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Neurotoxicosis in 4 Cats Receiving Ronidazole

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Tritrichomonas foetus is a protozoan that can cause chronic large-bowel diarrhea in cats.[1] Ronidazole, a nitroimidazole, has been shown to effectively treat *T foetus* in cats at doses of 30 to 50 mg/kg body weight twice daily for 14 days.[2] To our knowledge, adverse effects in cats have not been reported. This case series describes neurologic abnormalities suspected to be secondary to ronidazole administration in 4 cats.

Case 1 is a 2.5-year-old male castrated Domestic Shorthair that was presented with a chief complaint of chronic, intermittent, mucohemorrhagic diarrhea of 1.5 years' duration. The owner was unable to comment about the frequency or the urgency of defecation.

The cat, when 6 weeks of age, was adopted by the owner from a rescue organization and had been housed strictly indoors since then. He resided with 5 other cats, all of whom tested negative for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) and had no history of diarrhea. The only medical problems among the cats were occasional upper respiratory tract infections.

Serum biochemistry panel, CBC, and T4[a]; a blood smear to scan for *Mycoplasma hemofelis*; and (ELISA) for FeLV antigen and FIV antibody (FeLV/FIV test),[b] performed by the referring veterinarian (rDVM) were unremarkable. Coronavirus 7B antibody titers[c] were 1 : 80, 1 : 160, and 1 : 80 on 3 sequential serum samples in an 8-week period.

Initial physical examination (PE) revealed a bright, alert, responsive, and well-hydrated cat. He weighed 4.7 kg, with a body condition score (BCS) of 7 of 9. Rectal temperature was 102.9°F, and a small amount of frank blood was observed on the thermometer. The patient had a mild serous ocular and nasal discharge, as well as gingivitis, faucitis, and halitosis. The remainder of his PE was unremarkable.

Serum chemistry profile, CBC, urinalysis, abdominal ultrasound, and FeLV/FIV test[b] were all unremarkable. Fecal flotation and direct wet preparation were negative for intestinal parasite ova and motile protozoa; *Giardia* ELISA[d] was negative; stained direct preparations were unremarkable; and fecal cultures for *Salmonella*, *Yersinia*, and *Campylobacter* were negative. A rectal scrape revealed neutrophilic inflammation, with occasional cocci, diplococci, and a few sporulating bacteria consistent with *Clostridium* sp. A second fecal wet smear was positive for flagellated protozoa. Culture for *Tritrichomonas foetus*[e] was positive, and the patient was prescribed ronidazole[f] at a dose of 54 mg/kg PO q12h for 14 days.

Five days after starting ronidazole, the owner reported that the cat had normal stools, lethargy, a blank stare, and appeared to be in "slow motion." Neurologic evaluation of the cat was declined, and the ronidazole was continued for an additional 3 days. These clinical signs progressed, and the cat also developed an unsteady gait, pelvic-limb weakness, and trembling. Ronidazole therapy was discontinued, and the cat remained stable over several days, with gradual improvement. The patient was presented 7 days after discontinuation of ronidazole, and physical examination revealed a crouching, wide-based stance and mild ataxia in the pelvic limbs. The rest of the physical examination was unremarkable. The cat had complete resolution of its neurologic signs 1 month after discontinuation of ronidazole, and physical examination was unremarkable.

The hematochezia recurred several days after discontinuing the ronidazole. Direct wet preparation of feces for motile protozoa and culture for *T foetus* were negative; however, the owner elected to re-treat with ronidazole at a lower dose (30 mg/kg PO q12h). The hematochezia resolved quickly, but, 12 days later, the owner reported that the cat had been unsteady, stumbling, and "spacey" for several days and that she had been giving him only 1 dose daily during this period. Neurologic signs resolved over a period of weeks after discontinuation of ronidazole. The patient was returned for reevaluation approximately 6 weeks after discontinuing the second course of ronidazole, and the PE was unremarkable. Culture of fresh feces was negative for *T foetus*.

Case 2 is a 5-year-old female spayed Persian who was examined because of chronic mucohemorrhagic diarrhea since the cat was acquired from a breeder at 4 months of age. The diarrhea episodes initially occurred 6 to 8 times daily, and the cat was fecally incontinent. Routine deworming by the rDVM with pyrantel pamoate[g] and empiric antimicrobial administration with metronidazole had no effect on the diarrhea. Dietary trials with Royal Canin Innovative Veterinary Diet Green Peas and Venison, Hill's Prescription diet w/d, and Nestle Purina OM also had no effect on the diarrhea. The rDVM obtained multiple full-thickness biopsy specimens from the small and large intestines, which were characterized by mild lymphoplasmacytic inflammation. The cat was

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treated with prednisone (unknown dose and duration), with no improvement in the diarrhea. The frequency of diarrhea episodes gradually increased to approximately 20 times per day. The cat had a ravenous appetite and normal activity level.

