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Status epilepticus in dogs and cats, part 2: treatment, monitoring, and prognosis

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Abstract

Objective – To discuss current anticonvulsant drug options and advances in treatment of status epilepticus (SE) and to review the prognosis associated with SE.

Treatment – When treating a patient with SE, the main goals are to halt seizure activity, prevent further seizures, identify the cause of the seizures, and manage any complications. The veterinary literature indicates that benzodiazepines are the most common class of drugs used for the initial treatment of SE. Although many anticonvulsant drugs are currently available for treatment of SE, there is a lack of evidence demonstrating clear benefit to the use of specific therapeutics for benzodiazepine-refractory SE. Several multicenter, randomized, and placebo-controlled clinical trials are currently investigating the efficacy of new drugs, such as fosphenytoin, for use in canine SE. Another active area of research is the investigation of nonpharmacologic methods of seizure treatment including percutaneous vagal nerve stimulation and transcranial ultrasonic neuromodulation.

Monitoring – Electroencephalography (EEG) is underutilized in the management of veterinary seizure disorders. However, recent advances in EEG technology may allow for earlier and proactive therapeutic interventions in epileptic patients, provide objective data collection regarding treatment efficacy, and yield insight into the neurologic status of patients with SE. Most importantly, use of EEG in patients with SE will lead to increased recognition of nonconvulsive seizures and nonconvulsive SE.

Prognosis – Mortality associated with SE is as high as 25% in dogs due to direct and indirect causes of death. Dogs with seizure disorders have a decreased lifespan compared to the general population, and epileptic dogs with SE have a significantly abbreviated lifespan compared to epileptics that do not experience SE. In people, nonconvulsive SE has a higher morbidity and mortality than convulsive SE, regardless of patient age or underlying diagnosis.

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Abbreviations

cEEG	continuous electroencephalographic monitoring
CPP	cerebral perfusion pressure
CRI	continuous rate infusion
GABA	γ-aminobutyric acid
EEG	electroencephalography
IA	inhalational anesthetic
ICP	intracranial pressure
MAP	mean arterial pressure
NMDA	*N*-methyl-D-aspartate
RSE	refractory status epilepticus
SE	status epilepticus

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Initial Treatment and Stabilization of Status Epilepticus

The goals of treatment of status epilepticus (SE) include termination of seizure activity, prevention of further seizures, management of seizure complications, and management of underlying conditions causing seizure activity.[1] As with any acutely ill patient, airway, breathing, and circulation should be assessed first. Initial vital signs should be recorded. Intravenous catheterization allows for pretreatment blood sampling and delivery of drugs and intravenous fluids. At minimum, a small blood sample should be collected immediately for measurement of blood glucose concentration. Anticonvulsant drugs and dextrose, if appropriate, should be administered without delay. For patients receiving

maintenance anticonvulsant medications, appropriate blood samples should also be obtained for performance of therapeutic drug monitoring.

If hypoglycemia is noted, 0.5–1.0 mL/kg of 50% dextrose should be administered IV; this may be diluted to decrease phlebitis associated with hyperosmolar solution. Dextrose can then be added to intravenous fluids to make a 2.5% or 5% solution based on patient needs. Cooling measures should be employed if hyperthermia is noted. For most dogs, IV fluids and termination of seizure activity will result in normothermia. Intravenous crystalloid boluses may be needed for hypotension or hypovolemia. Hypotension should be avoided. Since cerebral perfusion pressure (CPP) depends on both mean systemic arterial pressure (MAP) and intracranial pressure (ICP; CPP = MAP – ICP), increased ICP or reduced MAP can impair it. Through autoregulation, the brain maintains normal cerebral blood flow with CPP ranging from 50 to 150 mm Hg; however, during SE autoregulation may be impaired, potentially compromising CPP if either systemic blood pressure is reduced.[2] Hypovolemia should be avoided since it contributes to hypotension and hypoperfusion. Low-volume resuscitation may be beneficial in patients that require resuscitation and have increased ICP and cerebral edema. Maintenance of normal blood oxygenation helps prevent intracranial hypertension, since hypoxemia ($PaO_2 < 50$ mm Hg) causes increased cerebral blood flow and increased ICP. A CBC, serum biochemistry profile, and acid-base analysis should be performed. Lactate concentration monitoring may be helpful to evaluate tissue perfusion. After initial clinicopathologic evaluation, fluid therapy should be initiated as appropriate to correct acid-base and electrolyte abnormalities and to maintain normotension and normovolemia.

