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Continuous rate infusion of midazolam as emergent treatment for seizures in dogs

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Abstract

Background: Midazolam delivered by continuous rate infusion (CRI) might be effective in dogs with cluster seizures (CS) or status epilepticus (SE).

Objective: To describe the use and safety of midazolam CRI in dogs with CS or SE.

Animals: One-hundred six client-owned dogs presenting to a veterinary teaching hospital with CS or SE.

Methods: Retrospective review of medical records for dogs with CS or SE treated with a midazolam CRI.

Results: Seventy-nine dogs presented with CS and 27 dogs had SE. Seizure control was achieved in 82/106 dogs (77.4%) receiving a midazolam CRI. The median dose associated with seizure control was 0.3 mg/kg/h (range, 0.1-2.5 mg/kg/h). The median duration of CRI was 25 hours (range, 2-96 hours). Seizures were controlled in 34/40 dogs (85%) with idiopathic epilepsy, 32/43 dogs (74%) with structural epilepsy, 12/16 dogs (75%) with unknown epilepsy, and 4/7 dogs (57%) with reactive seizures (P = .20). Seizure control was achieved in 81% of dogs with CS and 67% in dogs with SE (P = .18). Dogs with idiopathic/unknown epilepsy were more likely to survive than those with structural epilepsy (87% vs 63%, P = .009). Adverse effects were reported in 24 dogs (22.6%) and were mild in all cases.

Conclusions and Clinical Importance: Midazolam CRI is apparently safe and might be an effective treatment in dogs with CS or SE.

KEYWORDS

acute repetitive seizures, anticonvulsant, benzodiazepine, canine, cluster seizures, epilepsy, status epilepticus

1 | INTRODUCTION

Seizure disorders are among the most frequently seen neurological diseases in dogs, and include seizure emergencies such as cluster seizures (CS) and status epilepticus (SE). Status epilepticus is defined as continuous seizure activity lasting longer than 5 minutes, or recurrent

Abbreviations: CRI, continuous rate infusion; CS, cluster seizures; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; NCVH, NC State Veterinary Hospital; SE, status epilepticus.

seizures without interictal resumption of baseline central nervous system function. Cluster seizures are defined as 2 or more seizures within a 24-hour period.[1,2]

Approximately 20% to 40% of dogs with epilepsy do not have satisfactory seizure control and many of these dogs have CS or SE.[3,4] Status epilepticus is life threatening, with case fatality rates as high as 25.3% to 38.5%.[5-7] If not successfully treated, SE can lead to irreversible neuronal injury and systemic complications such as hyperthermia, acidosis, rhabdomyolysis, renal failure, and noncardiogenic pulmonary edema.[8,9] This illustrates the need for appropriate emergent treatment for SE and CS.

The underlying cause of seizures can also have an impact on response to treatment, or the tendency to become refractory to conventional treatment. These causes include idiopathic epilepsy (epilepsy having a genetic or suspected genetic etiology), structural epilepsy, unknown epilepsy, and reactive seizures (transient metabolic or toxic disturbance affecting an otherwise normal brain).[1,2,7,10] Dogs with structural or reactive etiologies are more likely to experience SE than those with idiopathic epilepsy[7,11] and dogs with structural epilepsy also have a lower probability of survival.[5,7]

Although SE and CS are considered medical emergencies requiring immediate treatment, the optimal treatment for SE and CS in dogs is unknown. There are multiple anticonvulsant drugs available for treatment, including benzodiazepines, phenobarbital, levetiracetam, propofol, and pentobarbital.[5,7,12-14] One potential treatment is a continuous rate infusion (CRI) of a benzodiazepine. In humans with SE and refractory SE (defined as SE that persists despite appropriate treatment with 2-3 anticonvulsant drugs), benzodiazepine CRIs, particularly midazolam, are frequently used.[15-19] In 1 study of children with refractory SE, similar efficacy was reported for diazepam and midazolam when used as a CRI.[20]

Although diazepam CRIs are frequently used in the management of SE and CS in dogs, there are few reports describing such use in the veterinary literature.[5,21] Adverse effects such as phlebitis, and concerns with diazepam's sensitivity to light and its compatibility with fluid solutions complicate the delivery of this drug as a CRI.[22] Use of midazolam as a CRI for the treatment of seizures in dogs is reported in a single dog.[23] The purpose of this retrospective study was to describe the use and safety of a midazolam CRI in a sample of dogs with SE or CS presenting to a single veterinary teaching hospital.