Physical examination revealed a quiet, yet alert and responsive cat who appeared adequately hydrated. The cat's temperature could not be determined because of an intolerance of a rectal thermometer. There was severe swelling, erythema, and pain of the anus. The cat weighed 2.3 kg and had a BCS of 3 of 9. The remainder of the PE was unremarkable.

Serum biochemistry profile, CBC, urinalysis, and FeLV/FIV test[b] were unremarkable. An abdominal ultrasound revealed mild enlargement of the mesenteric and sublumbar lymph nodes. However, there was no evidence of intestinal-wall thickening. Fecal direct wet preparation and centrifugation fecal flotation were negative. A fecal culture for *T foetus*[e] was positive for trophozoites and confirmed via PCR by using species-specific primers.[3,h] The PCR reaction amplified the 5.8S-ribosomal riboneucleic acid (rRNA) gene unit of *T foetus* and product identity was confirmed by sequencing.

Ronidazole was administered at a dosage of 40 mg/kg PO q12h for 10 days. The cat's fecal consistency improved within 3 days. A repeat fecal culture for *T foetus* on day 3 after initiation of ronidazole was negative. The owner reported no apparent problems with the cat 7 days after initiation of drug therapy, but the cat's appetite was notably decreased on day 8, and the cat became anorectic on day 9. In addition, the cat became extremely agitated and lethargic and was noted to have facial tremors and trembling of all extremities. Despite these signs, the owner completed the prescribed course of ronidazole therapy. The cat became progressively more unstable in the thoracic and pelvic limbs over the ensuing 48 hours until it became very weak and could no longer jump on the bed or walk up stairs. The cat remained inappetant for 7 more days, and the neurologic signs resolved over 14 days. Fecal culture for *Trichomonas*[e] was performed 4 days after completion of ronidazole therapy and was negative. In addition, the cat continued to have normal formed feces 3 months after completion of ronidazole administration.

Case 3 is an 18-month-old male neutered Abyssinian who was examined because of chronic intermittent mucohemorrhagic diarrhea of 12 months' duration. The cat was obtained from a breeder when the cat was 6 months of age, and the owner witnessed a bout of hematochezia within 2 days of purchase. The cat tested negative for FeLV and FIV,[b] and was subsequently dewormed with praziquantel and pyrantel embonate[i] and empirically treated with metronidazole and sulfadimethoxine, with no effect. The cat maintained an excellent appetite, despite the diarrhea, and had no history of vomiting.

Physical examination revealed a bright, alert, and responsive cat who weighed 4.6 kg (BCS, 5/9). The cat's temperature could not be determined, because the cat would not tolerate a rectal thermometer because of a painful anus. The rest of the PE was unremarkable.

Serum biochemistry profile, CBC, and abdominal ultrasound were unremarkable. Direct wet preparation, centrifugation fecal flotation, fecal culture for *Clostridium difficile*, *Campylobacter* spp., and *Salmonella* spp., ELISAs for detection of *Clostridium perfringens* enterotoxin[j] and *Clostridium difficile* toxin A,[k] and *Cryptosporidium*/*Giardia* direct fluorescent antibody test[l] were negative; however, fecal culture[e] was positive for trophozoites, confirmed to be *T foetus* via PCR.[h]

Ronidazole was administered at a dosage of 40 mg/kg q12h for 10 days. The cat was hospitalized for the first 3 days of ronidazole administration for close monitoring, and no abnormalities were detected during daily PEs. The cat did not defecate for 3 days after ronidazole administration. The cat continued to do well at home after discharge, and the owner reported that the cat's fecal consistency had improved dramatically within 5 days of starting ronidazole therapy. However, starting on day 9 of ronidazole administration, several new clinical signs were noted, including agitation, lethargy, anorexia, trembling of extremities, and instability in the thoracic and pelvic limbs. The owner also reported that the cat had become extremely hyperesthetic to external stimuli. The neurologic complications and hyperesthesia progressively resolved over an 8-day period after cessation of the drug. The cat regained its appetite 10 days after stopping the ronidazole, made a complete recovery, and continued to have well-formed stools. Additional fecal cultures[e] performed 3 days after initiating ronidazole therapy and 5 weeks after completion of ronidazole administration were negative.

Case 4 is a 2-year-old male neutered Domestic Medium Hair who was evaluated for persistent tenesmus, hematochezia, fecal incontinence, and extremely malodorous stools since being adopted from a shelter 1 year before presentation.

