CPD article

Managing canine status epilepticus in practice

Status epilepticus is a common emergency encountered in general practice, and one that can be daunting for many to manage. This review summarises the main considerations for patients presenting in status epilepticus, and discusses the treatment options available, specifically with regard to medications that are likely to be available to the general practitioner.

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Status epilepticus is a common emergency encountered in general practice, and one that can be daunting for many to manage. Not only must we expect these dogs to arrive at the clinic at unpredictable times, the presentation causes great distress to the accompanying owners, and we may not always have access to the full spectrum of recommended medications to treat it. This article will briefly review the disease as well as the common underlying causes and explore options for treatment available to most general practitioners. Specifically, this article will focus on patients who do not initially respond to first- and second-line interventions.

What is status epilepticus?

Status epilepticus is defined as seizure activity that lasts for longer than 5 minutes, or the occurrence of two or more seizures without complete recovery of consciousness in between. Two or more seizure episodes that occur within a 24-hour period with complete recovery of consciousness in between are termed cluster seizures (Berendt et al, 2015). Status epilepticus represents a life-threatening emergency that requires emergency intervention. Prolonged seizure activity is associated with cerebral damage, characterised by neuronal cell necrosis and gliosis (Shorvon and Ferlisi, 2011) as well as cerebral oedema secondary to blood–brain barrier disruption (Hong et al, 2004). These may contribute to longer durations of status epilepticus and becoming less responsive to anticonvulsant medication (Podell et al, 1995). Systemic effects of status epilepticus are mainly mediated by systemic release of catecholamines, commonly leading to hypertension, tachycardia, hyperglycaemia, hyperthermia, and subsequently can cause cardiac arrhythmias, acidosis, rhabdomyolysis, hypotension, shock, noncardiogenic pulmonary oedema, and acute tubular necrosis. If the seizure continues for over 30 minutes, the risk of hypoglycaemia, hyperthermia, hypoxia, respiratory failure, acidosis, hyperkalaemia, hyponatraemia, and uraemia increases (Tesoro and Brophy, 2010).

Table 1. Signalment characteristics that may have significance when considering the aetiology of seizures

Signalment points	Possible aetiological significance
Age of patient <6 months	Consider metabolic causes such as hepatic encephalopathy or inflammatory CNS disease
Age of patient >6 months or <6 years	Consider idiopathic epilepsy
Age of patient >6 years	Consider metabolic causes or structural brain disease
Breed	Border Collies, Labradors and German Shepherds may be over-represented in idiopathic epilepsy Middle-aged small and toy-breed dogs are more predisposed to inflammatory brain disease

What causes status epilepticus?

Any disease process that can cause a seizure may cause status epilepticus. A number of studies have tried to determine whether any specific underlying disease processes are more likely to cause status epilepticus than others, with one paper concluding that dogs presenting with status epilepticus are more likely to have secondary/reactive epilepsy than idiopathic/primary epilepsy (Platt and Haag, 2002). With this in mind, an understanding of the signalment and brief history of the patient is important to alert the clinician to an underlying cause, which may carry implications for the subsequent treatment (*Tables 1* and *2*).

Initial consideration

There are two main objectives of initial status epilepticus management:

- Control the seizure
- Protect the brain (and the rest of the body).

Table 2. Historical features that may have significance when considering the aetiology of seizures

Historical points	Possible aetiological significance
Seizure history	Previous isolated epileptic seizures with normal inter-ictal periods suggest idiopathic epilepsy
Toxin exposure	Known or suspected toxin exposure, especially insecticides, herbicides and prescription medication
Recent neurological signs	Acute onset multifocal signs preceding the seizure may suggest inflammatory disease Chronic progressive forebrain signs (mentation/ behaviour change, loss of trained behaviour) may suggest neoplastic disease
Recent systemic signs	Polyuria and polydipsia, polyphagia, weight loss/ gain, vomiting or inappetence may suggest underlying systemic disease
Known medical conditions/ medications	For example, hypoglycaemia secondary to exogenous insulin overdose
History of trauma	Recent history may alter to the possibility of depressed skull fractures or intraparenchymal haemorrhage Past history may suggest 'cryptogenic' epilepsy

In many respects, these aims are interwoven, as controlling the seizure alone will help to protect the brain from further damage. However, in cases of status epilepticus, additional treatment is often required to correct concurrent systemic changes, which if left untreated may lead to secondary brain injury. Full clinical and neurological examination is often not possible on first presentation of these patients, hence certain steps must be taken to control the seizure as a priority (*Figure 1*).

