

# SEIZE THE DAY: EMERGENT TREATMENT AND MANAGEMENT OF STATUS EPILEPTICUS

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## Definitions

- **Cluster seizures** – two or more seizures occurring within a 24-hour period.
- **Status epilepticus** – continuous seizure activity lasting longer than 5 minutes, or the occurrence of multiple seizures without recovery of baseline neurologic function between episodes.<sup>1,2</sup> Status epilepticus can be generalized or focal in nature, or in rare cases, can be nonconvulsive.<sup>3</sup>

## Pathophysiology and Goals of Treatment

The vast majority of seizures are self-limiting events, with eventual spontaneous return to resting or baseline neurologic function. However, during status epilepticus, a variety of changes occur within cells and networks of cells that result in a situation where the seizure activity becomes self-sustaining. These changes may be independent of the initiating cause of the seizure and involves a variety of molecular mechanisms. Repetitive seizures cause inhibitory GABA<sub>A</sub> receptors to move from the synaptic membrane to the cell interior, while excitatory N-methyl-D-aspartate (NMDA) receptors may be recruited to the cell surface.<sup>1</sup> Stores of inhibitory neurotransmitters may become depleted and increased expression of drug efflux transporters such as P-glycoprotein may occur.<sup>4</sup> After a period of time, these cellular alterations may lead to pharmacoresistance to first-line agents that would normally be effective in seizure termination at earlier phases, such as the benzodiazepines.

Generalized status epilepticus can cause profound acidosis, hyperthermia, cardiac arrhythmias, hypoxia, neurogenic pulmonary edema, rhabdomyolysis, myoglobinuria, renal failure, cerebral edema, elevated intracranial pressure and neuronal necrosis, and therefore constitutes a medical emergency.<sup>5</sup> The goals of treatment are to stop the seizures, support systemic organ functions, and protect brain function. Finally, ongoing seizure activity/seizure control should be closely monitored. These goals are described in greater detail below.

### 1) Stop the Seizures

The most critical and pressing goal of therapy is to stop the seizures, by any means necessary. The initial drug chosen is usually a benzodiazepine (diazepam or midazolam) but depends on the suspected underlying cause.

- If hypoglycemia is suspected (juvenile toy breed dog, hunting dog or insulin overdose), administer 1-2 ml/kg of 50% dextrose intravenously (IV) diluted 1:1 in saline. Oral dextrose may be used in animals able to swallow when intravenous access is not readily achieved.
- In small or toy breed dogs that have recently whelped and are nursing puppies, the administration of calcium gluconate may be considered to address potential hypocalcemia.

Animals with known idiopathic, symptomatic or probably symptomatic (acquired/cryptogenic) epilepsy and those with unknown etiologies typically receive a benzodiazepine as the first-line drug.

- Diazepam (0.5 mg/kg) can be administered IV, intranasally or rectally to control seizures. The dose can be repeated twice, if necessary. Anticonvulsant action only lasts about 15-30 minutes, and therefore some form of longer acting therapy is required if the seizures stop. Midazolam can be substituted for diazepam in this scenario, and lorazepam (0.2 mg/kg) may also be considered. These drugs may also be administered IV or intranasally but are not likely to be effective with rectal administration. In addition, unlike the others, midazolam can be successfully administered intramuscularly (IM).
- If the animal responds to a benzodiazepine bolus, phenobarbital may be considered for longer-term control. Naïve animals not previously receiving anticonvulsants can be loaded with 16-20 mg/kg divided into 4 doses and administered every 30-120 minutes (i.e., 4-5 mg/kg q 30-120 minutes). Epileptics already receiving phenobarbital may benefit from an additional "mini-loading dose" (5-10 mg/kg) depending on their serum levels of the drug. Phenobarbital should be continued at regular maintenance intervals (2-3 mg/kg IV, IM or PO q 12 hours or at the animal's regular dose) after this.
- Animals with severe cluster seizures or status epilepticus with some inter-ictal time (i.e., non-continuous) usually respond to a constant rate infusion (CRI) of diazepam (0.1-2.0 mg/kg/hour IV). The CRI can be started at the low end of the range (0.1-0.25 mg/kg) and gradually increased as necessary to control seizure activity. Once controlled, a seizure-free state is maintained for 12 hours, after which the infusion is gradually tapered (usually reduce dose by half every 4-6 hours) and stopped. The CRI can be administered with a syringe pump, if available, or by mixing with 0.9% saline in a small IV bag or Buretrol system. Diazepam is degraded by light and binds to plastic, and the syringe and tubing should be covered with brown plastic or aluminum foil, if possible. Midazolam can again be substituted in this scenario and is less likely to cause thrombophlebitis.
- Animals with continuous, prolonged seizure activity or those refractory to benzodiazepines may receive pentobarbital (3-15 mg/kg IV to effect), if available. This drug induces general anesthesia and is extremely effective in stopping the outward manifestation of the seizure. However, respiratory and cardiovascular function may be depressed, and these systems must be monitored very closely. Although intermittent bolus doses can be used, a CRI (2 mg/kg/hr adjusted to effect) may be more effective. Similar to benzodiazepine CRIs, animals may be kept seizure free for approximately 12 hours, and then weaned from the drug. It can be difficult to distinguish recovery from pentobarbital anesthesia from overt seizure activity. However, paddling movements of the limbs typically indicate the former, while seizure activity is usually characterized by overt tonic or clonic muscle contractions. Electroencephalography, if available, can help to differentiate these two scenarios. This medication also reduces the metabolic requirements of the brain and is considered to have neuroprotective effects.
- Propofol may be used as a substitute for pentobarbital if general anesthesia is required to control seizure activity. Due to its short duration of action, this drug must be given as a CRI (6 mg/kg initial bolus followed by 0.1-0.6 mg/kg/min). Substantial respiratory depression is common with this medication, and anesthesia must be closely monitored. In addition, propofol can have pro-convulsant effects in some patients. Some consider this to be the treatment of choice for patients in status epilepticus secondary to hepatic encephalopathy (typically after surgical repair of a portosystemic shunting vessel).