2 | MATERIALS AND METHODS

2.1 | Case selection

Dogs admitted to the NC State Veterinary Hospital (NCVH) for SE or CS that were treated with a midazolam (Heritage Pharmaceuticals, Ltd, East Brunswick, New Jersey) CRI were identified by a medical record search of dates between January 2007 and December 2014. For this study, SE was defined as continuous seizure activity lasting longer than 5 minutes, or recurrent seizures without interictal resumption of baseline central nervous system function. Cluster seizures were defined as 2 or more seizures within the 24-hour period before admission. Dogs with incomplete information within the medical record were excluded from the study.

2.2 | Data collection

Signalment, prior history of seizures, previous anticonvulsant treatment, and anticonvulsant blood concentrations were obtained from the medical record. If the owner or a veterinarian treated the dog for seizures before presentation at NCVH, the routes and types of medications administered were recorded and the results of therapeutic drug monitoring noted if available. The dog's seizures were classified as either SE or CS and the neurologic examination at presentation to NCVH was recorded as normal or abnormal.

Signalment, historical information, and the results of diagnostic testing, including complete blood count, serum biochemical analysis, urinalysis, cerebrospinal fluid (CSF) analysis, computed tomography (CT), magnetic resonance imaging (MRI), and necropsy results were used to classify each dog into an epilepsy category as well as a more specific etiology if possible. We used the International Veterinary Epilepsy Task Force Consensus Statements to guide classification,[1,10] with the exceptions that not all dogs classified with idiopathic epilepsy had urinalyses nor serum bile acid or blood ammonia measured and CT was used instead of MRI for some cases. Dogs were classified with idiopathic epilepsy (tier III evidence) if they had their first seizure between 6 months and 6 years of age, 2 or more unprovoked seizures >24 hours apart, a normal interictal neurologic examination, unremarkable CBC, serum biochemical analysis, intracranial imaging, and CSF analysis and electroencephalographic (EEG) evidence of seizure activity. Dogs fulfilling these criteria without EEG confirmation of seizures were classified as having idiopathic epilepsy (tier II) and those fulfilling these criteria but without EEG and both intracranial imaging and CSF analysis were classified as having idiopathic epilepsy (tier I). Dogs with a significant abnormality on brain imaging or CSF analysis were classified as having structural epilepsy. Those with unremarkable brain imaging and CSF analysis but falling outside of the age parameters determined for idiopathic epilepsy were classified with unknown epilepsy (tier II). Dogs not meeting the age parameters for idiopathic epilepsy (tier I) that did not have brain imaging or CSF analysis were termed unknown epilepsy (tier I). In some cases, dogs did not have brain imaging or CSF but did have a necropsy examination, which was substituted to assign a final tier II classification. Finally, dogs determined to have metabolic or toxic causes of their seizures were classified as having reactive seizures.

Additional anticonvulsant medications administered at NCVH were recorded as type of medication, dosage, route, and frequency of administration. Information regarding the midazolam CRI was gathered, and included the time from hospital admission to initiation of the CRI, initial dose, any dose increases and corresponding time frame, the dose that appeared to control seizure activity or the highest dose given, duration of the CRI, and duration of hospitalization. Seizures were considered completely controlled when no additional seizures were noted between initiation or escalation of the CRI and discharge from the hospital.

Seizures were considered largely controlled when a single isolated seizure was observed after initiation of the midazolam CRI that did not lead to escalation of the CRI before discharge from the hospital. Both completely and largely controlled seizures were considered successful seizure control in further analyses. Seizure activity while hospitalized was recorded as generalized or focal based on visual observations, with the aid of electroencephalography in some cases. Any adverse effects or complications noted in the medical record that may have been associated with the midazolam CRI were also recorded. The medical record was evaluated to determine survival to discharge vs death or euthanasia.

2.3 | Statistical analysis

Descriptive statistics and analyses were performed with commercially available software (Prism, Graphpad Software Inc, La Jolla, California). For comparisons between etiological groups, all categories of idiopathic epilepsy were combined with dogs in the unknown (tier II) group (to create a group termed idiopathic/unknown) and the unknown (tier I) group was excluded from statistical analyses. A chi-square test was used to compare the proportion of dogs whose seizures were controlled and those that survived to discharge between etiological groups. Pairwise comparisons were made between groups using chi-square tests with Bonferroni corrections. A Fisher's exact test was used to compare the proportion of dogs whose seizures were controlled when presenting with CS vs SE. All tests were 2-sided and a P value <.05 was considered significant.

