PRACTICAL MANAGEMENT OF SEIZURES IN CATS

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Introduction

Seizures are a common clinical problem representing 2-3% of all feline cases presenting to the veterinary practitioner. As with any other clinical problem it is important to clarify certain clinical features in order to determine the underlying etiology, prognosis, and appropriate treatment plan. Management of cats with seizures involves treatment of the underlying etiology when known and medication to control seizures.

Effective management of seizures in cats includes client communication. Often, clinical decisions are made based on historical information from the owner. Therefore, specific questioning is required to help differentiate seizures from seizure-like syndromes such as syncope, vestibular disease, or movement related paroxysmal problems. Differentiating these is not always possible. Having owners videotape an episode may help understand the problem. Other situations mandate broad diagnostic work-up. Also discussions should include ongoing management of cats with seizures including therapeutic drug monitoring, routine blood work, frequent drug adjustments, and the possibility of break-through seizures. They should also be prepared for emergency visits to their veterinarian in the event of status epilepticus.

Pathophysiology

The pathogenesis of a seizure is multifactorial. Conceptually, appropriate balance between neuronal excitation and inhibition normally prevents hypersynchronus abnormal electrical activity. When the balance is shifted towards excitation seizures can result. If focal neuronal excitation occurs in a discrete region of the brain partial seizures result. Depending on the location of this activity (frontal, parietal, occipital, limbic system) various manifestations of seizures could be seen. For example, motor seizure activity occurs when motor areas of the brain are affected. Less clear in veterinary medicine is the incidence of limbic seizures. These could manifest as behavior changes, episodes of absence, altered arousal, changes in appetite, and nausea. Because these are more difficult to observe in veterinary medicine, this type of seizure may be underreported. At times, focal seizure activity will secondarily generalize. Surrounding neurons and neuronal networks become involved in the hypersynchronus activity due to an upswing in excitatory neurotransmitters. What started as a focal (partial) seizure may become a generalized tonic colonic seizure. If seizure activity begins in or near the thalamus (a centralized switching station with diffuse neuronal networks) generalization may occur immediately or very quickly after onset. Likely, the incidence of partial seizure activity with secondary generalization is underreported since the initial partial seizures may go unrecognized by the evaluator.

Seizures can be generalized (whole body tonic and/or clonic) or partial (movement of face, single limb, ear, head, etc). As previously mentioned, some partial seizures may secondarily generalize. One report found that about half of the cats evaluated had generalized seizures while the remaining half had partial seizures with or without secondary generalization. Importantly, type of seizure is not a predictor of underlying etiology and should not be used to determine prognosis. Generally, it's been reported that cats with symptomatic or reactive seizures tended to have shorter survival times, while cats with no identifiable cause (idiopathic) had significantly longer survival. Cats with idiopathic seizures typically are younger than cats with other seizure types.

A universal system for classifying seizure etiology in cats has not been developed. However, one commonly used system classifies them into 3 distinct categories: reactive, symptomatic, and idiopathic. Reactive seizures are those caused by metabolic disease or toxin exposure. Renal and liver encephalopathy, electrolyte and glucose abnormalities, and CNS intoxication are examples of conditions that could cause reactive seizures. (**Table 1**) Symptomatic seizures are those caused by organic brain disease such as neoplasia, meningoencephalitis, cerebrovascular disease, and traumatic lesions. Symptomatic seizures are reportedly more common than reactive seizures in cats (50 – 60% vs. 20-30%, respectively). In cats, unlike dogs, a genetic basis for seizures has not been established. Therefore, the term "idiopathic" does not denote an inherited form of epilepsy, but rather implies that no underlying disease can be detected.

While symptomatic epilepsy is reportedly more common than reactive or idiopathic, the true incidence of various causes of seizures is not well known since most reports come from referral institutions where selection bias is unavoidable.

Common metabolic causes of seizures in cats	Hepatic encephalopathy Severe uremia Hypoglycemia Severe hyperthyroidism Polycythemia vera Severe anemia Hypocalcemia Hypertriglcyeridemia

Table 1. Common metabolic causes of reactive seizures in cats.

