"Not an Average Walk in the Park"

A Case Report of Metronidazole Toxicity in a Canid

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Introduction:

Metronidazole is a synthetic nitroimidazole and is a commonly utilized antibiotic/ antiprotozoal in veterinary medicine. It is used in the treatment various conditions such as inflammatory bowel disease (IBD), gastritis, giardiasis, diarrhea, and anaerobic infections.[4] Metronidazole has also been advocated for use in disease processes such as osteomyelitis and periodontal disease.[1] The therapeutic mechanism of action of the drug causes changes that lead to impaired function of microbial DNA and cell death.[6] Recommended doses of this drug generally range from 12-15mg/kg q12 hours for dogs and 10-25mg/kg q24 hours for cats.

Toxicity is thought to occur in animals receiving a high dose of the drug for short periods of time, as little as 5 days, or animals that are on a prolonged therapy. The maximum safe dose for any species is considered to be 50mg/kg/day.[3] Toxicity is iatrogenic in origin and is therefore avoidable in most instances though some animals may have a decreased resistance to its toxic effects. The lesions are commonly found in the brainstem of canids and the forebrain of felid patients with evidence of vasogenic or cytotoxic edema within the affected tissues.[3] Metronidazole toxicity has been noted in a wide range of species from mice, to domestic species, and also humans.[4]

History and Presentation:

On April 12, 2018 an approximately three year old female, spayed mixed breed dog presented to MSU-CVM Emergency service following a 48 hour history of a hyermetric gait, most notably in the hind limbs, that had progressed to the fore limbs over the preceding eight hours. The patient was seen three weeks prior to presentation by its primary veterinarian for a recheck examination following visiting an emergency clinic in the preceeding days for acute vomiting. The primary veterinarian denoted mild pain on abdominal palpation. Gastrointestinal

upset was suspected for which maropitant citrate and subcutaneous fluids were administered. The patient returned to its primary veterinarian the next day with no improvement in the present condition. No vomiting was noted, however the patient was inappetent and the owners had recently discovered the patient hiding under furniture, as well as reluctance to jump. The primary veterinarian noted a hunched posture and palpable evidence of pain at the thoracolumbar junction. The patient was suspected to have intervertebral disc disease (IVDD), and prescribed methocarbamol. The following day, the patient was re-presented to its primary veterinarian with no improvement in clinical status. Pain remained palpable at the thoracolumbar junction and as a result lateral spinal radiographs were performed. The resultant images were unremarkable. The patient was hospitalized overnight and received laser therapy at the thoracolumbar junction. In order to combat the persistent spinal pain Previcoxx, Gabapentin, and Tramadol were prescribed. The laser therapy was repeated over the next two days as an outpatient treatment. The patient once again presented to the primary veterinarian on March 27th, eight days after initial presentation, for a recheck following a second emergency visit. The patient had experienced a solitary vomiting episode in the days prior. Radiographs obtained by the emergency clinician were clinically unremarkable. The patient had been prescribed Miramaxx and Previcoxx by the emergency clinician. The owner initiated therapy with prednisone in addition to the aforementioned medications over the two day period prior to re-presentation to the primary veterinarian. The patient was lethargic and inappetant on presentation. The primary veterinarian noted grunts on abdominal palpation and firm stool in the distal colon in addition to loose tarry feces on rectal papation. The patient was also mildly dehydrated and exhibited no palpable spinal pain. The patient was hospitalized overnight and treated with intravenous fluids, cefazolin, and sucralfate. No change was noted in the patient's condition overnight. Lateral radiographs

revealed gas distention in the stomach and a barium study determined gastrointestinal motility to be decreased with no evidence of obstruction. Intravenous fluids were continued overnight. The next day, March 29th, the patient was discharged with an aggressive treatment protocol consisting of metoclopramide, famotidine, sucralfate, enrofloxacin, metronidazole, amoxicillin, and iron supplementation. The patient's clinical signs resolved, and two days prior to presentation to MSU-CVM, antibiotic therapy was completed, and the patient was only receiving sucralfate and famotidine. On April 11, 2018 the patient acutely developed hypermetria in the hind limbs, which progressed to the fore limbs by mid-afternoon on April 12, 2018. The patient was re-evaluated by its primary veterinarian, then referred to MSU-CVM Neurology service for further evaluation.

Upon presentation to MSU the patient was dull, alert, and responsive. The presenting weight was 12.7kg, temperature 99.6F, pulse 120 beats per minute, and respiratory rate 32 breaths per minute. Thoracic auscultation yielded muffled heart sounds, yet pulse oximetry was normal at 100% and ECG yielded a normal sinus rhythm. The patient was 5% dehydrated and blood pressure was mildly decreased at 97/48 (64). The patient was ambulatory but exhibited hypermetria and cerebellovestibular ataxia in all limbs. The remainder of the neurologic examination was unremarkable. The patient was given a vestibular/cerebellar neuroanatomic localization. Thoracic radiographs were taken and yielded no abnormalities. The patient remained hospitalized and was placed on intravenous fluids. A presumptive diagnosis of metronidazole toxicity was determined based on the history of metronidazole use, clinical signs and neuroanatomic localization.