- If pentobarbital and propofol are not available, the use of an inhalant anesthetic (e.g., isoflurane or sevoflurane) to maintain general anesthesia should be considered as a last resort. Both require close monitoring of respiratory and cardiovascular parameters.
- A parenteral formulation of levetiracetam is also available. Although its use in animals with status epilepticus or cluster seizures has been limited to date, it may prove useful in this role, based on reports in humans and preliminary experience in canine patients.<sup>1,6</sup> Pharmacokinetic studies in dogs suggest that a dose of 20-60 mg/kg IV results in blood concentrations within the range considered to be effective in humans (5-45 µg/ml) for greater than 8 hours.<sup>7,8</sup> Levetiracetam is approximately 100% bioavailable after IM administration and results in similar blood levels, although peak concentrations are not reached until about 40 minutes after the drug is given.<sup>8</sup>
- Reports of other medications for refractory status epilepticus are infrequent in veterinary medicine. There is a report of a dog with granulomatous meningoencephalitis and status epilepticus responding to intravenous ketamine infusion after failure to respond to diazepam and propofol.<sup>9</sup> This report follows several human case reports reporting similar efficacy for ketamine in the scenario of refractory status epilepticus, the rationale being blocking of NMDA receptors which may be responsible for the self-sustaining nature of this condition.<sup>1,6,10</sup> Ketamine infusions are gaining in favor for animals with refractory status epilepticus and dexmedetomidine has also been advocated in this scenario. Fosphenytoin is another newer medication that has been investigated for emergent seizure control in dogs. Additional therapies reported in refractory human cases include valproic acid, lidocaine, and topiramate.<sup>6,11,12</sup>
- A recent American College of Veterinary Internal Medicine consensus statement has developed a 3-tiered treatment system with documented levels of supporting evidence (Charalambous et al., 2023).

## 2) Support and Monitor Systemic Functions

As described above, status epilepticus can have profound effects on many body systems, and systemic functions must be closely monitored. These include:

- Mental status and level of consciousness
- Respiration, oxygen saturation and blood gases (if available)
- Cardiac rate and rhythm, blood pressure
- Body temperature
- Serum electrolytes, glucose, BUN and creatinine
- Fluid status and hydration
- Muscle damage and evidence of myoglobinuria (which may cause renal failure)

Intravenous fluid therapy is often indicated in order to maintain hydration and may help prevent renal damage if myoglobinuria is a concern. As severe seizure activity may lead to non-cardiogenic pulmonary edema, thoracic radiographs, pulse oximetry, and blood gas analysis should be considered in animals with compromised respiration. Aspiration pneumonia is also a concern, particularly in large recumbent dogs. Oxygen therapy may be administered in some of these patients. Active cooling should be considered in animals that are severely hyperthermic. Basic supportive nursing care must be performed in recumbent and stuporous animals, including applying artificial tears/lubrication to the eyes, providing adequate bedding/padding, periodically changing body position, turning from side to side, and passive range of motion of the limbs.

