Metronidazole Toxicosis (Canine)

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Synonyms

Flagyl® toxicosis
Metronidazole neurosis
Metronidazole overdose
Metronidazole poisoning

Disease Description

Definition

Metronidazole is a nitroimidazole antibiotic. It is commonly prescribed to treat anaerobic bacterial and protozoal infections that are associated with diarrhea, inflammatory bowel disease, or hepatic encephalopathy. Toxicosis can cause gastrointestinal (GI) and central nervous system (CNS) signs. In humans, both CNS signs and peripheral neuropathies have occurred. In dogs and cats, central vestibular and cerebellar dysfunction are most commonly reported. Hepatotoxicosis may also rarely occur.[1-4]

Etiology

Metronidazole toxicosis most commonly occurs when patients are placed on high-dose and/or long-term therapy.[5,13-15] Oral dosages >40 mg/kg/day (range 40-129 mg/kg/day, typically divided q 8-12 hrs) are associated with neurotoxicosis in dogs, although a few reports of dogs developing signs at dosages as low as 26 mg/kg/day have been noted.[1,4,15] Note that toxicosis at lower dosages tends to be associated more with chronic administration than acute dosing.[1,4,15] Typical dosage of metronidazole is 10-25 mg/kg PO q 12 hrs. Anecdotally, many veterinarians try to limit total daily dosage to 20-30 mg/kg/day to further avoid risk of toxicosis.[13,14]

Pathophysiology

Metronidazole is rapidly absorbed upon oral administration, usually within 1-4 hours. Bioavailability varies (i.e. 50-100%). Upon absorption, metronidazole is metabolized by the liver, exhibiting a half-life of 3-13 hours in the dog.[2,4,15] It distributes widely throughout the body, readily crossing the blood-brain barrier.[2]

Mechanisms of metronidazole hepatotoxicosis and neurotoxicosis are not fully understood. It is thought that metronidazole binds nucleic acids (i.e. DNA, RNA) within neurons of the CNS, inhibiting protein synthesis. This can lead to neuronal and axonal degeneration.[1,3] Neurotoxic effects of metronidazole are likely associated with inhibition of γ-aminobutyric acid (GABA) within the cerebellar and vestibular systems.[4,9,10,12] This theory is supported by observations that diazepam, a drug that also interacts with GABA receptors, can speed recovery of patients with metronidazole neurotoxicosis.[4]

Signs of neurotoxicosis are generally reversible upon discontinuation of metronidazole, suggesting only temporary CNS effects in most patients.[9,12,15] Not all patients recover. Histopathology and brain imaging have demonstrated axonal swelling and degeneration, neuronal necrosis, and demyelination (e.g. within vestibular-cerebellar white matter tracts, sometimes extending from diencephalon to medulla oblongata) in severely affected patients.[1,3,5]

Diagnosis

Physical Examination Findings/History: History of metronidazole administration may be reported. Findings can vary and may include lethargy, weakness, anorexia, vomiting, diarrhea, altered mentation/disorientation, vocalization, head tilt, vestibular ataxia, blindness, positional or vertical nystagmus, proprioceptive deficits, non-ambulatory tetraparesis, hypermetric gait, reduced menace, reduced pupillary light reflexes, tremors, rigidity, torticollis, opisthotonos, and seizures.[1,4,10,13,15] Signs of hepatotoxicosis may also rarely be seen.[4] Note that dogs tend to demonstrate signs associated with brain stem dysfunction (e.g. paresis, ataxia) more commonly than forebrain dysfunction (e.g. disorientation, seizures), which is seen more frequently in cats.[4,13,15]

Complete Blood Count: Lymphopenia and neutropenia are possible but not diagnostic.[4,15]

Biochemistry Profile: Findings are nonspecific. Increased alkaline phosphatase and/or bilirubin, as well as hypoproteinemia may be noted.[4,15]

Urinalysis: Hematuria may occur via rare, secondary cystitis. Also rare, brown to red discoloration may be noted in the urine, which is associated with water-soluble pigmentation formed during metronidazole metabolism. Latter finding may be more common in people than animals.[16,17]

Advanced Imaging: Magnetic resonance imaging may show bilaterally symmetrical hyperintensity as well as other lesions of the lateral nuclei in the cerebellar white matter. Alterations along vestibular-cerebellar white matter tracts may also be noted.[1,15]

Metronidazole Assay: Definitive diagnosis requires measurement of metronidazole concentrations in the blood. Such testing is rarely performed.[13]

Disease Description in This Species

Signalment

No breed, sex, or age predisposition has been noted.