Systemic hypertension in the mentally abnormal animal raises concern for increased ICP. Since CPP = MAP – ICP, patients with critically increased ICP develop increased MAP to maintain CPP. This is called the Cushing's reflex, and when it is seen, it should prompt immediate action to decrease ICP. Reflex bradycardia is sometimes seen along with the systemic hypertension of the Cushing's reflex, but is not reliable, particularly in animals with concurrent hypovolemia. For patients with presumed intracranial hypertension, hyperosmolar therapy should be instituted. Hyperosmolar therapy removes water from normal brain tissue and requires an intact blood-brain barrier.[3] Mannitol is an osmotic agent that increases plasma osmolality and creates an osmotic gradient between the intravascular space and extracellular space in the brain. This gradient causes electrolyte-free water to move from the cerebral parenchyma into the plasma, which reduces cerebral edema and ICP. Mannitol may also scavenge free radicals and minimize oxidative injury to the brain. A dose of 0.5–2.0 g/kg can be administered IV over 20–30 minutes through a filter. Reductions in ICP may occur within 30 minutes and may last for 6–8 hours.[4] Additional bolus doses can be administered as needed every 6–8 hours, but continuous rate infusion (CRI) is not recommended because the osmotic gradient responsible for removing water from the brain tissue is lost when the drug is given continuously. Mannitol induces free water diuresis and can lead to electrolyte derangements, hypovolemia, and cardiovascular collapse, and is therefore contraindicated in hypovolemic patients. Mannitol treatment should be followed by appropriate fluid therapy to prevent dehydration and hypovolemia. High doses of mannitol can lead to acute kidney injury, possibly through a combination of intrarenal vasoconstriction and hypovolemia.[3] Hypertonic saline also reduces ICP through osmotic effects. It causes intravascular volume expansion and may lead to volume overload and hypernatremia. A dose of 2–4 mL/kg IV can be given over 15–20 minutes. A meta-analysis of 5 human trials comparing hypertonic saline and mannitol in the treatment of increased ICP found mannitol to be more effective.[5] This comparison has not been investigated in veterinary medicine.

Anticonvulsant Therapy

Benzodiazepines

Benzodiazepines are the recommended first-line treatment of SE in human and veterinary medicine (Figure 1). Common drugs in this class include diazepam, lorazepam, and midazolam. Their anticonvulsant effect comes from enhancement of pre- and postsynaptic γ-aminobutyric acid (GABA)-ergic transmission that is mediated by a benzodiazepine-specific receptor.[6–8] This GABA agonism leads to a neuronal influx of chloride, which inhibits the transmission of nerve impulses by increasing the distance between depolarization threshold and resting membrane potential.[9] At higher doses, benzodiazepines also limit sustained repetitive neuronal firing, similar to phenytoin and carbamazepine.[6] Limitations to benzodiazepine therapy include respiratory and CNS depression and tachyphylaxis with prolonged use.[10]

Diazepam is lipophilic and thus crosses rapidly into the CNS. However, it has a large volume of distribution and rapidly redistributes into fat and muscle, which results in rapid decline of CNS concentrations; this can be associated with recurrence of seizure activity.[9] In people, diazepam has a distribution half-life of <1 hour. Repeat bolus dosing of diazepam causes accumulation in the CNS and high concentrations in the CSF and serum. This may lead to prolonged anticonvulsant activity, but also to unexpected CNS depression and cardiorespiratory

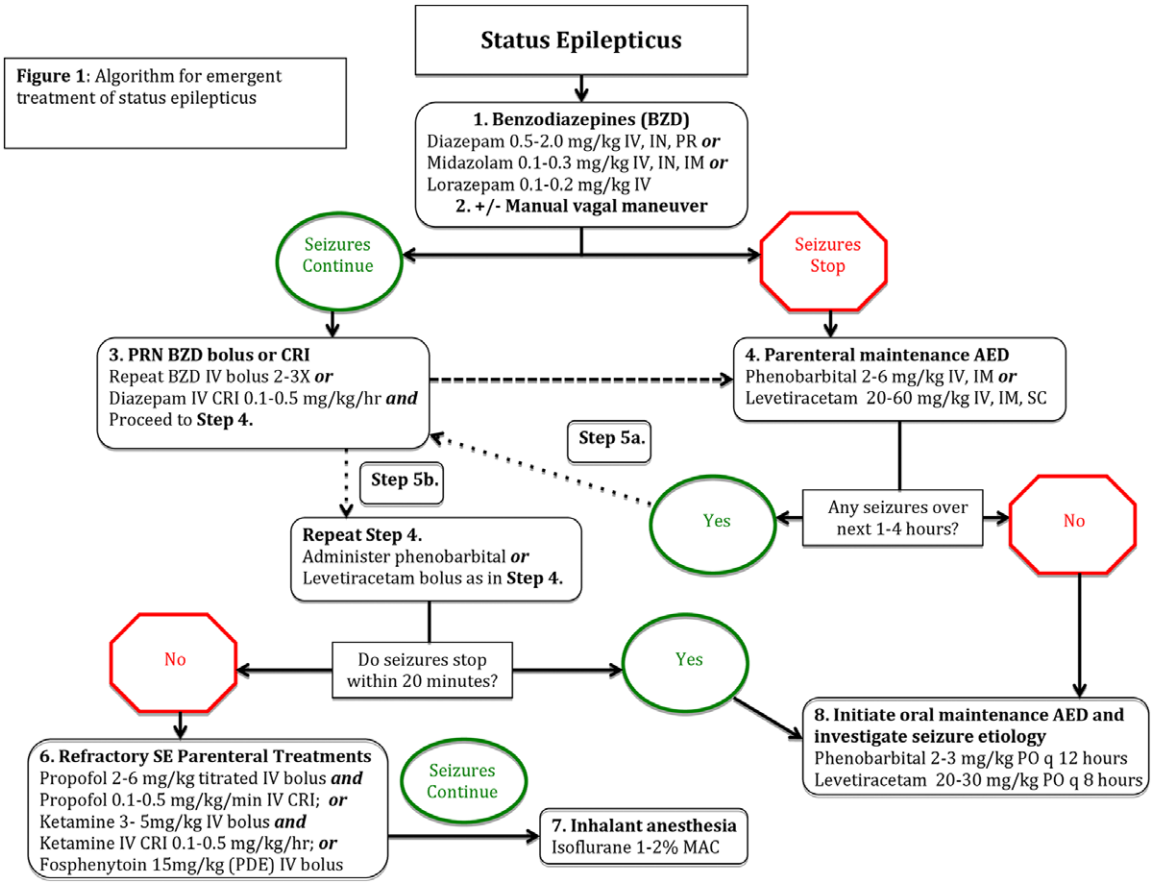

Figure 1: Algorithm for emergency treatment of status epilepticus.

collapse.[11] For this reason, after 2–3 boluses of diazepam, a CRI or another anticonvulsant drug should be considered.