Intravenous cannula placement is central to management of status epilepticus. Although this can be challenging to achieve in a dog having a seizure, intravenous (IV) access not only allows rapid administration of anticonvulsant medication (see later), blood samples can also be obtained through the cannula, and the patient started on intravenous fluid therapy. Other emergency triage steps to consider while other members of the team place a cannula include:

- Rectal temperature and cooling techniques as appropriate
- Assess oral cavity and airway for evidence of regurgitation, and suction when safe to do so
- Flow-by oxygen should be provided, as cerebral oxygen demand will be increased, and seizure activity is often associated with an erratic breathing pattern
- Emergency blood samples should ideally be run contemporaneously.
- Blood glucose should be assessed as not only a cause of the seizure, but also may be reduced secondary to prolonged metabolic demand. Supplement where required with IV glucose, or otherwise oral glucose syrups applied to the mucous membranes
- Packed cell volume (PCV)/total protein (TP) can give a crude indication of hydration status
- Electrolyte derangements should be noted, as early interventions may be required
- If available, blood gas and acid-base status of the patient should be assessed
- Intravenous fluid therapy should be started. Many of these patients will be hypoperfused on presentation and require initial bolus rates of balanced crystalloid solutions — the author's preference being Hartmann's solution.

Anticonvulsant medication

Benzodiazepines

Benzodiazepines are the first choice of anticonvulsant medication for use in status epilepticus. Two drugs are widely available in practice — diazepam and midazolam — with the former commonly available in oral, injectable, intranasal and per-rectum formulations. Benzodiazepines work by increasing the efficacy of the inhibitory neurotransmitter GABA at its receptor, hence stabilising neuronal membranes.

Diazepam can safely be given in doses of 0.5 mg/kg intravenously or per rectum. It can also be given intra-nasally, which may achieve anticonvulsant concentrations more rapidly than intrarectal administration, as it avoids hepatic first-pass metabolism (Musulin et al, 2011). Diazepam should not be given intramuscularly, as it is slowly and incompletely absorbed by this route. Dogs on long-term treatment with phenobarbitone will require higher initial doses of diazepam.

Midazolam is also commonly available, and its main advantage is its use intramuscularly, for those patients where IV access has not been possible. Doses of 0.2–0.3 mg/kg should be used. It has also been shown to be effective intranasally, however Charalambous et al (2017) used a mucosal atomisation device for administration, which is not widely available in practice.

It is also possible to use both as continuous rate infusions (CRIs), where necessary. Care should be exhibited in cases with status epilepticus secondary to suspected hepatic encephalopathy.

Phenobarbitone

In dogs that do not respond to benzodiazepine treatment, or those where the seizure rapidly recurs, phenobarbitone is the most widely available second-line anticonvulsant. The author would also argue that, in any dog presenting in status epilepticus, ongoing treatment with phenobarbitone would be appropriate, regardless of the response to benzodiazepines. Various formulations are available, including injectable (for intravenous and intramuscular use), oral tablets or oral suspensions. Phenobarbitone works in a similar way to the benzodiazepines, by potentiating the effect of the inhibitory neurotransmitter GABA, although its binding site is distinct from that of benzodiazepines.

An initial dose of 3 mg/kg can be given intravenously or intramuscularly, however the author will use doses of up to 6–8 mg/kg in some cases. When given intravenously, the injectable formulation should be diluted and given slowly. It takes around 20 minutes to cross the blood–brain barrier, so care must be taken with repeating doses too frequently, as excess sedation may

