Diazepam as a Treatment for Metronidazole Toxicosis in Dogs: A Retrospective Study of 21 Cases

Jason Evans, Donald Levesque, Kim Knowles, Randy Longshore, and Scott Plummer

The currently recommended treatment for metronidazole toxicity is drug discontinuation and supportive therapy. Reported recovery times are 1–2 weeks. The records of 21 dogs with metronidazole toxicosis were retrospectively analyzed to determine whether diazepam improved recovery. The dosage and duration of metronidazole therapy and the response and recovery times of 13 dogs treated with diazepam were compared to those of 8 dogs receiving only supportive care. Response time was defined as the time to resolution of the debilitating clinical signs. Recovery time was the time to resolution of all residual clinical signs. The average dosage and duration of metronidazole administration for the diazepam-treated and untreated groups were 60.3 mg/kg/d for 44.9 days and 65.1 mg/kg/d for 37.25 days. The protocol for diazepam administration consisted of an initial IV bolus and then diazepam PO q8h for 3 days. The average dosage of both the IV and PO diazepam was 0.43 mg/kg. The average recovery time for the diazepam-treated dogs was 13.4 hours compared to 4.25 days for the untreated group. Recovery time also was markedly shorter for the diazepam-treated dogs (38.8 hours) compared to the untreated group (11 days). Results of this study showed that dogs with metronidazole toxicosis recover faster when treated with diazepam. Although the mechanism of metronidazole toxicosis or how diazepam exerts its favorable effect is not known, it is likely related to modulation of the γ-aminobutyric acid (GABA) receptor within the cerebellar and vestibular systems.

Key words: Benzodiazepine; Cerebellar disease; Drug toxicity; γ-Aminobutyric acid; Vestibular syndrome.

Metronidazole is a nitroimidazole antibacterial and antiprotozoal compound used routinely in the treatment of giardiasis, anaerobic infections, and inflammatory bowel disease. It has high bioavailability for most tissues, including bone and the central nervous system. Metronidazole is metabolized by the liver and has a half-life of 3–13 hours in the dog. The adverse effects of metronidazole in humans, which include seizures, ataxia, peripheral neuropathy, and hematuria, are well documented. Adverse effects of metronidazole in the dog and cat have been reported and include vomiting, hepatotoxicity, neutropenia, and neurologic signs such as seizures, head tilt, falling, paresis, ataxia, vertical nystagmus, tremors, and rigidity. Neurologic adverse effects in cats have a greater tendency to reflect forebrain dysfunction (disorientation and seizures) than brain stem dysfunction.

Neurologic toxicity from metronidazole has been reported in dogs receiving >60 mg/kg/d for an average of 3–14 days, but reports of toxicity at lower dosages have been cited. The mechanism of the toxic effects of metronidazole has not been identified. The currently recommended therapy for treating metronidazole toxicosis is discontinuation of the drug and supportive therapy. No specific treatment to counteract the toxic effects of metronidazole has been reported. Reported recovery times of dogs with neurologic manifestations of metronidazole toxicosis are 1–2 weeks.

In humans, the centrally acting benzodiazepine diazepam has long been used in the symptomatic treatment of vertigo or disequilibrium secondary to diseases of the vestibular system such as benign paroxysmal vertigo (BPV) and endolymphatic hydrops (Meniere’s disease). Diazepam is believed to exert its antivertiginous effects by facilitating the effects of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) within the vestibular system. Diazepam is principally used in veterinary medicine for its anticonvulsant, muscle-relaxant, sedative, anxiolytic, and appetite-stimulating properties. It has been suggested for use as a sedative in animals with severe disequilibrium secondary to vestibular syndromes, but reports suggesting its application as an antidote to a specific toxicity are lacking.