Diazepam is carried in propylene glycol. Propylene glycol can cause hypotension with rapid administration and can cause phlebitis. A central venous catheter may be helpful in preventing phlebitis. If IV access is not available, rectal and intranasal administration are also effective at controlling seizure activity. Diazepam may be administered as a bolus of 0.5–2.0 mg/kg IV, intranasally or per rectum to dogs and cats; this bolus can be administered 2–3 times. Alternatively, a CRI can be delivered at 0.1–0.5 mg/kg/h. Coadministration of levetiracetam enhances the anticonvulsant effects of diazepam and may allow for control of seizure activity with lower doses of diazepam.[12]

Lorazepam is the preferred benzodiazepine in people. It is less lipid soluble than diazepam and binds more tightly to GABA receptors, leading to longer duration of action.[1] However, onset of action is slightly delayed compared to diazepam. Lorazepam has similar adverse effects as diazepam and is also manufactured in a propylene glycol vehicle.

Midazolam is gaining popularity in the treatment of SE due to decreased CNS and respiratory depression compared to diazepam and lorazepam. Midazolam is water soluble and becomes more lipophilic at physiologic pH, allowing prompt diffusion into the CNS.[9] Midazolam can be administered intramuscularly, buccally, or nasally in patients without venous access.[13–15] Midazolam has a short half-life (approx 1 h in the dog), so frequent dosing or CRI is required for effectiveness.

Barbiturates

Barbiturates bind to sites on GABA-regulated ion channels. The barbiturate binding site is distinct from the GABA and benzodiazepine binding sites. Barbiturates also block the α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) receptor, which is a subunit of the metabotropic glutamate receptor.[16] Binding of barbiturates to the GABA-A receptor increases the duration of chloride ion channel opening, resulting in increased influx of chloride ions into neurons and enhanced hyperpolarization of the postsynaptic neuron.[10] Barbiturates may also have neuroprotective effects and

lower body temperature, which may be protective in SE.[17]

Phenobarbital is a mainstay of treatment for convulsive SE in people and animals. Phenobarbital increases the threshold required for seizure discharge and decreases the spread of discharge to surrounding neurons.[18] In people, it has been used as a first-line SE treatment and in patients that do not respond to phenytoin and benzodiazepines.[19,20] Phenobarbital has been shown to be as effective as the combination of benzodiazepines and phenytoin, and superior to phenytoin alone.[21] In veterinary medicine, phenobarbital remains popular as a maintenance anticonvulsant. Due to decreased lipophilicity, it may take 20–30 minutes for phenobarbital to distribute to the CNS; this must be considered in patients that are actively seizing. A loading dose of phenobarbital can be administered to achieve rapid therapeutic serum concentrations in patients with SE who are naïve to the drug. A dose of 16–20 mg/kg IV can be divided into 3 or 4 increments and given every 30 minutes. Alternatively, the loading dose can be calculated as follows: loading dose (mg) = body weight (kg) × 0.8 × desired serum concentration (μg/mL).[7] Loading can also be accomplished through IM or PO administration. Parenteral use of phenobarbital is associated with significant hypotension and cardiorespiratory depression, especially in patients that have received benzodiazepines.[7] Other adverse effects that can be observed with chronic oral use include sedation, ataxia, polydipsia, polyuria, hepatotoxicity, neutropenia, dyskinesia, thrombocytopenia, decreased thyroxine and free thyroxine levels, and superficial necrolytic dermatitis.[18,22,23]

Pentobarbital is a short-acting barbiturate with negligible anticonvulsant properties that can be used to induce generalized anesthesia in patients with SE that do not respond to first-line anticonvulsant therapy.[7] Pentobarbital has negligible anticonvulsant activity at nonneurotoxic doses.[24] A dose of 3.0–15.0 mg/kg IV can be given to effect; extreme care must be taken not to overdose. Pentobarbital also has the ability to scavenge oxygen radicals and decrease cerebral oxygen demand.[18] Pentobarbital, like other barbiturates, has the potential to cause significant cardiorespiratory depression, hypothermia, and hypotension. Animals may paddle and vocalize during recovery, making it difficult to distinguish these movements from true seizure activity.[25]

