

CASE SERIES

Suspected benzodiazepine withdrawal-associated seizures in 3 young dogs undergoing mechanical ventilation

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Abstract

Objective: To describe new onset of generalized seizures in 3 young dogs following cessation of a benzodiazepine-containing sedation protocol to facilitate mechanical ventilation (MV) for hypoxemia.

Series Summary: Three dogs under 5 months of age underwent MV due to severe hypoxemia. All 3 dogs were sedated with a constant rate infusion of benzodiazepines as part of their sedation protocol to facilitate MV. All 3 dogs had an acute onset of generalized seizures within 36 hours of sedation cessation and weaning from MV. All 3 dogs' seizures were successfully managed with a slow, tapering course of benzodiazepines. One dog was additionally treated with levetiracetam at the time of initial seizure activity, which was discontinued 1 year following discharge and absence of ongoing seizure activity. All 3 dogs were discharged successfully with no reports of ongoing seizures or neurologic deficits after discharge.

New or Unique Information Provided: Young dogs managed with benzodiazepines to facilitate MV may have acute onset of generalized seizures following cessation, which can be successfully managed with short-term benzodiazepine therapy. The 3 cases in this series demonstrated a positive outcome and were successfully managed following acute onset of generalized seizure activity post-MV.

KEYWORDS

drug-related seizures, intravenous anesthesia, neurological complications

1 | INTRODUCTION

Mechanical ventilation (MV) is the mainstay of therapy for respiratory failure in both human and veterinary medicine.¹ MV is facilitated by a variety of IV sedation protocols, commonly including benzodiazepines and narcotics. Benzodiazepines act by potentiating gamma-aminobutyric acid receptor-mediated inhibition of the

central nervous system (CNS) and are commonly employed during MV due to their minimal cardiovascular effects.² While benzodiazepines are commonly used in sedation protocols, they have numerous documented side effects in people including prolonged ventilation, delirium, and chronic cognitive dysfunction.³⁻⁵ Benzodiazepine-induced delirium has been linked to morbidity, mortality, and cognitive impairment in adults. Benzodiazepines are additionally an independent risk factor in the development of CNS complications in critically ill pediatric patients, supporting the limitation of benzodiazepines in the pediatric population.⁶⁻⁹ CNS complications

Abbreviations: CNS, central nervous system; MV, mechanical ventilation; RI, reference interval.

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and other postventilation complications are not well documented in veterinary patients. This case series documents successful management of generalized seizures occurring as a transient complication associated with MV and withdrawal of sedation protocols in 3 young dogs.

2 | CASE DESCRIPTIONS

2.1 | Case 1

A 5-month-old female neutered mixed-breed dog weighing 16 kg presented for further evaluation of a pneumothorax identified after premedication for surgical repair of a tibial fracture, occurring secondary to an unknown trauma. The dog's neurologic status was unremarkable at the time of initial presentation with no evidence of traumatic brain injury or neurologic deficits. Prior to presentation, a left-sided thoracostomy tube was placed and the patient was transported under general anesthesia. Thoracic computed tomography scan revealed a diffuse alveolar pattern, bilateral mild pneumothorax, a gas-filled bullous lesion within the right caudal thorax, multiple pulmonary bullae, and a mild pneumomediastinum. Differentials for the alveolar pattern included pulmonary hemorrhage, contusions, or noncardiogenic pulmonary edema. A right-sided parasternal thoracotomy was performed and a mediastinal, gas-filled structure was identified in the caudodorsal aspect of the right hemithorax, a suspected bronchoesophageal fistula, which was ligated and removed. Histopathology of the removed tissue revealed diffuse lymphoplasmacytic and eosinophilic pleuritis. The dog demonstrated persistent severe hypoxemia and hypercapnia under anesthesia and was placed on a long-term MV postoperatively. Sedation and paralysis were maintained with constant rate infusions of fentanyl^a (3–20 µg/kg/h), midazolam^b (0.5–1.5 mg/kg/h), dexmedetomidine^c (0.5–1.5 µg/kg/h), and atracurium^d (0.1–0.3 mg/kg/h) titrated to effect, and intermittent boluses of propofol^e as needed. Other medications administered while undergoing MV included balanced isotonic fluid therapy, IV amino acid supplementation,^f dopamine,^g ampicillin-sulbactam,^h and metoclopramide.ⁱ Weaning from MV was attempted after 64 hours, at which time all sedative infusions were discontinued. Naloxone^j was administered at the time of weaning. Extubation was uneventful, after which the dog was oxygenating normally (SpO₂ of 100%) with a nasal oxygen canula flowing at 2 L/min. A venous blood gas following extubation showed a pH of 7.39 (reference interval [RI], 7.31–7.42), pCO₂ of 51 mm Hg (RI, 29–42 mm Hg), bicarbonate of 30.9 mmol/L (RI, 17–24 mmol/L), mild hyperglycemia 11.3 mmol/L (203 mg/dl) (RI, 3.9–6.7 mmol/L [70–120 mg/dl]), normal ionized calcium 1.22 mmol/L (RI, 1.20–1.39 mmol/L), and normal plasma lactate 0.6 mmol/L (RI, <2.5 mmol/L). Approximately 1 hour later, the dog began to show signs of cerebellar ataxia and subtle intention tremors but was ambulatory. Four hours after extubation, the dog developed a generalized seizure and was treated with 0.3 mg/kg of midazolam^b IV. No mentation or cranial deficits were noted prior or following seizure activity. The blood glucose 2 hours prior to the seizure was 9.7 mmol/L