At the Veterinary Neurological Center (VNC), dogs presenting with signs of metronidazole toxicosis that were treated symptomatically with diazepam appeared to have a more rapid resolution of clinical signs than dogs in various published reports that had been treated with conservative therapy alone. To evaluate potential differences in the recovery time between dogs with metronidazole toxicosis treated with diazepam and a similar group that did not receive diazepam as part of the therapy, the following parameters were compared: dosage of metronidazole, duration of therapy, time to resolution of the debilitating clinical signs (response time), and time to final resolution of all residual clinical signs (recovery time).

Although the exact mechanism of metronidazole toxicity is not known, the neurologic adverse effects are indicative of cerebellar and central vestibular dysfunction. The neuroinhibitory actions of benzodiazepines on the brain have been shown to be mediated by GABA. Because GABA is the major inhibitory neurotransmitter of the cerebellar and vestibular systems and because benzodiazepines such as diazepam have their major effect on this neurotransmitter, a possible relationship between metronidazole and diazepam was postulated. Further speculation for metronidazole’s affinity for the GABA receptor site was based on the similarity of both the chemical structure and clinical
signs of toxicity of metronidazole and the benzodiazepine antagonist flumazenil, which also is known to attach to the GABA receptor.21

Materials and Methods

Criteria for Case Selection

Medical records of 33 dogs at the VNC with a diagnosis of metronidazole toxicosis between 1997 and 2001 were reviewed. Twenty-one dogs were selected for this study on the basis of the availability of data regarding metronidazole dosage and duration of therapy before the onset of clinical signs, response time, and recovery time. Thirteen of the 21 dogs had been treated with diazepam, whereas the other 8 dogs had not received diazepam as part of their therapy. Response time was defined as the time to resolution of debilitating clinical signs and was determined by physical examination. For the purpose of this study, debilitating clinical signs were those signs that resulted in the loss of vestibular function, motor function, or both to the degree that ambulation, eating, or drinking could not be performed. Debilitating clinical signs typically were related to the profound disequilibrium often associated with vestibular syndromes. Recovery time was defined as the time to resolution of residual clinical signs of metronidazole toxicosis, which was the point at which the dog was considered normal by either clinical examination or owner evaluation. Data concerning breed, age, history, manifestations of metronidazole toxicosis, and previous treatments were collected but not considered in the statistical analysis.

Treatment

The treatment for 13 patients with a tentative diagnosis of metronidazole toxicosis at the VNC included an initial bolus of diazepam administered IV and then PO q8h for 3 days. Metronidazole was discontinued in all animals, and supportive care including IV fluid administration was given to animals that were admitted to the hospital. Treatment for the group of dogs that did not receive diazepam after a diagnosis of metronidazole toxicosis primarily consisted of discontinuation of the drug and supportive care. Summary information of the dosages of both IV and PO diazepam administered is listed in Table 1.

Diagnosis of Metronidazole Toxicosis

Blood concentrations of metronidazole were not measured, but all dogs in this study were diagnosed with metronidazole toxicosis on the basis of a history of having received metronidazole, clinical signs compatible with metronidazole toxicosis, absence of other clinical disease, and eventual recovery of all dogs upon discontinuation of metronidazole administration.

Table 1. Summary statistics of dogs with metronidazole toxicosis in the treated and untreated groups.*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated Group</th>
<th>Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>7.5 (3–13)</td>
<td>6.7 (0.8–13)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>13.4 (4.2–30)</td>
<td>20.4 (4.1–47.3)</td>
</tr>
<tr>
<td>Metronidazole dosage (mg/kg/d)</td>
<td>65.1 ± 23.3 (39.3–110)</td>
<td>60.3 ± 17.5 (33.3–83)</td>
</tr>
<tr>
<td>Metronidazole duration (days)</td>
<td>37.3 ± 34.9 (10–120)</td>
<td>127.5 ± 295.5 (7–1099)</td>
</tr>
<tr>
<td>Diazepam IV (mg/kg)</td>
<td>N/A</td>
<td>0.43 ± 0.14 (0.2–0.69)</td>
</tr>
<tr>
<td>Diazepam PO (mg/kg)</td>
<td>N/A</td>
<td>0.43 ± 0.13 (0.3–0.69)</td>
</tr>
<tr>
<td>Response timeb</td>
<td>4.25 ± 2.8 days (2–10)</td>
<td>13.05 ± 9.8 hours (0.3–24)</td>
</tr>
<tr>
<td>Recovery timeb</td>
<td>11.6 ± 5.9 days (5–21)</td>
<td>38.8 ± 15.6 hours (24–72)</td>
</tr>
</tbody>
</table>

