Status Epilepticus in Dogs

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Status epilepticus (SE) refers to sustained focal or generalized seizure activity lasting longer than 5 minutes or cluster seizure activity (i.e., multiple seizures characterized by lack of a defined interictal period). SE is a life-threatening emergency that requires immediate medical treatment. Initial management is focused on stopping seizure activity, most commonly with a benzodiazepine (e.g., diazepam, midazolam). Untreated generalized seizure activity can result in serious metabolic, cardiovascular, and respiratory dysfunction; permanent brain damage; and/or death.

Most dogs presenting with SE exhibit generalized motor seizure activity. Data gathered from limited epidemiologic studies regarding populations of dogs presenting for SE indicate that the majority of dogs have primary (idiopathic) or secondary (acquired) epilepsy (i.e., epilepsy secondary to intra- or extracranial disease). Gathering a thorough history from the client is imperative in determining the potential cause of SE in a given patient and will aid in formulating appropriate diagnostic and therapeutic plans and in establishing the prognosis. The longer SE remains untreated, the less the chance for response to initial seizure control and the poorer the prognosis for a positive clinical outcome.

DIAGNOSTIC CRITERIA

Historical Information

Gender Predisposition: None.

Age Predisposition
- Congenital abnormalities (e.g., portosystemic shunt, hydrocephalus) should be considered as an underlying cause in young (<1 year) toy breeds.
- Infectious inflammatory diseases can occur in dogs of any age but are most common in dogs younger than 1 year.
- Idiopathic epilepsy should be considered as an underlying cause in dogs 1 to 5 years of age.
- Intracranial neoplasia and metabolic diseases are most common in dogs older than 5 years.
- Toxic, metabolic, and noninfectious inflammatory disorders can occur at any age.

Breed Predisposition: Breeds with a proven or highly suspected genetic predisposition for idiopathic epilepsy include beagles, German shepherds, Labrador retrievers, golden retrievers, vizslas, Belgian Tervurens, and English springer spaniels, but the condition can occur in any dog.

Owner Observations
- Clients may observe either one continuous prolonged seizure episode (lasting longer than 5 minutes) or multiple seizures between which the dog does not regain full consciousness.
- Seizure activity may consist of generalized convulsive or focal seizures.

Other Historical Considerations/Predispositions
- History of idiopathic (primary) epilepsy.

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7 Electrocautery and Electrical Cord Injury
• History of known intracranial disease (e.g., previously diagnosed space-occupying lesion, meningoencephalitis).
• Past history of SE.
• Known toxin ingestion.
• Head trauma.
• Known metabolic disorder.

Physical Examination Findings
The presentation of SE and the associated physical examination findings may differ from case to case because of the variable etiology and clinical behavior of SE.
• Continuous generalized or focal seizure activity may be observed on presentation.
• In cases of prolonged SE in which cerebral autoregulation has failed, the patient may present in a comatose state and only occasional muscle twitching may be observed.
• Focal or multifocal neurologic deficits may be present and may be attributable to either the underlying cause of the seizures (especially with intracranial disease) or to postictal neurologic impairment (cortical blindness, disorientation, lethargy).
• An elevated rectal temperature may be present in cases of prolonged convulsive seizures.
• External signs of cranial trauma, such as soft tissue injury, broken teeth, or palpable skull fractures, may be detected.
• It is important to note that in rare situations, mechanically “quiet” seizures (nonconvulsive epilepsy) can occur, in which an animal shows no outward signs of seizure (e.g., tonus, urination, defecation, clonus) but is still experiencing the cerebral overactivity associated with a seizure. Thorough neurologic examination may reveal neurologic deficits or other abnormalities (e.g., pupil asymmetry or abnormal pupillary light reflex, abnormal oculocephalic reflex, subtle focal muscle twitching) in a nonresponsive patient, which may lead one to suspect this form of seizure is occurring. This type of seizure is as damaging to the cerebral cortex as the more common generalized (systemic) seizure and needs to be treated as aggressively. Unfortunately, this electromechanical dissociation is impossible to diagnose without an electroencephalogram (EEG).

Laboratory Findings
Initial diagnostics should include a complete blood count, serum chemistry profile, urinalysis, electrocardiography (ECG), blood pressure measurement, arterial or venous blood gas analysis, partial or complete coagulation profile (especially if the patient is significantly hyperthermic or signs of disseminated intravascular coagulation [DIC] are present), and measurement of antiepileptic drug (AED) levels if the patient is receiving phenobarbital or potassium bromide (KBr). Depending on the underlying cause of SE, the following abnormalities may be present on clinical laboratory testing:

KEY TO COSTS
$ indicates relative costs of any diagnostic and treatment regimens listed.
$ costs under $250
$$ costs between $250 and $500
$$$ costs between $500 and $1,000
$$$$ costs over $1,000
Hypoglycemia: Generally accepted as glucose levels below 60 mg/dl (reference range, 80–100 mg/dl), although clinical signs may not be evident until concentrations become extremely low (< 30 mg/dl). Also, the severity of central nervous system (CNS) signs is generally a result of the rapidity of the drop in blood glucose rather than the actual concentration.

