

## CASE REPORT

# Successful treatment of severe baclofen toxicosis initially refractory to conventional treatment

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### Key Clinical Message

After ingesting a dose of baclofen thought to be lethal, a patient with severe neurologic signs was successfully managed despite initially being refractory to treatment. Patients with persistent neurologic abnormalities may still have an excellent prognosis despite lack of initial response. Additionally, we present a potential case of benzodiazepine withdrawal.

### Keywords

Baclofen, canine, midazolam, toxicity

## Introduction

Baclofen (Novartis Pharmaceuticals, East Hanover, NJ) is a synthetic derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Although the exact mechanism is unknown, its effects are thought to be secondary to depression of afferent reflex activity at the level of the spinal cord by acting as an inhibitory neurotransmitter. Baclofen is postulated to depress mono- and polysynaptic reflex transmission by stimulation of GABA<sub>β</sub>-receptors leading to inhibition of excitatory amino acid action. In humans, baclofen is commonly used as a skeletal muscle relaxant in conditions such as multiple sclerosis and spinal disorders [1, 2]. In dogs, baclofen has been used in the treatment of urinary retention and gastroesophageal reflux; however, its clinical use is infrequent due to a narrow margin of safety [2].

Once orally administered, baclofen is rapidly absorbed from the gastrointestinal tract. In humans, the bioavailability is 70–80% in oral form. Elimination is achieved via the kidneys and to a lesser extent the liver. In humans, the plasma elimination half-life is approximately 2–6 h [1, 2]. Baclofen does not readily cross the blood–brain barrier; therefore, the cerebrospinal fluid contains

very low concentrations of the drug when used at therapeutic dosages. However, with overdoses, the plasma concentrations increase and the central nervous system may be affected from changes in excitatory and inhibitory neurotransmitters [3]. No definitive dose for the consistent onset of neurologic signs has been determined.

In the veterinary literature, there are various reports of baclofen toxicosis. Ingested doses have ranged from 0.61 to 61 mg/kg in small animal patients. Clinical signs have been observed at doses as low as 0.7 mg/kg, and death has been reported following ingestion of 2.3 mg/kg [4]. Clinical signs vary with degree of intoxication, and primarily involve the respiratory, cardiac, and the central nervous system. Common clinical signs include depressed mentation, vocalization, coma, lethargy, ataxia, and hypersalivation. Less commonly reported signs include bradycardia, miosis, urinary incontinence, tachypnea, hypotension, and nystagmus. Current treatment recommendations include gastrointestinal decontamination, intravenous fluid therapy, intravenous lipid emulsion (ILE, Baxter Healthcare, Deerfield, IL), hemodialysis, hemoperfusion, and mechanical ventilation [4–8].

Midazolam (Bedford Laboratories, Bedford, OH) is a parenteral benzodiazepine commonly utilized in

veterinary medicine for sedation and seizure control [9]. In mechanically ventilated patients, benzodiazepines are often used in protocols in combination with other medications for long-term sedation. In human patients, a syndrome of benzodiazepine withdrawal is recognized in patients receiving a constant rate infusion over an extended period of time, in some cases between 3 and 7 days. The syndrome is characterized by symptoms including nervous system instability (seizures, tremors), gastrointestinal (vomiting, diarrhea), and autonomic dysfunction (fever, tachycardia, and tachypnea). Signs are commonly seen when there is abrupt discontinuation or rapid tapering of continuous infusions [10, 11]. A diagnosis of benzodiazepine withdrawal is difficult to make due to lack of definitive diagnostic criteria. In human medicine, the diagnosis is typically made when patients exhibit typical clinical signs in the face of rapid tapering or discontinuation of benzodiazepines which resolve with the reinstatement of benzodiazepines [10]. This syndrome has not previously been documented in veterinary medicine. This case study describes a patient with compatible clinical signs after abrupt discontinuation of a benzodiazepine, and resolution of signs with reinstatement of therapy, suggesting this syndrome may occur in veterinary patients as it does in human medicine.