Clinical examination

Clinical examination can help prioritize a list of differential diagnoses. It is important to note that any cat, despite the underlying cause of seizure, may have neurological abnormalities during the period following the seizure (post-ictus). Post-ictal intervals are variable, lasting hours to days. Up to 50% of cats have post-ictal deficits including: central blindness (absent menace with

normal PLR's), decreased postural reactions, altered mentation, anisocoria, and ataxia. Therefore, repeated neurological evaluations should be performed. Many cats with seizure disorders have unremarkable neurological evaluations during the inter-ictal period. Unfortunately, this is not a good predictor of underlying etiology and consideration of symptomatic, reactive, and idiopathic causes should still remain on the list of rule-outs.

In cats with persistent asymmetric neurological abnormalities, especially during the inter-ictal period, symptomatic epilepsy should be suspected. Examples of neurological abnormalities of the prosencephalon are listed in **Table 2**. Differential diagnoses for cats with structural disease causing symptomatic epilepsy include neoplastic, inflammatory, vascular, and traumatic diseases. Neoplasia may be primary (originating from tissue within the brain) or metastatic. Inflammatory disease may be infectious (viral, bacterial, protozoal, or fungal) or non-infectious (meningoencephalitis of unknown etiology). Vascular disease (ischemic or hemorrhagic infarct) could be the result of a systemic problem such as hypertension, hypoproteinemia, systemic inflammatory disease, endocarditis, endocrine disease, or toxic disease. Occasionally, adherent parasite migration (cuterebra, etc) has been reported.

Prosencephalic signs	Circling Head pressing Contralateral hemiparesis Contralateral menace deficit Blindness Altered mentation Delayed or absent knuckling Hyper or hyporexia Aggression

Table 2. Common signs suggestive of structural prosencephalic brain disease

Various metabolic diseases can lead to reactive seizures. The most common include diseases of the liver and kidney, and diseases that cause electrolyte or glucose abnormalities. Reported clinical features of cats with portosystemic vascular anomalies include copper colored irises and ptyalism, however these clinical findings are neither senisitive nor specific. Myriad toxic insults should also be considered. A complete list of CNS toxins can be found in several texts.

Diagnostic evaluation

Diagnostic work-up is highly dependent on individual clinical situations including age of cat, other medical history, and the financial situation of the client. Ideally, a complete diagnostic evaluation would include tests to screen for metabolic and structural disease. Magnetic resonance imaging (MRI) is currently the gold-standard in evaluating the structure of the brain.

Management of cats with seizures varies considerably based on owner philosophy and expectations, underlying cause of the seizure, concomitant illness, and financial constraints. It is

important to remember that ongoing cost and time commitments are often necessary to properly monitor drug levels and organ function and to make emergency visits to a veterinarian in the case of break-through seizures. Prior to initiating an extensive diagnostic plan, the owner should be aware of the future commitments.

Treatment of the primary underlying disease should occur whenever possible. Each of these conditions carries its own prognosis, treatment plan, and financial consideration. Simultaneous treatment of the seizures is also important.

Antiepileptic drugs

The decision to initiate pharmacologic therapy for seizures balances many factors including, severity and frequency of seizures, underlying disease process, and type of seizure (partial vs. generalized). In general, it should be the goal to minimize or stop all seizure activity. Criteria for deciding when to begin drug treatment can be found in **Table 3**.

Antiepileptic drugs (AED) should ideally control seizures with no or minimal side-effects and be affordable to clients. Unfortunately, no single AED fits all of these criteria. Currently, a handful of AED's are commonly used in cats. These drugs are summarized in **Table 4**.

Phenobarbital is still commonly used and remains the drug of choice in many situations. With serum drug monitoring and vigilant patient management successful long-term seizure control is possible with minimal side-effects. Hepatotoxicity is uncommon when appropriate serum drug levels are maintained. Increased eating, drinking, urinating, and lethargy are usually short-term side-effects, but raise concern in many owners.

