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Metronidazole-induced neurotoxicity in 26 dogs

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Background Metronidazole is an antibacterial, antiprotozoal and anthelmintic medication commonly used in veterinary medicine. We describe cases of neurotoxicity associated with the drug's administration.

Methods Medical records between 2004 and 2017 from four referral veterinary hospitals were reviewed. Inclusion criteria were the presence of neurological signs compatible with metronidazole toxicity, clinical history supporting recent metronidazole therapy and resolution of clinical signs upon discontinuation of metronidazole administration.

Results A total of 26 dogs were identified with clinical signs supporting a diagnosis of metronidazole toxicity. Median age at presentation was 7.2 years (range, 0.1–12 years); median duration of treatment was 35 days (range, 5–180 days); median treatment dosage was 21 mg/kg BID (range, 13–56 mg/kg every 12 h); median resolution of the clinical signs upon discontinuation of metronidazole was 3 days (range, 1–26 days). Magnetic resonance imaging (MRI) of the brain was performed in 19 cases and only one dog had brain lesions affecting the dentate nuclei, which resembled the MRI appearance of this disease in humans.

Conclusions We found evidence of neurotoxicity in dogs at much lower doses than previously reported and we suggest caution when administering metronidazole at doses > 40 mg/kg every 24 h, regardless of the duration of the treatment.

Keywords dogs; metronidazole; neurotoxicity

Abbreviations CSF, cerebrospinal fluid; FLAIR, fluid attenuated inversion recovery; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; T2W, T2-weighted

Metronidazole is an antibacterial, antiprotozoal and anthelmintic medication approved for veterinary use and commonly used to treat systemic and enteric obligate anaerobic bacterial and some protozoal infections.[1–4] Metronidazole belongs to a class of antibiotics known as nitroimidazoles. It induces loss of helical structure and strand breakage in bacterial and protozoal DNA and inhibits nucleic acid synthesis, resulting in cell death. It has a primarily hepatic metabolism via several pathways.[5] It is a highly lipid-soluble drug and following oral administration its bioavailability is approximately 50–100%, with serum concentrations peaking within 1–2 h and rapid distribution to most body tissues and fluids, including the central nervous system because of its ability to penetrate the blood–brain and blood–cerebrospinal fluid (CSF) barriers.[6] It is only slightly bound to plasma proteins (< 20%) in humans and metabolites are excreted by both the renal and biliary routes.[2] The elimination half-life in dogs is 4–6 h.[7,8]
Various sources state that the metronidazole dose in canine patients for anaerobic infectious and gastrointestinal conditions is 10–15 mg/kgevery 12 hand the dose for protozoal infections is 25 mg/kg every 12 h for 5 days.[2,4,9–12]

Metrobactin™ (Le Vet Beheer B.V., The Netherlands) is a veterinary product that contains metronidazole licenced for the treatment of gastrointestinal tract infections caused by *Giardia* spp. and *Clostridia* spp. (i.e. *C. perfringens* or *C. difficile*) in dogs and cats. The recommended dose is 50 mg/kg for 5-7 days. The daily dose may be divided equally for twice daily administration (i.e. 25 mg/kg every 12 h). The manufacturer states that this dose rate, written in the Summary of Product Characteristics, was considered 'acceptable' by all Member States involved in the assessment of the application (25 EU Member States); however, no references to support the use of this dose are provided. Furthermore, there is no veterinary drug licenced in the UK to treat giardiasis in dogs and the high metronidazole dosages lack evidence of suitability and efficacy.

The *BSAVA Small animal formulary* (9th revised edn, British Small Animal Veterinary Association; 2017) is widely used in general veterinary practices in the UK. It states the same doses as above, but without any guidance on the duration of metronidazole treatment.

In one study, the dose to treat canine giardiasis was stated as 25 mg/kg every 24 h for 5 days.[13] We were unable to find any other veterinary research study that specifically states the use of this drug at a higher dose or longer duration.

It has been advocated that metronidazole should be the drug of choice in cases of concurrent *C. perfringens* overgrowth, as it is effective against *Clostridium* spp. In cases of concurrent nematode and/or cestode infestation, other drugs such as fenbendazole should be used.[14]

Adverse side effects are not common; however, neurotoxicity has been described in dogs receiving acute high doses, such as > 65 mg/kg every 24 h for acute infection[8,15] or chronic therapy.[16] Common signs of neurotoxicity include tremors, rigidity, ataxia, head tilt, vertical nystagmus and convulsions. Neurotoxicity has been anecdotally reportedin some animals with dosages as low as 30 mg/kg every 24 h and, occasionally, as soon as 3 days after the initiation of the treatment.[17]

In this study, we present evidence of metronidazole neurotoxicity at much lower doses than has previously been published and the drug's pharmacodynamic and pharmacokinetic profiles are discussed.