(174 mg/dl). The dog was administered 23.4 mg/kg of levetiracetam^k orally approximately 3 hours after the initial seizure. Six hours after the initial seizure, the dog had a second generalized seizure that was treated with an additional dose of midazolam^b as well as 18.75 mg/kg of levetiracetam^k IV. Approximately 3 hours later, the dog experienced a third generalized seizure, which was treated with 0.25 mg/kg midazolam^b IV followed by initiation of a constant rate infusion of midazolam^b at 0.2 mg/kg/h. A neurology consultation was performed the following day that revealed the dog to be alert and interactive but with intermittent impaired mentation. Occasional head pressing was noted in addition to subtle intention tremors. Proprioceptive positioning was absent in the right thoracic and pelvic limbs and nasal sensation was reduced on the right side. The neurologic exam findings were most consistent with a left forebrain lesion with possible cerebellar involvement. Biochemistry results were within RI with no evidence of systemic or hepatic causes for the neurologic signs. Due to ongoing improvement, further imaging and diagnostics were not pursued. Based on the lack of systemic signs and improving neurologic signs, top concerns for the dog's seizures and neurologic deficits were related to sedation protocols, previous hypoxemia, or secondary to an ischemic or hemorrhagic lesion. The midazolam^b infusion was continued at 0.2 mg/kg/h for 10 hours and then slowly weaned over the following 31 hours before discontinuing. Levetiracetam^k was continued at 23.4 mg/kg PO every 8 hours. The dog experienced no additional witnessed seizure activity over the next 48 hours prior to discharge from the hospital. The dog experienced no seizures for the following year and levetiracetam^k was tapered and discontinued with no reported seizures following discontinuation.

2.2 | Case 2

A 2-month-old intact male Golden Retriever weighing 6.4 kg presented for acute respiratory distress following an episode of coughing and vomiting. On presentation, the dog was dyspneic and hypoxemic (PaO₂ 49 mm Hg on room air and an A-a gradient of 53.5 mm Hg) with harsh lung sounds and crackles bilaterally, worse on the left side. Anesthesia was induced and the dog was placed on a MV. Thoracic radiographs revealed a bilateral caudodorsal interstitial pattern, with differentials including noncardiogenic pulmonary edema, hemorrhage, infectious bronchopneumonia, and acute respiratory distress syndrome. Sedation and paralysis were maintained with continuous infusions of fentanyl^a (5–36 µg/kg/h), midazolam^b (0.3–0.6 mg/kg/h), propofol^e (50–125 µg/kg/min), dexmedetomidine^c (1–5 µg/kg/h), and atracurium^d (4 µg/kg/min) titrated to effect, and intermittent bolus doses of ketamine^l as needed. The dog was maintained on the mechanical ventilator and ventilation was successfully discontinued after approximately 39 hours. A dose of naloxone^j was administered at the time of weaning. Approximately 1 hour after extubation, an arterial blood gas showed a respiratory acidosis with a pH of 7.20, pCO₂ of 65 mm Hg, and bicarbonate of 25.4 mmol/L. The dog's SaO₂ was 99% and PaO₂ was 149 mm Hg while supplemented with flow-by oxygen via face mask. The dog experienced 2 generalized seizures, 1 hour apart,



