

Status Epilepticus and Cluster Seizures



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KEYWORDS

• Dog • Epilepsy • Seizures • Diazepam • Phenobarbital • Levetiracetam

KEY POINTS

- First-line (emergent initial) therapy for dogs or cats with prolonged (>5 min) seizures or seizures without recovery between should be initiated as soon as possible with a benzodiazepine drug at home (dogs) or in the veterinary hospital.
- Following first-line therapy, urgent therapy with parenteral loading doses or miniloading doses of a long-acting antiepileptic drug such as phenobarbital, levetiracetam (LEV), or bromide (dogs only) should be given to rapidly attain therapeutic levels of a chronic therapy drug.
- The etiology of status epilepticus (SE) should be diagnosed and treated as soon as possible.
- For companion animal patients failing to respond to first line therapy, second-line therapy should be attempted with nonanesthetizing doses of intravenous phenobarbital and/or intravenous LEV and/or a constant rate infusion (CRI) of diazepam or midazolam.
- Companion animals in refractory SE because they have failed to respond to first- and second-line treatments should be anesthetized with a CRI of propofol or pentobarbital or other anesthetic as third-line therapy.

DEFINITIONS

Status Epilepticus

Status epilepticus (SE) in the current veterinary and human literature is most often defined as a single seizure lasting 5 minutes or longer, or 2 or more seizures without recovery between.¹ Previous definitions had often been seizure activity lasting for at least 30 minutes due to the clear-cut potential for permanent damage at that point. The rationale for a shorter duration for the definition has been the need for urgent and aggressive treatment early in the process well before the 30-minute mark.²

Generalized Seizure

This type of seizure is one in which the first clinical changes indicate the initial involvement of both cerebral hemispheres.³

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Focal Seizure

A focal seizure is one that originates within neuronal networks limited to 1 hemisphere. Such networks may include cortical and subcortical structures.⁴

Convulsive Status Epilepticus

Convulsive SE (CSE) is SE with convulsions that are associated with rhythmic jerking of the extremities such as generalized tonic-clonic movements and/or mental status, impairment and/or neurologic deficits.⁵

Nonconvulsive SE

Nonconvulsive SE (NCSE) is defined as prolonged seizure activity seen on electroencephalography (EEG) without the clinical findings associated with CSE, with either a wandering and confused patient or a patient with severely impaired mental status.⁵ Although NCSE could be common, it has rarely been recognized in veterinary patients to date; therefore this article will not address NCSE beyond this section. Continuous intensive care unit (ICU) EEG monitoring is routinely done for human SE patients. Similar monitoring for NCSE has been done in some canine and feline patients and proposed to be further investigated,⁶ but it is not standard practice in veterinary ICUs at this time.

Acute Repetitive Seizures and Cluster Seizures

Acute repetitive seizures (ARS) in people have been variably defined, but an accepted definition is 3 or more seizures in the 5 to 12 hours prior to presentation.^{7–10} In dogs, frequent seizures (ie, ARS) have usually been defined as cluster seizures (CS). Definitions of CS in dogs have been inconsistent between publications, but they generally have been defined as a bout of multiple seizures occurring over a short period of time that is different from the patient's typical seizure pattern. A useful clinical definition of CS is 2 or more seizures occurring within a 24-hour period, in which the patient regains consciousness between the seizures.¹¹

Refractory SE

Refractory SE (RSE) in people is defined as continuation of either clinical or EEG-defined seizures after receiving adequate doses of initial benzodiazepines followed by a second acceptable antiepileptic drug (AED).⁵ Patients with RSE usually require anesthetic agents at anesthetic doses as third-line treatment.

Super RSE (SRSE)

Super RSE (SRSE) is SE that goes on 24 hours or more after the onset of anesthesia¹²; because of financial constraints and other considerations, companion animals are often euthanized before SRSE occurs.

Recently, several definitions regarding seizures in companion animals have been proposed (Box 1).¹ These proposed definitions are based on, but not identical to current definitions for people.