Hypocalcemia (serum ionized calcium [iCa\(^{2+}\)] < 0.8 mg/dl; reference range, 1.34 ± 0.05 mg/dl).

Polycythemia (packed cell volume > 55%; reference range, 37% to 55%) and hyperproteinemia (>7.5 g/dl; reference range, 5.1–7.3 g/dl) may be present and indicate dehydration.

Elevated creatine kinase activity (>368 U/L; reference range, 92–367 U/L) due to skeletal muscle damage secondary to prolonged generalized seizures. Muscle damage may also result in myoglobinuria.

Metabolic acidosis (blood pH < 7.31; reference range, 7.31–7.42; bicarbonate < 17 mEq/L; reference range, 17–24 mEq/L; or total carbon dioxide < 14 mEq/L; reference range, 14–26 mEq/L), especially in cases of ethylene glycol toxicosis.

In severe cases of SE, prolonged coagulation times (prothrombin time > 10.1 sec; reference range, 6.1–10.1 sec; activated partial thromboplastin time > 14.4 sec; reference range, 8–14.4 sec) accompanied by thrombocytopenia (< 200 x10\(^3\)/µl; reference range, 200–500 x10\(^3\)/µl), decreased fibrinogen (<100 mg/dl; reference range, 100–300 mg/dl), and elevated fibrin degradation products (>10 µg/ml; reference range, 0–10 µg/ml) may be present and indicate DIC is occurring.

A variety of other laboratory abnormalities indicating disease of a major organ system (e.g., liver, kidneys) may be present depending on the etiology.

Other Diagnostic Findings

Cerebrospinal fluid (CSF) analysis: Requires general anesthesia. Nonspecific findings are common, but inflammatory CNS disease can quickly be ruled in. Total nucleated cell count, cytology, protein analysis, and possible infectious disease titers are indicated. There is a risk of cerebral or cerebellar herniation after CSF collection in animals with increased intracranial pressure (ICP). This risk is higher in older animals in which an intracranial space-occupying lesion is suspected.

Skull radiography: Indicated if cranial trauma is suspected.

Computed tomography: Indicated in patients suspected of having a structural intracranial abnormality or skull trauma and is optimal for visualization of bony changes. Disadvantages include cost, the need for general anesthesia, and suboptimal visualization of parenchymal lesions.

Magnetic resonance imaging: Indicated in patients suspected of having a structural intracranial abnormality and is preferred for visualization of parenchymal changes, such as soft tissue masses, vasogenic edema, and potential focal or multifocal inflammatory lesions. Changes may also be evident due to the seizure activity itself. Disadvantages include cost and need for general anesthesia.

EEG monitoring: This is generally performed in a specialized hospital setting and can be used to diagnose nonconvulsive epilepsy and to monitor response to treatment in patients being treated for SE.

Summary of Diagnostic Criteria

Continuous focal or generalized seizure activity lasting longer than 5 minutes or a history of cluster seizures without return to full consciousness between episodes.

History of known primary or secondary epilepsy (intracranial versus extracranial disease) or known toxin ingestion.

Clinical pathology findings consistent with metabolic diseases that may induce seizures; alternatively, CSF or diagnostic imaging findings consistent with CNS disease.

Differential Diagnosis

Idiopathic epilepsy.

Intracranial disease: Neoplastic, cerebrovascular, infectious inflammatory (e.g., distemper, toxoplasmosis), or noninfectious inflammatory (e.g., granulomatous meningoencephalitis).

Toxin ingestion: Ethylene glycol, organophosphates, carbamates, strychnine, lead, metaldehyde, pyrethrins, pyrethroids, or rodenticides are commonly incriminated toxins.

Cranial trauma or cerebral anoxia.

Hypoglycemia.

Hypocalcemia.

Hepatic encephalopathy.

Uremic encephalopathy.

Tetanus.

TREATMENT RECOMMENDATIONS

Initial Treatment

In any emergency situation, the ABCs (airway, breathing, and circulation) should be assessed and appropriate action initiated.

An intravenous (IV) catheter should be placed.

If the patient is hypoglycemic (blood glucose < 60 mg/dl), an IV bolus of dextrose and an IM dose of thiamine (vitamin B\(_1\)) can be administered.
— 50% dextrose: 1.0 ml/kg IV (diluted 1:2 in IV fluids) over 10 minutes. This dose can be repeated as necessary, ideally guided by serial blood glucose determinations.