Physical examination was unremarkable, although the cat was deemed to be overweight (5 kg; BCS, 6/9). Results of a serum chemistry profile and CBC were unremarkable. Repeated centrifugation fecal flotation and *Cryptosporidium*/*Giardia* direct fluorescent antibody tests[l] were negative. *T foetus*–associated diarrhea was suspected, despite negative fecal culture.[e]

Ronidazole was administered empirically at a dosage of 40 mg/kg PO q12h for 10 days. The cat was hospitalized for the first 3 days of ronidazole administration for close monitoring. The cat became extremely agitated and hyperesthetic after 3 days of ronidazole therapy and was difficult to restrain. The cat was described as a "mellow" animal normally, and the owner was alarmed at the cat's profound hyperesthesia to touching and any sudden movements by people. The drug was discontinued after an additional 3 days of therapy because of the progressive behavioral changes and lack of any improvement in fecal quality. The cat's agitation and hyperesthesia resolved over the ensuing 8 days.

T foetus has been recognized as a cause of chronic diarrhea in cats.[1,4,5] Many antibiotics and antiprotozoal agents have been used in an effort to treat *T foetus* diarrhea, without consistent success. Ronidazole has

been identified as a treatment for *T foetus* in cats, when other drugs have been unsuccessful or deemed unsafe.[1,2,4,6,m] It is a nitroimidazole, similar to metronidazole and is used as a treatment for trichomoniasis in birds.[7] Currently, there is no commercially available pharmaceutical product in the United States, but the chemical is available through Sigma-Aldrich Pharmaceuticals at greater than 99.9% purity, and many pharmacies will compound the drug into capsules. This compound is not approved for use in cats by the Food and Drug Administration.

To the authors' knowledge, there is no published information about the pharmacokinetics, pharmacodynamics, or adverse effects profile of ronidazole in cats. In other species, ronidazole and its metabolites are excreted in urine and feces.[8,9] It is readily absorbed from the gastrointestinal tract and biodegraded, and is found in its intact form only in muscle.[10,11]

The primary mechanism of action of most nitroimidazoles (including ronidazole) is thought to be related to production of nitro anion radicals,[12,13] leading to destabilization of deoxyribonucleic acid. Hydrogenosomes are specialized double-membrane–bound organelles responsible for the production of adenosine triphosphate (ATP) by a process that involves generating hydrogen and are found in some eukaryotic microbes that inhabit oxygen-deficient environments. Within hydrogenosomes, an electron transport system using ferredoxin oxidoreductase and the electron carrier ferredoxin transfers electrons to the nitro group of 5-nitroimidazoles.[14] However, ferredoxin oxidoreductase is absent in *T foetus* organisms that are resistant to metronidazole,[15,16] suggesting that ronidazole may have other mechanisms of action and is likely cidal to *Trichomonas* via other unknown reductive pathways.

The World Health Organization has summarized multiple published and unpublished experiments exploring the effects of orally administered ronidazole in dogs, mice, and rats.[17] Research on dogs has identified numerous adverse effects at doses of 50–200 mg/kg/d 5 days per week, including seizures, opisthotonos, fine tremors, ataxia, hindquarter stiffness, dry mouth and gums, mild tachycardia, and slow and shallow respiration. These signs were first observed in the dogs within 1–2 weeks of therapy at high doses (100–200 mg/kg/d), and after 5–8 weeks with a dose of 50 mg/kg/d. A dose of 25 mg/kg/d 5 days per week was well tolerated for up to 17 weeks (the duration of the study). Long-term studies also revealed neurologic effects at much lower doses. At 10 mg/kg/d occasional fine tremors were noted; dogs administered 20 mg/kg/d were hyperreactive; and dogs administered 30 mg/kg/d suffered anorexia, weight loss, ataxia, and clonic-tonic seizures. At postmortem examination, all dogs receiving ≥20 mg/kg/d, 5 days a week for 1 to 2 years had gross lesions, including slight hydrocephalus; subdural hemorrhage; and pale yellowish coloration of the brain, and histopathologic lesions, including focal hemorrhage of the cerebellum, leukomalacia, vascularization, and neurophagia. Other findings included cardiac hemorrhage, testicular atrophy, aspermatogenesis, and oligospermia. Similar testicular changes have been noted in rats receiving similar doses for 2 years. No neurologic changes were reported in rodents; however, a significant decrease in survival of rats at ≥20 mg/kg/d was reported.

