Emergency seizures – status and clusters

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Abstract: In this session we will discuss a step by step treatment protocol for emergency seizures in dogs and cats. We will outline what to do if the seizures don't stop when treated in a standard manner.

Keywords: Status epilepticus, cluster seizures, diazepam, midazolam

The goals of anticonvulsant therapy in SE are to achieve cessation of clinical and electrical seizure activity and prevent its recurrence. Intravenous drug treatment for SE should be started without delay. This is necessary based upon the relationship between duration of SE and the extent of neurologic morbidity. This approach is also based upon experimental animal models that suggest that SE becomes progressively less responsive to treatment with diazepam.

Diazepam

Diazepam remains the first drug of choice for the treatment of SE in dogs and cats. With its relatively brief duration of action, diazepam is not a definitive therapy for SE. It has been recommended to use 0.5 to 1.0 mg/kg intravenously, up to a maximum dose of 20 mg, in dogs and cats. This dose can be repeated to effect or twice within two hours. If the diazepam does not control the seizures, the use of phenobarbital should be considered. Probably the most common and most dangerous error made in the management of SE is to treat repeated seizures with repeated doses of IV diazepam without administering an adequate loading dose of a longer-

acting anti-epileptic drug. In this situation, the patient will continue to have seizures, toxic concentrations of diazepam or diazepam metabolites will accumulate, and serious morbidity may result from diazepam over-dosage. Intravenous administration of diazepam may not be possible in some patients. It can be administered intramuscularly (IM), although absorption is not predictable. Rectal administration of diazepam may be considered initially at a dose of 0.5 to 2.0 mg/kg body weight depending upon whether the animal was being treated with phenobarbitone before the onset of SE. It may be necessary to use the higher dose in dogs receiving long-term phenobarbitone therapy. In previously untreated dogs, a per rectum diazepam dose of 1 mg/kg results in a mean time to peak plasma concentration of approximately 14 minutes.

Midazolam

Midazolam is a recently developed water-soluble benzodiazepine which is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Midazolam has been shown to have a wide margin of safety and a broad therapeutic index. Unlike diazepam, with erratic and incomplete intramuscular absorption, midazolam is rapidly absorbed following IM injection, with a high bioavailability, an early onset of sedation, and early clinical effects. The peak plasma concentration in dogs after IM administration was seen within 15 minutes. The dose for cats and dogs is 0.066 - 0.3 mg/kg IM or IV.

PHENOBARBITAL

Phenobarbital (PB) is a safe, inexpensive drug that may be administered orally, intravenously or intramuscularly. Phenobarbital increases the seizure threshold required for seizure discharge and acts to decrease the spread of the discharge to neighboring neurons The recommended loading

dose is 12 to 24 mg/kg IV, if immediate therapeutic concentrations are desired but this can induce a profound stupor with concurrent suppression of the cardiovascular and respiratory. Alternatively, the dose can initially be 2 mg/kg IV, repeating the dose every 20 - 30 minutes to effect and to a maximum total 24-hour dose of 24 mg/kg. The parenteral form can also be given IM, which is recommended if diazepam has already been administered. This will avoid the potentiation of profound respiratory and cardiovascular depression. The depressant effects of PB on respiratory drive, level of consciousness, and blood pressure may complicate management of the SE patient, especially when administered after benzodiazepine.

Propofol

In human cases of refractory SE, the use of IV infusions of anesthetic doses of propofol, 2,6-diisopropylphenol, has become standard. This approach has recently been evaluated in veterinary patients. Propofol has barbiturate- and benzodiazepine-like effects on the (GABA)A receptor and can suppress CNS metabolic activity. Propofol can be administered by IV bolus (1-4 mg/kg) or by constant rate infusion (0.1-0.6 mg/kg/min titrated to effect or up to 6 mg/kg/hr). The advantages of this drug over the barbiturates are its rapid clearance, chiefly eliminated by hepatic conjugation to inactive metabolites, and less profound hypotensive effects. However, this drug should be used with caution, preferably in settings where definitive airway control and hemodynamic support is possible, as hypoxemia secondary to apnoea is a primary side-effect as is myocardial depression.

Levetiracetam

Levetiracetam is the *S*-enantiomer of the ethyl analogue of piracetam that has broad-ranging, unique but incompletely understood mechanisms of action against seizures. Its main mechanism may be in decreasing the onset of a seizure through enhanced GABA activated Cl^- conductance. The pharmacodynamic effect is believed to outlive the known half-life of the drug. In dogs, this drug has a half-life is approximately 4-6 hours, is liver cytochrome P450 independent and is excreted unchanged by the kidneys. The dose range documented for dogs is estimated to be 5-25 mg/kg q 8-12hrs PO. Levetiracetam has been documented as the most well tolerated anti-epileptic drug in humans, with adverse reactions equal to that of placebo. Overall, this drug is proven to be a highly effective adjunctive therapy in humans to control seizures. In 2006, levetiracetam was approved in humans as the first of the newer anticonvulsive drugs for intravenous administration and has been trialed for its use with status epilepticus. It has been shown that it is an effective drug in people with this condition and is well tolerated at high doses. Recent pharmacokinetic studies in dogs have demonstrated that IV administration of this drug is well tolerated when administered as a bolus at 60 mg/kg and rapidly achieved suggested therapeutic levels. Clinical veterinary trials are underway for this drug.

Ketamine

Experimental animal work has indicated that NMDA glutamate receptor antagonists may be used to treat the so called self-sustaining status epilepticus (SSSE). This type of status exists after approximately 10 minutes to 1 hour and may have a different underlying pathophysiology to that of the initial SE in that NMDA receptors may be over stimulated by excessive glutamate concentrations. Ketamine is a NMDA receptor antagonist which has been used in humans with refractory or SSSE and has been shown to be effective in a dog with SSSE.

Inhalational Anesthesia

Inhalational anesthetics have been recommended as a last resort in cases of resistant SE. The equipment and personnel necessary to administer inhalational anesthesia may not be readily available and can be cumbersome. Isoflurane, an inhalational general anesthetic agent, may be efficacious in the treatment of resistant SE. Not all of the volatile anesthetic agents have anti-epileptic potential, however; enflurane may actually increase seizure activity. Isoflurane does not undergo hepatic metabolism, has a rapid onset of action and has been extensively studied. Obviously, isoflurane therapy necessitates ventilation and intensive-care monitoring, and hypotension may occur during therapy.