Pathophysiology:

Metronidazole is highly bioavailable with peak concentrations reached 1 hour post administration.[1] The drug is lipophilic and is readily absorbed from the gastrointestinal tract with increased concentrations being achieved in the plasma, bone, peripheral tissues and central nervous system.[3] Metronidazole undergoes hepatic metabolism and primarily renal excretion, however it may also be excreted fecally. The elimination half-life of metronidazole is about 3-13 hours in the dog and cat.[1] The therapeutic mechanism of action requires anaerobic conditions and is suspected to be governed by reductive activation accomplished via the electron transport chain within the microbial organism.[2] The reduced form of the drug then binds the microbial DNA and leads to the loss of the helical structure of the DNA and strand breakage.[6]

The mechanism of neurotoxicity is unknown but there are two putative theories. Mechanism one involves modulation of the gamma-aminobutyric acid (GABA) receptor. The second mechanism involves the production of neurotoxic radicals following interactions of metronidazole with catecholamine neurotransmitters. These radicals cause damage to the GABA receptor. Both mechanisms are similar in the fact that they both point to the GABA receptor as the target leading to neurotoxic effects; with one detailing competitive binding with the GABA receptor and the other, destruction of the receptor by neurotoxic radicals.[2] Metronidazole is believed to have an affinity to the GABA receptor based on its similar clinical structure with the benzodiazepine antagonist flumazenil and the clinical signs associated with its toxicity. Like flumazenil, metronidazole has an imidazole component and may bind sites on the GABA receptor leading to hyperexcitability secondary to inhibition loss.[2] Toxicity generally occurs in animals that are administered a high dose for short periods of time or those administered an appropriate dose for prolonged periods of time. In dogs a dose as low as 60mg/kg over a 3-14

day period can lead to toxic effects and a dose of 250mg/kg can lead to acute signs of toxicosis. In the feline patient a dose as low as 58mk/kg daily for 6 months can lead to toxicity as well as a dose of 111mg/kg/day for 9 weeks.[3] Neuronal disturbance can be noted within 1-12 weeks following administration of metronidazole.[6]

Common clinical signs seen with a toxic dose of this drug in canids include lethargy, ataxia, positional nystagmus, muscle spasms, head tilt, conscious proprioception deficits, mydriasis, and opisthotonus.[3] Clinical signs seen in the felid resemble signs of a forebrain lesion indicating forebrain involvement with signs such as ataxia, weakness, disorientation, seizures, decreased postural reactions, and blindness. Clinical signs are often progressive and begin with lethargy and potentially intermittent vomiting and quickly progress to generalized ataxia and nystagmus.[3]

Diagnostic Approach:

As with any toxicity a definitive diagnosis begins with a thorough history and physical exam. Following a complete physical exam, a neurological exam should also be performed. In many cases, the presence of clinical signs, no history of access to toxins, and knowledge that metronidazole has been utilized as medical therapy in the patient, lead the clinician to prophylacticly treat for metronidazole toxicity. Resolution of clinical signs is often diagnostic of this toxicity.[3] Though this is the common way metronidazole toxicities are diagnosed there are diagnostic approaches that can be taken to allow for definitive diagnosis of this condition prior to treatment.

A diagnosis of metronidazole toxicity can be further established by assessing plasma concentration of the drug. Blood plasma concentrations are not commonly assessed in veterinary

private practice for diagnosis of metronidazole toxicity.[3] Studies in the human patient suggest that neurotoxicity does not correlate with cerebrospinal fluid (CSF) or serum concentrations of metronidazole; additional studies in domestic species are required to determine if a correlation truly exists.[4] Serum and CSF metronidazole measurements are evaluated utilizing high performance liquid chromatography (HPLC). This method separates different components of a mixture and determines their identity based on their reaction with a specific absorbent material.[4] Elevated protein levels may also be noted on CSF evaluation.[1] Based on the neurological signs associated with the toxic effects of metronidazole, computed tomography (CT) may be performed to rule out other conditions that can lead to similar signs, most notably a stroke, neoplasia, or an infarct.[4] Magnetic resonance imaging (MRI) is a useful mode of imaging that can differentiate metronidazole toxicity from other toxins, metabolic disease, neuronal disorders, or neoplasms.[3] Data from previous studies on rats yielded lesions in the cerebellum similar to those associated with thiamin deficiency and when carbon labeled metronidazole was administered, the drug was detectable in the rat's cerebellum.[6] Studies in humans have shown T2 hyperintense lesions of the cerebellar dentate nucleus, midbrain, dorsal pons, medulla, corpus callosum, and cerebral white matter.[4] These lesions correspond to vasogenic and cytotoxic edema resulting from the toxic effects of the drug.[5] The drug is believed to react similarly in canids, felids, rats, and humans based on clinical and histological findings.[6] Though metronidazole toxicity, with adequate treatment, does not generally end in death, post mortem changes can also be identified to confirm a diagnosis. Post mortem histological examination reveals axonal swelling and degeneration within the vestibulocebellar pathway and brainstem leukoencephalomalacia.[1] Purkinje cell loss may also be noted. Changes noted on post mortem

