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Suspected adverse drug interaction between spinosad and milbemycin oxime in a cat

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Abstract

Case summary A 12-year-old male neutered Tonkinese cat was presented for acute ataxia, weakness, altered mentation and generalised tremors. The cat had been administered oral spinosad (140 mg; 33.5 mg/kg) 48 h prior to the onset of clinical signs, and an oral anthelmintic containing milbemycin oxime (16 mg; 3.8 mg/kg) and praziquantel (40 mg; 9.6 mg/kg) 12 h before the onset of clinical signs. On physical examination, dull-to-obtunded mentation, tetraparesis, ataxia and mild tremors of facial, limb and trunk muscles were noted. Serum biochemical changes and urinalysis were consistent with haemoconcentration. The results of a complete blood count, urine culture and serology for feline leukaemia virus, feline immunodeficiency virus and cryptococcal antigen were negative. The patient was monitored in hospital and all clinical signs resolved within 24 h.

Relevance and novel information The neurological signs in this case were consistent with macrocyclic lactone neurotoxicity, which is suspected to have occurred from an adverse drug interaction between spinosad and milbemycin oxime. This report serves to highlight the potential for this adverse drug interaction between these commonly used prophylactic drugs.

Keywords: Milbemycin oxime; spinosad; adverse drug interaction; P-glycoprotein

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Introduction

Spinosad, a macrocyclic lactone (ML) belonging to the spinosyn class of insecticides, is indicated for treatment and prophylaxis of fleas (*Ctenocephalides felis*).^{1–3} Its mechanism of action is activation of nicotinic acetylcholine receptors (nAChRs) causing motor neuron activation manifesting as involuntary muscle contractions, tremors, paralysis and death.^{1–3} Differential sensitivity of insect vs vertebrate nAChRs results in selective toxicity to insects only. Spinosad is not known to interact with binding sites of other nicotinic or gamma-aminobutyric acidergic insecticides, including milbemycins.¹ There are no contraindications to the use of spinosad, but caution is recommended with concomitant extra-label use of ivermectin.^{1,3} A field study reported that administration of spinosad with other frequently used veterinary products, including tapeworm anthelmintics and heartworm preventatives containing ivermectin, was safe.¹

Milbemycin oxime and praziquantel are indicated for the treatment and control of intestinal worms (*Toxocara cati*, *Toxascaris leonina*, *Ancylostoma tubaeforme*, *Dipylidium caninum* and *Taenia* species) and heartworm (*Dirofilaria immitis*) in cats. Milbemycins, along with avermectins, are ML parasiticides. In invertebrates, MLs bind to glutamate-gated chloride channels, causing

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hyperpolarisation of neurons via an influx of chloride ions, resulting in paralysis and death.^{4,5}

The aim of this report is to describe a suspected adverse drug interaction between spinosad and milbemycin oxime in a cat.

Case description

A 12-year-old male neutered 4.18 kg Tonkinese cat was referred to the Valentine Charlton Cat Centre at the University Veterinary Teaching Hospital, Sydney, for ataxia. Over the course of a few hours, the cat had become subdued and developed a slow gait, weakness and ataxia (see Video S1 in the supplementary material). Subtle tremors of the facial muscles, trunk and limbs had been observed. The cat was housed indoors with supervised outside access. There was no known access to neurogenic toxins. The cat had been administered oral spinosad (Comfortis; Elanco [140 mg; 33.5 mg/kg]) 48 h prior to the onset of clinical signs, and an oral anthelmintic (Milbemax; Elanco) containing milbemycin oxime (16 mg; 3.8 mg/kg) and praziquantel (40 mg; 9.6 mg/kg) 12 h before the onset of clinical signs. The cat had been in previous good health. There had been no change in appetite and the cat had eaten on the morning of presentation. Five weeks earlier, abnormalities detected on routine health check, complete blood count (CBC) and serum biochemistry (including total thyroxine) were a mild non-regenerative anaemia with haematocrit 0.24 l/l (reference interval [RI] 0.25–0.48 l/l); mild lymphocytopenia $0.8 \times 10^9/l$ (RI $0.9\text{--}7.0 \times 10^9/l$); increased symmetric dimethylarginine 17 $\mu\text{g}/\text{dl}$ (RI 0–14 $\mu\text{g}/\text{dl}$); and mild azotaemia (urea 11.7 mmol/l [RI 5–15 mmol/l] and creatinine 190 $\mu\text{mol}/l$ [RI 80–200 $\mu\text{mol}/l$]).