— Thiamine: 50 mg IM once after dextrose administration in patients suspected of having thiamine deficiency. However, any patient receiving glucose supplementation may be given this water-soluble cofactor as a preventive measure against inducing acute thiamine deficiency secondary to dextrose infusion. Thiamine is an important cofactor in neuronal glucose metabolism and has the potential to become rapidly depleted with an acute increase in glycolysis.

• An attempt should be made to control seizures with diazepam or midazolam (0.5 mg/kg IV bolus). $

— Bolus can be repeated once or twice if the patient does not respond.

— The dose of diazepam may need to be increased in dogs that have received phenobarbital long-term (related to enhanced hepatic clearance of diazepam).

— If an IV route is not available, 1.0 mg/kg of either drug may be administered per rectum (PR). Dogs that have been on long-term phenobarbital therapy may require higher doses of diazepam (up to 2 mg/kg PR). Intranasal administration of diazepam (0.5 mg/kg) has been shown to result in therapeutic plasma drug concentrations as well.

• Supplemental oxygen should be provided by flow-by, nasal insufflation, or intubation as needed.

• Rectal temperature should be monitored; if it exceeds 103.5°F, the patient should be cooled:
  — IV fluid administration and seizure control are generally sufficient.
  — Placing ice packs or other cooling devices directly onto the patient should be avoided as the resulting peripheral vasoconstriction can impede total body cooling.
  — Cooling measures should be discontinued when the patient’s temperature has reached 102°F.

• Known toxin exposure/ingestion should be treated accordingly. Contact your regional poison control center for more information.

Alternative/Optional Treatments/Therapy

Phenobarbital $

If seizures persist despite a 1.0 to 2.0 mg/kg cumulative dose of diazepam or midazolam, an attempt should be made to initiate phenobarbital therapy.

• In an animal not already receiving phenobarbital, a cumulative dose of 20 to 25 mg/kg IV is divided into three or four increments, with a wait time of 15 to 30 minutes between administration of each dosage increment. Diazepam or midazolam boluses (0.5 mg/kg IV) can be given as needed to control seizure activity that may occur between administrations of phenobarbital dosage increments. Diazepam and midazolam are relatively safe drugs (reported LD$_{50}$ of 720 mg/kg PO in mice for diazepam; reported LD$_{50}$ of 86 mg/kg IV in mice for midazolam), but significant CNS depression can occur with overdosage. Alternatively, a loading dose of phenobarbital can be given with the goal of rapidly establishing a therapeutic drug level in serum: Loading Dose (mg) = Body Weight (kg) x 0.8 x Desired Serum Concentration (µg/ml).

• In animals already receiving phenobarbital, it is imperative that the dose of phenobarbital be decreased. The following formula can be used in
such animals: Loading Dose (mg) = Body Weight (kg) × 0.8 × (Desired Serum Concentration – Current Serum Concentration [µg/ml]). A pretreatment serum sample should be saved for phenobarbital concentration determination.

- If phenobarbital is not available, a loading dose of KBr (400 mg/kg PO or PR divided over 2–4 days) may be attempted. However, the long half-life of KBr prevents acute seizure control. Some measure of refractory seizure therapy (see below) may have to be employed while waiting for a therapeutic serum concentration to be established.

Refractory Seizure Therapy

If seizure activity persists after phenobarbital loading, refractory seizure therapy should be initiated.

- Diazepam or midazolam continuous-rate infusion (CRI) may be attempted first: 0.5 to 1.0 mg/kg IV cumulative loading dose to effect; if seizures respond to the loading dose, a dosage of 0.5 to 1.0 mg/kg/hr CRI is used initially but may be adjusted to fit individual patient needs. Isotonic saline should be used as the base fluid because diazepam may precipitate with other crystalloids.

- General anesthesia may be required for patients refractory to a diazepam or midazolam CRI.
  - Propofol CRI: 2.0 to 8.0 mg/kg IV cumulative loading dose to effect; if seizures respond to the loading dose, a dose of 0.1 to 0.6 mg/kg/min CRI is used.
  - Pentobarbital: 3.0 to 15.0 mg/kg IV cumulative dose slowly to effect. This dose can be repeated to induce full anesthesia in refractory patients. There is a major caveat in using this drug to control seizures: Normal animals will often paddle and vocalize when waking up from pentobarbital-induced anesthesia, which allows for potential confusion between this response and true seizure activity; thus, pentobarbital may be a difficult drug to use in cases of SE.
  - Isoflurane anesthesia: The patient should be intubated and minimum alveolar concentration (MAC) adjusted accordingly.