INTRODUCTION

Most seizures in dogs and cats are self-limiting and last a couple of minutes or less. Seizures that last more than a few minutes or occur back-to-back without recovery between are emergencies and should be treated promptly, aggressively, and with a systematic plan. If 30 to 60 minutes of continuous seizure activity occur, irreversible neuronal damage begins, mainly because of excitotoxic cell injury related to excessive glutamate release.¹³ Resulting autonomic and endocrine dysfunction can lead

Box 1**Proposed definitions for companion animal seizures¹ that relate to seizure emergencies****Status Epilepticus:**

- A seizure that persists for greater than 5 minutes or
- Recurrent seizures without interictal resumption of baseline central nervous system function

Cluster Seizure

- Two or more seizures within a 24-hour period.

Duration

- Time between the beginning of initial seizure manifestations and the cessation of observed seizure activity. Does not include prodrome or postictal states but might include aura.

Data from Mariani CL. Terminology and classification of seizures and epilepsy in veterinary patients. Top Companion Anim Med 2013;28:34–41.

to loss of normal brain homeostasis, kindling, functional and structural hippocampal changes, neurodegeneration, and altered distribution of ion channels and neurotransmitter receptors on a cellular level.⁶ Systemically, prolonged or frequent seizures can result in hyperglycemia, hypertension¹¹ neuronal necrosis, hyperthermia, cardiac arrhythmias, kidney damage, metabolic acidosis, disseminated intravascular coagulation, cardiorespiratory failure, and a predisposition to further seizure episodes.⁴ Consequently, aggressive and safe early intervention is important.

About 40% to 60% of dogs with genetic (idiopathic, primary) epilepsy suffer CS or SE,^{11,14–17} and CS can evolve into SE.

In people, SE and ARS are common reasons for presentation to emergency rooms, with approximately 152,000 cases per year and 42,000 annual deaths in the United States.^{18,19} Reported mortality rates in people range from 8% to 38%, depending on the underlying cause and patient age, with an overall mortality rate of 22%.^{18,20}

To date, several detailed retrospective studies evaluating SE and CS in dogs have been published.^{14–17} Although the designs differed, particularly for the underlying cause of SE, many similar conclusions were reached:

- The incidence of CS in dogs with genetic (idiopathic) epilepsy has been reported to be as high as 41%.¹⁶
- The prevalence of SE in dogs admitted for seizures has been documented to be 16%.¹⁴
- The incidence of SE in dogs with primary epilepsy was found to be 2.5%¹⁶ in 1 study, whereas in another study it was found to be up to 59%.¹⁵
- Overall mortality rates (mostly from euthanasia) for dogs with episodes of SE were 23%,¹⁴ 32%¹⁵ and 38%,¹⁷ with death occurring in a relatively small number of cases (2%–5%) (these estimates of morbidity and mortality are roughly comparable to those reported in studies in people).
- The underlying causes identified were genetic (idiopathic) epilepsy (26.8%–37.5%), structural (symptomatic, secondary) epilepsy (35.1%–39.8%), and reactive epileptic seizures (6.7%–22.7%).^{14,17}

THERAPY OF SE***General Considerations for SE Care for Companion Animals***

The initial management of SE should utilize basic principles of life support and drug administration to stop the seizures. Sedating antiseizure drugs can lead to loss of

pharyngeal tone and risk of aspiration. Oral or nasal administration of oxygen is therefore needed in some patients, and when anesthetic drugs are used, intubation and ventilator support are required. Intravenous access should be obtained as soon as possible and blood collected for glucose measurement and therapeutic monitoring in patients already on AED therapy. Temperature, pulse oximetry, electrocardiogram (ECG), and blood pressure should be monitored, and any abnormalities, such as hyperthermia, hypoglycemia, or hypocalcemia should be quickly treated.¹¹ As the SE is being treated with drugs, efforts should also be made to diagnose the etiology as quickly as possible and start treatment for any causes with specific therapies.