This case describes the highest documented known ingestion of baclofen in the medical literature. The patient was successfully treated with intravenous fluid therapy, ILE, multiple hemodialysis treatments, and several days of mechanical ventilation. In addition, the patient exhibited clinical signs suggestive of benzodiazepine withdrawal syndrome upon abrupt discontinuation of a midazolam infusion. We suggest therefore that treatment of patients with significant neurologic compromise from baclofen ingestion should not be considered futile if minimal improvement is noted with initial treatment.

## Case Summary

### Day one

A seven-month-old male castrated Goldendoodle weighing 21.2 kg was referred for mechanical ventilation. Earlier in the day, the dog ingested approximately eighty twenty-milligram tablets of baclofen, equivalent to a total ingestion of 75 mg/kg. The dog was initially brought to his primary veterinarian. On presentation, he was drooling and recumbent with periods of vocalization. An IV catheter was placed, and a 0.5 mg/kg dose of Diazepam (Abbott Laboratories, North Chicago, IL) was administered along with 1 L of intravenous Lactated Ringers (Abbott Laboratories, North Chicago, IL). Further decontamination procedures were not performed due to the patient's recumbent state.

He was subsequently transferred to a referral center for further care. Upon arrival at the initial referral center, he was obtunded. Cranial nerve examination revealed miotic pupils; remaining cranial nerve exam was normal. A CBC and chemistry panel were within normal limits with the exception of an increased cholesterol level (349 mg/dL [131–345]). Systolic blood pressure ranged between 120 and 175 mmHg and ECG revealed normal sinus rhythm. Intravenous lipid emulsion (ILE) was administered as a bolus (1.7 mL/kg), followed by a CRI (16.5 mL/kg) over 1 h. Cyproheptadine (Par Pharmaceutical Inc, Woodcliff Lake, NJ) (1.2 mg/kg) was administered rectally. Mentation did not improve following administration of ILE. The dog was assessed to be comatose with decreased chest wall excursions. An oxygen saturation (SpO<sub>2</sub>) reading was 88%. No pCO<sub>2</sub> level was available. Harsh lung sounds were auscultated bilaterally. Due to concern for hypoventilation, aspiration pneumonia, and the perceived need for assisted ventilation, the dog was intubated. Intravenous Ampicillin (Auromedics LLC, NJ) (24 mg/kg IV) and enrofloxacin (Baytril, Bayer Healthcare LLC, KS) (11 mg/kg IV) were administered prior to referral.

The dog presented to the author's clinic approximately 8 h after the initial ingestion. Initial neurologic examination revealed miotic pupils with absent pupillary light reflexes (PLR), menace and palpebral reflexes bilaterally. The patient was comatose with an absent gag reflex. Copious amounts of green to yellow nasal discharge were present in both nares. An initial arterial blood gas, fraction of inspired oxygen (FiO<sub>2</sub>) of 1.0, was obtained and revealed pH 7.248, pCO<sub>2</sub> 50.9 mmHg, pO<sub>2</sub> 358.7 mmHg, bicarbonate 21.7 mmol/L, sodium 161.8 mmol/L, potassium 4.43 mmol/L, calcium 1.24 mmol/L, chloride 128 mmol/L, glucose 106 mg/dL, and lactate 2.38 mmol/L. PCV/TS was 42% /6.0 g/dL. A systolic blood pressure was 137 mmHg. CBC, chemistry panel, and urinalysis were within normal limits. Three view chest radiographs revealed an interstitial to alveolar pattern in the left cranial and caudal lung lobes. Pressure assist control, continuous mandatory ventilation (840 Ventilator Systems, Nellcor Puritan Bennett, Pleasanton, CA) was started shortly after presentation. Peak inspiratory pressure was set at 14 cm H<sub>2</sub>O with positive end-expiratory pressure (PEEP) at 3.0 cm H<sub>2</sub>O. End-tidal carbon dioxide (ETCO<sub>2</sub>) was 34 mmHg with a FiO<sub>2</sub> of 0.50. An 11.5 French, 24 cm Dialysis Catheter (Covidien, MN) was placed. The patient was administered 1 g/kg Mannitol (Hospira Inc., Lake Forest, IL) IV with no change in neurologic status. Intermittent hemodialysis was performed over 4 h. Mentation was reassessed after dialysis and was unchanged. Overnight one dose of diazepam (0.625 mg/kg IV) was administered for sedation. Antibiotics were continued, and additional ILE was not administered due to lipemia.

