Cats with Seizures—What Drugs to Use?

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Information on efficacy of antiepileptic treatment in cats is limited. Maintenance therapy with antiepileptic drugs is recommended for most cats with idiopathic epilepsy (IE) when seizures occur more frequently than once every 3 months and in all cats whenever seizures occur in a cluster (>1 seizure/24 h), when status epilepticus occurs, or when seizure frequency increases over time. The recommendation to treat based on seizure frequency in cats with IE is controversial and should be somewhat flexible. Owner preferences must be taken into consideration and a seizure frequency of one seizure every 6 weeks may be tolerable if that can be maintained without having to administer twice daily drugs. When the decision is made to treat chronic recurrent seizures with drugs, a short period without drugs is often recommended to establish baseline seizure frequency before initiating treatment, but there is some evidence that each seizure event has the potential to worsen the disease in the brain and early treatment may result in better long-term control. Lifelong therapy should also be recommended whenever seizures occur post-trauma or when potentially progressive structural forebrain disease (neoplasia, inflammation, hippocampal necrosis) has been identified or is suspected as the reason for the seizures. Even when the primary cause of the seizures can be treated specifically, therapy for the seizures is necessary. Chronic therapy is also recommended in cats presenting with an acute onset of repetitive seizures caused by a non-progressive intracranial disorder such as a stroke; in some of these cats chronic treatment can be gradually tapered and discontinued following weeks or months without seizure recurrence.

DRUGS

Phenobarbital

Phenobarbital (PB) is the most commonly used anti-seizure medication and seems efficacious in cats with idiopathic and symptomatic (structural) epilepsy. Ideal therapeutic serum concentrations of PB in cats are 20–30 mg/ml (90–129 mmol/l), which are slightly lower than the range for dogs, although many laboratories use the same therapeutic range as for dogs (15–45 mg/ml). Some cats will have good seizure control at subtherapeutic levels of PB, so chronic serum monitoring and dosage adjustments are usually only recommended in cats with unacceptable seizure control. Adverse clinical effects are more likely to occur when serum PB concentrations are above the recommended therapeutic range. PB is a very effective drug in cats. Therapeutic serum PB concentrations can be achieved following chronic transdermal administration of compounded PB gel, but

absorption and actual serum concentrations attained are variable and this formulation is not yet commercially available.

Adverse effects associated with chronic PB administration are minimal in most cats but can include sedation, ataxia, polyphagia and weight gain. Polyuria and polydipsia are less marked in cats compared with dogs being treated with PB. Blood dyscrasias occasionally occur, leading to granulocytopenia or thrombocytopenia that is usually mild and reversible with discontinuation of PB therapy. Hepatotoxicosis progressing to hepatic failure, has not been reported in cats. Mild increases in alanine aminotransferase and alkaline phosphatase activities are expected in 10–30% of cats treated with PB, but do not seem to be clinically significant.

A recent study including 36 idiopathic epileptic cats reported seizure eradication in approximately 45% of cats, good (1–5 seizures/year) to moderate (6–10 seizures/year) seizure control in approximately 25% of cats, and poor (>10 seizures/year) seizure control in 30% of cats following PB treatment. Similar results (44% seizure free, 31% adequate seizure control, 25% inadequate seizure control) were reported in another study including 16 epileptic cats. In the larger study, seizure duration and severity (based on owner assessment) decreased in 72% and 69% of cats, respectively. Quality of life was considered good by the owners in 72% of cats. Early initiation of PB treatment was significantly associated with a more favorable outcome than delayed treatment. In one study including predominantly cats with symptomatic (structural) epilepsy, treatment of the underlying seizure aetiology as well as antiepileptic treatment (PB and/or diazepam) resulted in seizure eradication or low seizure frequency in 57% (17/30) of cats with a follow up of 3 to 21 months.

Levetiracetam

Levetiracetam (LEV) is a novel drug that is rapidly absorbed following oral administration and has an oral bioavailability of nearly 100% whether administered to fasted or fed cats. Peak plasma concentrations are achieved within approximately 2 h, with an elimination half-life of 3 h; however, the effect of the drug seems to persist longer than its presence in the bloodstream. Most of the drug (70–90%) is eliminated by the kidneys through glomerular filtration so the dose should be decreased in cats with renal insufficiency. As LEV does not undergo any hepatic metabolism it is a good choice for cats with liver disease.