With respect to the case series presented here, it is important to note that ronidazole toxicity was not definitively confirmed in any of these cases. Ronidazole levels were not measured, and other potential concurrent diseases were not completely ruled out. However, resolution of signs with discontinuation of ronidazole, as well as a recurrence of the same signs with the reintroduction of the drug in the first case lends support to the hypothesis that ronidazole was responsible for these cats' neurologic signs. Neurologic signs were consistent with those reported in other species and were similar to adverse effects reported with use of other medications within the same drug class. These 4 cats received no other medications during the ronidazole treatment period, and there were no other obvious causes for the signs.

Because ronidazole is in the same class of drugs as metronidazole, some of the adverse effects may be similar to those of metronidazole. Neurotoxicosis secondary to metronidazole administration has been reported in dogs, cats, and humans.[18–21] Neurotoxicity in mammals secondary to use of 5-nitroimidazoles has been theorized to be because of the formation of superoxide radicals, hydrogen peroxide, nitrofurantoin radicals, and semiquinone radicals from catecholamine reduction of these drugs under aerobic conditions.[22] Other research indicates that the cytotoxic mechanism of nitroimidazoles in anaerobic protozoa also occurs in hypoxic mammalian cells in vitro.[23] Cytotoxicity of aerobic cells does not occur because of the low redox potential of 5-nitroimidazoles.

In the 4 cases described here, ronidazole was used to treat documented or suspected trichomonad infections. Adverse effects attributed to ronidazole in these cats included decreased appetite, altered mentation, trembling, weakness, ataxia, and hyperesthesia. No seizures were observed in any of the cats. Neurologic signs started between 3 to 9 days after initiating ronidazole therapy and lasted between 1 and 4 weeks, gradually diminishing after discontinuation of the medication. Continuation of ronidazole therapy in 3 cases after signs were noted may have affected the duration of signs in these cases. It is also worth noting that in the 3 cases in which trichomonad infections were documented, diarrhea resolved after ronidazole treatment and post-treatment *Trichomonas* cultures were negative.

The dose of ronidazole used to treat the cats in this report was equal to or greater than 60 mg/kg/d in all cases. A recent study of the efficacy of ronidazole for treatment of *T foetus* infection in cats found that a dose of 20 mg/kg/d (divided) was associated with relapsing infection in all cases, whereas doses of 60 mg/kg/d or 100 mg/kg/d (divided) resulted in clearance of infection for the duration of testing (21–30 weeks).[2] The effective doses of 60–100 mg/kg/d are significantly higher than the doses at which toxic effects were consistently seen in

other species. It is not possible to determine from these cases whether the toxicity of ronidazole in cats might be dose-dependent as suggested by experimental studies involving dogs and rats. However, additional studies are warranted to determine the efficacy of ronidazole administration at doses between 20 and 60 mg/kg/d.

Based upon clinical signs exhibited by the cats described in this series, it appears likely that adverse effects of ronidazole reported in dogs may also occur in cats. The aim of this report is to alert veterinarians to these potential adverse neurologic effects of ronidazole in cats. Although all cats had complete resolution of their neurologic signs, it may be prudent to discontinue use of ronidazole even if only mild neurologic abnormalities are seen. Clearly, further investigation of ronidazole activity and side effects in felines is necessary. At present, we recommend that the use of ronidazole be limited to confirmed cases of *T foetus* infection and that owners be educated about the potential adverse effects of this medication.

Footnotes

[a] Antech Diagnostics, Atlanta, Ga
[b] SNAP Combo Test, Idexx Laboratories, Westbrook, ME
[c] Antech Diagnostics, Atlanta, Ga
[d] Giardia SNAP ELISA, Idexx Laboratories, Westbrook, ME
[e] InPouch TM TF, BioMed Diagnostics, White City, OR
[f] Sigma Chemical Company, St. Louis, MO
[g] Nemex, Pfizer Animal Health, Exton, PA
[h] University of California, Davis, School of Veterinary Medicine, CA
[i] Drontal, Bayer HealthCare LLC, Animal Health Division, Shawnee Mission, KS
[j] *C perfringens* enterotoxin test, Techlab Inc, Blacksburg, VA
[k] Triage Micro *C difficile* panel Toxin A and common antigen (glutamate dehydrogenase (GD), Biosite Inc, San Diego, CA
[l] Merifluor, Meridian Bioscience, Inc, Cincinnati, OH
[m] Levy MG, Gookin JL, Poore MF, et al. Intestinal trichomonosis in cats: pathology, diagnosis and susceptibility to antiprotozoal drugs. Proceedings of the Joint Meeting of the American Society of Parasitologists and the Society of Protozoologists 2000, San Juan, Puerto Rico, 108 (abstract)

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