Materials and methods

This study was a retrospective analysis of recorded data from necessary clinical procedures. The medical records of dogs admitted at one hospital and three referral centres between 2005 and 2017 were reviewed. Inclusion criteria were the presence of neurological signs compatible with metronidazole toxicity, clinical history supporting recent metronidazole therapy and resolution of clinical signs upon discontinuation of metronidazole administration. Signs of metronidazole toxicity typically include vestibulocerebellar ataxia, head tilt, positional nystagmus, tremors and seizures.[2]

We recorded the signalment, age at presentation, reasons for metronidazole therapy, dose and length of metronidazole therapy, clinical signs, concurrent disorders if present, details of investigations performed, time for resolution of the clinical signs and eventual treatment used.

Results

A total of 26 dogs were identified with clinical signs supporting a diagnosis of metronidazole toxicity. Breeds represented were German Shepherd Dogs (8), Labrador Retrievers (6), Shih Tzu (2), and 1 each of Border Collie, Boxer, French Bulldog, Great Dane, Hungarian Vizsla, Labrador–Mastiff cross, Patterdale Terrier, Soft Coated Wheaten Terrier, Weimaraner and West Highland White Terrier.

Median age at presentation was 7.2 years (range, 0.1–12 years); median duration of treatment was 35 days (range, 5–180 days); median treatment dosage was 21 mg/kg every 12 h (range, 13–56 mg/kg). The reasons for metronidazole therapy are presented in Table 1; 14 of the dogs (54%) were presented with diarrhoea (Table 1).

The main clinical signs of neurotoxicity included cerebellovestibular ataxia in 22 dogs, (Figure 1), pathological nystagmus (13 dogs), upper motor neuron paresis (8 dogs) and hypermetria (8 dogs) (Table 2, Supplementary Video 1). Other signs included disorientation, seizures, audiorory and visual hyperaesthesia, and reduced palpebral reflex in 1 dog each, 2 dogs were obtunded and 2 dogs had increased myotactic reflexes. Reduced postural reactions were not reported.

Haematology and serum biochemistry profiles were obtained and urinalysis performed in 14 cases and the results were abnormal in 5 cases, showing bilirubinuria (case 3), elevations of urea, total bilirubin and alanine aminotransferase (case 8), hypoproteinaemia, (cases 9 and 12) and decreased urea (case 16) (Supplementary Table 1).

Blood ammonia concentration was assessed in two cases (nos 8 and 16) and found to be elevated (~130 and 171 μmol/L, respectively; reference range, 0–70 μmol/L). Bile acid evaluation and abdominal ultrasonography were performed in both cases and the dogs were found to be normal.

One case (no. 8) was positive for *Neospora*-like oocysts on faecal flotation prior to referral; however, protozoal DNA was notdetected by PCR. Serology or PCR was performed for *Toxoplasma gondii* in 8 cases and *Neospora caninum* in 7 cases; all results were negative. Case 16 (Patterdale Terrier) had genetic testing for late-onset ataxia and spinocerebellar ataxia; the dog was homozygous for the normal genes.

Magnetic resonance imaging (MRI) of the brain and CSF analysis were performed in 19 and 16 cases, respectively (1.5-T Siemens Symphony Tim System, Enlangen, Germany). MRI was normal in 17 dogs and abnormal in 2 dogs. The abnormal findings were pronounced cerebral cortical atrophy (case 7, Weimaraner, 8 years old) and bilateral symmetrical hyperintensity within the dentate nuclei on T2-weighted (T2W) and T2W FLAIR images (Figure 2) with no enhancement following gadolinium administration in one German Shepherd Dog (case 2). CSF analysis was normal in 15 dogs and abnormal in 1 dog (case 12). In the abnormal case, CSF was obtained via lumbar puncture and the result showed a mild mononuclear pleocytosis with concurrent iatrogenic blood contamination (Supplementary Tables 1, 2). Occasional reactive lymphocytes were noted. This dog manifested thoracolumbar spinal hyperaesthesia and MRI of the spine showed multiple dehydrated intervertebral discs throughout the thoracolumbar spine with mild protrusions at the level of T11–T12 and L1–L2 intervertebral discs.

Occasionally, other tests such as serum trypsin-like immunoreactivity, folate and cobalamin concentrations and thyroid function (thyroid-stimulating hormone and thyroxine) were performed. Folate was found to be elevated in case 24 (Supplementary Table 1) and cobalamin serum concentration was reduced in case 2 (166 ng/L; reference range, 250–900 ng/L).