### Day two

The following day, a neurologic examination revealed unchanged comatose mentation, absent menace, PLRs, dazzle, palpebral, gag reflex, and facial sensation. The patient's signs were neurolocalized to the prosencephalon and/or brainstem. Sedation was provided, via a diazepam (0.50–1.0 mg/kg/h) constant rate infusion (CRI), along with intermittent Propofol (Abbott Laboratories, North Chicago, IL) (1 mg/kg IV) and dexmedetomidine (Dexdomitor, Zoetis Inc., Kalamazoo, MI) (1 mcg/kg IV) boluses to minimize patient-ventilator asynchrony. SpO<sub>2</sub> was 95–98%, ETCO<sub>2</sub> 38–42 mmHg, and venous pCO<sub>2</sub> 29–37.2 mmHg. A second hemodialysis treatment was administered. Chest radiographs revealed worsening pulmonary infiltrates. An endotracheal lavage was performed; cytology revealed septic suppurative inflammation with intracellular rod bacteria, extracellular yeast organisms, and foreign material consistent with aspiration of gastric contents. Due to the concern for progression of pneumonia, antibiotics were transitioned to Meropenem (Meropenem, Hospira Inc., Lake Forest, IL) (12 mg/kg IV Q8) pending the results of aerobic culture and sensitivity. A carbapenem (Meropenem) was chosen based on historic bacterial culture results from patients with ventilator associated pneumonia in the author's clinic.

### Day three

On the third day, the patient was transitioned to continuous positive airway pressure ventilation with pressure support (7 cm H<sub>2</sub>O). A third hemodialysis treatment was performed. Neurologic examination following hemodialysis revealed resolving miosis, with intact direct and indirect PLRs bilaterally. The remainder of the examination was unchanged. Diazepam infusion was discontinued, and no further sedation was required. The patient's spontaneous ventilatory efforts were initially deemed sufficient following dialysis, and mechanical ventilation was discontinued. Flow-by oxygen was provided, and the dog was kept intubated with ETCO<sub>2</sub> monitoring. During the evening, the dog became tachypneic at 80–100 breaths per min and SpO<sub>2</sub> decreased to 94% from 99%. Midazolam (0.5–1 mg/kg/h) and propofol (0.1 mg/kg/min) were initiated, and the dog was started back on mechanical ventilation.

### Day four

The following day neurologic examination revealed intact palpebral and dazzle reflexes. Spontaneous limb movement was observed with weak spinal reflexes present. Gag

reflex and remainder of the examination was unchanged. Midazolam CRI (0.5 mg/kg/h) was continued along with mechanical ventilation.

### Day five

Neurologic examination revealed an intact gag reflex, spontaneous blinking with orientation of eyes in response to sound and stimuli. A second endotracheal wash was performed; cytology revealed neutrophilic inflammation with fungal structures consistent with *Candida spp.* The sample was submitted for aerobic bacterial culture. In the afternoon, the patient's spontaneous ventilatory efforts were again deemed to be adequate, and ventilatory support was discontinued. The dog remained intubated with flow-by oxygen and ETCO<sub>2</sub> monitoring. Overnight, the dog was extubated. Oxygen was provided via face mask. Sedation was continued with a midazolam CRI (0.20 mg/kg/h). SpO<sub>2</sub>, venous pCO<sub>2</sub>, and respiratory rate remained within normal limits.

### Day six

In the morning, the midazolam CRI was discontinued abruptly from 0.20 mg/kg/h. Thirty minutes later, the dog was noted to be hyperesthetic to noise and stimuli. Approximately 2 h later, a generalized seizure was observed lasting thirty seconds. Midazolam (0.25 mg/kg IV) was administered and resulted in immediate termination of seizure activity. A midazolam CRI was started again at 0.1 mg/kg/h. No further seizures were noted. Recheck chest radiographs revealed an improving alveolar pattern.