examination are consistent with the clinical signs seen in patients suffering from metronidazole toxicity.[3]

Treatment and Management:

Current treatment for metronidazole toxicity include discontinuation of drug administration along with supportive therapy and diazepam.[4] Diazepam is commonly used in veterinary medicine as an anticonvulsant, muscle relaxant, sedative, anxiolytic, and appetite stimulant. Diazepam is believed to dramatically aid in the resolution of clinical signs by facilitating the effects of the inhibitory neurotransmitter GABA.[2] GABA is the principle neurotransmitter of the central nervous system. Activation of its receptors increases chloride conductance at the postsynaptic membrane which induces hyperpolarization of the membrane.[3] This decreases the excitement within the vestibular system leading to a resolution of clinical signs.[4] As previously discussed, it is postulated that metronidazole binds to the GABA receptor preventing inhibition. Diazepam is believed to compete with metronidazole for the receptor site or support GABA propagation via unaffected receptors.[2] Not surprisingly, the use of diazepam in the treatment of this condition greatly improves speed at which clinical signs are resolved in patients suffering from metronidazole toxicity. A dog that is treated with diazepam following a diagnosis of metronidazole toxicity on average has a 13 hour response time with a 39 hour average recovery time. Whereas, when diazepam is not utilized in the treatment protocol, there is an average response time of 4.25 days with an average time to recovery of 11.6 days.[2] In the feline patient diazepam administration may cause a behavioral change and can also be associated with hepatic failure. Therefore, its use in cats is controversial. Average response time in cats with drug discontinuation and supportive therapy alone is approximately 48 hours.[1]

Case Management:

The current case was managed utilizing conservative therapy under the presumed diagnosis of metronidazole toxicity. The patient's metronidazole regimen was completed two days prior to presentation. The current medical therapy consisting of sucralfate and famotidine was discontinued, and the patient was placed on intravenous fluid therapy and diazepam (loading dose of 0.3 mg/kg IV and 0.5 mg/kg PO q8 hours). The following morning, April 13th, the patient was noted to be significantly improved, only exhibiting mild residual ataxia. The clinical improvement in under 24 hours following initiation of therapy was indicative of effective treatment. The patient remained in hospital overnight for continued therapy. On the morning of April 14th the patient had an episode of diarrhea, and subsequently became lethargic and laterally recumbent. Subsequently, bloodwork was performed revealing hyponatremia, hyperkalemia, mild normocytic normochromic anemia, hypoalbuminemia, and mildly elevated serum lactate at 1.1mg/dl. Based on these findings, intravenous fluid therapy was continued, a baseline cortisol was performed and found to be decreased at <1.0 μg/dl. Addison's disease was suspected in addition to the presumptive diagnosis of metronidazole toxicity. As a result, intravenous glucocorticoid theray (dexamethasone sodium phosphate) was also initiated. Given this additional information, sucralfate, maropitant citrate, and pantoprazole were added to the treatment protocol. As a prophylactic therapy, fenbendazole administration was initiated as whipworm infection is a common differential for the associated electrolyte abnormalities noted on the patient's bloodwork. There was no significant change noted in the patient's status on day four. On April 16, 2018 the patient was transferred to the MSU-CVM Internal Medicine service for further evaluation of suspected Addison's disease, which was confirmed with an ACTH

stimulation test. The next day, April 17th, the patient was discharged. The take home medications consisted of prednisone, maropitant, omeprazole, tylosin, sucralfate, and deoxycorticosterone (DOCP). The patient was scheduled for a recheck examination in two weeks to assess electrolyte status.

Case Outcome:

At the time of discharge the patient displayed complete resolution of clinical signs. Unfortunately the patient did not return for her two week checkup, however, the primary veterinarian was contacted to obtain follow-up information. The primary veterinarian has confirmed continued resolution of the patients clinical signs. The patient was seen for an electrolyte recheck on July 24th at which time no abnormalities were noted. The glucocorticoid therapy has also since been decreased with no evident adverse effects.

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