3 | RESULTS

3.1 | Case population

A total of 106 dogs were included in the study, representing 129 separate visits when a midazolam CRI was administered. Thirteen dogs received a midazolam CRI on multiple hospital visits, comprising 10 dogs that received a CRI on 2 separate occasions, 2 dogs that received a CRI on 4 separate occasions, and 1 dog that was admitted for seizures 8 times and received a CRI each time. In dogs with multiple visits, only the earliest chronological visit was used for data analysis and reporting. The median age at the time of presentation was 6.0 years (range, 4 months to 17 years). Three dogs (2.8%) were younger than 6 months and 54 (50.9%) were older than 5 years of age. The median weight was 15.1 kg (range, 1.3-73.3 kg). The most frequently documented breeds were Golden Retriever (7 dogs), Labrador Retriever (7), Boston Terrier (6), mixed breed (6), Australian Shepherd (5), Maltese (5), and Beagle (5). There were 52 castrated male dogs, 8 intact males, 41 spayed females, and 5 intact females.

There were 79 dogs (74.5%) with CS and 27 dogs (25.5%) with SE. In 85 dogs (80.2%), the neurological examination was abnormal at the time of admission. Of the dogs with CS, 1 dog had 2 seizures, 35 dogs had 3 to 5 seizures, and 42 dogs had >5 seizures. One dog did not have the exact number of seizures recorded. Of the dogs in SE, 21 dogs had a single seizure 15 minutes or longer in duration and 6 dogs had 2 to 5 seizures without return to baseline neurologic function.

Advanced diagnostics were performed in 61 dogs (57.5%) and included MRI and CSF analysis in 36 dogs, MRI alone in 18 dogs, CSF analysis alone in 4 dogs, and CT and CSF analysis in 3 dogs. Necropsy was used to confirm the absence of an identifiable structural lesion in 2 dogs with idiopathic epilepsy and 2 dogs with unknown epilepsy. Seizure etiology was classified for each dog (Table 1). Sixty-three dogs (59.4%) had a previous history of seizures, for which 55 dogs (51.9%) received maintenance anticonvulsant medication(s) and 43 dogs (40.6%) had routine blood concentrations monitored (37/43 [86.0%] were within the reported therapeutic range at the most recent evaluation). Forty-three dogs (40.6%) presented for their first occurrence of seizure activity.

3.2 | Emergent treatment in addition to CRI administration

Sixty-four dogs (60.4%) received emergent treatment for their seizures before referral to NCVH. This included 11 dogs treated by their

TABLE 1 Seizure etiologies in dogs included in the study

Category	Number of dogs
Idiopathic epilepsy	40
Tier I[a]	26
Tier II[b]	12
Tier III[c]	2
Unknown epilepsy	16
Tier I[d]	11
Tier II[e]	5
Structural epilepsy	43
Meningoencephalitis	21
Brain tumor	18
Intracranial anomaly	1
Cerebrovascular accident	1
Trauma	1
Polioencephalomalacia	1
Reactive seizures	7
Toxin	4
Metabolic cause	3
Total	106

[a]Based on age >6 months and <6 years, 2 or more unprovoked seizures >24 hours apart, a normal interictal examination and normal CBC and serum biochemical evaluation.
[b]Based on criteria above in addition to unremarkable intracranial imaging and cerebrospinal fluid (CSF) evaluation.
[c]Based on criteria in b in addition to electroencephalography.
[d]Based on a normal CBC and serum biochemical evaluation but lack of intracranial imaging and CSF evaluation.
[e]Based on age <6 months or >6 years, normal CBC, normal serum biochemical evaluation and unremarkable intracranial imaging and CSF evaluation or necropsy examination.

owners and 53 dogs treated by a referring veterinarian. The treatment administered is detailed in Table 2. Immediately upon presentation to NCVH, 73 dogs (68.9%) received a midazolam bolus given IV (68 dogs), intranasally (3 dogs), or both intranasally and IV (2 dogs). After the midazolam bolus, 11 dogs (10.4%) received additional anticonvulsant medications PO during the hospital visit, 47 (44.3%) received additional IV anticonvulsant medications, and 8 (7.5%) received a combination of additional PO and IV medications (see Table 3). Of the 33 dogs (31.1%) that did not receive a midazolam bolus at presentation, 9 were given additional PO anticonvulsant medications during the hospital visit, 16 received other IV anticonvulsant medications, and 2 received a combination of additional PO and IV anticonvulsant medications (see Table 3).

3.3 | Use of midazolam CRI

The median time from hospital admission to initiation of the midazolam CRI was 4.0 hours (range, 0-44 hours). The median initial dose rate of the midazolam CRI was 0.25 mg/kg/h (range, 0.1-0.75 mg/kg/h). Sixty-four dogs (60.4%) did not receive dose escalation of the CRI and 42 dogs (39.6%) were escalated. The median highest dose rate received was 0.4 mg/kg/h (range, 0.1-2.5 mg/kg/h).