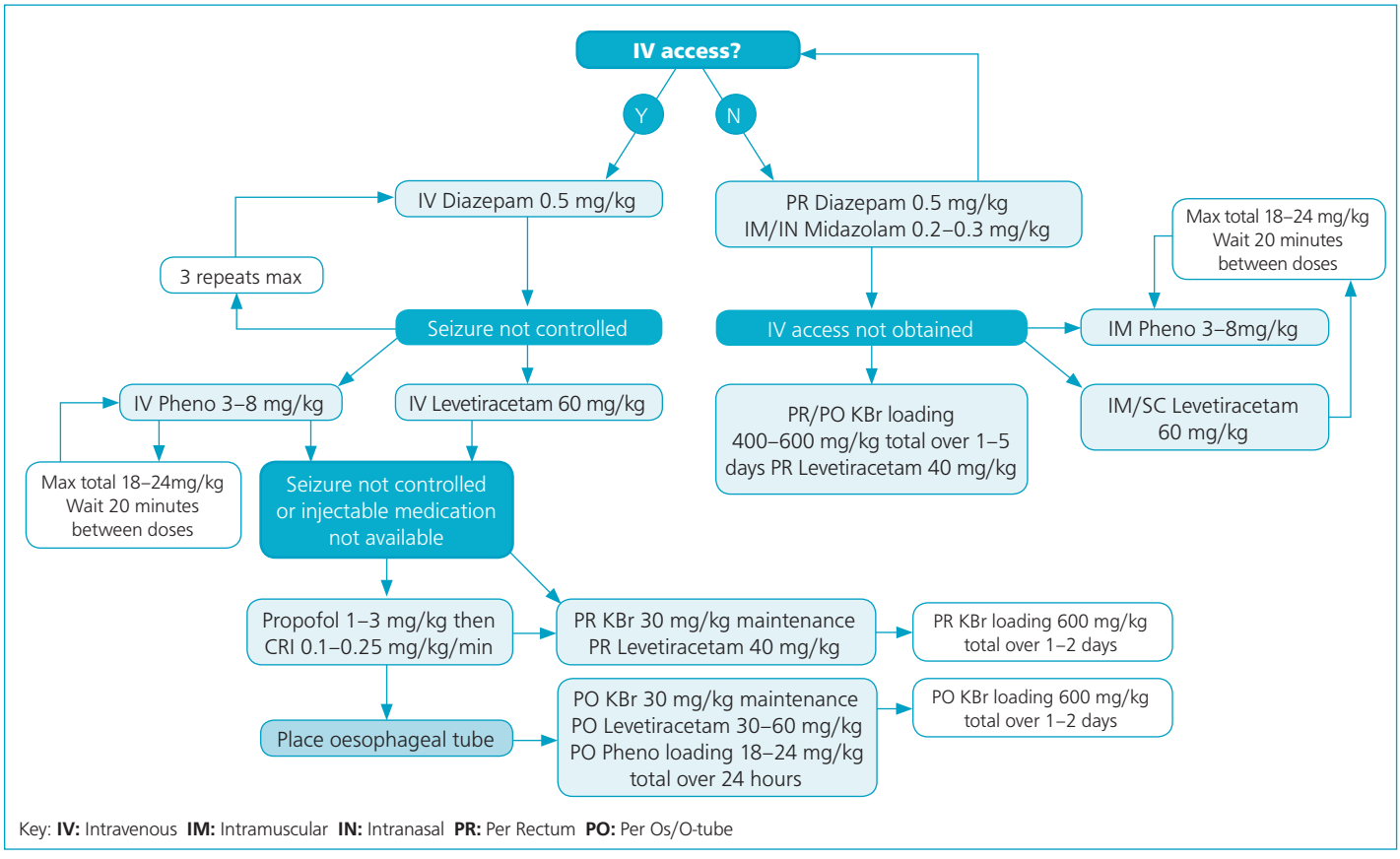

Figure 1. Treatment algorithm for management of status epilepticus in practice.

occur. If the seizures are recurring after this time, the dose can be repeated in this fashion, up to a maximum total of dose of 18–24 mg/kg for patients that are naïve to phenobarbitone treatment. In patients already receiving phenobarbitone treatment, a single IV dose of 3 mg/kg may be given.

Levetiracetam

In patients where phenobarbitone is contraindicated (for example, dogs with hepatic disease), or in those where an acute toxicity is suspected, many clinicians prefer the use of levetiracetam. This is a more expensive drug, and is available in injectable formulation for intravenous, intramuscular and subcutaneous use, and as oral tablets. The mechanism of action is not completely understood, but appears to interfere with neurotransmitter release at synapses, and is distinct from that of other anti-epileptic drugs (AEDs).

