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HOW I TREAT STATUS EPILEPTICUS

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INTRODUCTION
Status epilepticus (SE) is a life-threatening neurologic emergency characterized by prolonged seizure activity. SE has been defined as an epileptic seizure or sequence of recurrent seizures persisting for at least 30 minutes during which the patient does not regain normal consciousness. A stricter criterion includes the presence of electrical seizure activity of at least 10 minutes duration, even if consciousness is not impaired. Data from human patients, however, indicates that seizures lasting for at least 5 minutes are unlikely to stop on their own without pharmacologic intervention. Many epileptic dogs exhibit recurrent generalized epileptic seizures within a 24-hour period, termed cluster seizures. Since little information is available on the electrical activity of the brain of these dogs during these events, coupled with the fact that many of these cluster seizures are intermixed with partial seizures and abnormal behavior, it is possible that many of these affected animals are exhibiting a form of SE unique to this species. Failure to control these seizures cannot only be a life-threatening event, but also may also contribute to poor long-term seizure control.

INITIAL APPROACH AND DIAGNOSIS
The cause of SE is often related to whether previous epilepsy has been diagnosed. In general, there has been no definitive evidence correlating SE to specific etiology. A higher proportion of dogs with previous seizures in the age range of 1 to 5 have idiopathic epilepsy. Approximately 25% of the SE cases in one study were idiopathic in nature. Many of these animals develop SE or cluster seizures due to inadequate antiepileptic drug (AED) therapy, drug tolerance, or recent changes in therapy. In contrast, dogs with new onset of seizure activity, that are younger (<1 years) or older (>7 years), are more likely to have symptomatic epilepsy due to a predisposing underlying brain disease. Younger animals are more susceptible to toxicity, metabolic encephalopathies (e.g., portosystemic shunts) and encephalitic diseases as a cause for seizures. Older cats and dogs, however, are more likely to suffer from underlying brain neoplasms, cerebrovascular disease, as well as metabolic encephalopathy from advancing renal or liver disease.

Immediate diagnostic testing should revolve around the current physiologic status of the seizuring animal. Basic cardiopulmonary resuscitation requirements of ensuring that there is an open airway with adequate blood oxygenation with a pulse oximeter and/or blood gas, and providing fluid support to maintain normal blood pressure is critical. Minimal STAT testing includes analysis of blood glucose, electrolytes (sodium, potassium, calcium, chloride), and PCV/TP. Optimal STAT testing includes a complete blood count, serum chemistry panel (to include creatine phosphokinase), blood gas analysis, and existing AED serum concentrations. The latter tests, however, are typically not available to most emergency clinics. Serum should be collected in a non-serum separator tube at the time of admission for future submission of AED serum concentrations.

Once the patient is stable, the next level of diagnostic testing involves the physical and neurologic examination of the patient. Although neurologic examination is expected to be abnormal due to the post-ictal state of the animal, the examination is important to allow for evaluation of possible underlying brain disease, obtain a baseline measurement of neurologic function, and to determine if cerebral herniation may be impending or present. A minimal evaluation includes determination of the level of consciousness, notation of any abnormal extensor rigidity of the neck or limbs, pupillary light reflex testing, corneal reflex, and the oculocephalic reflex. Signs of impeding or existing brain herniation include one or more of the following: 1. Opisthotonus with extensor rigidity of all limbs (decerebrate posturing), or thoracic limbs only with hypotonia of pelvic limbs (decerebrate posturing); 2. Anisocoria with a fixed and dilated pupil(s); 3. Bradycardia with or without underlying systemic hypertension. The loss of a corneal reflex (cranial nerves V and VI) and oculocephalic reflex (cranial nerves III, IV, VI, and VIII) is suggestive of underlying brainstem disease or damage (if not due to drug influences). If brain herniation is suspected, appropriate treatment is required (see below).

Delayed or advanced diagnostic testing entails determination of the underlying cause for the seizures as well as evaluation of existing serum AED levels as applicable. These tests include thoracic and abdominal radiographs, possible abdominal ultrasound, and any follow-up biochemical testing as indicated by the initial laboratory testing. Advanced imaging of the brain (i.e., MRI scan) is strongly recommended for any new onset seizure dog over the age of 7 years and for any cat proven not to have a metabolic disease. Collection of cerebrospinal fluid is typically dependent upon results of the imaging. Results of neuroimaging can be abnormal as a consequence of SE in a high proportion of dogs.

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TREATMENT

The goals of treating SE are simple: stop the seizures, protect the brain from further damage, and allow full recovery from the episode of SE. The longer an animal seizures, the greater the chances are that neuronal injury will occur. Brain damage in the epileptic patient begins at the subcellular level, progresses to the cellular level, and overtime, will result in overt pathologic changes to the brain that may lead to permanent changes in brain function. With the onset of a seizure, several mechanisms occurring simultaneously can lead to neuronal death. Understanding the effect of these changes on the brain is important when planning proper emergency seizure therapy. Several factors lead to direct cytotoxicity, to include hypoxemia, ischemia, and excitotoxicity. The latter is due to an excessive activation of glutamate receptors, an excitatory neurotransmitter, resulting in an excessive and prolonged influx of intracellular calcium that disrupts the normal metabolic activity of the cell.