Seizures were considered successfully controlled in 82 dogs (77.4%). This included 49 dogs (46%) in which seizures stopped after initiation of the CRI and 25 dogs (24%) where seizures stopped after escalation of the dose rate. There were 8 additional dogs (8%) that had a single isolated seizure between initiation of the CRI and hospital discharge and were considered largely controlled. Midazolam treatment was unsuccessful in 24 dogs (22.6%), including 17 dogs (16%) that continued to have seizures despite dose escalation and 7 dogs (7%) that died or were euthanized before dose escalation was attempted. The median dose rate that resulted in a successful outcome was 0.3 mg/kg/h (range, 0.1-2.5 mg/kg/h) and the median time to seizure control was 0 hours (range, 0-60 hours; mean, 5.8 hours). Of the 57 dogs (53.8%) that had additional seizures after initiation of the CRI, 24 dogs had generalized motor seizures, 23 dogs had focal motor seizures, 6 dogs had both generalized and focal motor seizures, and 4 dogs had electroencephalographic activity consistent with seizures without observable muscle activity and were considered to be in nonconvulsive SE. In the dogs whose seizures were not immediately

TABLE 2 Emergent treatment of SE or CS before referral to NCSUVH

Location	Route	Medication	Number of dogs
Home	Oral	Phenobarbital PO	4
		Levetiracetam PO	2
		Diazepam PO	1
		Zonisamide PO	1
		Potassium bromide PO	1
	Parenteral	Diazepam PR	3
		Midazolam IN	3
		Diazepam IV	1
		Midazolam PR	1
RDVM	Oral	Phenobarbital PO	12
		Levetiracetam PO	3
		Diazepam PO	1
	Zonisamide PO	1	
		Potassium bromide PO	1
	Parenteral	Diazepam IV	39
		Phenobarbital IV	21
		Propofol IV	8
		Diazepam PR	7
		Midazolam IV	3
		Isoflurane (inhaled)	2
		Levetiracetam IV	1
		Ketamine IV	1
		Pentobarbital IV	1
		Thiopental IV	1

Notes: Medications listed as PO were those given in addition to maintenance treatment. Note that numbers exceed the total number of dogs as some dogs received multiple interventions.

Abbreviations: CS, cluster seizures; IN, intranasal; PR, per rectum; RDVM, referring veterinarian; SE, status epilepticus.

TABLE 3 Emergent treatment of status epilepticus (SE) or cluster seizures (CS) after NCSUVH admission

Initial midazolam bolus	Route	Medication	Number of dogs
Yes	Oral	Levetiracetam PO	4
		Zonisamide PO	2
		Levetiracetam + zonisamide PO	2
		Phenobarbital PO	1
		Phenobarbital + levetiracetam PO	1
		Potassium bromide PO	1
		Total Oral Only	11
	IV	Phenobarbital IV	22
		Phenobarbital IV, levetiracetam IV	9
		Levetiracetam IV	6
		Phenobarbital IV, propofol IV	6
		Propofol IV	1
		Phenobarbital IV, pentobarbital IV	1
		Phenobarbital IV, propofol IV, levetiracetam IV	1
		Phenobarbital IV, propofol IV, levetiracetam IV, sodium bromide IV	1
		Total IV Only	47
	Oral and IV	Levetiracetam IV, zonisamide PO	1
		Phenobarbital IV, levetiracetam PO	1
		Levetiracetam IV, phenobarbital PO	1
		Phenobarbital IV, zonisamide PO	1
		Phenobarbital IV, potassium Bromide PO	1
		Phenobarbital IV, zonisamide PO, levetiracetam PO	1
		Phenobarbital IV, levetiracetam IV, zonisamide PO	1
		Levetiracetam IV, phenobarbital IV, sodium bromide IV, potassium bromide PO	1
		Total Oral and IV	8
No	Oral	Zonisamide PO	3
		Levetiracetam PO	2
		Phenobarbital PO	1
		Phenobarbital PO, zonisamide PO	1
		Phenobarbital PO, levetiracetam PO	1
		Gabapentin PO, potassium bromide PO	1
		Total Oral Only	9
	IV	Phenobarbital IV	12
		Phenobarbital IV, levetiracetam IV	3

TABLE 3 (Continued)

Initial midazolam bolus	Route	Medication	Number of dogs
		Levetiracetam IV	1
		Total IV Only	16
	Oral and IV	Phenobarbital IV,	
		levetiracetam PO	1
		Phenobarbital IV, diazepam IV,	
		zonisamide PO	1
		Total Oral and IV	2

controlled at the initial dose rate, the median time to seizure control was 13 hours (range, 1-60 hours).