In case 2, electrodiagnostic testing were performed and indicated a reduced motor nerve conduction velocity (tibial nerve: 41 m/s and ulnar nerve: 57 m/s; reference range, 60 ± 10 m/s), together with reduced amplitude of the compound muscle action potential. Electromyographic abnormalities were not identified in this dog. Acetylcholine receptor antibody titres were negative and the cobalamin serum concentration was reduced (Table 1).

All affected dogs improved rapidly, becoming ambulatory with minimal ataxia and were discharged within a median of 3 days (range, 1–26 days) once the metronidazole therapy was discontinued, with the exception of cases 8 and 14, in which the resolution of the clinical signs was 26 and 12 days, respectively. Supportive care such as intravenous fluid therapy was used and oral diazepam was instituted in 19 cases in order to improve the speed of recovery,[2] at a median dose of 0.4 mg/kg every 8 h for a median duration of 3 days (Table 1).

Discussion

We report the occurrence of metronidazole neurotoxicity at considerably lower dosages than previously recorded and at dosages within the recommend range in many texts, albeit at the high end. As previously stated, it is widely known that high metronidazole doses such as > 65 mg/kg daily may result in neurotoxicity;[2,8] however, our study results suggested that this may be evident when using much lower doses (~20 mg/kg every 12 h) and following a variable length of treatment with a median duration of 35 days (range, 5–180 days).

The mechanism of metronidazole toxicity is still unknown; however, it may be related to modulation of the inhibitory neurotransmitter gamma-aminobutyric acid receptor within the cerebellar and vestibular systems. Metronidazole has a large volume of distribution and penetrates sufficiently into most tissues, as well as the blood–brain and blood–CSF barriers.

In our study, the results of ancillary tests such as haematology, serum biochemistry and urinalysis showed minor changes unrelated to metronidazole toxicity and were, therefore, considered not significant.

MRI performed on the dog in case 2 revealed bilateral symmetrical hyperintensity on T2-weighted and FLAIR images within the dentate nuclei. The dentate (or lateral) nucleus is a cluster of neurons located within the deep white matter of each cerebellar hemisphere, responsible for the planning, initiation and control of voluntary movements. These MRI findings are a very characteristic feature of metronidazole-induced neurotoxicity in humans.[18,19] Studies in rats have demonstrated that large doses of metronidazole can bind to the RNA of nerve cells to inhibit protein synthesis, thereby resulting in axonal degradation.[20] As the clinical findings in the present cases were reversible, a more likely aetiology is that the acute toxic insult leads to axonal swelling with increased water content, resulting in T2 signal prolongation.[16,21] Furthermore, metronidazole requires reduction by pyruvate–ferredoxin oxidoreductase to become active; in fact, bacteria and protozoa that do have alterations in their enzymes or metabolic pathways are resistant to metronidazole.[22] The dentate nucleus is one of the deep iron-rich nuclei in the cerebellum[23] and when metronidazole activation occurs, we theorise that reduced cytotoxic compounds may be formed that bind to proteins, membranes and DNA in target cells, causing severe damage. Furthermore, the dentate nucleus is one of the structures that appears to be particularly vulnerable to injury and it is frequently involved in neurodegenerative, ischemic and metabolic disorders.[22,24]

The dog in case 2 showed also hypocobalaminaemia, which may result in axonal sensorimotor polyneuropathy caused by axonal degeneration as well as demyelinating features in the spinal cord (i.e. myeloneuropathy).[25,26] Supplementation with vitamin B12 was provided; however, this dog quickly improved upon discontinuation of metronidazole (Table 1) and therefore the hypocobalaminaemiawas considered non-clinically significant in this case.[27] Furthermore, the motor nerve conduction velocity results were mild and likely attributed to physiological changes seen in older dogs.[28,29]

The dog in case 7 had cerebral cortical atrophy on MRI of the brain (Supplementary Table 2), but this finding was thought to be related to neuroparenchymal loss associated with ageing and was, therefore, considered an incidental finding.

The dog in case 12 showed abnormal CSF with mild mononuclear pleocytosis; the dog also had multiple thoracolumbar intervertebral disc herniations, and spinal cord injury caused by chronic thoracolumbar intervertebral disc disease has been associated with an increase in CSF mononuclear cells.[30]

Two young dogs (Supplementary Tables 1, 2) presented with moderate elevations in ammonia concentration. This was measured only in these two cases because portosystemic shunt was initially suspected because of their young age. In both cases, abdominal ultrasonography and normal bile acids ruled out the presence of a shunt. In addition, ammonia is not a reliable test[31] and these patients recovered completely upon discontinuation of metronidazole and without any specific treatment.