Physical examination revealed mild tachycardia (208 beats per min), normal respiratory rate (20 breaths per min), normothermia (rectal temperature 37.8°C), pink and moist mucous membranes, and normal capillary refill time. Indirect systolic blood pressure with Doppler sphygmomanometry was 140 mmHg. There was a grade 3/6 left parasternal systolic heart murmur with no arrhythmia or gallop rhythm. Neurological examination showed dull-to-obtunded mentation; tetraparesis and ataxia; occasional, subtle, spontaneous tremors of the facial muscles, limbs and trunk; sluggish-to-absent oculocephalic reflexes; and normal-to-delayed placing reflex of the right forelimb. Postural reactions were present in all four limbs, although weak in the hindlimbs. The Modified Glasgow Coma Scale (MGCS) was 16/18.

Abnormalities on a CBC and serum biochemistry panel included marginal neutrophilia, $12.2 \times 10^9/l$ (RI $3.8\text{--}10.1 \times 10^9/l$), mild azotaemia (creatinine 212 $\mu\text{mol}/l$ [RI 71–212 $\mu\text{mol}/l$], urea 12.2 mmol/l [RI 5.7–12.9 mmol/l]) and mild hypercholesterolemia (7.93 mmol/l [RI 1.68–5.81 mmol/l]). All other parameters, including bilirubin, liver enzyme activities and electrolytes, were

within the RIs. Urinalysis was normal, with a urine specific gravity (USG) of 1.040 (pH 8.0), normal sediment examination and negative urine culture. Serology for feline leukaemia virus antigen, feline immunodeficiency virus antibody (Witness; Zoetis) and cryptococcal antigen (latex agglutination) were negative.

An intravenous catheter was placed and the cat was hospitalised. Although neurotoxicity from the combined parasiticide treatment was suspected, treatment for toxoplasmosis was commenced with clindamycin (17.9 mg/kg PO q12h) and *Toxoplasma* serology was submitted. The following day, the cat's neurological examination was normal (see Video S2 in the supplementary material). Clindamycin was discontinued, *Toxoplasma* serology was cancelled and the cat was discharged home. The neurological signs did not recur. The cat re-presented 4 days later for echocardiography to assess the heart murmur. The heart was structurally normal.

Discussion

The clinical signs of ML toxicity include neurological depression, ataxia, mydriasis, blindness, vomiting, tremors, hypersalivation, disorientation and coma.^{4,5} In a study of 139 cats treated with spinosad, adverse reactions included vomiting, lethargy, anorexia, weight loss and diarrhoea.¹ Side effects of oral praziquantel at recommended dose rates are rare in adult cats, with either no side effects or salivation and diarrhoea being reported in safety and evaluation studies and field trials.^{6–8} The manufacturers of a combined praziquantel and pyrantel embonate worming product report transient lethargy and incoordination in a small number of oriental breed cats, but it is unknown whether these clinical signs are caused by praziquantel, pyrantel embonate or the combination.⁹

The clinical signs of ataxia, lethargy, obtundation and tremors observed in this case were consistent with ML central nervous system (CNS) toxicity. However, these signs are not specific and other differential diagnoses included intracranial disease such as cerebrovascular accident, neoplasia, infectious disease (*Toxoplasma gondii*, *Cryptococcus* species), inflammatory disease, trauma or extracranial disease, such as thiamine deficiency or other neurotoxins. Given the rapid improvement with no specific treatment and the unremarkable clinical pathology results, toxicity was considered to be the most likely cause of the cat's clinical signs. Exposure to other toxins was unlikely as the cat did not have free outdoor access, and there was no known exposure to household toxins such as cleaning products.