### **3) Protect Brain Function**

Prolonged, severe seizure activity can lead to cerebral edema, increases in intracranial pressure and neuronal necrosis. Select cases may benefit from oxygen therapy, mannitol (0.25-1.0 g/kg IV over 10-20 minutes) or hypertonic saline (4-5 mg/kg of 4% or 7.2% solution IV) in order to address these effects. Compression of the jugular veins, coughing and sneezing all increase intracranial pressure, and should be avoided in animals where this is suspected to be increased. Therefore, jugular catheters, collection of blood from the jugular vein, neck bandages, nasogastric tubes, and nasal oxygen catheters should all be avoided. Intravenous lidocaine should be considered to reduce the coughing reflex if intubation is required. Elevation of the head approximately 30 degrees from the horizontal is a simple way to promote venous return from the brain and potentially reduce intracranial pressure. Pentobarbital administration, in addition to stopping seizure activity, also has the advantage of reducing cerebral metabolism, which can have neuroprotective effects in patients with status epilepticus.

### **4) Monitor ongoing seizure activity**

Patients should be closely monitored to ensure the cessation of seizures and for the recurrence of seizure activity after initial therapy. This is typically done by visual observation and examination of animals for motor activity consistent with seizures. Whenever possible, cessation of seizure activity should be confirmed electrophysiologically with the aid of electroencephalography (EEG). This may detect animals whose outward motor manifestations of the seizure activity have stopped, but who continue to have abnormal electrical brain activity, known as nonconvulsive status epilepticus (NSE). Although NSE has rarely been reported in veterinary patients,<sup>9</sup> this is likely a reflection of the infrequency with which veterinary clinicians perform EEG in this setting. The author has documented a number of canine patients with apparent NSE after prolonged convulsive status epilepticus or presenting with a primary complaint of altered mentation (Mariani, unpublished observations). An EEG is part of the routine diagnostic evaluation of human patients presenting with stupor or coma, and in the author's opinion, the same should be offered to veterinary patients wherever possible.

### **At-Home Therapy for Cluster Seizures**

Some owners can be taught to administer benzodiazepines in the home environment in order to reduce the number of seizures in dogs (or cats) prone to cluster seizure events. The goal is usually to prevent further seizures, reduce the number and severity of subsequent seizures, and avoid an emergency visit to the veterinary hospital. Diazepam has been used most often via the rectal route; a standard dose (0.5 mg/kg) can be administered, although in some animals on chronic phenobarbital therapy, a higher dose (1-2 mg/kg) may be required due to increased metabolism of the drug.<sup>13,14</sup> Drugs administered rectally in the dog undergo a substantial first-pass effect and hepatic metabolism as the majority of absorbed drug enters the portal circulation.<sup>15</sup> As a result, the bioavailability of diazepam after rectal administration is only about 2.7-7.4% at doses of 0.5 and 2.0 mg/kg respectively in dogs not receiving phenobarbital.<sup>16</sup> However, some anticonvulsant effect is achieved as the main metabolites of diazepam (desmethyldiazepam and oxazepam) possess 20-50% of the activity of the parent drug.<sup>17-19</sup> Lorazepam is unsuitable for rectal administration, as its primary metabolite (lorazepam glucuronide) does not have anticonvulsant activity.<sup>15</sup> Midazolam does have a metabolite with reported pharmacologic activity (1-hydroxymidazolam), although the contribution of this reported activity is controversial.<sup>20</sup>

Intranasal (IN) administration of benzodiazepines avoids several of the shortcomings of the rectal route. The IN route avoids substantial first pass metabolism, and drug is directly absorbed into the systemic circulation thorough the dense vascular plexus present in the nasal passages.<sup>21</sup> In addition, there is evidence for direct movement of drug through the cribriform plate and into the central nervous system.<sup>22-24</sup> Several studies suggest that the bioavailability of diazepam is much higher after IN administration than after rectal.<sup>25,26</sup> and this route has been used successfully by the author in several emergent clinical cases (0.5 mg/kg). Preliminary experience suggests that intranasal lorazepam (0.2 mg/kg) may also be useful as an alternative to rectal diazepam for at-home use by owners.<sup>27</sup> Intranasal or IM midazolam (0.5 mg/kg) is another option available for these scenarios.

Lastly, pulse dosing of a novel anticonvulsant (i.e., one that the animal is not taking as a maintenance drug) can be effective in controlling cluster seizures and avoiding a visit to the hospital. The author typically recommends a loading dose, followed by administration of the pulse therapy for 48-72 hours. Options for such therapy include levetiracetam (60 mg/kg once then 20 mg/kg q 8 hrs) and pregabalin (4 mg/kg once then 2-3 mg/kg q 8-12 hrs).

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