The diagnosis of metronidazole toxicity was made on the basis of a history of recent metronidazole therapy, clinical signs compatible with metronidazole toxicosis, absence of other clinical disease and resolution of clinical signs upon discontinuation of metronidazole administration.[2] Based on these criteria, we excluded the diagnosis of idiopathic geriatric vestibular disease in some cases where this condition was the main differential diagnosis. The dogs in cases 8 and 14 had slow recovery times and we are unable to provide an explanation for such a long recovery in case 8 (Table 1); however, the National Institute for Health and Care Excellence[32] states the use of metronidazole in paediatric human patients at lower doses than in adults and perhaps the young age (2 months old) or light body weight (2.5 kg) of the dog in case 8 may have influenced the metabolic clearance of the drug. The combination of the duration of antibiotic therapy (42 days) with the presence of chronic gastroenteric disease in case 14 may be associated with the delay in clinical improvement, despite the use of diazepam therapy.

All dogs (except in case 8) received a long course (defined as ≥ 7 days) of metronidazole; 54% presented with chronic diarrhoea, but only three dogs had a diagnosis for the cause of gastrointestinal dysfunction (Table 1). Furthermore, 43% of the dogs with diarrhoea were German Shepherd Dogs and this breed has been shown to have an increased risk for developing inflammatory bowel disease (IBD).[33] Metronidazole is commonly used in cases of IBD and secondary small intestinal bacterial overgrowth. Other antibacterial drugs such as oxytetracycline, tylosin[34] and, more recently, rifaximin[35] have been indicated for their use in IBD and they may be a better alternative to metronidazole. In addition, we have also found a high incidence of metronidazole toxicity in Labrador Retrievers and Labrador-crosses; however, metronidazole therapy was instituted to treat various pathologies (Table 1) and Labradors are also the most common breed in UK.[36] Therefore, the apparent breed predisposition should be viewed with caution. For both breeds of dog, we are not aware of any breed-related specific susceptibility to metronidazoletoxicity, which was therefore considered incidental. These findings highlight the need for a stepwise diagnostic work-up in order to identify the underlining aetiology and deliver the most appropriate treatment.[37]

Because of the varying dosages and duration of diazepam therapy, we were not able to formulate any conclusion regarding its usefulness.

Study limitations

The main limitations of this study are its retrospective nature and the additional lack of specific screening tests, such as high-performance liquid chromatography to determine serum concentrations of metronidazole.[38] However, the latter test is not easily available and we were unable to identify any laboratory or hospital able to perform it. Furthermore, in humans, this test does not seem sufficient to diagnose metronidazole toxicity, because of the lack of correlation between neurotoxicity signs and drug concentration.[15,38,39] Further studies are necessary to understand the benefits of this screening test in veterinary medicine.

In summary, neurotoxicity may occur at lower doses and during shorter treatment periods than previously reported. Because of the retrospective nature of this study, we were unable to reach any conclusion regarding dosages or duration of treatments. However, we would recommend caution with the use of metronidazole at dosages > 40 mg/kg every 24 h. The use of alternative drugs and/or more extensive work-up is encouraged,[40] avoiding the use of high or repeated doses without scientific and medical evidence in cases of clinical signs persisting. A randomised double-blind study of the use of metronidazole is needed in order to evaluate the safety, risks and side effects of this drug.

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Conflicts of interest and sources of funding

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Supporting information

Additional supporting information can be found in the online version of this article at the publisher's website: https://doi.org/10.1111/avj.12772

Figure 1. Patient (case 9) showing wide-based stance related to vestibulocerebellar ataxia secondary to metronidazole toxicity.

Figure 2. Case 2. Mid-sagittal T2W (A) and transverse T2W FLAIR (B) and T2W (C) images at the level of the 4th ventricle demonstrating bilateral symmetrical hyperintensity within the dentate nuclei (black arrows). FLAIR, fluid attenuated inversion recovery; T2W, T2-weighted.

