Treating the epileptic patient

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Nursing the epileptic patient can be very demanding, stressful and sometimes frustrating for the practising veterinary professional and requires a calm and focused frame of mind. Here, we will learn to understand the nature of epilepsy, handling that all-important emergency call, patient presentation, emergency stabilisation and treatment, differential diagnosis, diagnostics and long-term management of the epileptic cat and dog

It is important we grasp a basic understanding of the term epilepsy in order to develop and carry out the appropriate care and treatment plan for our patients. Epilepsy is a common chronic neurological disorder in dogs and cats and refers simply to the state of recurrent seizures. Epilepsy is caused by abnormal brain activity, an electrical short-circuit of one or more brain areas which might be followed by contractions of skeletal muscles. Epilepsies can be genetic in nature, be symptomatic or cryptogenic and can be further classified as either Intra-cranial or extra-cranial in nature with generalised or focal seizure activity.

Type & Classification of Epilepsy

Intra Cranial Epilepsies	Type	Nature	Causes		
Idiopathic	Primary Epilepsy	Functional	Forebrain Disorder	Normal Inter Ictal Period	No other Abnormalities
Symptomatic	Secondary Epilepsy	Structural	Developmental anomaly, neoplasia , inflammatory or infectious disease, traumatic or vascular		
Cryptogenic	Secondary Epilepsy	Structural	Previous head trauma, post-encephalitis changes, undetected hypoxic/vascular events		
Extra Cranial		Reactive	Specific organ failure (hepatic or renal), electrolyte imbalance (hypo/hypernatraemia and/ or hypocalcaemia), hypoglycaemia, hypoxia, hypertension, polycythemia, thiamine deficiency, toxicity (lead, organophosphates, ethylene glycol or metaldehyde)	With or without a normal or abnormal inter-ictal period	No underlying brain disorder

PRIMARY GENERALISED SEIZURE

Primary generalised seizures activate the whole brain right from the start. Generalised seizures might be tonic, myoclonic, clonic, atonic, tonic-clonic or absences.

Phase of seizure	Appearance
Tonic	Sustained, increased muscle contraction, animal usually becomes recumbent in this phase
Myoclonic (myoclonus)	Sudden, brief, involuntary, single or multiple contractions of muscles or muscle groups.
Clonic (clonus)	Regularly repetitive myoclonus, which involves the same muscle groups, and is prolonged.
Atonic	Sudden loss of muscle tone, usually lasting 1-2 seconds or more.
Tonic-clonic (previously known as gran mal?)	Sequence consisting of a tonic phase, followed by a clonic phase. Autonomic manifestations,such as hypersalivation, urination or defecation, are common
Eventually absences (previously known as petit mal?)	Brief impairment of consciousness without loss of muscle tone

FOCAL SEIZURE

Focal seizures (partial seizures) affect one part of the cerebrum of the brain and may cause abnormal movements of specific body parts or abnormal behaviour and are the most common seizure in cats. Any type of focal-onset seizure can evolve into a generalised seizure.

Complex-partial or psychomotor seizures	Behavioural seizures	Abnormal behaviour (hysteria,rage, hyperaesthesia, fly-biting or tail-chasing)
Focal-onset sensory seizures	Abnormal sensations	Hyperaesthesia, tingling or visual hallucinations
Focal autonomic seizures	Autonomic manifestations	Diarrhoea, vomiting or apparent abdominal pain

SEIZURES CAN HAVE FOUR STAGES

Prodrome	**Behaviour changes that occur hours or days before the seizure**
Aura	**Event prior to seizure characterised by sensory, psychosensory and experiential symptoms in humans, and indicative of a sensation. Humans describe sensations such as fear, déjà vu, a smell sensation or a typical taste**
Ictus	**The seizure event itself**
Post-ictal phase	**Disorientation, behaviour changes hours or days after the seizure**

Status epilepticus (SE) can be defined as either a continuous seizure lasting at least five minutes or two or more discrete seizures between which there is incomplete recovery of consciousness. There are as many types of status epilepticus as there are types of seizures. Multiple seizures within a short period of time with full recovery of consciousness between the seizures does not meet the strict definition of status epilepticus but instead would be considered as cluster, serial, or acute repetitive seizures which occur within a 24hr period and represent a serious condition that may evolve into SE and should be treated as such.

THE CALL

This can be a difficult one to handle, particularly if this is a new experience. Observing a seizuring pet can be extremely distressing, even more so if the owner has never seen this activity before. Keeping a composed and controlled tone on the phone will help instil calm and confidence in the client. Reassure the owner that you are there to help and you need to ask some questions in order to ensure the pet gets the appropriate treatment required. Emphasise that, during the seizure episodes, the pet may not be in any pain or aware of what's happening.

First, ask how long the seizure activity has been, and is the pet still seizing? This will tell us if the animal requires immediate veterinary attention as research shows that prolonged SE episodes of five minutes or more can damage the brain.

Should you be faced with a patient in SE or cluster seizures, then immediate drug therapy is required by administering IV/Rectal Diazepam to control the seizure. Once initial control is achieved then patient history and details can be obtained.