An initial dose can be given IV of 60 mg/kg, with continued doses of 20–30 mg/kg given every 6–8 hours. In dogs where the injectable formulation is not available, Cagnotti et al (2019) recently reported the use of 40 mg/kg of rectal levetiracetam. While this study used pure levetiracetam powder for suspension, the authors found no difference when compared with suspension made with commercially available tablets.

Potassium bromide

Bromide is only available in a tablet formulation as potassium bromide, however it is very commonly accessible in general practice. The mechanism of action is suspected to be mediated through neuronal cell hyperpolarization secondary to Br- influx through GABA-gated Cl- channels. Steady-state concentrations can take 80–120 days in dogs, hence loading doses are frequently used when managing status epilepticus or cluster seizures in practice.

Doses of 400–600 mg/kg KBr should be administered in divided doses over 1–5 days (Gindiciosi et al, 2014). In patients with status epilepticus, these doses can be administered in suspension per-rectum. Clinicians should be aware of possible profound sedation that can be an effect of KBr loading, as well as gastrointestinal side effects of per os/rectal dosing.

Propofol

Propofol infusions are commonly used early-on in the management of status epilepticus in practice given its wide availability and rapid onset of action; however, it is important for the clinician to consider other mechanisms of controlling the seizure on top of the infusion. Should additional anti-epileptic strategies not be employed, it is common for the seizure to recur during weaning of the infusion. Steffen and Grasmueck (2000) reported good response to treatment in dogs with intracranial disorder, when combined with treatment with phenobarbitone/pentobarbitone.

An IV bolus of 1–3 mg/kg should be followed by a CRI of 0.1–0.25 mg/kg/min. Mechanical ventilation must be provided, as well as cardiovascular and thermoregulatory support.

KEY POINTS

- Status epilepticus is a condition that can be managed with the medications available in most general practices.
- Consideration should be given, through the signalment and history, as to the possible cause of a presenting seizure.
- Management of the seizure should include protective measures for the brain and other organs, including intravenous fluid therapy, flow-by oxygen and blood glucose assessment.
- Benzodiazepines should be the first choice anticonvulsant, ideally following establishment of intravenous access.
- Per rectun administration has been shown to be effective in several anti-convulsant medications, including potassium bromide and levetiracetam.
- If anaesthetised, consider placing an oesophageal feeding tube in these patients to facilitate oral administration of medications.

This plane of anaesthesia gives the clinician the opportunity to place an oesophageal feeding tube, to allow administration of oral anticonvulsant medications, or otherwise to administer previously discussed treatments per-rectum.

Other therapies

Once the initial seizure is managed, further investigations of the underlying cause of the status epilepticus should be performed. For many, referral would be necessary for this to permit cross-sectional imaging. The authors have experienced many cases where motivated owners and general practitioners have transported dogs while anaesthetised, in order to facilitate specialist input and further investigations. This, however, is not always possible or appropriate, and these cases may require empirical interventions to be considered by the general practitioner. A brief list of other therapies includes:

- **Corticosteroids**. In cases where inflammatory or neoplastic aetiologies are suspected based on a history of acute progressive signs, age or breed, corticosteroids such as dexamethasone 0.2 mg/kg IV should be used.
- **Mannitol.** Given the risk of cerebral oedema secondary to status epilepticus, if available an infusion of 0.5 g/kg mannitol given over 20 minutes could be considered once hydration status has been corrected. Mannitol is also useful in cases of suspected hepatic encephalopathy.
- **Lactulose and antibiosis**. In cases where hepatic encephalopathy is suspected on the basis of signalment and history (as well as comprehensive blood profile), lactulose retention enemas of 30% lactulose and 70% water at 20 ml/kg for 15–20 minutes can be used. Oral antibiosis (metronidazole or amoxicillin-clavulanate) can also be used.

Conclusions

Status epilepticus is a challenging clinical presentation, however imaginative use of the anticonvulsant medications at our disposal can achieve good outcomes. While an infusion of propofol will give a rapid improvement in the clinical signs in front of us, thought should be given to the ongoing plan for the patient, both in the short and longer term. Consideration should be given to the most appropriate medications to choose, having assessed the likely aetiology based on the signalment and history (and diagnostic tests that can be performed in practice). Use of per-rectal drug administration, or placement of an oesophageal feeding tube in the event that the patient is anaesthetised, can vastly increase the range of medications available for use by the general practitioner. CA

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