Supportive Treatment

- Patients that respond to initial treatment with diazepam or midazolam, or to phenobarbital loading, should be started on a maintenance AED, such as phenobarbital or KBr, while the underlying cause for their seizures is determined.

- Patients requiring treatment for refractory seizures also require intensive monitoring and supportive care. Whether the patient responded to initial pharmacotherapy or is undergoing refractory seizure therapy, the following should be performed according to patient needs:
  - Ensuring airway patency/stabilization, including intubation if necessary (especially in patients without a gag reflex).
  - Providing well-padded bedding and rotating the patient from side to side every 4 hours.
  - Lubricating the eyes every 4 to 6 hours.
  - Maintaining adequate patient hydration with isotonic IV fluids.
  - Providing adequate nutritional support, whether via oral feedings, feeding tube, or partial or total parenteral nutrition, in animals unable to voluntarily eat within 48 hours.

- If phenobarbital is not available, a loading dose of KBr (400 mg/kg PO or PR divided over 2–4 days) may be attempted. However, the long half-life of KBr prevents acute seizure control. Some measure of refractory seizure therapy (see below) may have to be employed while waiting for a therapeutic serum concentration to be established.

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  - Isoflurane anesthesia: The patient should be intubated and minimum alveolar concentration (MAC) adjusted accordingly.

- Additional parameters to monitor in patients undergoing treatment for refractory seizures:
  - Arterial blood gas analysis, with appropriate adjustments in ventilation or oxygen therapy if possible.
  - Urine output.
  - Coagulation status: A complete coagulation profile or individual tests of coagulation may be performed periodically if DIC is suspected as a sequela to seizure-induced hyperthermia.
  - Brain activity may be monitored with an EEG in a specialized hospital setting.

- Patients receiving maintenance therapy (i.e., patients with a history of epilepsy being managed with an AED): Serum drug concentrations of AEDs should be evaluated to determine whether a therapeutic level existed before treatment of SE and/or whether a therapeutic level was established if phenobarbital or bromide loading were attempted.
  - Therapeutic range of phenobarbital: 20 to 40 µg/ml; serum drug concentration should be checked after loading and 2 weeks after any dose alteration.
  - Therapeutic range of KBr: 1.0 to 3.0 mg/ml (if used as the sole AED); serum drug concentration should be checked 2 to 3 days after administering a loading dose and 3 months after any dose alteration. The therapeutic range of KBr may be lower (0.8–2.4 mg/ml) in animals concurrently receiving phenobarbital.
The underlying cause of the seizure activity should be investigated to facilitate appropriate treatment planning and long-term prognosis.

**Home Management**
- Seizure control (a discussion of long-term seizure management is beyond the scope of this article).
- Removal of known toxicants from the home environment or closer observation (or confinement) to prevent the dog from consuming such items in the future.
- If a potential episode of SE arising at home is a concern, clients may be instructed about how to administer diazepam PR (1.0 mg/kg PR; may repeat once). Clients should be instructed to seek immediate emergency care if seizure activity does not respond to this treatment.

**Milestones/Recovery Time Frames**
- Within the first 5 to 10 minutes of initial pharmacotherapy: Significant decrease or arrest of seizure activity.
- Within the first 24 to 48 hours: Improved neurologic function and nonrecurrence of seizure activity.

**Treatment Contraindications**
- Anesthetic drugs that may increase ICP (e.g., ketamine, halothane) should be avoided.

**PROGNOSIS**

Prognosis for return to normal neurologic function or acceptable quality of life depends heavily on the expediency and aggressiveness of treatment, initial response to seizure control, and underlying etiology. As with other neurologic emergencies, the earlier SE is detected and stopped, the greater the chance of a positive clinical outcome. Once the decompensated stage of SE is reached (as generally occurs with SE lasting more than 30 minutes), prognosis for a positive outcome decreases substantially. Prolonged SE can result in profound systemic complications, permanent brain damage, and possibly death.

**Favorable Criteria**
- Response to initial treatment with diazepam or midazolam (e.g., significantly reduced or no seizure activity).
- Rectal temperature not exceeding 105.0°F.
- No recurrence of seizure activity within a 24-hour period.
- Return of complete neurologic function.

**Unfavorable Criteria**
- Persistence of seizure activity despite initial treatment with diazepam/midazolam or phenobarbital.
- Loss of seizure control within 6 hours of initially successful pharmacotherapy.
- Rectal temperature in excess of 105.0°F.
- Coagulation profile abnormalities.
- Persistent neurologic deficits despite adequate seizure control.
- Presence of underlying diseases such as neoplasia or granulomatous meningoencephalitis.
- Nonconvulsive epilepsy.

**RECOMMENDED READING**


Dr. Smith is currently an Adjunct Instructor in the Department of Biomedical Sciences, College of Veterinary Medicine, Iowa State University.