The dose range documented for cats is estimated to be 10–30 mg/kg q 8 h PO. Overall, this drug is proven to be a highly effective adjunctive therapy in humans to control seizures refractory to treatment. Four studies have assessed the efficacy of levetiracetam as a

monotherapy agent or in combination to phenobarbital (three studies), providing a total group size of 43 cats. In two of the studies, 50% of the study population was treated successfully. An injectable formulation of LEV is also available and is well tolerated in cats, with pharmacokinetics similar to the oral preparation. This drug can be administered (20–60 mg/kg intravenous bolus) to stop seizures in patients with acute seizures or status epilepticus. The anticonvulsant effect is rapid and is maintained for several hours. Patients do not become sedate, simplifying support and monitoring

Diazepam

Diazepam is a benzodiazepine that is very effective for the treatment of seizures in cats, whether administered as the only drug or as an add-on medication when PB is ineffective or contraindicated. Oral diazepam has a long elimination half-life (15–20 h) in cats; and, unlike dogs, cats do not appear to develop a functional tolerance to the drug. Diazepam monotherapy (0.5–2.0 mg/kg q 8–12 h) has been reported to be effective in cats with idiopathic epilepsy, with 40% of treated cats in one study becoming seizure-free and another 40% showing good control (>50% decrease in seizure frequency); 20% were resistant to treatment. The most common adverse effects are sedation, physical dependence and the potential for withdrawal seizures. The administration of oral diazepam to cats has also occasionally been associated with potentially fatal idiosyncratic hepatotoxicosis seen in some cats as early as 5 days after initiating therapy; so if a clinician does choose to administer oral diazepam to a cat they should monitor clinical signs and hepatic enzymes 5–7 days after starting the drug and then periodically during treatment for at least 6 months, with plans to discontinue the diazepam if any adverse effects occur.

Zonisamide

Zonisamide (ZNS) is a sulfonamide-based drug that has been used anecdotally in cats. ZNS is well absorbed after oral administration and peak concentrations are achieved in approximately 4 h in cats. The drug is metabolized primarily by hepatic microsomal enzymes and has a long elimination half-life of 33 h in cats, reaching steady state within 7 days. The half-life may be significantly shortened in cats concurrently receiving PB or other drugs that increase the hepatic microsomal enzyme p450. Therapeutic serum levels have not been established in cats but due to its long half-life, some have recommended once daily administration of a 5–10 mg/kg body weight dose for cats; however, further studies are needed. Three of five cats with refractory seizures when treated with PB alone had a >50% reduction in seizures when ZNS was added, at a mean dose of 11.54 mg/kg q 24 h. ZNS has a wide therapeutic index but adverse effects reported in dogs include sedation, ataxia and

loss of appetite. A dose of 20 mg/kg q 24 h caused adverse reactions in 50% of treated cats, including anorexia, diarrhea, vomiting, somnolence and ataxia.

Gabapentin/Pregabalin

One pharmacokinetic study in cats showed an elimination half-life of 2.5–3.5 h and suggested that administration of 8 mg/kg orally q 6 h would be expected to result in plasma concentrations similar to those recommended in humans. An oral dose of 5–10 mg/kg q 8–12 h has been used with limited success in cats. Pregabalin is a newer generation anticonvulsant in the same class as gabapentin but with increased potency due to a greater affinity for the binding site. The recommended dose in cats is 1–2 mg/kg given orally q 12 h. The most common adverse effects include sedation and ataxia, and it is possible that these can be reduced by starting at a lower dose (0.5 mg/kg q 12 h) with gradual increments over a few weeks.

Potassium Bromide

Bromide was initially thought to be a safe and desirable drug in cats due to its lack of hepatic metabolism and its long elimination half-life (approximately 11 days), allowing for once daily dosing. Administration of potassium bromide (KBr) at 30 mg/kg q 24 h or 15 mg/kg q 12 h controls seizures in approximately 35–50% of treated cats. Mild adverse effects can occur in cats treated with KBr, including polydipsia, vomiting and sedation. Unfortunately, nearly 40% of cats receiving KBr have been shown to develop clinical signs similar to bronchial asthma, with chronic cough, mild to marked peribronchial infiltrates and inflammatory bronchoalveolar lavage with eosinophilic predominance. The respiratory signs can be severe, and do not always resolve when KBr is discontinued, progressing to severe bronchiolitis/pulmonary fibrosis and death in some cats. Therefore the use of KBr is contraindicated in cats.

Emergency Seizures

The goals of anticonvulsant therapy in status epilepticus (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 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 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.

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/h). 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 apnea is a primary side-effect as is myocardial depression.

Levetiracetam

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 cats have demonstrated that high doses of this drug is well tolerated and may be a good option for refractory SE in cats.

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.

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.

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