Clinical Signs

Metronidazole toxicosis can cause mild GI signs, such as vomiting, anorexia, nausea, and diarrhea.[4] Dogs are often presented with a wide-based stance and inability to walk.[15] Clinical signs may also include lethargy, vertical or positional nystagmus, ataxia, upper motor neuron paresis, reduced menace and pupillary light response, hypermetria, extensor rigidity of limbs, intention tremors, head tilt, torticollis, opisthotonos, tremors, and seizures. Although rare, signs of hepatotoxicosis may also be noted.[1,4,10,13,15]

Etiology

Metronidazole

Breed Predilection

None

Sex Predilection

None

Age Predilection

None

Clinical Findings

AFEBRILE
Anorexia, hyporexia
ATAXIA, INCOORDINATION, DYSMETRIA
BLINDNESS OR OTHER VISUAL DEFICIT
Central nervous system (CNS) signs
Cerebellar signs
Circling
Collapse of patient or syncope
Coma, unconsciousness

Cutaneous hyperesthesia
Dehydration
Dementia, altered mentation
Depression, lethargy
DIARRHEA
Disorientation
Exercise intolerant, reluctant to move
HEAD TILT
Hematuria
HEMORRHAGE
Intention tremors
Limbs extended
Nausea
NYSTAGMUS
Nystagmus vertical
Opisthotonos, opisthotonus
PARALYSIS OR PARESIS
Paraparesis, paresis
Proprioception abnormal
Pupillary light reflex absent
Pupillary light reflex decreased
SEIZURES, CONVULSIONS
Tetraparesis, quadriparesis
Torticollis, neck twisted
TREMORS
Urine discolored, cloudy
Vocalization increased
VOMITING
Weakness: Asthenia or Paresis
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Diagnostic Procedures

Diagnostic Procedures:	Diagnostic Results:
Complete blood count (hemogram)	Lymphopenia, blood lymphocytes decreased Neutropenia, neutrophils decreased
Urinalysis	Red blood cells present in urine
Serum biochemistries	Alkaline phosphatase (ALP) increased Hyperbilirubinemia, bilirubin increased Hypoproteinemia
Necropsy	Swelling of axon sheaths in vestibular-cerebellar white tracts

Treatment / Management

IMMEDIATE THERAPY

Manage any life-threatening clinical signs (e.g. seizures) first. Consider GI decontamination within 1 hour of large oral overdoses.

Decontamination

Induce emesis using one of the following:

1) Apomorphine can be given at 0.02-0.05 mg/kg IV or 0.08 mg/kg IM, SC. Half of a 6 mg tablet can be crushed and placed into the conjunctival sac of one eye, with tablet residue flushed out with saline for 2-3 minutes as soon as emesis occurs.[6,16]

2) Ropinirole can be administered topically to the eye at 3.75 mg/m^2 according to this dosing chart.[7]

3) Hydrogen peroxide 3% is given at 2 mL/kg PO or 1 mL/Lb, up to maximum of 45 mL, and may be repeated once. Feeding a few pieces of bread prior to administration provides bulk that may increase vomiting and aid in more thorough evacuation of the stomach. Walking afterwards may aid in emesis. Note that risk exists of causing esophagitis, hemorrhagic gastritis, and air embolism. Because of such risks, many clinicians no longer recommend its use.[8,16]

Activated charcoal may be given at 1-5 g/kg PO. For large ingestions, consider a second dose 4-6 hrs later.[6,16]

SPECIFIC THERAPY

Discontinue metronidazole until signs fully resolve. If it is necessary to resume metronidazole therapy, use a lower dosage (<30 mg/kg/day).

Diazepam at 0.43 mg/kg (range 0.2-0.69 mg/kg) IV, followed by the same dose given orally, q 8 hrs for 3 days may enhance recovery time because of diazepam's effects on GABA in the vestibular system.[4,13,15,16] In one study of 21 dogs experiencing metronidazole toxicosis, diazepam administration resulted in positive responses within 24 hours compared to 2-10 days among dogs not given diazepam. Full recovery occurred within 72 hours for the diazepam group compared to 5-21 days in the control group.[4]

SUPPORTIVE THERAPY

Fluid therapy may be necessary for several days. Ensure that ataxic patients are kept in an appropriately-sized kennel and assisted when walking.[13]

MONITORING and PROGNOSIS

Monitor neurologic function, body temperature, blood pressure, and respiration. Prognosis is typically excellent. Clinical improvement usually occurs within 2-14 days after discontinuing metronidazole; however, some neurological effects may take weeks to months to fully resolve. Severely affected patients may die, but this is rare.[4,13]

Preventive Measures

Avoid high-dose and/or long-term metronidazole therapy whenever possible. Use lower dosages in patients with pre-existing hepatic disease.[4,10,13,15]

Special Considerations

Other Resources

Recent Message Boards discussions on metronidazole toxicosis
Recent Proceedings on metronidazole toxicosis
Small Animal Diagnoses algorithm on Head Tilt/Nystagmus

Veterinary Partner article on Metronidazole

VIN Veterinary Drug Handbook monographs on:
Metronidazole
Diazepam

Differential Diagnosis

Alcohol toxicosis
Bromethalin toxicosis
Brain abscess
Diabetic ketoacidosis
Ethylene glycol toxicosis
Fungal granuloma
Encephalitis
Head trauma
Hepatic encephalopathy
Lead toxicosis
Macrocyclic lactone toxicosis, e.g. ivermectin, moxidectin
Marijuana toxicosis
Mercury toxicosis

Neoplasia, intracranial
Vestibular disorders, e.g. otitis interna, idiopathic vestibular disease

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