Short and long acting benzodiazepines are also useful in cats. Diazepam is generally safe, but has been associated with idiosyncratic hepatic necrosis (rarely). Clonazepam is also safe, longer acting, and has not been associated with hepatic necrosis.

Criteria for starting anticonvulsant drug therapy
➢ Symptomatic epilepsy is diagnosed per imaging or CSF analysis ➢ Status epilepticus event ➢ >2 isolated seizure events within a 6-9 month period ➢ >2 isolated cluster seizure events (cluster = two or more seizures within a 24-hour period) ➢ Seizures develop after severe exogenous trauma ➢ Post-ictal deficits are severe or prolonged

Table 3. Criteria for deciding when to begin anticonvulsant drug therapy in cats.

A couple of novel AED's developed for use in humans, levetiracetam (Keppra®) and zonisamide have been used more frequently over the last few years. Levetiracetam has a poorly understood mechanism of action, but it is thought to work on different ion channels than standard AED's.

Studies in cats demonstrate that it is well absorbed orally and excreted by the kidneys relatively unchanged. Cats with renal disease may theoretically require dose reductions. Since there is no hepatic metabolism it could be used in cats with hepatic disease. Additionally, it appears to have a large safety margin with only inappetance and lethargy noted at high doses. While it has been evaluated as an add-on medication with phenobarbital, many have used it as a sole agent. Serum levels approximating those reported as therapeutic in people were achieved with doses of approximately 20 mg/kg orally every 8 hours. Lacking are randomized placebo controlled prospective studies to determine short and long-term efficacy in cats.

Zonisamide was effective in a laboratory setting at stopping convulsions in cats with various types of induced seizures. It also appears to be safe in cats. At this time, zonisamide has been used with success in cats with refractory epilepsy. Again, controlled studies are lacking. As more cats are treated with this medication, information will become available regarding side-effects and efficacy. Generally, it may be a drug used in cases that are refractory to other treatment.

Gabapentin can also be used in cats. It is excreted by the kidneys and has a relatively high safety margin. The most common reported side effect is sedation. Some authors recommend gradually increasing dosing over a period of a couple of weeks to mitigate this side-effect. Gabapentin has been used most commonly as an add-on drug, but it has also been used as a sole agent.

Drug	Starting dose	Monitoring	Side Effects
Phenobarbital	1-2mg/kg/d PO q12-24h	Serum levels 10-20 mcg/ml; monitor liver function	Polyuria, polydipsia, polyphagia, hepatotoxicity, blood dyscrasia, dermatitis, altered behavior.
Diazepam	0.5-2.0mg/kg PO divided 2 or 3 times per day; use rectally for active seizuring.	N/A – response to treatment	Not for use with Phenobarbital; idiopathic hepatic necrosis; withdrawal seizures
Clonazepam	0.5 mg PO q12-12h	N/A – response to treatment	Hepatic necrosis not reported.
KBr	Not recommended	N/A	Acute pneumonitis
Gabapentin	5-10mg/kg PO q12h	Not determined for cats	Sedation
Zonisamide	10 -20 mg/kg	Therapeutic levels not well established	GI related, ataxia, lethargy
Levetiracetam	20mg/kg PO q8 h	Therapeutic levels not well established	Lethargy inappetance

Table 4. Commonly used antiepileptic drugs (AED) for managing seizures in cats.