The median CRI duration was 25 hours (range, 2-96 hours). In the 49 dogs with immediate seizure control upon initiation of the CRI, the median CRI duration was 24 hours (range, 7-48 hours). In the dogs that had additional seizures after initiation of the CRI but ultimately achieved control, the median CRI duration was 39.5 hours (range, 16-96 hours). The median duration of hospitalization for all dogs was 2.5 days (range, 0.5-10 days).

Seizure control was achieved in 34/40 dogs (85%) with idiopathic epilepsy, 32/43 dogs (74%) with structural epilepsy, 4/5 dogs (80%) with unknown epilepsy (tier II), and 4/7 dogs (57%) with reactive seizures (Figure 1A). There was no difference in the proportion of dogs controlled between these groups (P = .20). Seizures were controlled in 8/11 dogs (74%) with unknown epilepsy (tier I). Seizures were considered uncontrolled in 24 dogs, of which 15 dogs had CS, and 9 dogs had SE. There was no difference in seizure control for dogs with CS vs SE (P = .18). Seventy-seven dogs (73%) survived to discharge, 25 dogs (24%) were euthanized, and 4 dogs (4%) died spontaneously. Three dogs with CS were not controlled with a midazolam CRI but survived to discharge; these dogs were discharged despite continued seizure activity. There was a significant difference in survival to discharge between etiological groups (P = .02), as 35/40 dogs (88%) with idiopathic epilepsy survived, compared to 27/43 dogs (63%) with structural epilepsy, 4/5 dogs (80%) with unknown epilepsy (tier II), and 4/7 dogs (57%) with reactive seizures (Figure 1B). Seven of 11 dogs (64%) with unknown epilepsy (tier I) survived to discharge. After Bonferroni correction, the only comparison that remained significant involved dogs with idiopathic/unknown epilepsy, which were more likely to survive to discharge than those with structural epilepsy (P = .009).

In this study, there were 24 dogs in which a midazolam CRI was considered unsuccessful and 21 of these dogs did not survive to discharge. Of the 3 dogs that were discharged without achieving seizure resolution, 1 was an idiopathic epileptic (tier III) already receiving 3 maintenance anticonvulsant medications, and 2 had unknown epilepsy (tier I). Overall, 29 dogs did not survive to discharge, despite seizure control in 8 of these individuals. All 8 dogs were euthanized. In 6 dogs this decision was based on a diagnosis of intracranial neoplasia. One dog with meningoencephalitis was euthanized when it failed to return to a normal mental state and 1 dog was euthanized because of progressive myelomalacia secondary to concurrent thoracolumbar myelopathy.

Adverse effects were recorded in 24 dogs (22.6%), and included sedation (11 dogs, 10.4%), vomiting or diarrhea (6 dogs, 5.7%), hyperexcitability (3 dogs, 2.8%), ataxia (2 dogs, 1.9%), and polyphagia (2 dogs, 1.9%). There were no reports of phlebitis. Of the 6 dogs with vomiting or diarrhea, 5 had SE lasting longer than 30 minutes. The CRI dose was reduced in 4 dogs (3.8%) because of adverse effects including sedation (2 dogs, 1.9%), ataxia (1 dog, 0.9%), and vomiting (1 dog, 0.9%). The CRI was discontinued in 2 dogs (1.9%) as a result of adverse effects, because of either sedation (1 dog) or diarrhea (1 dog).

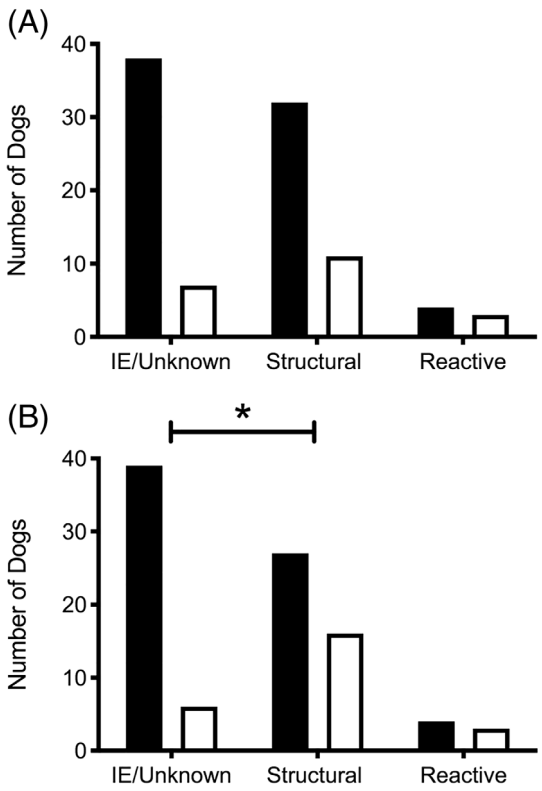

FIGURE 1 A, Seizure control in dogs by etiology. Black bars indicate dogs with seizures that were controlled in hospital. White bars indicate dogs with uncontrolled seizures. There was no difference noted between groups (P = .20). B, Survival to discharge by etiology. Black bars indicate dogs that survived to discharge. White bars indicate dogs that died or were euthanized in hospital. Dogs diagnosed with idiopathic/unknown epilepsy were more likely to survive to discharge than those with structural epilepsy (*P = .009)