Phenytoin/Fosphenytoin

Phenytoin is commonly used in human medicine as a parenteral agent in SE.[26] It exerts its anticonvulsant effect by blockage of voltage-gated sodium channels and calcium fluxes across neuronal membranes.[27] Oral formulations also exist for maintenance therapy.[28] In dogs, phenytoin has poor oral bioavailability and short half-life, and is not an ideal drug choice.[29] Adverse effects of parenteral phenytoin include cardiac dysrhythmias and hypotension, likely related to the propylene glycol vehicle. Injection site pain and phlebitis have also been noted, and tissue necrosis may occur with extravasation.[28] To minimize these risks, slow infusions are typically administered, which leads to delayed onset of action. Phenytoin and phenobarbital are frequently administered together in human epileptics. However, phenytoin and phenobarbital are both potent inducers of hepatic microsomal enzymes. In dogs, therapeutic levels are difficult to achieve with combination therapy due to enzyme induction, and the formation of epoxide and other toxic metabolites may lead to cholestatic liver injury.[29]

Fosphenytoin is a prodrug of phenytoin that was developed to limit complications of phenytoin. There are no known drugs that will interfere with conversion of fosphenytoin to phenytoin, and the anticonvulsant effects are those of phenytoin.[27,28] Fosphenytoin is water soluble, compatible with most parenteral solutions, and safe for intramuscular administration.[27,30] Dosing is based on phenytoin equivalents. Fosphenytoin can be infused more rapidly than phenytoin. However, due to the time required to convert fosphenytoin to phenytoin, improvement in time needed to reach therapeutic levels has not been demonstrated.[27,30] Fosphenytoin tends to cause less adverse injection site problems, but hypotension and dysrhythmias may still be seen. The increased price associated with fosphenytoin has limited its use in human medicine.[31] It has been demonstrated that fosphenytoin, when administered at 15 mg/kg IV to dogs, produced unbound phenytoin plasma concentrations in the range used to treat SE in people without significant side effects. Eighty percent of fosphenytoin was converted to phenytoin within 30 minutes, similar to metabolism observed in people.[32] In a recent study of dogs with convulsive SE, 63% of dogs that received 15 mg/kg phenytoin equivalent of fosphenytoin had no further seizures, compared to 22% of dogs that received placebo. No hypotension was noted in this group, with vomiting being the only significant adverse effect.[33]

Levetiracetam

Levetiracetam is a novel anticonvulsant drug. Structurally, it is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide and similar to piracetam, a racetam drug that is thought to improve cognitive function.[34] Levetiracetam binds to the synaptic vesicle protein 2A, a protein that governs the amount of available secretory vesicles and enhances neurotransmission.[35,36] Binding

of levetiracetam to synaptic vesicle protein 2A leads to decreased release of neurotransmitters during high-frequency bursts that are commonly observed during seizures.[37] However, the primary anticonvulsant effect of levetiracetam comes from a presynaptic decrease in glutamate-mediated excitatory transmission.[38] Levetiracetam has been shown to have neuroprotective properties. It affects the expression of genes that are upregulated in epilepsy and modulates excessive neuronal calcium release, which may lead to decreased neuronal excitability.[34,39–42] Other anticonvulsant effects may be derived from inhibition of the Na-dependent Cl/HCO_3 exchange and lowering of neuronal pH in hippocampal CA3 neurons.[43] Reduction of neuronal hypersynchronization in epileptic neurons has also been demonstrated.[34,44–46] Levetiracetam does not directly bind to GABAergic or glutaminergic receptors but has indirect effects on GABAergic neurotransmission. It has been shown to out-compete GABA antagonists and reverse inhibition of GABA- and glycine-gated currents.[47,48]

Levetiracetam has gained popularity in recent years as an anticonvulsant. In a 2008 study of epileptic dogs that were resistant to phenobarbital and bromide therapy, the addition of levetiracetam resulted in a 77% decrease in seizure frequency in 8 of 14 responders.[49] In an unpublished study, the addition of levetiracetam resulted in a 54% decrease in seizure frequency in dogs resistant to phenobarbital and bromide.[50] However, in another study of resistant epileptic dogs the addition of levetiracetam did not significantly reduce seizure frequency when compared to placebo, but owner-perceived improvement in quality of life was reported.[51] Levetiracetam undergoes little hepatic metabolism, does not cause sedation, and interacts minimally with other drugs.[52] However, concurrent phenobarbital use increases levetiracetam clearance. Monitoring of serum levetiracetam concentrations and dose adjustments may be needed when the drugs are used together.[53]

Levetiracetam has been evaluated in human and veterinary medicine as a second-line anticonvulsant in SE and is safe to use in patients where oral administration is not possible. In people with SE who have failed benzodiazepine therapy, the efficacy of levetiracetam in controlling seizures has been reported as 44–94%.[54] A 2014 meta-analysis estimated the mean efficacy of levetiracetam to be 68.5% when used as a second-line agent in people, while a 2015 prospective study found that levetiracetam terminated seizures in 76.6% of patients.[55,56] Levetiracetam has been shown to be equally effective as a second-line treatment for SE in people when compared to phenytoin or valproate.[57,58] When administered intravenously to dogs at a dose of 60 mg/kg, therapeutic levels of levetiracetam can be achieved for up to 8 hours.[59] Safe IM and SC administration has also been demonstrated.[60] In a 2012 prospective study of 19 dogs with SE or acute repetitive seizures (cluster seizures), diazepam was administered to stop seizure activity. After receiving diazepam, dogs received either levetiracetam or placebo. Fifty-six percent of dogs that received levetiracetam had no additional seizure activity, compared to 10% of dogs that received placebo, but this was not found to be statistically significant.[61] A 2011 retrospective study found a significantly decreased risk of postoperative seizures and death when dogs received levetiracetam for a minimum of 24 hours before portosystemic shunt attenuation.[62] Studies on the use of levetiracetam as initial treatment for SE in veterinary medicine are lacking. In a small study of elderly people with nonconvulsive and convulsive SE, levetiracetam effectively terminated seizure activity when used as a first-line treatment.[63] Recently, target serum concentrations of levetiracetam were achieved after rectal administration in 6 healthy dogs, with the only adverse effect being mild and transient sedation.[64]