### Day seven to nine

Over the next days, the dog's mentation steadily improved. Conscious proprioceptive reflexes were normal, and he was able to ambulate with minimal assistance. The midazolam CRI was slowly decreased from 0.1 mg/kg/h over the next two days to 0.02 mg/kg/h then discontinued. No further seizure activity was noted. Endotracheal lavage culture revealed an *Enterococcus species* and *Candida tropicalis*. Meropenem was discontinued, and the patient was prescribed Chloramphenicol (Bimeda Inc, Le Sueur MN) (50 mg/kg PO Q8).

### Day ten

On the final day of hospitalization, the patient was assessed to be neurologically normal. Five months after discharge, the owner reports that he is doing well with no neurologic or respiratory abnormalities.

## Discussion

In this case study, we present the clinical sequelae of the highest reported dose of baclofen ingested in the medical literature. The severity of intoxication resulted in a protracted clinical course, but ultimately the patient responded to aggressive supportive care, suggesting that treatment of patients with high dose ingestion should not be considered fruitless. In the first veterinary report of baclofen toxicosis, a possible ingestion of 4–8 mg/kg was suspected. The dog was administered IV fluids and required intubation, with no assisted ventilation, for 6 h. On day six, the patient was discharged [7]. In two additional veterinary case studies, higher doses of baclofen were ingested (21–52 mg/kg and 20 mg/kg). Both dogs required less than one day of mechanical ventilation and one hemodialysis/hemoperfusion treatment [6, 8]. In one retrospective observational study looking at a population of 145 cases of baclofen toxicosis, doses ranged from 0.61 to 61 mg/kg. CNS depression and dyspnea were observed with doses as low as 0.7 mg/kg and death at 2.3 mg/kg [4].

The authors theorize that the higher concentration of baclofen ingested in the current report necessitated a significantly longer duration of treatment. Our patient underwent treatment with conventional therapy including intravenous fluids, ILE, mechanical ventilation, and hemodialysis. The dog's clinical signs were minimally mitigated by these treatments. Although it required a significantly longer duration of hospitalization, multiple hemodialysis treatments, and multiple days of mechanical ventilation, his signs ultimately resolved with supportive therapy.

Intravenous lipid emulsion can be used to treat patients with hemodynamic and neurologic complications from ingestion of lipophilic medications. The exact mechanism is not fully known, but ILE is thought to aid in increased plasma clearance of the toxin. The most likely mechanism discussed in the literature is the "lipid sink" theory. This theory involves the neutralization of lipophilic toxic drugs due to extraction from target receptors upon delivery of lipid emulsion IV [12, 13]. Side effects reported include lipemia, elevations in amylase, aspartate aminotransferase, triglycerides, phosphorus, and creatinine. In one study, an eight-week-old puppy ingested a maximum dose of 25 mg/kg of baclofen. The patient received gastrointestinal decontamination and IV fluids. ILE was initiated due to deteriorating mentation. Thirty minutes after infusion (1.5 mL/kg bolus followed by 1 mL/kg/h), her mentation improved. A CRI was continued for 14 h, and the dog was discharged 48 h after presentation [14]. In our patient, no improvement was noted after ILE treatment. This may be due to the higher dose ingested or possibly

the shorter duration of administration. Based on the veterinary literature, response to ILE therapy is variable with some dogs failing to respond [15]. We suspect that due to the larger dose ingested, there was decreased binding availability of the lipid for drug neutralization. However, serum baclofen levels were not available in the patient to confirm this suspicion.

Hemodialysis is used in baclofen toxicosis to help increase drug elimination. Hemodialysis is useful in hastening elimination of low molecular weight compounds with low protein binding. Baclofen has a small molecular weight and low protein binding (<30%) making it ideal for removal via hemodialysis. At this time, there is not a definitive consensus on the benefit of hemodialysis with baclofen in the human literature [16–18].