4 | DISCUSSION

This study describes a cohort of dogs with SE or CS treated with a midazolam CRI in a single referral practice. Most dogs were diagnosed with idiopathic (37.7%) or structural (40.5%) epilepsy. Seizure control was considered successful in 77.4% of dogs in the study. There was no difference in the response to treatment between etiological groups although there was a difference in the proportion of dogs that survived to discharge.

There are a variety of options for emergent seizure treatment in dogs. The first line drug of choice is generally a benzodiazepine, typically chosen for its availability and rapid movement into the CNS after parenteral administration.[7,24,25] Animals responding to an initial benzodiazepine bolus can be loaded on a maintenance anticonvulsant drug such as phenobarbital or levetiracetam if they are naïve to such treatment and the suspected cause of the seizures warrants long-term treatment. Animals already on maintenance treatment that is suspected to be subtherapeutic may receive additional maintenance drug to increase their blood concentrations. In some animals, such interventions might be adequate to control an episode of CS or SE.[7,24]

However, these strategies will not control all dogs and dogs commonly experience CS or SE while on maintenance medications resulting in blood concentrations considered to be therapeutic. In these scenarios, additional treatment is required, and generally consists of a benzodiazepine CRI[5] or the induction of general anesthesia. General anesthesia can be induced with the use of pentobarbital, propofol, or less commonly inhalant anesthetics.[7,13,14,23,25-27] Although anesthesia is usually effective in controlling CS or SE, it introduces additional monitoring requirements for dogs as well as significant risk of additional morbidity and mortality. A benzodiazepine CRI can be an attractive alternative in these dogs, with the potential to control seizures while avoiding anesthesia or even significant sedation.

Diazepam has been utilized most frequently in this regard and can be effective for the treatment of CS and SE in dogs.[5] However, concerns with the use of diazepam as a CRI include its poor aqueous solubility, the formation of deposits of sparingly soluble material, and sorption on polyvinyl chloride bags and tubing.[20,28,29] Humans report a high incidence of thrombophlebitis and pain during intravenous diazepam injection,[22] which has also been anecdotally observed in dogs. These less desirable characteristics have not been reported with midazolam.[29] Midazolam has an imidazole ring that is open at low pH, which allows it to dissolve in water, improving mixing properties and concurrent administration with fluids.[30] However, at physiological pH, this ring closes, dramatically altering the drug's lipid solubility and allowing it to rapidly penetrate the blood-brain barrier and exert its anticonvulsant effect.[31] Intranasal midazolam was shown to be more efficacious than rectal diazepam and at least as efficacious as IV midazolam when administered to dogs with status SE.[32,33] Administration of a midazolam CRI is an efficacious treatment for emergent seizures in humans.[15,17-20] To our knowledge, the use of a midazolam CRI for this indication in dogs has only been reported in a single dog.[23]

In the current study, seizures were considered controlled in 77.4% of dogs receiving a midazolam CRI. It is not possible to determine the true efficacy of this intervention because of the administration of concurrent anticonvulsants in these dogs. It is also difficult to compare the control achieved in this study to other interventions, as most previous veterinary studies do not explicitly report the efficacy of treatment. However, there are exceptions. Hardy et al reported that 1/10 dogs (10%) receiving a single IV diazepam bolus for CS were controlled over a 24-hour period compared with 5/9 dogs (56%) receiving a diazepam bolus followed by a bolus of IV levetiracetam.[12] Steffen and Grasmueck reported that propofol administration controlled 10/12 dogs (83%) with seizures refractory to a diazepam bolus with or without the addition of a barbiturate[14] and several small case series report the successful control of SE occurring after portosystemic shunt ligation with propofol.[23,25,34]

An indirect measure of seizure control can be obtained by examining survival to discharge, which is described in several other reports.[5,7,13,27] The survival rate in dogs treated with a midazolam CRI compares favorably to these other studies, particularly when considering those studies that included dogs with structural epilepsy.[5,7,13] The survival rates typically underestimate the efficacy of anticonvulsant treatment in such reports (including ours), as many dogs with structural epilepsy will be euthanized regardless of seizure control.

