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Case Report
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Successful management of fipronil toxicosis in two pet rabbits

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Abstract
Background: Antiparasitic drug toxicosis is commonly described in dogs and cats, but reports on the management of antiparasitic drug toxicities in pet rabbits are scarce. Here, we describe the successful clinical management of two pet rabbits with fipronil toxicosis.
Cases Description: The first case was a 5-month-old, intact female, rabbit that presented with the acute onset of seizures, obtunded mentation, and in lateral recumbency, while the second rabbit was a 1-year-old, intact male, rabbit that presented with anorexia and lethargy. In both cases, the owners reported to have administered a 0.5 ml fipronil vial topically on the skin as an antiparasitic drug between 4 and 6 hours prior to presentation. Complete blood count and serum biochemistry were unremarkable and both rabbits tested negative on *Encephalitozoon cuniculi* serology. Both animals were decontaminated by bathing with tepid water and dishwashing soap. The rabbit with seizures received on admission intravenous midazolam. In both cases, overnight hospitalization, intravenous isotonic crystalloid fluids, and assisted-feeding by oral syringe were provided until voluntary feeding was resumed. Both rabbits rapidly improved approximately 12 hours of initiating supportive care. Complete resolution of clinical signs and return of normal appetite and defecation occurred within 24 hours of hospitalization in both animals. No recurrence of neurological signs was reported in the rabbit presenting with seizures on a follow-up period of 1 month.
Conclusion: The outcome of these cases suggests that supportive treatment of fipronil toxicity in pet rabbits can be successful if administered promptly.
Keywords: Pet rabbit, Fipronil, Antiparasitic, Toxicosis, Management.

Introduction

Antiparasitic drug toxicosis (e.g., permethrin) is commonly described in dogs and cats (Merola and Eubig, 2012; Seitz and Burkitt-Creedon, 2016), but reports on the management of antiparasitic drug toxicities in pet rabbits are scarce (Meredith and Richardson, 2015). Fipronil is a topical antiparasitic drug belonging to the phenylpyrazole family, and exerts its toxic effect through blockage of the chloride channels of the gamma-aminobutyric acid receptors causing neuronal excitation and neurological signs (Elhawary *et al.*, 2018). Its selective neurotoxicity in insects compared to mammals makes it a commonly used antiparasitic in dogs and cats for the treatment of several ectoparasitoses, such as flea, tick, lice, burrowing, and non-burrowing (fur) mite infestation (Elhawary *et al.*, 2018; Petriz and Chen, 2018). However, its use in rabbits is not recommended due to reported toxic effects, including seizures, tremors, anorexia, lethargy, and death, especially in young, debilitated, and underweight rabbits (Cooper and Penaliggon, 1997; Beck, 2000; Johnston, 2008; Fehr and Koestingler, 2013; Petriz and Chen, 2018). History of exposure, occurrence of compatible clinical signs, and exclusion of differential diagnosis causing similar clinical presentations (e.g., seizures) may help achieve a final diagnosis. There is no specific antidote for fipronil toxicosis in rabbits so the most important part of treatment is provision of appropriate supportive care (Petriz and Chen, 2018). Here, we describe the successful clinical management of two pet rabbits with fipronil toxicosis.

Case Details

Two unrelated rabbits belonging to two different owners presented between 4 and 6 hours after topical application of a 0.5 ml fipronil vial (Frontline® Spot-On for cats, 100 mg/ml, Boehringer Ingelheim, Milan, Italy) on the skin as an antiparasitic drug. Both pets were housed indoors, had free roam of the household (while under supervision) and had no known exposure to toxins. They were fed a diet of commercial rabbit pellets, a variety of grass hays *ad libitum*, with the daily addition of fresh vegetables. Fresh tap water was provided in a bottle or a cup. Neither of the patients had a previous history of illness, and both were regularly vaccinated for myxomatosis and rabbit hemorrhagic disease (RHD).

Case 1

The first case was a 5-month-old, intact female, lop-eared rabbit weighing 1.1 kg that presented with a history of acute onset of tonic-clonic seizures, and on

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clinical examination was in lateral recumbency and had marked obtundation. During the physical examination, the rabbit was in good body condition. The rectal temperature was slightly elevated (40.2°C; reference interval 38.3°C–40.0°C) (Oglesbee, 2006a); the mucous membranes were pink (capillary refill time less than 2 seconds); and she was tachypneic (respiratory rate of 110 breaths per minute; reference interval 30–60 breaths/minute) and tachycardic (350 beats per minute; reference interval 103–325 beats/minute) (Oglesbee, 2006a). The remainder of the clinical examination was unremarkable. Complete blood count and serum biochemistry were unremarkable and the rabbit tested negative on *Encephalitozoon cuniculi* serology (IgM and IgG). Total exposure was 45.5 mg/kg.

Case 2

The second case was a 1-year-old, intact male, Lionhead rabbit weighing 1.2 kg that presented with anorexia and lethargy. On admission, the patient was in good body condition, alert, and responsive. The rabbit was estimated to be slightly dehydrated (5%) based on a prolonged skin tent. The mucous membranes were pink, the rectal temperature, and respiratory (40/minute) and heart rates (210/minute) were within normal limits. Thoracic auscultation and other physical examination findings were unremarkable. Complete blood count and serum biochemistry were unremarkable and the rabbit tested negative on *E. cuniculi* serology (IgM and IgG). Total exposure was 41.7 mg/kg.