Propofol/Fospropofol

Propofol (2,6-diisopropylphenol) is an alkylphenol that is most commonly used as an injectable anesthetic. It has a very short elimination half-life, and allows for rapid control of anesthetic depth with rapid recovery.[65,66] Propofol is a GABA-A agonist and acts at sites different from those targeted by benzodiazepines and barbiturates.[66,67] It reversibly inhibits *N*-methyl-D-aspartate (NMDA) receptors and modulates slow calcium ion channels.[67,68] Propofol is an effective treatment for refractory SE in people.[66,69,70] In veterinary medicine, propofol has been used to control seizure activity after ligation of portosystemic shunts and in SE when benzodiazepines and barbiturates have failed.[71–73] Due to its short duration of action, propofol should be administered as a CRI. The authors recommend an intravenous loading dose of 2–6 mg/kg followed by a CRI of 0.15–0.4 mg/kg/min. The infusion should be continued for at least 6 hours. If seizure activity returns, consider continuing the infusion for 24 hours. PropoFlo-28[a] is a formulation of propofol with the addition of 2% benzyl alcohol as a preservative to prolong shelf life. No significant cardiovascular or neurologic differences were noted between cats receiving propofol with or without 2% benzyl alcohol up to 24 mg/kg.[74] However, due to the benzyl alcohol addition, Propoflo-28 is not labeled for use as a CRI. Adverse effects of propofol include injection site pain, cardiovascular compromise, respiratory depression including apnea, and loss of gag reflex that may predispose patients to aspiration pneumonia.[75] As such, the cardiovascular and respiratory status of these patients must be

carefully monitored and endotracheal intubation may be beneficial. Repeated propofol infusions in cats may lead to Heinz body formation and increased recovery time.[76] Propofol-infusion syndrome has occurred with prolonged anesthesia in people but has not been seen in veterinary patients. This syndrome manifests clinically as acidosis, rhabdomyolysis, hyperkalemia, and cardiac dysfunction, and is associated with high morbidity and mortality.[65]

In people and dogs, numerous reports exist of seizure-like phenomena associated with propofol administration; these phenomena are thought to be caused by glycine antagonism in the spinal cord.[73,77] Seizure-like phenomena have been observed most often during anesthetic induction or emergence and may be related to changes in propofol concentrations in the blood or brain.[78] Some studies have demonstrated epileptic activity on EEG monitoring associated with seizure-like phenomena, while others have demonstrated no cortical epileptic activity.[79,80] For this reason, EEG monitoring would be beneficial during propofol treatment.

Fospropofol is a water-soluble prodrug that is hydrolyzed by alkaline phosphatases to yield propofol, formaldehyde, and phosphate. Fospropofol does not cause injection site pain. The necessary conversion of fospropofol to propofol causes delayed onset and longer duration of sedation.[81] Potential advantages of fospropofol include lower dosing to achieve EEG changes representative of general anesthesia when compared to propofol emulsion and possibly longer duration of action. Fospropofol is widely available and may be useful in treating status epilepticus, but veterinary experience is lacking.

Ketamine

Ketamine is a noncompetitive NMDA glutamate receptor antagonist. It is frequently used in small animals for general anesthesia and analgesia. The use of ketamine to treat seizures and when its use should be considered during refractory status epilepticus (RSE) is controversial. Ketamine, along with other NMDA antagonists, has been shown to have neuroprotective effects in a rat model of SE, whether seizure activity was terminated or not.[82] Numerous studies have demonstrated that ketamine is effective in controlling seizure activity in prolonged SE.[83–86] In a 2006 case report, ketamine was used to treat a Yorkshire Terrier with RSE from inflammatory CNS disease. In this dog, clinical seizure activity was eliminated with a propofol CRI but EEG revealed persistent seizure pattern. The patient received 2 boluses of ketamine and then was placed on a continuous rate infusion to achieve a burst suppression pattern.[87] For refractory SE, a bolus of ketamine can be administered at 3–5 mg/kg IV, followed by a continuous rate infusion of 0.1–0.5 mg/kg/h. Despite the findings of these studies, conflicting evidence exists about the safety of ketamine and potential long-term effects. In small animals, ketamine should be avoided or used cautiously in patients with increased ICP or preexisting seizure disorder, and has been shown to cause seizure activity in dogs.[88]

It has been demonstrated that ketamine and other NMDA antagonists cause potentially irreversible degenerative changes in pyramidal neurons of the posterior cingulated and retrosplenial cortices. These changes can be prevented by treatment with anticholinergic agents or GABA agonists. This toxicity has been explained by an indirect mechanism working through a trisynaptic circuit. Glutamate, when acting at an NDMA receptor on a GABAergic interneuron in a cingulate neuron, normally inhibits release of acetylcholine. Antagonism of the NDMA receptor leads to uncontrolled cholinergic stimulation, and this leads to cholinergic excitotoxicity in the cingulate neuron.[87,89]

In a 2003 case study, ketamine was administered to a man with refractory SE. Electroencephalographic evidence of seizure activity was controlled, but the patient developed diffuse cerebellar and cerebral atrophy and neurologic defects that persisted during 15 months of follow-up.[90] Cerebral atrophy was also demonstrated in a 13-year-old girl who received ketamine after prolonged seizure activity.[91] Long-term follow-up was not reported. However, it remains to be proven whether the neurologic changes in these patients were directly caused by ketamine, by the duration of seizure activity, or another factor.