N/A, not applicable.

* The response and recovery times for the untreated group are listed in days, and the response and recovery times for the treated group are listed in hours.

Statistical Analysis

All statistical comparisons between the 2 groups were made by the Student’s t-test. The level of significance was chosen as P < .05. Correlation analysis was applied to the scatterplot (Fig 1) to measure the correlation coefficient (r) of the relationship between dosage and duration of metronidazole administration and the onset of clinical signs of metronidazole toxicosis.

Results

The ages of the dogs in this study ranged from 10 months to 13 years, and the weight of the dogs ranged from 4.1 to 47.3 kg. Only 1 breed of dog (Shih Tzu) was represented more than once (twice) in this study.

The results of routine physical examinations did not identify any other major abnormality except for the neurologic signs. Nearly all of the neurologic problems were acute, and the dogs were presented to a veterinarian within 24 hours of the onset of signs. Additionally, the final dose of metronidazole had been given to all dogs within 24 hours of presentation to the VNC for examination. CBCs and serum biochemistry were performed in 11 of 21 dogs, and the most common abnormalities were mild-to-moderate increases in alkaline phosphatase activity and stress leukograms. Serum titers for Coccidioides immitis and Ehrlichia canis had been performed on 7 and 8 dogs, respectively, and were negative. In addition, serum bile acid concentrations had been measured in 3 dogs, whereas computed tomography brain scans and cerebrospinal fluid analyses were performed on 2 dogs. All results were within normal limits.

The most common neurological signs were vertical nystagmus (17 of 21), truncal ataxia (15 of 21), inability to walk (10 of 21), upper motor neuron (UMN) paraparesis (7 of 21), hypermetria (5 of 21), extensor rigidity of all 4 limbs (5 of 21), UMN tetraparesis (5 of 21), intention tremors (4 of 21), right head tilt (2 of 21), left head tilt (1 of 21), right torticollis (2 of 21), and opisthotonus (2 of 21). Of the 10 dogs that were nonambulatory, 5 were unable to walk without assistance because of cerebellovestibular dysfunction, but these dogs were not tetraparetic.

The most common reasons for administration of metronidazole were for treatment of gastrointestinal signs such as diarrhea (7 of 21) or vomiting (4 of 21), for suspected inflammatory bowel disease (5 of 21), for high liver en-
zyme activities (2 of 21), for giardiasis (2 of 21), and for
dental disease (1 of 21). Before the diagnosis of metroni-
dazole toxicosis, medical treatments for the neurologic
signs consisted of one or more of the following: corticoste-
roids (16 of 21), antibiotics (8 of 21), methocarbamol (5
of 21), carprofen (3 of 21), meclizine (2 of 21), and but-
torphanol (2 of 21).

Table 1 lists the summary statistics of dosages and du-
ration of metronidazole administration, dosages of IV and
PO diazepam, if applicable, and response and recovery
times for dogs in the untreated and treated groups.

The average daily dosage of metronidazole for dogs that
received diazepam was 60.3 mg/kg/d; for dogs that were
not treated with diazepam, the average daily dosage of met-
ronidazole was 65.1 mg/kg/d. The range of the individual
dosages of metronidazole for dogs that were given diaze-
pam was 33–83 mg/kg/d. The range of the metronidazole
dosages for dogs in the untreated group was 45–110 mg/
kg/d. The average daily dosage of metronidazole was not
significantly different between the 2 groups (P > .05).