CURRENT AND HISTORICAL DRUG THERAPY FOR SE

Human SE

In the 19th century, starting in the 1860s, bromides were given hypodermally, rectally, or orally. Intravenous barbiturates, including phenobarbital, were introduced in the 1920s. Phenytoin was first used by intravenous injection in 1958. Benzodiazepines were introduced for SE in 1965, and the therapy of SE remained mainly unchanged for more than 40 years until the recent introduction of intravenous levetiracetam (LEV), intravenous valproate, and intravenous lacosamide.²¹

Despite the high levels of morbidity and mortality associated with human SE (HSE), there is a relative paucity of prospective, controlled research to determine the optimum treatment regimens for people. To date, 4 prospective, randomized, double-masked studies have been performed for first-line therapy for HSE. The most notable findings are:

- Intravenous lorazepam is superior to intravenous diazepam for first-line treatment.²²
- Intravenous lorazepam is superior to intravenous phenytoin alone and is comparable to intravenous phenobarbital treatment and combination intravenous diazepam with intravenous phenytoin treatment.²³
- Intramuscular midazolam is equivalent to intravenous lorazepam in prehospital treatment by paramedics.²⁴

The most current published guidelines for HSE by a panel of experts⁵ indicate

- **First-line (initial emergent) therapy for HSE.** When available, intravenous therapy is preferred with intravenous lorazepam. When intravenous access is not available, midazolam is the preferred intramuscular agent (and can also be given nasally or buccally), and diazepam is the preferred drug for rectal administration.
- **Urgent control.** Additional antiepileptic drug (AED) treatment should be given following benzodiazepines unless the immediate cause of HSE is known and corrected. The goal is rapid attainment of therapeutic levels of an AED and continued dosing for maintenance therapy.
- **Second-line therapy for HSE for patients who continue to have motor or EEG seizures.** The preferred agents include intravenous fosphenytoin/phenytoin, intravenous valproate sodium, intravenous phenobarbital, intravenous LEV, or CRI of midazolam. Of these agents, fosphenytoin may be preferred for most patients, with the exception of patients, particularly children, with a history of primary generalized epilepsy, in whom valproate would be the best choice.
- **Third-line therapy for (human) RSE (induction of general anesthesia).** AEDs most often recommended for use as a continuous infusion are midazolam,

propofol, and pentobarbital; in some countries, thiopental is also used. At present, there are insufficient data to suggest whether midazolam, propofol, or pentobarbital is the preferred agent. Alternatives for RSE include inhalant anesthesia, corticosteroids, ketamine, hypothermia, and neuromodulation.⁵

Canine SE

Although there are some recommended guidelines for the emergency treatment of seizures for companion animals, only 1 prospective controlled study in dogs evaluating the efficacy of AEDs for SE has been published to date.²⁵ Current treatment recommendations for seizure emergencies in dogs and cats are based on clinical experience and the results of human or rodent studies. One published algorithm²⁶ recommends diazepam as first-line therapy followed by phenobarbital as second-line therapy. Additional recommended medications are diazepam or midazolam CRI, and/or general anesthesia with pentobarbital, propofol, thiopental (if available), or inhalant anesthesia.² Other treatment options include mannitol for elevated intracranial pressure, and ketamine has been used in some refractory cases.²⁷ In addition to in-hospital therapy, at-home therapy with rectal (1.0–2.0 mg/kg, 2.0 mg/kg if on phenobarbital)²⁸ and intranasal administration of diazepam (0.5 mg/kg) have also been recommended. The pharmacokinetics of intranasal midazolam (0.2–0.5 mg/kg) and intranasal lorazepam (0.2 mg/kg) have also been studied in dogs. It should be noted that lorazepam per rectum may not be useful AED therapy because of rapid conversion to inactive metabolites and first pass hepatic metabolism,²⁹ and that there is erratic systemic availability of midazolam when given per rectum.³⁰