Zonisamide

Zonisamide is a sulfonamide derivative that is biochemically similar to serotonin.[92,93] It is thought that zonisamide inhibits seizure activity through inhibition of neuronal voltage-gated sodium and T-type calcium channels, and weak inhibition of carbonic anhydrase.[92,94] Zonisamide may also modulate GABA, dopamine, serotonin, and acetylcholine.[93,95]

Zonisamide is most commonly used as an add-on drug when seizures are not well controlled with traditional anticonvulsants. The addition of zonisamide may allow reduced doses of other anticonvulsants, leading to decreased frequency of undesirable side effects.[96] In a 2004 study of dogs with idiopathic epilepsy, 58% of dogs had decreased seizure frequency when zonisamide was added to phenobarbital and potassium bromide.[95] Of interest is that phenobarbital may increase the clearance of zonisamide for up to 10 weeks.[97]

Zonisamide may also be used alone for seizure control. A 2012 study of 10 dogs with idiopathic epilepsy

found that 60% achieved good seizure control for at least 12 months with zonisamide therapy alone.[94]

Rectal absorption of zonisamide at a dose of 10 mg/kg has been demonstrated in healthy dogs. Bioavailability was higher when zonisamide was housed in polyethylene glycol compared to water, but both rectal formulations resulted in lower maximum zonisamide concentrations compared to oral administration. The time to maximum concentration was over 7 hours for rectal administration, which is undesirable in SE.[98] A dose of 30 mg/kg may be effective in SE but should not be used as a sole treatment. This may allow initiation of maintenance therapy in patients that are not stable to receive oral medications.

Dose-dependent ataxia, lethargy, vomiting, and keratoconjunctivitis sicca were noted after zonisamide therapy in 50% of dogs with idiopathic epilepsy in a 2004 study.[95] Case reports of hepatic necrosis, hepatopathy, and renal tubular acidosis have also been published, as well as anecdotal reports of immune-mediated hemolytic anemia and thrombocytopenia.[92,93,99]

Etomidate

Etomidate is a carboxylated imidazole anesthetic agent that has been used to treat RSE in people.[100,101] Etomidate is a GABA-A agonist that enhances postsynaptic binding of GABA-A receptor agonists.[102] This leads to an inward chloride flux and hyperpolarization that decreases neuronal excitability.[103] Etomidate also decreases the cerebral metabolic rate and oxygen consumption, and lowers ICP while maintaining normal arterial pressure.[103] The effect on cerebral metabolism has been suggested to improve the brain's tolerance to ischemia.[104] Etomidate causes less respiratory depression than propofol or barbiturates and few cardiovascular effects, even in the presence of cardiovascular disease.

Etomidate inhibits cortisol synthesis by suppression of the adrenocortical response to ACTH, which has been associated with increased mortality in people.[105–107] Etomidate has been associated with an increased incidence of postoperative nausea and vomiting in people and pain on injection. Etomidate may also cause involuntary myoclonic movements and has been associated with an increase in EEG epileptiform activity in human epileptic patients.[103,108] Interestingly, etomidate has been used to induce seizure activity in people to guide surgical resection.[109] Because of its adverse effects and proconvulsant properties, etomidate use in people with SE is reserved for cases that are refractory to conventional therapy. Etomidate may be less expensive than other anticonvulsant agents and causes less cardiovascular and CNS depression compared to a propofol infusion or a loading dose of phenobarbital or phenytoin. A dose of 1–2 mg/kg IV can be administered to effect, followed by a CRI of 0.5–2 mg/kg/h IV. However, studies on the use of etomidate to treat seizures in veterinary medicine are lacking.

Inhalational anesthetic agents

Inhalational anesthetic (IA) agents enhance inhibitory GABA-A receptor-mediated currents and decrease thalamic neuronal membrane excitability.[110,111] They also increase cerebral blood flow and ICP while decreasing cerebral oxygen consumption.[112] Isoflurane and desflurane produce dose-dependent depression of spontaneous epileptiform discharges.[113,114] In human medicine, the use of IA agents is reserved for the treatment of RSE. Halothane has previously been used in RSE but carries a risk of hepatotoxicity due to generation of toxic metabolites.[115] Sevoflurane may also produce toxic metabolites and can have epileptogenic properties. Isoflurane and desflurane undergo less metabolism and therefore carry a reduced risk of organ damage, making them the preferred IA agents used in treatment of RSE.[116] In a case series of 7 people with seizure activity that was resistant to midazolam, propofol, and pentobarbital, isoflurane and desflurane terminated seizure activity and produced a burst suppression EEG pattern. Inhalational agents were administered for an average of 11 days.[116] However, 2 patients receiving isoflurane for RSE developed brain magnetic resonance imaging signal abnormalities in the thalamus, cerebellum, and medulla that disappeared or improved after isoflurane was discontinued.[117] However, these patients received isoflurane for prolonged periods of time.

