median, 3 days; range, 2-9).

There were no interactions between methocarbamol treatment and presence of muscle tremor (P=0.175) or whole body bathing (P=0.14) as independent variables and the length of hospitalization as the dependent variable.

DISCUSSION

This is the largest description of permethrin toxicosis in cats in Israel and the first to evaluate the effectiveness of methocarbamol treatment in cats with this toxicosis. In most cats, signs of toxicity had occurred after exposure to spot-on insecticide products intended for dogs, inadvertently applied by their owners, likely because of ignorance or disregard to the intended use of such products. This exemplifies the need for owner education by their veterinarians. The most common commercial brand that caused the toxicosis herein was Advantix, despite being the most appropriately labeled product amongst the insecticide recorded in this study, including a rather large warning against use in cats, both on the package and on each individual ampoule. Advantix is a leading insecticide brand for use in dogs in Israel, which is likely why it was the most common brand involved in the toxicosis cases in the present study. Another contributing factor is possibly the similarity between its name and that of Advantage (Bayer Health Care, Kansas City, KS), which is approved for use in cats, but does not contain permethrin or other pyrethroids.

In a retrospective study of 42 permethrin toxicosis cases of cats, most exposures were due to permethrin spot-on flea products intended for dogs, applied directly to cats by their owners (8). In the present study, the results are similar, with 39 exposures (89%) through similar products. Veterinary permethrin-containing spot-on products for dogs are popular, and available over the counter in many pet stores in Israel, as well as worldwide. To the best of our knowledge, in Israel, no regulations exist prohibiting their sale in pet stores, despite their potential hazard to cats. Most products are labeled by their manufacturer as contra-indicated or unsafe in cats. Nevertheless, the label is often small, potentially being unnoticed by some pet owners. In addition, some products are not appropriately labeled. For example, the outer package may contain a warning against use in cats, while the inner package does not. In a survey in Australia (11), most permethrin toxicosis cases occur when using insecticide products purchased in supermarkets or pet stores, most likely because the owners were not educated properly. We strongly believe that insecticide products potentially hazardous to cats, as well as those with low safety margins should not be sold over the counter, and that regulatory measures should be considered, advancing owner education when these products are sold in pet stores and at veterinary clinics.

Cats that presented with permethrin toxicosis herein were mostly young, similar to previous findings (8). In a retrospective study of 87 permethrin toxicosis cases, clinical signs were evident only in cats aged <4 years, while >50% of the cats were aged <12 months (12). It is uncertain whether

younger cats are more susceptible to permethrin toxicity, or whether applying inappropriate flea-control products is done more commonly to younger cats due to unawareness amongst new cat owners, or because younger cats are infested by fleas more commonly than older ones, possibly because of outdoors access.

The nature and proportions of the clinical signs described herein, including seizures (30%), ataxia (16%), ptyalism (11%) and mydriasis (10%), are in agreement with previous findings (1,8). While the proportion of muscle tremor and twitching (90%) is similar to some previous studies (1,8), it is higher compared to another (13), as were the proportions of hypothermia (39%) (13) and tachypnea (25%) (8). Temporary blindness, previously reported (8), was unrecorded herein. Such differences between studies possibly result from the limited cohort sizes, or from misinterpretation of certain clinical signs by cat owners and veterinarians (e.g., generalized tremor and twitching vs. seizures), differences between the commercial insecticide products involved, or might be incidental.

The proportion of hypothermia at presentation was surprisingly relatively high (39%) despite the common occurrence of increased muscle activity (i.e., tremor and twitching, 90% and seizures, 30%), which is expected to lead to hyperthermia (14). This discrepancy possibly because in some cats, especially those requiring sedation when presented with severe signs, the rectal temperature was measured only after sedation or general anesthesia and whole-body bathing, in hospital or in referring clinics, which have lowered their body temperature. In addition, some cats were referred and were possibly administered sedatives prior to presentation to the hospital, and lastly, presence of shock, as a potential cause of hypothermia in some cats cannot be ruled out (8). Because permethrin acts on neuronal cell membrane sodium channels, hypothermia might increase its toxicity by increasing sodium channel activity, warranting rectal temperature monitoring, and actively warming hypothermic cats sustaining permethrin toxicosis (8).

This is the first study, to the best of our knowledge, to evaluate the effectiveness of methocarbamol treatment in cats with permethrin toxicosis. Methocarbamol, a skeletal muscle relaxant, belongs to a heterogeneous drug group commonly used to treat upper motor neuron syndrome-associated spasm and musculoskeletal conditions causing tenderness in humans and in dogs (15,16). In addition, methocarbamol appears to decrease the hospital stay of human trauma patients sustaining rib fractures (17). It is also reportedly used to treat metaldehyde, strychnine, carbamate, and tremorgenic mycotoxin toxicosis in dogs (18–21). The frequency of methocarbamol-related adverse reactions in cats is unknown; however, the likely side effects in dogs and cats include sedation, hypersalivation, emesis, lethargy, weakness, and ataxia (3, 22). This study includes, to the best of our knowledge, the largest cohort of methocarbamol-treated cats. Methocarbamol treatment in cats with permethrin toxicosis herein appeared safe, with no recorded adverse reactions, and was associated with a significantly shorter hospitalization period in general, and particularly in cats presenting seizures, suggesting that this drug might be recommended for treatment of this toxicosis in cats, and warranting future, prospective studies. The impression of many emergency clinicians is that cats with permethrin toxicity respond better to methocarbamol treatment compared to administration of benzodiazepines to "tone down" the extent of tremors, although both methocarbamol and benzodiazepines are skeletal muscle relaxants, and this study somewhat supports this clinical impression. Because the true mortality rate of this toxicosis could not be assessed in this study, we could not test weather methocarbamol decreased mortality rate; however, it may be worth mentioning that eight of the incomplete medical records that were lost during the earlier period of this study, prior to methocarbamol use, were of cats that died or were euthanized.

The major limitation of this study is the retrospective search methods for the medical records, which resulted in the selection bias towards cats that had survived the toxicosis. Hence, the 100% survival rate recorded herein should be accepted very cautiously, because some non-survivors were not included in this study. Nevertheless, the present results suggest that the outcome of permethrin toxicosis in cats in Israel is good, as no medical records were lost from 2017 onward, and among these cases there were no deaths. Our results differ from previous findings (11). In a survey amongst Australian veterinarians in 2010, 760 permethrin toxicosis cases were included, with 166 deaths (21%), which were all generally toxicosis-related, however, 39 cats (59% of all deaths) were euthanized prior to treatment due to owners' financial constraints (11), suggesting that in Israel euthanasia is performed less commonly based on limited finances in this toxicosis. The technical difficulties of searching for medical

records has also led to loss of cases, limiting the cohort size, while the retrospective nature of the study resulted in additional data loss, both of which had weakened the power of some statistical analyses. Lastly, this study was performed in a single academic teaching veterinary hospital, admitting both first opinion cases as well as referral, and its results should be applied cautiously to other clinical settings.

In conclusion, permethrin toxicosis is a potential threat to cats. In Israel it mainly occurred via inadvertent direct application of canine spot-on insecticide products by cat owners, warranting better education of cat owners and possibly stricter regulation of the sales of insecticide products through un-professional stores. Muscle tremors and twitching and seizures are the most common clinical signs. Permethrin toxicosis should be treated by supportive care, whole body bathing and anti-convulsive drugs and muscle relaxants. Methocarbamol appears to be very safe in cats, and was an effective treatment for permethrin toxicosis being associated with shorter hospitalization period.

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