The median midazolam CRI time to initiation of 4 hours reflected the initial administration of benzodiazepine boluses along with other anticonvulsants such as phenobarbital or levetiracetam before considering the use of a CRI in many dogs. The median midazolam CRI dose that achieved seizure resolution was 0.3 mg/kg/h. Most dogs were started at 0.1-0.25 mg/kg/h although a number of dogs were started at 0.5 mg/kg/h, which was based primarily on clinician preference and the severity of both seizures and sedation at presentation.

Midazolam CRIs were well tolerated by the dogs in this study, with sedation reported as the primary adverse effect. However, it was not possible to separate sedation or ataxia occurring secondary to midazolam from the results of excessive seizure activity or the administration of other drugs commonly known to cause these effects. Some dogs had vomiting or diarrhea, but most of these animals experienced prolonged SE, which could also have contributed to gastrointestinal upset because of hyperthermia, hypoperfusion, or other systemic alterations. There were no serious adverse effects attributable to midazolam CRI, and infusion durations up to 96 hours were well tolerated.

These observations are consistent with prior reports of midazolam use in dogs and other species. In a toxicity study in healthy dogs, IV doses up to 6 mg/kg were given daily for 5 weeks without observable adverse effects.[35] Two studies of intranasal midazolam in dogs with SE concluded that midazolam was safe in this scenario but was associated with some sedation and ataxia.[32,33] In humans, midazolam is considered safer and is associated with lower complication rates than other emergent seizure treatments including barbiturates, propofol, and inhalant anesthesia.[15,16,36] Midazolam reduces the need for mechanical ventilation and vasopressor use, and allows a more rapid return to consciousness than these other protocols.[16] Although not directly compared in the veterinary literature, benzodiazepine CRIs likely provide similar advantages to dogs. Such advantages might in turn result in shorter

durations of treatment, quicker return to normal neurologic status, and reduced costs of hospitalization.

Our study has several limitations. Given its retrospective nature, a standardized protocol for administration of the midazolam CRI was not employed, and decisions on initial dose rate, escalation of dose and discontinuation of treatment were made at the discretion of the managing clinician. In addition, dogs received a variety of other anticonvulsant treatments both at referring veterinary hospitals as well as at our facility. A control population was not evaluated in this study and it is possible that some dogs would have achieved seizure control without the use of the midazolam CRI. Although the rates of seizure control and survival to discharge with the midazolam CRI seemed to compare favorably to previously published therapies for CS and SE in dogs, this study was not designed to directly compare anticonvulsant protocols, and conclusions in this regard await further study.

In conclusion, the use of a midazolam CRI appears to be safe and might be an effective treatment in dogs with CS or SE. Such use can be considered in dogs with reactive seizures while awaiting clearance of a toxic agent or resolution of a metabolic encephalopathy. This strategy might also be useful as a bridge treatment to control seizures whereas a structural condition is addressed or to allow the adjustment of maintenance anticonvulsant medications. Based on the preliminary data, the authors suggest a starting dose of 0.1 to 0.25 mg/kg/h with subsequent dose escalation as required to control seizure activity, to a maximum of 2 mg/kg/h.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflicts of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

This study was retrospectively conducted using medical records generated during the course of routine hospital visits; IACUC approval is not required for such studies at our institution.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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REFERENCES