Veterinary studies regarding the use of IA agents in status epilepticus are lacking. Some authors advocate the use of isoflurane as a treatment of last resort for patients with RSE.[118] The required isoflurane vaporizer setting varies by individual, and is affected by comorbidities, current medications, and drug history. Patients under inhalant anesthesia may require vasopressor therapy due to hypotension caused by decreased systemic vascular resistance. Electroencephalography can be used to titrate IA to seizure suppression; this may allow more conservative IA use, which can help decrease adverse effects.

Alternative methods of seizure treatment

Vagal nerve stimulation using either manual methods or implanted, programmable electrical generators may aid in the treatment of seizures in dogs.[119,120] Manual vagal maneuvers such as ocular compression and carotid message are potential helpful interventions that can be easily and simultaneously administered to the seizing patient while vascular access is being obtained. Objective data

regarding manual maneuvers are lacking, but these interventions are unlikely to harm the patient. Vagal nerve stimulation appears to reduce cerebral extracellular glutamate concentrations in a rodent migraine model; vagal maneuvers may exert antiseizure effects by the same mechanism.[121] A handheld, transcutaneous device has been developed that allows for nonpainful stimulation of the vagal nerve in animals.[b] The device is currently being evaluated as treatment to abate seizures in multicenter veterinary clinical trial.

Transcranial ultrasonic stimulation has been used to safely modulate brain activity. An ultrasonic neuromodulation system has recently demonstrated its utility for cessation of EEG-documented seizure activity in a murine seizure model.[122] Ultrasonic brain stimulation offers several significant clinical advantages such as compact system size, rapid and noninvasive administration of pulses, and superior spatial resolution compared to other noninvasive methods such as transcranial magnetic stimulation. These advantages make ultrasonic brain stimulation attractive for use in the ICU.[122]

Electroencephalographic Monitoring: Guiding Therapy

In people, EEG has been indispensable in the diagnostic evaluation of seizures for nearly 90 years.[123,124] The EEG is an essential tool in the differentiation of seizure disorders from other paroxysmal events that impair consciousness, since psychogenic events, metabolic/toxic events, and movement disorders can look similar to SE.[124,125] In epileptic people, EEG provides important information about background rhythms, location of epileptogenic foci, and epileptiform discharges, and is necessary for the diagnosis of specific electroclinical syndromes.[124,126] Data from EEG studies can provide important prognostic information, guide the rational selection of antiepileptic medication, and assist the clinician in determining treatment end points.[124] Although EEG studies have been reported to provide similar, valuable diagnostic information in dogs with epilepsy, EEG examinations are not routinely performed during the evaluation of veterinary patients with seizures.[127–129]

Continuous electroencephalographic monitoring (cEEG) is frequently used in critically ill people. The use of cEEG in ICUs has focused primarily on seizure detection and the potential significance of specific EEG patterns in particular patient populations. Studies have demonstrated that nonconvulsive seizures and nonconvulsive SE are common in critically ill people.[130–132] Continuous EEG can provide dynamic information about brain function that may permit early detection of changes in neurologic status associated with intracranial hypertension and brain ischemia, which is particularly useful in comatose patients in whom the clinical examination is limited.[132,133] However, cost effectiveness and impact of cEEG on patient prognosis is unclear at this time.[131,134–136] There are also important limitations of cEEG that should be addressed in future studies; for example, while information gathered from cEEG monitoring is frequently used to initiate treatment in cases of nonconvulsive seizures and SE, periodic and rhythmic EEG patterns are frequently identified in the critically ill that are of unknown significance.[130,131,134,137]

Continuous EEG is commonly used for decision making and to define therapeutic end points; however, how cEEG results are used varies among neurologists. Some consider the elimination of ictal EEG patterns and clinical seizure activity to be the end point target, while others prefer burst-suppression patterns or complete suppression of EEG background activity.[134,136,137] A burst suppression pattern has been defined by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology as a pattern of delta and/or theta waves intermixed with faster waves and intervening periods of quiescence. Burst suppression results from the hyperpolarization of 95% of cortical neurons, and the presence of such a pattern is thought to be neuroprotective.[138,139] Further studies are needed to determine which cEEG treatment end points are most clinically relevant for improved patient outcomes.

In veterinary medicine, few studies have investigated cEEG; however, existing reports highlight the diagnostic utility of cEEG.[127,138,140] In a report of 10 veterinary patients with SE, cEEG monitoring identified nonconvulsive SE in all 10 animals. Nonconvulsive SE manifested as epileptiform EEG discharges that persisted after termination of gross motor seizures following administration of general anesthetics. In this study, epileptiform activity was also noted when attempting to wean anesthetic medications after 6 hours. A burst suppression pattern was noted in 5 of 10 patients.[138] Recently, cEEG was used to diagnose nonconvulsive SE in a cat and guide successful, high-dose phenobarbital treatment using a burst suppression EEG pattern as a therapeutic end point.[140]

Newly developed implantable, ambulatory, telemetric cEEG microsystems have the potential to improve seizure monitoring and treatment in dogs and cats. The premise of these devices is that when the implanted cEEG detects impending seizure activity, either an alert is sent to the caretaker's mobile device prompting a specific medical intervention, or the cEEG device activates another implanted device that delivers treatment. A prototype example of this technology was subdurally implanted in 6 dogs with epilepsy and was able to successfully record the cEEG.[127] The device was generally well tolerated and allowed detection and

characterization of a variety of epileptiform events.[127] Developers would like to produce units capable of transcranial EEG monitoring, and to produce dynamic and real-time biofeedback circuits that would allow for intervention prior to the onset of the ictus.