Practical Summary

Let's now take the above information and boil it down to a practical approach to the seizuring cat. A couple of scenarios may highlight some important "take home" points. Scenario 1. You are presented with a cat that the owners claim has had a seizure. Questions characterize the event as one that sounds like seizure activity and not a "seizure-like" episode. If this is not clear diagnostics may also evaluate the cardiovascular system, musculoskeletal system, and screen for non-seizure neurological dysfunction. Naturally, the first goal is to determine the underlying etiology of seizures. Consideration of reactive, symptomatic, and idiopathic causes should be done. Typically, ruling out metabolic causes (reactive) first allows you to move from least costly and least invasive tests to more costly/invasive. Routine laboratory data will answer most questions regarding metabolic status. Adding a liver function test like bile acids (fasted and 2-hour post prandial) would, in most circumstances, cover all bases for metabolic disease. If, upon questioning or examination, you are suspicion of toxin exposure than appropriate treatment and diagnostics could be carried out. Typically, you'll need to target a very specific toxin in order to get any valuable information or select an effective treatment. General non-specific treatment could be carried out if a toxin exposure is suspected.

In those cases that are normal metabolically, then consider a structural problem (i.e., symptomatic epilepsy) next. Gold-standard work-up for these cats would include a MRI and cerebrospinal fluid analysis. Computed tomography can demonstrate some lesions, but is less sensitive than MRI. Typically, CSF is collected after imaging, this allows the clinician to have knowledge prior to the tap about the primary lesion or brain herniation. Cases in which the MRI is very characteristic of a specific diagnosis or in those suspected of having high intracranial pressure, a tap may be avoided. CSF can allow characterization of certain inflammatory or neoplastic conditions, however, a specific diagnosis is rarely determined. CSF allows the clinician a minimally invasive method for sampling the CNS and allows that sample to undergo culture, titer testing, or other biochemical analysis.

Scenario 2. You are presented with a cat that is actively seizuring. In this case immediate action should be taken to halt the seizure. This can usually be done with rectal diazepam. Most cats require 1 – 2 ml to stop the seizure. In other cases, the dose will have to be repeated. Don't be bashful about using diazepam. You can repeat several times in most cases without risk of major side effects. In cats with a portosystemic vascular anomaly, diazepam could make them severely sedated due to altered hepatic metabolism of the drug. If this occurs ventilatory assistance may be required. Flumazonil can be used to reverse the effects of diazepam. In those cases that do not responds to diazepam try using levetiracetam (Keppra; 20 mg/kd IV). This has been shown to be effective at stopping seizures acutely. Propofol, pentobarbital, and inhalant gases have all been used to stop seizures as well.

After stopping the seizure, assessment of body temperature, respiration, blood pressure and heart rate should be done. This is a good time to place a catheter (saving a sample of blood while

placing a catheter is a good idea). For longer term management of the convulsions a diazepam CRI may be necessary in addition to starting the cat on another AED. As a starting point for diazepam, use the same dose per hour as the amount of diazepam required to stop the seizure. For example, if you gave two 1 ml rectal doses to stop the seizure, then start the CRI at a rate of 2 ml/h. This rate is easily adjusted as necessary. Remember that diazepam binds to plastic and will breakdown in light. (Running a small amount of diazepam through a line saturates the benzodiazepine receptors.) Loading with phenobarbital or starting a drug like Keppra could also be initiated at this time.

After stabilization of the patient proceed with the plan described in scenario 1.

In reality, many clients will be unable or unwilling to pursue all of the available diagnostics, especially imaging. At a minimum a metabolic workup should be done (this may be an easier sell after quoting an approximate cost for a MRI - $1500 to 1800). Ultimately, you may have to manage the seizures without knowing the underlying etiology. Generally, phenobarbital is still the drug of choice unless there is a specific contraindication (hepatic disease). If so, I generally choose levetiracetam as a good front line sole agent. Remember to warn the clients about ongoing serum monitoring, break-through seizures, constant drug adjustments in the early phase of treatments, and the fact that the underlying etiology may make seizure control difficult.

Conclusion

Overall, a standard approach to cats with seizures should be used since it is difficult to predict the underlying etiology based on clinical features alone. Working them up in a logical step wise fashion insures that the client incurs the least cost and the patient only undergoes what is absolutely necessary. Management of seizures can be frustrating for many because there is frequently ongoing cost and time commitments. However, depending on the nature of the underlying disease, managing the seizures themselves can lead to an improved quality of life.

SUGGESTED READING:

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