The average duration of metronidazole administration for
dogs treated with diazepam was 127 days, with a range of
7–1,099 days. The average duration of metronidazole ad-
ministration was 37 days for animals in the untreated group,
with a range of 10–120 days. If the data from dog 13 of the
diazepam-treated group that had been on metronidazole
therapy for 1,099 days are disregarded, the average duration
of metronidazole use for the diazepam-treated group be-
comes 44 days. The resulting calculation is closer to the
37-day average of the untreated group; however, including
the data from this dog does not alter the statistical analysis
in comparing the 2 groups. The duration of metronidazole
administration was not significantly different between the 2
groups (P > .05).

The average single, initial IV dosage of diazepam was
0.43 mg/kg, and the average subsequent PO dosage was
0.43 mg/kg. The range for IV and PO administration of
diazepam was 0.2–0.625 and 0.31–0.69 mg/kg, respective-
ly.

Dogs treated with diazepam had an average response
time of 13 hours and an average recovery time of 38.7
hours. The response times for dogs treated with diazepam
ranged from 20 minutes to 24 hours, and the recovery times
ranged from 24 to 72 hours. Dogs that were not treated
with diazepam had an average response time of 4.25 days
and an average recovery time of 11.6 days. Response times
for the dogs in the untreated group ranged from 2 to 10
days, and recovery times ranged from 5 to 21 days. Both
the response and recovery times for the animals treated with
diazepam were significantly shorter than those for the un-
treated group (P < .05).

Discussion

The neurologic adverse effects of metronidazole are well
documented in humans and companion animals. There
is currently no recommended treatment other than with-
drawing the drug and providing supportive care. Diazepam,
a centrally acting benzodiazepine, is used in human medi-
cine for symptomatic treatment of signs of vestibular sys-
tem dysfunction, but reports have not indicated any
curative effect for an underlying disease or toxicity. In one
study, guinea pigs undergoing unilateral labyrinthectomy
and treated with diazepam had milder signs than the un-
treated group, but there was no marked difference between
the groups in the time to complete vestibular compensa-
tion. Similar findings regarding vestibular compensation
are reported in humans with BPV treated with diazepam. Diazepam has been recommended for alleviating signs of
vestibular dysfunction in humans and animals, but indica-
tions for the use of diazepam other than for palliative ther-
apy have not been reported.

The results of this investigation demonstrate that diaze-
pam dramatically improves recovery times for dogs with
metronidazole toxicosis. Recovery times for dogs in this study that did not receive diazepam were consistent with previous reports. Dogs 1 and 3 in the untreated group had prolonged recovery times, which greatly increased the average overall recovery time for animals in this group. Both of these dogs suffered pronounced paraparesis, which lingered long past the resolution of the acute vestibular signs. Although these 2 dogs may have adversely influenced the average overall time to clinical resolution for the untreated group, there was still a marked difference in the response and recovery times compared to the diazepam-treated animals if data from these 2 dogs are discarded.

The results of this investigation show a positive correlation between dosage and duration of treatment relative to the time of onset of signs of metronidazole toxicosis (Fig 1). There did not appear to be an increased susceptibility to adverse effects of metronidazole administration on the basis of either age or breed. The average dosage of metronidazole that induced toxicity in the dogs of this study (60.3 and 65.1 mg/kg/d for diazepam-treated and untreated groups, respectively) was consistent with published reports.

Ours was a retrospective study, and a specific protocol for the administration of diazepam was not used. All animals in the diazepam-treated group, however, received an initial, single IV bolus and then diazepam PO q8h for 3 days. The average dosage of both the IV and PO diazepam was 0.43 mg/kg, but there was no apparent correlation between the dosages of either the IV or PO routes and the response or recovery times.