1. Berendt M, Farquhar RG, Mandigers PJ, et al. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. *BMC Vet Res*. 2015; 11:182.
2. Mariani CL. Terminology and classification of seizures and epilepsy in veterinary patients. *Top Companion Anim Med*. 2013;28:34-41.
3. Lane SB, Bunch SE. Medical management of recurrent seizures in dogs and cats. *J Vet Intern Med*. 1990;4:26-39.
4. Monteiro R, Adams V, Keys D, Platt SR. Canine idiopathic epilepsy: prevalence, risk factors and outcome associated with cluster seizures and status epilepticus. *J Small Anim Pract*. 2012;53:526-530.
5. Bateman SW, Parent JM. Clinical findings, treatment, and outcome of dogs with status epilepticus or cluster seizures: 156 cases (1990-1995). *J Am Vet Med Assoc*. 1999;215:1463-1468.
6. Saito M, Munana KR, Sharp NJ, et al. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990-1996). *J Am Vet Med Assoc*. 2001;219:618-623.
7. Zimmermann R, Hulsmeyer V, Sauter-Louis C, et al. Status epilepticus and epileptic seizures in dogs. *J Vet Intern Med*. 2009;23:970-976.
8. Haley A, Platt S. Status epilepticus. In: Platt SR, Garosi LS, eds. *Small Animal Neurological Emergencies*. London: Manson Publishing, Ltd; 2012:417-432.
9. Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998; 338:970-976.
10. De Risio L, Bhatti S, Munana K, et al. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. *BMC Vet Res*. 2015;11:148.
11. Platt SR, Haag M. Canine status epilepticus: a retrospective study of 50 cases. *J Small Anim Pract*. 2002;43:151-153.
12. Hardy BT, Patterson EE, Cloyd JM, Hardy RM, Leppik IE. Double-masked, placebo-controlled study of intravenous levetiracetam for the treatment of status epilepticus and acute repetitive seizures in dogs. *J Vet Intern Med*. 2012;26:334-340.
13. Raith K, Steinberg T, Fischer A. Continuous electroencephalographic monitoring of status epilepticus in dogs and cats: 10 patients (2004-2005). *J Vet Emerg Crit Care*. 2010;20:446-455.
14. Steffen F, Grasmueck S. Propofol for treatment of refractory seizures in dogs and a cat with intracranial disorders. *J Small Anim Pract*. 2000; 41:496-499.
15. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. *Pediatr Neurol*. 2008;38: 377-390.
16. Gilbert DL, Glauser TA. Complications and costs of treatment of refractory generalized convulsive status epilepticus in children. *J Child Neurol*. 1999;14:597-601.
17. Hayashi K, Osawa M, Aihara M, et al. Efficacy of intravenous midazolam for status epilepticus in childhood. *Pediatr Neurol*. 2007; 36:366-372.
18. Koul R, Chacko A, Javed H, al Riyami K. Eight-year study of childhood status epilepticus: midazolam infusion in management and outcome. *J Child Neurol*. 2002;17:908-910.
19. Ozdemir D, Gulez P, Uran N, Yendur G, Kavakli T, Aydin A. Efficacy of continuous midazolam infusion and mortality in childhood refractory generalized convulsive status epilepticus. *Seizure*. 2005;14:129-132.
20. Singhi S, Murthy A, Singhi P, Jayashree M. Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus. *J Child Neurol*. 2002;17:106-110.
21. Platt SR, McDonnell JJ. Status epilepticus: patient management and pharmacologic therapy. *Compend Continuing Ed Small Anim Pract*. 2000;22:722-728.
22. Graham CW, Pagano RR, Conner JT. Pain and clinical thrombophlebitis following intravenous diazepam and lorazepam. *Anaesthesia*. 1978; 33:188-191.

23. Yool DA, Kirby BM. Neurological dysfunction in three dogs and one cat following attenuation of intrahepatic portosystemic shunts. *J Small Anim Pract*. 2002;43:171-176.
24. Podell M. Seizures in dogs. *Vet Clin North Am Small Anim Pract*. 1996; 26:779-809.
25. Tisdall PL, Hunt GB, Youmans KR, et al. Neurological dysfunction in dogs following attenuation of congenital extrahepatic portosystemic shunts. *J Small Anim Pract*. 2000;41:539-546.
26. Hardie EM, Kornegay JN, Cullen JM. Status epilepticus after ligation of portosystemic shunts. *Vet Surg*. 1990;19:412-417.
27. Zimmermann R, Steinberg TA, Raith K, Hülsmeyer V, Fischer A. Canine status epilepticus due to acute intoxication. *Tierarztl Prax Ausg K Kleintiere Heimtiere*. 2010;38:285-294.
28. Kowaluk EA, Roberts MS, Polack AE. Factors affecting the availability of diazepam stored in plastic bags and administered through intravenous sets. *Am J Hosp Pharm*. 1983;40:417-423.
29. Martens HJ, De Goede PN, Van Loenen AC. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm*. 1990;47:369-373.
30. Fountain NB, Adams RE. Midazolam treatment of acute and refractory status epilepticus. *Clin Neuropharmacol*. 1999;22: 261-267.
31. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology*. 1985;62:310-324.
32. Charalambous M, Bhatti SFM, Van Ham L, et al. Intranasal midazolam versus rectal diazepam for the management of canine status epilepticus: a multicenter randomized parallel-group clinical trial. *J Vet Intern Med*. 2017;31:1149-1158.
33. Charalambous M, Volk HA, Tipold A, et al. Comparison of intranasal versus intravenous midazolam for management of status epilepticus in dogs: a multi-center randomized parallel group clinical study. *J Vet Intern Med*. 2019;33:2709-2717.
34. Heldmann E, Holt DE, Brockman DJ, Brown DC, Perkowski SZ. Use of propofol to manage seizure activity after surgical treatment of portosystemic shunts. *J Small Anim Pract*. 1999;40:590-594.
35. Schlappi B. Safety aspects of midazolam. *Br J Clin Pharmacol*. 1983;16 (Suppl 1):37S-41S.
36. Trinka E, Kalviainen R. 25years of advances in definition, classification and treatment of status epilepticus. *Seizure*. 2016;44:65–73.

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