Spinosad and milbemycin were both administered as per label recommendations in this case. Milbemycin had been administered without spinosad several times previously to this cat, with no adverse effects. Toxicity studies have demonstrated no adverse effects when milbemycin is administered to cats at dose rates up to

12.7 mg/kg.⁴ An idiosyncratic reaction to milbemycin cannot be excluded in this case, but the authors consider it more likely that an adverse drug interaction occurred as a consequence of administering milbemycin 36 h after the administration of spinosad.

The pharmacokinetic profile of spinosad in cats is not described. In dogs, spinosad reaches peak concentrations within 2–3 h, undergoes hepatic metabolism, has a half-life of approximately 10 days and 70–90% is eliminated from the body in faeces via bile within 24 h.^{2,3} In rats, it reaches peak concentrations in 1–6 h and has a half-life of 25–42 h.^{2,10} Milbemycin also undergoes hepatic metabolism and is excreted in the bile.⁴ If the pharmacokinetic profile of spinosad in cats is similar to that in dogs and rats, it would be expected that most of the spinosad would have been eliminated prior to the administration of milbemycin, making an adverse drug interaction unlikely. Also, although not specifically tested, this cat had no signs to suggest liver dysfunction, so altered hepatic metabolism of the drugs is unlikely.

The minimum recommended doses for both spinosad and milbemycin are higher for cats (50 mg/kg and 2 mg/kg, respectively) than dogs (30 mg/kg and 0.5 mg/kg, respectively).^{1,11,12} These different recommendations are presumed to relate to species differences in pharmacokinetics and pharmacodynamics but raise the question as to whether the higher doses recommended for cats increase the risk of adverse effects. If the pharmacokinetic profile of spinosad in cats is different to that in rats and dogs, spinosad administration may have contributed to the development of signs consistent with ML toxicity in this case.

The mild serum biochemical abnormalities present in this case were unlikely to be related to the neurological signs observed. The azotaemia with a USG of 1.040 was most likely prerenal due to haemoconcentration and dehydration. Elimination of spinosad and milbemycin should be unaffected by reduced renal perfusion because these drugs are eliminated predominantly via hepatic metabolism and biliary excretion. The mild hypercholesterolaemia was likely due to postprandial blood collection.

In mammals, MLs bind to gamma (γ)-aminobutyric acid type A-gated chloride channels (GABA_A receptors). These receptors are only found in the CNS, and are normally protected from MLs by the blood–brain barrier (BBB).⁵ With overdosage or *ABCB1* mutations, MLs cross the BBB and bind to GABA_A receptors. *ABCB1* codes for permeability glycoprotein (P-gp), an important component of the BBB, which extrudes substances that have entered endothelial cells in the brain back across the membrane.⁵ When MLs evade the BBB and bind to GABA_A receptors, glycine- and voltage-gated chloride channels, they hyperpolarise neurons via chloride influx, causing decreased excitation manifesting in signs such as ataxia and CNS depression.⁵ This is seen more

commonly with avermectins than milbemycins but can occur with both.

Several mechanisms by which spinosad may interact with milbemycin in cats to result in signs consistent with ML toxicity can be postulated. In dogs given ivermectin and spinosad together, spinosad pharmacokinetics are unaffected, but there is an increased maximum plasma concentration, increased area under the curve and a decreased clearance of ivermectin compared with dogs given ivermectin alone.¹³ Additionally, in vitro spinosad is both a substrate and inhibitor of human P-gp whereby it reduces the hepatic and/or intestinal secretion of MLs, increasing their systemic concentration, and increasing their neurotoxicity through inhibition of P-gp at the BBB.¹³ In dogs, spinosad is listed as an inhibitor of P-gp and milbemycin a substrate of P-gp.¹⁴ Potent inhibition of P-gp by spinosad has been demonstrated in an in vitro study in dogs.¹⁵ Contrary to this, scintigraphic imaging of six healthy adult dogs using radiolabelled P-gp substrate showed that spinosad did not affect P-gp function 48 h following administration.¹⁶ Also, another study found no signs of toxicity in dogs with *ABCB1* mutations given three or five times the labelled dose of spinosad and up to 10 times the heartworm preventative dose of milbemycin.¹⁰ It was concluded that milbemycin likely has relatively poor affinity for P-gp compared with avermectins.¹⁷