Additional diagnostic considerations

Once the patient has been stabilized, additional diagnostic work-up should be considered to rule out underlying structural or metabolic disease. Magnetic resonance imaging of the brain and collection and analysis of CSF are recommended in patients that experience SE. Depending on the specifics of the case, additional initial diagnostic tests may include serologic or polymerase chain reaction testing for infectious diseases, toxicology screening, serum bile acids concentrations, insulin:glucose ratio, thoracic radiographs, or abdominal ultrasound. For full discussion of the diagnostic battery used to determine the underlying cause of SE, please see the accompanying Part I article.

Basic Monitoring and Nursing Care of the Hospitalized Patient

For patients that are neurologically compromised or anesthetized to control seizures, nursing care can be intensive and 24-hour monitoring is generally required. The patient should have a baseline neurologic examination upon presentation. Frequent neurologic reassessment is important as changes in neurologic status may occur rapidly. Level of consciousness, response to stimuli, cranial nerve reflexes, spinal reflexes, and posture should be evaluated during neurologic examination.[141] However, assessment can be complicated by sedative effects of anticonvulsant medications.

While performing the neurologic examination, careful attention should be paid to the size, symmetry, and responsiveness of the pupils. Bilateral miosis may be associated with a diencephalic lesion or diffuse CNS disease. Mydriatic pupils may indicate an irreparable midbrain lesion or caudal transtentorial herniation. Increased sympathetic tone, which is common in critically ill patients, can contribute to mydriasis. Progression from miotic to mydriatic pupils may indicate rising ICP and should prompt immediate intervention.[141,142] Posture should be monitored and documented during treatment. Decerebrate rigidity, characterized by extension of all 4 limbs and opisthotonus, may indicate brainstem compression secondary to severe intracranial hypertension or herniation. Decerebellate rigidity, or extension of the thoracic limbs with pelvic limb flexion, is associated with a cerebellar lesion such as cerebellar herniation.[4]

Close monitoring of blood pressure, hydration status, oxygenation, ventilation, heart rate, and body temperature is necessary. Alterations in these parameters may be secondary to anticonvulsant drug administration or may be related to the underlying disease process. Trends in heart rate and blood pressure should be tracked because systemic hypertension in the neurologically impaired animal is consistent with the Cushing's reflex (see above), which indicates critically elevated ICP. Nonconvulsive SE may manifest as subtle changes in heart rate, respiratory rate, or pupil size. Arterial blood gas analysis allows for evaluation of both oxygenation and ventilation. If blood gas analysis is not available, pulse oximetry can be used to monitor oxygenation. For patients that are intubated, end-tidal CO_2 can be used to evaluate ventilatory status.[143] Continuous EEG monitoring may be indicated for some patients. Blood glucose, electrolyte, and lactate concentrations should be evaluated frequently.[141]

Recumbent patients require soft, padded bedding and should have their position changed at least every 4 hours for comfort and to prevent lung atelectasis and bed sores.[144] The patient should be monitored closely, and auditory and visual stimuli minimized. Clustering treatments and interventions together may help to minimize patient stress, and interventions that may lead to increased ICP (jugular venipuncture, nasal lines, neck wraps) should be avoided.[145,146] The urinary bladder should be emptied by expression or intermittent catheterization every 4–6 hours or as needed to keep the patient clean and dry. Lubricant eye drops or gel should be applied frequently in sedated or anesthetized patients or in patients with a decreased ability to blink. As with any critically ill patient, nutritional supplementation may be needed for alert but anorexic patients or for those with neurologic abnormalities making them prone to aspiration. If a feeding tube is in place, intermittent aspiration of esophageal or stomach contents may help reduce the incidence of regurgitation and aspiration pneumonia. Prokinetic and antiemetic agents may be used as needed. Pain medications should be administered to the patient exhibiting signs of pain or with a known chronic painful condition, since uncontrolled pain may lead to increased cerebral metabolic rate and ICP.[147] A reversible or short-acting analgesic agent is preferred.

Prognosis

The true mortality rate of patients with SE is difficult to determine, as many patients are euthanized. In a retrospective study of 156 dogs with either SE or cluster seizures, approximately 25% of dogs died or were euthanized during hospitalization. Upon follow-up, 59% of dogs had died or were euthanized. The prognosis was significantly and negatively associated with

granulomatous meningoencephalitis, loss of seizure control after 6 hours of hospitalization, and the development of partial SE.[148] In a 2012 study of 407 dogs with epilepsy, approximately two-thirds were euthanized due to epilepsy.[149] Dogs with epilepsy have a decreased lifespan when compared to the general population, and survival time is even lower in epileptics that experience SE.[150,151]

Footnotes

[a] Propoflo 28, Abbott Laboratories, Abbott Park, IL.
[b] www.youtube.com/watch?v = 1TJ4_BFMe8E.

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