Trseatment and outcome

Both animals were decontaminated by bathing with tepid water and dishwashing soap, and then dried with towels and a hair dryer to prevent hypothermia. The rabbit with seizures (which occurred at home) received on admission a bolus of intravenous midazolam (0.5 mg/kg; Midazolam, BBraun, Melsugen, Germany). In both cases, overnight hospitalization, intravenous isotonic crystalloid fluids (NaCl 0.9%; AltaSelect Srl, San Giovanni Lupatoto, Italy, and Lactate Ringer solution; BBraun, Milan, Italy), at a maintenance rate of 4 ml/kg/hour IV, and assisted-feeding (20 ml/kg every 8 hours Oxbow Critical Care, Oxbow Animal Health, Omaha, NE) by oral syringe was provided (after the patient's mentation had improved to ensure it could swallow) until voluntary feeding was resumed. Both rabbits rapidly improved approximately 12 hours of initiating supportive care. Complete resolution of clinical signs and return of normal appetite and defecation occurred within 24 hours of hospitalization in both animals. No recurrence of neurological signs was reported in the rabbit presenting with seizures on a follow-up period of 1 month.

Discussion

Toxicoses are an uncommon presentation to practitioners dealing with pet rabbits (Johnston, 2008) and only a few cases of antiparasitic drug toxicosis of pet rabbits exist (Cooper and Penaliggon, 1997; Oglesbee, 2006b). Fipronil toxicity seems to be more severe in rabbits due to the 10 times higher dermal absorption in this species compared to rats (Elhawary *et al.*, 2018). However, fipronil ingestion following topical application can also result in severe signs (Anadon and Gupta, 2012). A study investigating the toxicity of fipronil for the treatment of rabbit ear mite infestation found that the purposeful topical administration of fipronil 5%, 1 vial/10 kg body weight (b.w.) (5 mg/kg), resulted in the death of 1 out of 5 rabbits (20%), whereas 1 vial/5 kg b.w. (10 mg/kg) caused the death of 3 out of 5 rabbits (60%) (Elhawary *et al.*, 2018).

In the present report, a dose of approximately 50 mg/kg was unintentionally used and did not result in the death of any rabbit. Possible explanations for this discrepancy could be the prompt decontamination that avoided additional absorption of the drug, a continuous supportive care that contrasted anorexia as well as fluid administration that promoted elimination of the drug absorbed. As rabbits rapidly groom any product applied topically off their hair coat, attention should be paid to the possibility of ingestion in addition to dermal absorption. In the present cases, the antiparasitic vials were applied to the back of the dorsal neck (behind the ears), in an area not directly accessible to the rabbits' mouth and as the owners reported to have monitored their rabbits after administration without noticing cleansing of that area, ingestion of the antiparasitic drug was considered unlikely.

In other species (e.g., cats), treatment of antiparasitic (e.g., permethrin) toxicosis includes stabilization, decontamination, supportive care, and tremor and seizure control when indicated (Seitz and Burkitt-Creedon, 2016). The latter can require different therapies depending on the severity, ranging from methocarbamol for tremors and benzodiazepine bolus and eventual constant rate infusion to total intravenous anesthesia for seizure control (Yozova and Wierenga, 2021). Similarly, in rabbits exposed to fipronil in the last 48 hours, the treatment includes bathing to remove any residual drug from the surface of the skin, intravenous benzodiazepines (e.g., diazepam or midazolam) to control neurological signs (e.g., seizures), and parenteral fluids and nutritional support to treat anorexia (Johnston, 2008; Petriz and Chen, 2018). In severe cases, propofol constant rate infusion and barbiturates can be used to manage neurological signs.

In the present cases, supportive therapy proved to be effective in managing the affected animals. Prognosis of rabbits after fipronil intoxication is reported to be generally poor and depends on the severity of toxicosis and exposure, time from administration to presentation, and severity of neurologic signs (Johnston, 2008; Meredith and Richardson, 2015; Petriz and Chen, 2018). The outcome of these cases suggests that supportive treatment of fipronil toxicity in pet rabbits can be successful if administered promptly.

A literature review found no cases of fipronil toxicosis diagnosed and successfully treated in pet rabbits. The absence of any clinicopathological abnormalities emphasizes the importance of history collection in rabbits presenting with neurological or aspecific clinical signs (e.g., anorexia and lethargy), which could be misleading and point toward gastrointestinal disorders. Fipronil toxicity should be part of the differential diagnosis for rabbits with either neurological or aspecific signs (e.g., anorexia and lethargy), and particular attention should be paid to investigate any particular drug exposure in the history, specifically in relation to the use of off-label antiparasitic medications in this species. Prompt decontamination (to avoid additional absorption of the drug) as well as continuous supportive care including syringe feeding (to contrast anorexia and avoid gut stasis) and fluid administration (in the attempt to promote elimination of the drug absorbed and maintain patients' euhydration) are strongly recommended. Further studies are needed to determine the prognostic factors for survival of pet rabbits with fipronil intoxication.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

DdO: Data collection and manuscript preparation. SC: Manuscript preparation and revision.

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