General Standard of Practice for Companion Animal SE (Box 2)

There has not yet been an expert panel consensus statement for the treatment of companion animal SE. There does seem, however, to be fairly similar recommendations from a number of sources^{11,26,31} that can be generally summarized as

First-line therapy should be with a benzodiazepine, which is most often is intravenous diazepam, but can be by other routes and/or with midazolam, or lorazepam. There have not been any published studies comparing the benzodiazepines to each other in dogs or cats as there has been for people. Shortly after the benzodiazepine, there should be intravenous loading or mini loading doses of intravenous phenobarbital or intravenous LEV to start chronic therapy, for when the short acting benzodiazepines wear off.

In second-line therapy for continuing seizure activity, intravenous phenobarbital or intravenous LEV or a CRI of diazepam or midazolam should be given. The author has found that 2 or more of these second-line therapies can potentially be given to the same patient.

Third-line therapy of RSE to induce general anesthesia can be with intravenous propofol or pentobarbital. In some instances, IV ketamine or inhalant anesthesia has been administered.

Feline SE

Most of the data and studies for SE in companion animals have been performed in dogs. The same general recommendations, with some exceptions (Box 2), are generally valid for cats at this time, but more retrospective analysis and prospective studies are needed in cats to be able to confidently make specific recommendations for treating feline SE.

Box 2**Generally recommended doses and staged plan for parenteral AED therapy for canine SE****First-line (initial emergent) therapy^a**

Diazepam 0.5–2.0 mg/kg intravenously up to 3 times,¹¹ intranasally,³² per rectum²⁸

or

Midazolam 0.06–0.3 mg/kg intravenously, intramuscularly,³³ 0.2 mg/kg intranasally³⁴ not per rectum

or

Lorazepam 0.2 mg/kg intravenously,²⁹ intranasally³⁵ not per rectum

Second-line therapy

Phenobarbital 2–6 mg/kg intravenously,³³ every 20 to 30 minutes to effect; maximum dose 24 mg/kg³³

or

Diazepam CRI 0.1–0.5 mg/kg/h, 0.5–2.0 mg/kg/h.³³ Use with caution, as diazepam can crystallize in solution and adsorb to polyvinyl chloride tubing, or midazolam 0.1–0.2 mg/kg/h

or

LEV 30–60 mg/kg intravenously in dogs,²⁵ 20 mg/kg intravenously in cats³⁶

Third-line therapy for RSE by induction of general anesthesia.

Propofol 1–4 mg/kg intravenous bolus slowly to effect³³

0.1–0.6 mg/kg/h CRI^{37,38}

or

Pentobarbital 3–15 mg/kg intravenously to effect³³

0.5–4 mg/kg/h CRI³⁷

Other anesthetic therapies

Isoflurane 1%–2% minimum alveolar concentration³¹

or

Ketamine 2–8 mg/kg intravenous bolus²⁷

Other drugs with very little published data to date

Bromide 3% sodium bromide 800 mg/kg/24 h intravenous loading³⁹ (not cats)

Fosphenytoin 15 mg/kg phenytoin equivalent (PE) intravenously, dog⁴⁰

LEV 60 mg/kg subcutaneously at home, dog^{2,41}

Lacosamide 3 mg/kg/15 min³⁹ intravenous loading dose, dog only

^a Be sure to load or miniload with a long-term chronic AED soon after initial therapy.
Data from Refs. ^{2,11,27–29,31–37,39–41}

Recent Prospective Studies of SE in Dogs**Levetiracetam**

LEV was approved in the United States in 1998 for the oral treatment of partial-onset seizures in adult people. An intravenous formulation was approved in 2006 for use as bridge therapy in people.²⁵ Since that time, there have been increasing reports of the off-label use of LEV in people for the treatment of seizure emergencies with variable response rates. In adults, success rates for the treatment of HSE

have ranged from 44% to 71% with LEV with few reported adverse effects.^{42–45} A wide safety margin and minimal drug-drug interactions have led to LEV use in children, the elderly, and critically ill patients with SE. The author's group completed a randomized controlled trial of LEV for SE and CS for dogs in 2012 indicating that 30 to 60 mg/kg LEV intravenously for second-line therapy may be safe and effective.²⁵