After 30 minutes of seizure activity, physiologic complications can arise to further jeopardize neuronal health. As seizure activity becomes more prolonged, an animal will exhibit hyperthermia, hypoxia, cerebral edema and brain ischemia. Eventually, intracranial pressure becomes elevated due to disruption of the blood-brain-barrier and the presence of cerebral edema. If the seizures are not stopped, a vicious cycle of progressive cerebral edema, increasing intracranial pressure, decreased cerebral perfusion, and eventual cellular death ensues. Thus, the acute pathogenesis of brain injury during seizures dictates therapy designed to stop the ictal event, reduce intracranial pressure by decreasing cerebral edema, and provide the care to support neuronal metabolic activity.

As a consequence of severe or prolonged seizure events, animals can develop detectable neurologic deficits during the immediate and extended post-ictal time period. More severe immediate post-ictal abnormalities include vision loss, circling, paresis, profound disorientation, aggressive personality changes, and other dementing behaviors. Some of these changes may last for several days to weeks. Fortunately, practically all of these abnormalities are reversible over time. Management of SE is most effective when a pre-established protocol is followed. While individual variations in treatment protocols exist in both human and veterinary medicine, the key to a successful outcome is three-fold: 1) Establish physiologic supportive care; 2) Provide effective and immediate acting AED therapy; and 3) Institute AED therapy that will maintain prolonged antiepileptic action.\(^7,8\) The protocol listed in Table 1 provides a sequential plan of action starting from initial care through complete anesthesia, as needed. Specific AED therapy revolves around the ability of the drug to rapidly enter the brain, provide effective and immediate seizure cessation, possess no to minimal adverse systemic or neurologic effects, and be retained in the brain to prevent future seizures. Unfortunately, no one drug possesses all of these criteria. Therefore, a combination of AEDs is used to control immediate seizures and prevent the onset of seizure recurrence.

A recently developed protocol in people with SE introduces the use of single agent benzodiazepine therapy with lorazepam for rapid seizure cessation followed by rapid intravenous bolus infusion of levetiracetam for prolonged antiepileptic drug therapy.\(^9,10\) The advantages of this protocol include reduced respiratory suppression, low seizure recurrence rate, and overall reduced hospitalization time. I have used successfully in dogs with SE with an initial dose of lorazepam of 0.2 mg/kg IV followed by a bolus loading dose of levetiracetam of 60 mg/kg.

MONITORING AND SUPPORTIVE CARE

Generalized convulsive SE is a dynamic condition, with a progressive diminution of convulsive activity as the seizures continue. Thus, observation alone may be an inadequate method of determining seizure control. Monitoring of electroencephalographic (EEG) activity has been instituted provides the ability to ensure that complete cessation of all epileptic activity has been achieved. Improvements in seizure control, and eventual outcome, can be related to the ability to determine cessation of all epileptic brain activity. Other parameters to monitor include: heart rate, blood pressure, and serial neurologic examinations. Supportive care revolves around stabilizing the patient and reversing the physiologic sequelae of prolonged or recurrent seizure activity (Table 1). Within the first 30 minutes of SE, animals develop arterial hypertension, increased cerebral blood flow, hypoxemia, hypercarbia, hyperglycemia, and lactic acidosis. Subsequent changes may include arterial hypotension, decrease in blood pH, pyrexia, hyperkalemia, myoglobinuria, and hypoglycemia. The combination of circulatory collapse, organ hypoperfusion, and energy depletion can lead to severe, irreversible organ failure (renal, cardiac, hepatic). Therefore, it is critical that all cases of SE are treated as "trauma" patients: that is, maintain a patent airway, support proper breathing patterns and oxygenation, and provide circulatory support. Rectal temperature should be closely monitored during the first hour. Animals should be cooled with ice and cold water if body temperature is > 104°F. Cooling should stop when rectal temperature is 102°F, to prevent rebound hypothermia. Thiamine (250-500 mg IM) should be administered, as this B-vitamin is an important co-factor for aerobic glycolytic metabolism. Dextrose containing solutions should NOT be administered unless hypoglycemia is documented. Hyperglycemia in the face of reduced oxidative phosphorylation in the brain results in CNS lactic acidosis and resultant neuronal necrosis. Mannitol at 1 gm/kg IV over a 15-minute period along with steroid therapy is...
HOME TREATMENT

Financial and emotional constraints of recurrent emergency therapy are often the limiting factor in an owner’s decision to continue treating their pet. A safe, affordable home treatment for cluster seizures would reduce owner cost, decrease patient morbidity and contribute positively to the overall AED therapy.

Diazepam per rectal (DZPR) therapy by owners of dogs with primary epilepsy and generalized cluster seizures using a dose of 0.5 mg/kg was associated with a significant decrease in the number of cluster seizure events in a 24 hour period, and a decrease in the total number of seizure events when compared to an identical time period without such therapy. As a consequence of this change, there was a significant decrease in the total cost in emergency care per dog. Administration of DZPR at 2 mg/kg proved to achieve effective plasma benzodiazepine concentrations above 300 µg/L in dogs on chronic phenobarbital with minimal adverse effects. This dose can be given up to three times within 24 hour period, but should not be given within 10 minutes of prior dose. No information is reported for rectal AED therapy in the cat.

REFERENCES