There are no equivalent studies in cats so it remains unknown whether spinosad or milbemycin acts as a substrate and/or inhibitor of P-gp in this species. In this case, the cat recovered quickly, which would suggest spinosad may not necessarily have a high affinity for P-gp. *ABCB1* mutations resulting in defective P-gp have been reported in cats,¹⁸ but their incidence and clinical significance in the feline population is unknown. Genetic testing for this mutation was not pursued in this case.

This case was discussed on a social media group for Australian veterinarians, where it was reported, anecdotally, that similar signs have been seen in cats given spinosad and milbemycin together. A case of adverse drug interaction between ivermectin, spinosad and milbemycin was reported in a dog treated with ivermectin for 1 month before application of a topical preparation containing spinosad and milbemycin.¹⁹ Clinical signs in that case were muscle tremors, dull mentation, ptialism and blindness, with a MGCS of 12/18. The interaction between ivermectin and spinosad was thought to be responsible for these clinical signs.

There are no previously published reports of a possible adverse drug interaction between spinosad and milbemycin in dogs or cats. Numerous field and laboratory studies have shown that the combination of spinosad and milbemycin is safe when administered to dogs, with occasional minor side effects (mainly vomiting) but no neurological adverse events.^{20–30} There are two licensed products containing spinosad and milbemycin

in combination (Trifexis [Elanco] and Combogard [Vethical]) registered for dogs only in the USA.^{31,32} There are no equivalent products registered for cats and no published studies to assess the safety and/or efficacy of this drug combination in cats. The findings of the current case raise questions about the safety of concomitant spinosad and milbemycin administration in cats, and species-specific pharmacokinetics and pharmacodynamics of these drugs, potentially through P-gp affinities and/or inhibition, may explain the adverse interaction seen.

It is not known whether all cats might be at risk of the same interaction, or whether other factors contribute to this such as genetic predisposition, comorbidities or age. One study demonstrated a 72% decrease in P-gp expression in dogs aged >100 months vs dogs aged 23–36 months, suggesting that aged dogs may have impaired ability to eliminate MLs from the BBB.³³ It is possible that geriatric cats, such as the one in this case report, may be similarly affected. More studies are necessary to determine if decreased expression of P-gp increases susceptibility to ML toxicity.

In this case, owing to the mild nature of the clinical signs, no specific treatment was given to manage the suspected ML toxicity. Methods of decontamination such as inducing emesis or administering activated charcoal were unlikely to be effective given the timing of milbemycin administration. Treatment with intravenous lipid emulsion therapy has been described to treat lipophilic drug toxicities,¹⁹ but it can cause hyperlipidaemia and/or hypersensitivity reactions.³⁴ If more severe neurotoxic signs such as seizures or coma were observed in this case, lipid emulsion therapy would have been considered, along with anticonvulsant therapy.

Conclusions

This case has been reported to raise awareness about a potential adverse drug interaction between spinosad and milbemycin oxime in cats. Further studies are required to assess the incidence of such an interaction and, if it is proven, the mechanism by which it occurs.

Supplementary material

The following files are available: Video S1: Cat at home day 1. Video S2: Cat at University Veterinary Teaching Hospital Sydney on day 2.

Conflict of interest The authors declare that the subject of this report belonged to veterinarian Natalie J De Souza. The authors declare no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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