Neither the mechanism of metronidazole toxicity nor the precise mechanism of action of diazepam in the reversal of signs is known. Because the neurological effects of metronidazole are referable to both cerebellar and central vestibular dysfunction, literature regarding the histology and physiologic of these systems was reviewed for a relationship between metronidazole and diazepam.

Histological examinations of brain tissue in dogs with metronidazole toxicosis have demonstrated Purkinje cell loss, axonal degeneration in vestibular tracts. Histopathologic studies in mice given toxic dosages of metronidazole showed cerebellar Purkinje cell loss and degenerative changes in the vestibular, cochlear, deep cerebellar, and olivary nuclei as well as in the rostral colliculi. These nuclei and their associated tracts are involved primarily with equilibrium, hearing, and fine motor control. These nuclei, particularly the Purkinje cells, mediate an inhibitory influence on postsynaptic receptors, and their principal neurotransmitter is GABA, which is the major inhibitory neurotransmitter of the central nervous system. Activation of the GABA receptor by GABA or GABA mimetics, such as benzodiazepines, increases chloride (Cl\(^{-}\)) conductance at the postsynaptic membrane, resulting in hyperpolarization (Fig 2). The majority of GABA-minergic receptors in the central nervous system are located between the neurons of the cerebellum and their associated brainstem nuclei, especially the Purkinje cells and the lateral vestibular nuclei. Other major sites of GABA receptors are in the tracts between the vestibular nuclei and the trochlear motor neurons and within the olfactory bulbs, cuneate nuclei, hippocampus, and lateral septal nuclei. GABA also facilitates inhibitory transmission in the cerebral cortex and between the substantia nigra and caudate nucleus.

Because of the prevalence of GABA-minergic receptors in those tracts damaged by metronidazole and the known relationship of GABA receptors and benzodiazepines, the following mechanism may be postulated: benzodiazepines, such as diazepam, potentiate GABA influence on chloride conductance, thereby enhancing an inhibitory effect on excitatory neurons. Conversely, inhibition of GABA release, such as seen in the neurological adverse effects of enrofloxacin, ciprofloxacin, and imipenem, can lead to hyperexcitability of the central nervous system, resulting in seizures or tremors. It may therefore be speculated that interference of the GABA receptor at the postsynaptic membrane also may result in central nervous system hyperexcitability.

The benzodiazepines have specific binding sites on GABA receptors within the brain, particularly in the cerebellum, cerebral cortex, and limbic system. The imidazobenzodiazepine flumazenil is a selective, competitive antagonist (also known as an inverse agonist) of the benzodiazepine receptor. Both flumazenil and metronidazole have an imidazole component, and it is possible that metronidazole also may bind specifically to benzodiazepine sites on GABA receptors in the cerebellar and central vestibular systems, resulting in loss of inhibition, similar in effect to flumazenil (Fig 3). That the adverse reactions of flumazenil in humans, such as seizures, vertigo, and ataxia, are similar to the neurological adverse effects of metronidazole in dogs lends additional credence to this proposed mechanism of metronidazole toxicity. Regardless of whether metronidazole specifically binds to the benzodiazepine receptor inhibiting the effects of GABA or selectively destroys these cells by another mechanism, it is the GABA-dependent interactions of the cerebellar and central vestibular systems that are affected. It can be therefore postulated that diazepam either competes with metronidazole for the benzodiazepine receptor site or supplements GABA propagation via unaffected receptors, whereas the remain-
der of the metronidazole in the system is metabolized. It is more likely that diazepam at therapeutic concentrations competitively reverses the binding of metronidazole to the benzodiazepine site on the GABA receptor, because rebound manifestations of metronidazole toxicosis were not observed in the dogs of this study (Fig 4).