starting approximately 4 hours following cessation of sedative drugs. Blood glucose was slightly increased at 7.2 mmol/L (129 mg/dL) (RI, 3.9–6.7 mmol/L [70–120 mg/dL]). A venous blood gas at the time of the first seizure showed an improved respiratory acidosis (pH of 7.39, pCO₂ of 54 mm Hg) and no other significant abnormalities to explain the seizure activity. Neurologic exam was within normal limits prior to the onset of the generalized seizure and following the postictal period. Biochemistry profile was performed and was unremarkable with no evidence of systemic causes of seizure activity. A blood ammonia concentration was slightly increased at 42 μmol/L (RI, 10–30 μmol/L) but not suspected to be high enough to explain the seizure activity. Both seizures were treated with midazolam^b 0.25 mg/kg IV. Following the second seizure, a continuous infusion of midazolam^b was initiated at 0.3 mg/kg/h. The infusion was continued at this rate for 24 hours, slowly weaned over the next 12 hours, and discontinued after a total of 36 hours. The dog experienced no additional witnessed seizure activity during the subsequent 72 hours prior to discharge from the hospital. The dog was successfully discharged 72 hours after weaning from MV with no neurologic deficits or seizure activity noted. Follow-up at 1-week postdischarge revealed no ongoing neurologic signs or seizure activity.

2.3 | Case 3

A 4-month-old intact male Labrador Retriever weighing 20 kg presented for acute respiratory distress. Prior to referral, the dog was hospitalized for 24 hours following an acute onset of lethargy, anorexia, vomiting, and wheezing. An abdominal exploratory laparotomy did not reveal any abnormalities, but at the time of intubation, severe left-sided laryngeal edema causing partial upper airway obstruction was identified. A temporary tracheostomy tube was placed and the dog was initially eupneic while breathing room air. The dog became severely dyspneic following obstruction of the tracheostomy tube, and thoracic radiographs revealed a bilateral, diffuse alveolar pattern, suspected to represent noncardiogenic pulmonary edema secondary to airway obstruction. Due to persistent hypoxemia and hypercapnia, the dog was referred for MV. MV was initiated shortly after presentation and sedation was maintained with constant infusions of fentanyl^a (20–40 μg/kg/h), midazolam^b (0.5 mg/kg/h), and ketamine^l (25–50 μg/kg/min) titrated to effect, and intermittent bolus doses of atracurium^d and propofol^e as needed. Other therapeutics administered over the duration of ventilation included balanced isotonic crystalloids, intravenous amino acid supplementation,^f ampicillin–sulbactam,^h enrofloxacin,^m clindamycin,ⁿ norepinephrine,^o metoclopramide,ⁱ and dexamethasone.^p Computed tomography of the head and neck revealed multifocal abscesses within the left retropharyngeal soft tissue. The dog was successfully discontinued from the ventilator after approximately 48 hours and maintained a SpO₂ of 98% in an oxygen cage at 40%–42% oxygen concentration. Approximately 35 hours after cessation of sedative drugs, the dog experienced a generalized seizure and was treated with midazolam^b (0.25 mg/kg IV). At the time of the seizure, the dog's SpO₂ was 97% breathing room

air. Blood glucose was slightly increased immediately following the seizure (7.1 mmol/L [128 mg/dL]; RI, 3.9–6.7 mmol/L [70–120 mg/dL]). Neurologic examination was otherwise normal following the seizure. Biochemistry profile was within RI and no evidence of systemic causes or hepatic dysfunction was noted. The dog was placed on a midazolam^b constant rate infusion at 0.25 mg/kg/h that was slowly weaned over the subsequent 24 hours. The dog experienced no additional seizure activity and did not require any other anticonvulsant therapies. The dog was successfully discharged 24 hours following MV discontinuation. Follow-up at 2 days postdischarge revealed no ongoing neurologic signs or seizure activity.

3 | DISCUSSION

Positive-pressure ventilation and MV for the management of respiratory failure and fatigue in veterinary medicine are facilitated through multimodal sedation and anesthesia.^{1,10} Protocols of MV in human and veterinary medicine include a combination of analgesia and sedation, including opioids and benzodiazepines, which cause a dose-dependent suppression of awareness and anxiolysis.² Additional protocols often include propofol, dexmedetomidine, ketamine, and varying use of neuromuscular blocking agents. Overall goals of sedation protocols include treatment of pain and anxiolysis while minimizing adverse cardiovascular and neurologic effects.