Fosphenytoin

Fosphenytoin is the most often-used second-line agent in people. The author's group has published that intravenous fosphenytoin at 15/mg/kg intravenous PE at a rate of 50 mg/min PE infusion is generally well tolerated in normal dogs, with minor vomiting in some dogs.⁴⁰ The author and colleagues have just completed a randomized clinical trial of diazepam and placebo versus diazepam and 15 mg/kg PE of fosphenytoin for canine SE in 31 cases.⁴⁶ The results of this study are in preparation for article submission, and the author expects they should be published in the coming year. Based on the full results of this study and possibly other future studies, fosphenytoin might be a possible additional nonanesthetizing choice for second-line therapy of SE for dogs.

CS Recommendations

Because of the lack of consistent definitions of CS for companion animals, and lack of published information, there are not clear-cut recommendations that can be unequivocally made for monitoring and treatment of CS. In the author's experience, dogs or cats with 2 or more generalized seizures with recovery between within a 12- to 24-hour period should at a minimum be monitored carefully, and can be given per rectum or intranasal diazepam at home by the owner to try to prevent the need for hospitalization. If benzodiazepines are ineffective at home, and/or the seizures continue, then in-hospital monitoring and possible treatment as for SE are recommended. It has been advocated by a number of specialists to give an extra dose or doses of chronic therapy drugs such as phenobarbital, zonisamide, or levetiracetam at home when the patient is awake enough to swallow safely, in order to break cluster seizures. There are not any published studies of this strategy in dogs, although reasonable additional doses of chronic AEDs are unlikely to cause significant harm, and future studies of pulse therapy in dogs are indicated to determine if this practice is truly helpful for cluster seizures prior to possible hospitalization.

Open Question—Single-Agent Versus Combined Therapy for Initial Treatment of SE?

It has been suggested by some that first-line therapy be with 2 nonanesthetizing drugs immediately rather than benzodiazepines first and then second-line therapy. Synergy between LEV and diazepam has been shown in both rodent models of SE, and in a clinical population of human patients with acute repetitive or prolonged seizures. In rats with electrical stimulation-induced SE, the combination of LEV and diazepam as first-line therapy was superior to either drug alone, even when plasma concentrations were well below the therapeutic range of either drug alone.⁴⁷ Two reasons for possibly utilizing intravenous LEV combined with benzodiazepines as first-line therapy are the high safety profile of LEV and favorable pharmacokinetics. Compared with all other AEDs, LEV has the widest safety margin of an AED.⁴⁸ Doses as high as 1200 mg/kg/d by mouth have been shown to cause only mild adverse effects in long-term oral dosing studies in dogs.⁴⁹ Future controlled prospective trials are needed to determine whether early combination therapy might be more effective and still safe compared with benzodiazepine therapy only.

FUTURE POSSIBILITIES

In the last 10 years there have been evolving potential therapies for SE beyond the benzodiazepines, which open the hope for new treatments, and if successful would be paradigm shifts; these include but are not limited to neurosteroids,⁵⁰ gene therapy, optogenetics (light control of neurons through light-sensitive proteins), use of antagonists (inhibitors of micro RNAs that affect gene expression),²¹ and new biochemical targets such as adenosine.⁵¹

FINAL SUMMARY

SE in companion animals is an emergency and should be quickly treated by recommended first-line (emergent) therapy with benzodiazepines followed by loading doses of chronic therapy drugs, and then second-line, and third-line (refractory) therapy when needed. CS can evolve into SE, and therefore at-home treatment with per rectum or intranasal benzodiazepines and longer-acting oral AEDs for dogs is often recommended, and if not effective, then hospitalization for observation and treatment as for SE are recommended.

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