The average response time for the resolution of debilitating clinical signs in animals receiving diazepam in this study was 13 hours, with a final resolution of the remaining clinical signs (usually mild ataxia) over the next 24–48 hours. The plasma half-life of metronidazole in the dog is 3–13 hours, given this fact, the question of why the clinical signs in animals receiving diazepam in this study was thought to be minimal to nonexistent. The 2 dogs that had received the H1-antagonist meclizine, which generally is used to treat signs of motion sickness in humans,48 and the 2 dogs that underwent general anesthesia all were in the untreated group. Four dogs from each group had been given either an aminopenicillin or a 1st-generation cephalosporin; meclofenamic acid had been given to 3 dogs of the treated group and 2 dogs of the untreated group; and butorphanol had been administered to 1 dog from each group. Neurological adverse effects such as seizures, sedation, and ataxia have been described for each of these medications, but these adverse effects have been reported rarely and only with prolonged use or very high dosages.42,49–51 Corticosteroids, which had been administered to 6 of 8 dogs in the untreated group and to 10 of 13 dogs in the diazepam-treated group, could theoretically have induced the oxidative metabolism of metronidazole,52 but the effect of corticosteroids was not believed to be important because their use was common in both groups, and only 1–2 doses had been given. All dogs in this study had neurological manifestations consistent with metronidazole toxicosis before administration of any of these drugs and were diagnosed with metronidazole toxicosis within 24 hours of the onset of the neurological signs. Administration of the above ancillary medications was discontinued after the diagnosis was established, making it unlikely any medication other than diazepam influenced the outcome of these dogs.

A dose-dependent or duration-dependent relationship between actual neuronal cell death or leukomalacia of the vestibulocerebellar tracts and metronidazole administration could not be determined from this study because no histopathologic evaluations were performed. Clinical and experimental studies reported neuronal changes in subjects receiving much higher dosages than the 60.3-mg/kg/d dosage received by dogs in this investigation.8,30,31 Vestibulocerebellar axonal degeneration with no loss of neurons, however, has been reported in dogs receiving 63 mg/kg/d.8 All
though the animals in this investigation recovered, the potential for permanent, subclinical damage to neurons and white matter tracts in all cases of metronidazole toxicosis exists, thereby increasing the probability that these animals will be more susceptible to the adverse effects of metronidazole in the future. Administration of metronidazole to animals previously diagnosed with metronidazole toxicosis is not recommended.8–11

Although the exact mechanism is not known, the use of diazepam markedly improved the recovery of animals with metronidazole toxicosis. Consequently, we recommend the use of diazepam for the treatment of metronidazole toxicosis in dogs.

Footnotes

a Metronidazole, Flagyl®, GD Searle & Co, Chicago, IL
b Diazepam, Valium®, Roche, Division of SmithKline Beecham, Exton, PA
c Flumazenil, Romazicon®, Roche, Division of SmithKline Beecham, Exton, PA
d Model 9800 GE HiLite Advantage® CT Scanner, GE Medical Systems, Milwaukee, WI
e Methocarbamol, Robaxin®, Fort Dodge Animal Health, Fort Dodge, IA
f Carprofen, Rimadyl®, Pfizer Animal Health Inc, New York, NY
g Meclizine, Antivert®, Solvay Animal Health Inc, Mendota Heights, MN
h Butorphanol, Torbugesic®, Fort Dodge Animal Health, Fort Dodge, IA
i Enrofloxacin, Baytril®, Miles Inc, Shawnee, KS
j Ciprofloxacin, Cipro®, Miles Inc, Shawnee, KS
k Imipenem-Cilastatin, Primaxin®, Merck & Co, West Point, PA

References

4. Metronidazole toxicosis. Consequently, we recommend the use of diazepam for the treatment of metronidazole toxicosis in dogs.
6. Enrofloxacin, Baytril®, Miles Inc, Shawnee, KS.
7. Ciprofloxacin, Cipro®, Miles Inc, Shawnee, KS.
8. Imipenem-Cilastatin, Primaxin®, Merck & Co, West Point, PA.