Upon discontinuation of MV and sedation protocols, side effects reported, specifically in critically ill children, include overstimulation of the CNS, anxiety, agitation, muscle twitching, disorientation, and seizures.^{11,12} This iatrogenic withdrawal syndrome occurs during abrupt discontinuation or rapid tapering of sedative drugs.¹³ Mechanisms of CNS complications related to benzodiazepine withdrawal include alterations in gamma-aminobutyric acid receptors and increased neuronal excitability.¹⁴ The occurrence and timing of withdrawal symptoms are related to pharmacologic properties of the drug, dosage, and duration of use and can develop within the first 24–48 hours after discontinuation and have been associated with poor outcomes.^{16,17} Iatrogenic withdrawal syndrome and subsequent CNS signs occur in both the human adult and pediatric population with an incidence of 16.7%–55% in adult patients and 7.5%–100% in pediatric patients with a higher overall incidence of withdrawal signs and higher incidence in primarily neurologic signs, including seizures, in younger patients.^{13,15} Treatment of benzodiazepine withdrawal-associated CNS signs in both adult and pediatric human patients includes reintroduction of benzodiazepines and subsequent slow taper with resolution of withdrawal signs.^{18,19} Neurologic signs, including tonic–clonic seizures, have also been reported in dogs following abrupt cessation of chronic benzodiazepine administration.²⁰

All dogs in this case series developed generalized seizures within 4–35 hours following sedation and MV discontinuation. While seizures associated with benzodiazepine withdrawal are noted in human adult and pediatric patients, seizures were only noted in young dogs undergoing sedation for MV, which may be related to gamma-aminobutyric acid receptor physiology in young patients. Two out of the 3 dogs had

no other neurologic deficits noted at or around the time of seizure activity and no systemic causes of seizure activity based on biochemistry results were appreciated. The dog in case 1 did have lateralizing signs; therefore, other differentials for the seizures remain possible including a hemorrhagic or ischemic lesion. No dogs had any identifiable systemic causes of generalized seizures based on physical examination, neurologic examination, or blood glucose, biochemistry, or blood gas evaluation. While benzodiazepine withdrawal is the most likely explanation for the acute onset of generalized seizures in these cases, other potential causes of neurologic signs include cerebral complications of severe hypoxemia, which was present in all cases at the time of MV initiation. While hypoxemia is a potential cause for the neurologic signs in these cases, it is less likely based on the lack of other neurologic deficits to support a diagnosis of hypoxic brain injury. Additionally, while these dogs received multiple sedatives, withdrawal of these drugs, including opioids and alpha antagonists, is associated with signs such as tremors and agitation but has not been associated with seizures, making benzodiazepine withdrawal the most likely scenario in all 3 cases.²¹ Due to the temporary lateralizing neurologic deficits in case 1, it is possible that the cause of this dog's seizures was multifactorial including the combination of a forebrain lesion and acute benzodiazepine withdrawal.

This case series describes 3 cases of young dogs, under the age of 5 months, that experienced generalized seizures following discontinuation of MV and sedation protocols including benzodiazepines. All seizures were controlled with re-institution of benzodiazepine boluses and constant rate infusions that were slowly tapered. One dog was started on levetiracetam following the second generalized seizure. Two out of the 3 dogs were discharged without ongoing antiepileptic therapy, while 1 dog was discharged on levetiracetam, which was ultimately discontinued 1 year following discharge. No dogs had ongoing seizures or neurologic deficits following discharge. In conclusion, benzodiazepine sedation protocols should be used with caution in young dogs undergoing MV. In the event that benzodiazepines are used as part of the sedation protocol, young dogs should be observed and monitored closely for an onset of seizure activity within 48 hours of withdrawal. With aggressive management, the occurrence of seizures in this patient population did not affect short-term prognosis or outcome.

OFFPRINTS

Offprints will not be available from the authors.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ENDNOTES

- ^aFentanyl citrate, Hospira Inc., Lake Forest, IL.
^bMidazolam, Hospira Inc., Lake Forest, IL.
^cDexmedetomidine, Zoetis LLC, Kalamazoo, MI.
^dAtracurium, Meitheal Pharmaceuticals, Chicago IL.
^ePropofol, Hospira Inc, Lake Forest, IL.
^fAmino acid solution, Braun Medical Inc, Irvine, CA.

^gDopamine, Hospira Inc, Lake Forest, IL.

^hAmpicillin-sulbactam, Auromedics Pharma LLC, E. Windsor, NJ.

ⁱMetoclopramide, Hospira Inc., Lake Forest, IL.

^jNaloxone, Mylan Institutional LLC, Rockford, IL.

^kLevetiracetam, Westward, Eatontown, NJ.

^lKetamine, MWI, Boise, ID.

^mEnrofloxacin (Baytril injectable), Bayer Healthcare LLC, Shawnee Mission, KS.

ⁿClindamycin, Pfizer, New York, NY.

^oNorepinephrine, Baxter Healthcare, Deerfield, IL.

^pDexamethasone SP, West-ward, Eatontown, NJ.

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