Table 1. Details of signalment, duration of clinical signs, metronidazole dosage, time for resolution of clinical signs, eventual use of diazepam as part of the treatment and the reason for metronidazole therapy

Case no.	Breed	Sex	Age at presentation (years)	BW (kg)	Treatment duration (days)	Average dosage (mg/kg per 12 h)	Time of resolution (days)	Diazepam (dosage & duration)	Reason for therapy
1	German Shepherd Dog	F	5.0	28.8	58	20	1	0.5 mg/kg IV once, 0.5 mg/kg three times daily PO for 3 days	Diarrhoea caused by exocrine pancreatic insufficiency
2	German Shepherd Dog	FN	9.0	43.1	84	20	4	-	Diarrhoea
3	Labrador Retriever	MN	5.0	34.4	37	17	3	-	Chronic hyperplastic pododermatitis
4	Labrador × Mastiff	MN	2.5	40	23	20	3	0.25 mg/kg IV once, 0.2 mg/kg three times daily PO 3 days	Infection post tibial plateau levelling osteotomy
5	Border Collie	FN	9.8	14.6	10	40	4	n/a	Infection post tarsal fracture repair
6	Soft Coated Wheaten Terrier	FN	7.5	15.1	47	27	3	0.2 mg/kg four times daily PRN	Diarrhoea caused by lymphocytic plasmacytic enteritis
7	Weimaraner	MN	8.0	35	35	27	4	-	Endocarditis caused by urinary tract infection and secondary septicaemia
8	French Bulldog	M	0.1	2.5	5	20	26	-	Diarrhoea
9	Hungarian Vizsla	M	8.9	24.6	180	44	2	0.4 mg/kg three times	Diarrhoea

								daily PO 3 days	
10	Great Dane	M	2.4	78	20	20	3	0.2 mg/kg three times daily PO 3 days	Anal gland infection
11	German Shepherd Dog	M N	8.4	55	75	22	5	1 mg/kg IV once, 0.5 mg/kg three times daily 3 days	Chronic diarrhoea
12	Shih Tzu	FN	12.0	5.7	150	20	1	-	Chronic diarrhoea
13	German Shepherd Dog	F	4.0	42.3	21	30	5	Dose n/a three times daily 3 days	Chronic diarrhoea
14	German Shepherd Dog	FN	7.0	46	42	15	12	0.5 mg/kg IV once, 0.5 mg/kg three times daily 5 days	Chronic diarrhoea
15	Labrador	FN	11.3	20	60	20	6	0.5 mg/kg TID 3 days	Chronic diarrhoea
16	Patterdale terrier	M	0.3	4.5	7	22	2	0.5 mg/kg IV twice, 45 min apart	Diarrhoea
17	WHWT	FN	9.1	8.9	14	56	3	0.5 mg/kg three times	Abscess under eye

								daily PO 3 days	
18	Labrador	MN	11.1	34.8	21	20	1	0.4 mg/kg three times daily PO 4 days	Jaw wound
19	Labrador	FN	9.1	29.4	29	26	2	-	Septic arthritis
20	Labrador	FN	2.4	36.6	20	22	1	0.4 mg/kg three times daily PO 3 days	Chronic diarrhoea
21	Labrador X	MN	7.7	65	28	21	3	0.4 mg/kg three times daily PO 5 days	Arthritis
22	German Shepherd X	FS	5.9	26	28	23	2	0.2 mg/kg three times daily PO 7 days	Bronchopneumonia
23	German Shepherd Dog	FS	5.1	30	35	13	3	0.3 mg/kg three times daily PO 14 days	Anal furunculosis
24	Boxer	FS	7.8	28.1	42	21	2	0.25 mg/kg TID PO 7 days	Wound dehiscence post mast cell tumour removal
25	German Shepherd Dog	M	3.3	32.9	35	30	2	0.3 mg/kg three times	Diarrhoea caused by inflammatory bowel disease

								daily PO 8 days	
26	Shih Tzu	M N	6.6	6.6	152	20	4	-	Chronic diarrhoea

BID, twice daily; BW, body weight; FN, female neutered; MN, male neutered.

Table 2. Most common clinical signs of metronidazole toxicity in 26 dogs

Case no.	Cerebellovestibular ataxia	Wide-based stance	Non-ambulatory	UMN paresis	Hypermetria	Tremors	Nystagmus	Head tilt	Reduced PLR	Reduced menace
1	✓	✓			✓					
2	✓			✓				✓		
3	✓		✓				✓	✓		
4	✓	✓		✓						
5	✓					✓	✓			
6	✓	✓	✓			✓	✓		✓	
7	✓									
8	✓									
9	✓				✓					✓
10				✓	✓		✓			✓
11	✓						✓			✓
12	✓			✓		✓			✓	✓
13	✓			✓	✓		✓			✓
14			✓	✓			✓			
15			✓	✓			✓			✓
16	✓								✓	
17	✓		✓			✓				
18	✓		✓		✓					
19	✓			✓		✓	✓			
20	✓				✓		✓			

21	✓									
22	✓						✓			
23	✓				✓		✓			✓
24										
25	✓						✓	✓		
26	✓				✓					

PLR, pupillary light reflex; UMN, upper motor neurone.