In two case reports of veterinary patients receiving hemodialysis/hemoperfusion for baclofen toxicosis, each patient exhibited significant neurologic improvement following one hemodialysis/hemoperfusion treatment [6, 8]. Our patient underwent three hemodialysis treatments before a significant improvement in his neurologic status was evident. We suspect this was due to the high dose ingested (75 mg/kg vs. 20 mg/kg and 21–52 mg/kg) in our patient, and the altered pharmacodynamics occurring secondary to the high dose ingestion [6, 8]. However, based on the few reported cases in the veterinary literature, it is unknown whether the previously reported patients would have recovered within the same time duration without the use of hemodialysis. We did not obtain plasma levels of baclofen in our patient to compare pre- and postdialysis concentrations. In one study evaluating serum baclofen kinetics in dogs, the half-life after hemodialysis/hemoperfusion decreased from 5 to 1.5 h in the initial 2 h of treatment [6]. That patient had a possible ingestion of 21–52 mg/kg which was smaller than that consumed by our patient. This may explain why our dog remained neurologically inappropriate for multiple days and required three hemodialysis treatments, while the previously reported patient improved significantly following only one treatment.

In some cases of baclofen toxicosis, mechanical ventilation is required due to profound respiratory muscle weakness that causes decreased chest wall excursions. In one human study, patients ingesting over 200 mg of baclofen had higher ICU admission rates, higher rates of mechanical ventilation, and prolonged hospitalization. Clinical signs observed in patients with high ingestion (>200 mg) included delirium, coma, and seizures. Intubation and ventilation were required for eleven of twenty-three patients, with a median of 32 h [19]. Mechanical ventilation was essential in our patient due to hypoventilation and aspiration pneumonia. Our patient was ventilated for just over four days. In a human case series describing

multiple adolescents that ingested baclofen, a linear relationship was observed between dose ingested and days ventilated [20]. In comparison with previous veterinary case reports, our patient required prolonged ventilation which we suspect was due to the higher dose of baclofen ingested.

Baclofen is primarily renally excreted, with only a small portion (15%) being metabolized by the liver. Small amounts of baclofen are capable of crossing the blood–brain barrier at therapeutic doses; however, at higher doses, significant drug concentrations can accumulate within the cerebrospinal fluid, leading to coma and respiratory depression. At therapeutic doses, baclofen undergoes first-order elimination kinetics with a half-life of 2–6 h [1, 3, 19]. In first-order elimination kinetics, a constant fraction of drug is eliminated per unit time. The time required for the drug concentration to fall by one half-life ( $t_{1/2}$ ) is therefore constant; within five  $t_{1/2}$ , over 95% of the drug should be eliminated. When first-order elimination mechanisms become saturated, a transition to zero-order kinetics may occur. In zero-order kinetics, a constant amount, rather than a constant fraction of drug, is eliminated per unit time. Therefore, the serum half-life of the medication is constantly changing. In drug overdoses, this can result in prolonged elimination of a drug. Baclofen may transition to zero-order elimination kinetics in high dose ingestion, which might explain a prolonged duration of clinical signs following ingestion. However, measurement of serial baclofen levels following toxic ingestions in the human literature suggests that a transition to zero-order kinetics is not responsible for persistent CNS signs in that species. It is not uncommon for human patients to have serum baclofen levels within the therapeutic range while exhibiting profound neurologic abnormalities following overdose. Neurologic signs are theorized to persist in patients due to delayed clearance of baclofen from the CNS [19–21]. In experimental studies examining the elimination kinetics of intravenous radiolabeled baclofen in rats, blood baclofen levels decreased significantly faster than brain tissue levels, supporting the notion that the neurologic abnormalities could be due to persistence of drug within those tissues. [22] Unfortunately, until serial serum baclofen levels are consistently measured, and ideally correlated to brain tissue levels, and to a standardized metric of brain function, such as the Glasgow Coma Score, a definitive etiology for the persistence of neurologic signs in human patients will remain unknown. Moreover, the lack of currently available data makes it impossible to determine whether either of these mechanisms could be responsible for the clinical sequelae of baclofen toxicity in our patients.

The oral pharmacokinetics of baclofen in veterinary patients is poorly described. One study evaluated IV

baclofen administration in dogs with single and multiple doses. Those receiving a single dose (3 mg/kg) had minimal clinical signs noted. Those with multiple doses (~3.8 mg/kg) exhibited emesis, ataxia, and in one patient loss of response to noxious stimuli. Maximal concentration of baclofen did not correlate to peak clinical effects due to suspected delayed distribution within the CNS. Mean distribution and elimination  $t_{1/2}$  were 11 and 222 min [23]. In a case of oral baclofen toxicity, hemodialysis was utilized to shorten the half-life from 5 to 1.5 h in the first 2 h of treatment [6]. Although we did not look at plasma levels of baclofen in our patient, we suspect that the prolonged neurologic signs were due to delayed elimination of baclofen from the CNS and possibly transition to zero-order kinetics.

To our knowledge, there are no clinical reports of suspected benzodiazepine withdrawal syndrome in canine patients. In this report, we observed a seizure episode shortly after discontinuation of midazolam. Based on the known half-life of baclofen, our patient's improvement of neurologic signs, and the timing of the seizure in relation to the cessation of midazolam, we suspect benzodiazepine withdrawal as the etiology in this patient. Benzodiazepine withdrawal was initially described in psychiatric patients administered chlordiazepoxide daily for one to seven months. Eleven patients abruptly switched to a placebo medication exhibited clinical signs including depression, aggravation, insomnia, poor appetite, and seizure episodes [10, 11]. In one human case report, a patient was being administered a midazolam CRI. On two occasions (day 6 and 16), the CRI was abruptly discontinued and resulted in agitation and anxiety. Based on the improvement once midazolam was initiated, it was suspected that abrupt midazolam cessation precipitated the events [24]. Similar signs can be observed in patients with baclofen withdrawal; however, these signs do not usually resolve solely with administration of a benzodiazepine.

In our patient, a benzodiazepine CRI (midazolam) was started, continued for almost 72 h, and then abruptly discontinued. A few hours after discontinuation, a seizure was observed that ceased with midazolam administration. Initially, this patient was on a diazepam CRI. This CRI was continued for less than 24 h and abruptly discontinued. No clinical signs of withdrawal were suspected at that time. We suspect that the increased duration of administration of midazolam puts this patient at risk for withdrawal symptoms. In human medicine, clinical signs are observed with withdrawal when there is rapid tapering or discontinuation of benzodiazepines which resolve with the reinstatement of benzodiazepines. A diagnosis of benzodiazepine withdrawal is difficult to make due to lack of definitive diagnostic



criteria. No previous reports are noted in the veterinary literature.

Baclofen withdrawal has also been reported in the human literature with similar clinical signs that include seizures, rigidity, fever, change in level of consciousness, rhabdomyolysis, and death. The majority of these cases involve patients receiving intrathecal baclofen. In one retrospective human study, the duration of exposure prior to withdrawal was 6 weeks to 6.5 years. Severe withdrawal signs were observed 1–2 days after baclofen discontinuation. Some of these patients did experience seizure activity refractory to high doses of benzodiazepines. The majority of patients required reintroduction of baclofen for seizure termination [25]. Our case had an acute ingestion; seizure activity did not occur until day six of hospitalization shortly after cessation of midazolam. Seizure activity terminated promptly with benzodiazepine treatment alone. Due to the timeframe of seizure onset, and termination with reinitiation of midazolam, we do not suspect baclofen withdrawal as a cause for seizures in our patient.

## Conclusion

This case study describes the highest reported dose ingestion of baclofen in a canine patient. In comparison with other cases, our patient required a longer duration of hospitalization and mechanical ventilation, as well as three hemodialysis treatments. ILE therapy was also instituted but did not result in appreciable improvement in the patient's clinical signs. Additionally, the patient exhibited signs consistent with benzodiazepine withdrawal after abrupt discontinuation of a midazolam CRI. Based on the past literature, response to treatment has been noted shortly after institution of therapy [4–8]. This case suggests that in patients with high dose ingestions and minimal initial response to therapies, further treatment should not be considered fruitless. When provided with ongoing intensive treatment and care, the long-term prognosis can still be excellent.

## Conflict of Interest

The authors claim no conflict of interest. No results or information from this manuscript has been presented at a scientific meeting.

## Authorship

CM: the primary contributor to the writing and editing of the manuscript. MD: also aided in manuscript writing and editing.

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