Should the episode be isolated, of very short duration (1-2min), or the patient has recovered then the following advice can be provided and patient history obtained. Instruct the owner to remove any nearby dangers from the pet. It is important to avoid interfering with them and, instead, start timing and observing the event from a distance. Removing all external stimuli can be of assistance. If indoors, close curtains/blinds and switch off lighting and any electrical equipment i.e. T.V/radio. A recording of the pet's seizure can also be invaluable to the

diagnosis process.
If the patient has had a single seizure episode lasting less than three minutes, a prudent course of action may be to observe the animal and allow the patient to recover at home. Advising the owner to update the practice of the patient's behaviour throughout the day, a short isolated episode may not require medical intervention initially as it is unlikely that leaving such seizures untreated affects the progression of epilepsy.
Some animals will resume normal activity within minutes of an epileptic seizure, while others may take hours, with some being disoriented or confused for up to 24 hours post-episode. For this reason, it is important not to transport a recovered patient too soon for a physical exam and diagnostic tests, as unduly stressing the patient so soon after an episode could potentially exacerbate the condition. The practitioners will advise on a suitable time for examination possibly hours later and when the surgery is quieter in order to reduce patient stress further.

If the patient has a history of epilepsy and is currently receiving anti-convulsive medication, and has been prescribed a valium suppository for use in the event of an epileptic seizure, the owner can be instructed to administer the valium immediately during the seizure activity and monitor closely as discussed above. It is not advised to administer benzodiazepines during post-ictal state unless another seizure occurs.

PATIENT HISTORY

- Time/length of the seizure (the seizures may appear longer than they actually are)
- Breed
- Gender
- Age
- Diet
- Vaccination status
- Prescription details
- History of epilepsy/seizures/trauma/toxins etc

Developing a practice epilepsy questionnaire can aid in diagnosis and history taking.

THE INPATIENT

Should you be faced with a scenario where the patient is experiencing prolonged SE or cluster seizures and must be admitted for treatment, the following steps will aid you in preparing for the patient's arrival and intensive care:

Quite Kennel Area

If possible prepare a kennel area where there are no other noisy barking patients, creating a quiet and environment with minimal stress is crucial. If possible, provide an area where lighting can also be dimmed during resting periods.

Plenty of Absorbent Bedding

Plenty of Vetbeds are required; seizuring patients will often lose control of the bladder and bowel during episodes, as can heavily sedated or anaesthetised patients. Heavy bedding will also prevent any injuries should the patient begin fitting whilst kennelled. As with all recumbent or anaesthetised patients, regular movement is required by turning the patient every 30-60mins and gentle massage increasing peripheral circulation will help prevent hypostatic pneumonia and decubital ulceration.

Fans to Cool the Patient

These may also be needed depending on the patient's core temperature. The seizure process can cause the core temperature to rise significantly. It may also be necessary to use cool wet towels to dampen the patient's fur. The use of ice or ice water is not advised as it will cause constriction of the blood vessels of the skin which impedes the cooling process. Do not leave wet towelling covering the patient as this will rapidly warm from the patient's increased body temperature resulting in a detrimental insulating layer further increasing the body temperature. Cooling the body too quickly will also lead to the patient shivering, thus causing the patient's core temperature to remain elevated.
It is vital to monitor patient temperature regularly, as once the seizure activity is controlled, the patient can rapidly become hypothermic.

FIRST AID TREATMENT

Equipment

Prepare the following equipment for arrival, having everything at hand will ensure speedy treatment and increase positive patient outcome.

- Clippers – for aseptic IV prep
- Skin prep solution
- Intravenous catheters of appropriate size – vital to maintain constant IV access
- Zinc tape/adhesive tape to secure and maintain catheter placement.
- DugSoft – comfort and padding of IV catheter
- Cohesive Bandaging – secure IV access and administration lines
- Blood collecting tubes – Lithium Heparin, plain tubes, EDTA, capillary tubes.
- Glucometer (AlphaTrak)
- T-piece injection port (optional) – allows ease of IV access without disturbing IV Cannula
- IV giving set – fluids & CRI administration
- IV extension set – provide extra line to maintain IV patency during excessive movement.
- Thermometer – monitor CBT
- Pen torch – monitor PLR

Emergency Medication

- Benzodiazepines – (Diazepam/Midazolam), – Anticonvulsant
- Rectal Diazepam (Stesolid®) – Anticonvulsant often used initially due to ease of access
- Phenobarbital (Phenoleptil®), AED (anti-epileptic drug)
- KBr - Potassium Bromide – (Libromide®), AED

- IV Fluids – for maintenance & replacement fluids, correction of metabolic imbalances
- IV Propofol (Propoflo®) – used for management of prolonged/cluster seizures with CRI.

Diazepam

Rectal +/- Intravenous, IM administration of 0.5mg – 1mg/kg up to maximum of 20mg and can be repeated to effect or twice within two hours. After which, should control not be achieved, alternative drug therapy is required. An initial higher dose of rectal diazepam of 2mg/kg may be required for patients receiving long-term phenobarbital therapy. Midazolam can also be used in place of Diazepam at a dose of 0.066-0.3mg/kg IM or IV.

Phenobarbital

Loading doses can be administered shortly for treatment of SE or shortly following SE or cluster episodes in order to rapidly raise the serum concentrations.

- Step 1. Administer 3 mg/kg intravenously every 30 minutes until a total dose of up to 20 mg/kg has been given.
- Step 2. Reduce the dose to 3 mg/kg intravenously every six hours for 24 hours.
- Step 3. Reduce the dose to 2.5mg – 3mg/kg orally twice daily for continued long-term use (Phenoleptil®).

Note: animals will be very sedated during this time and will need to be hospitalised, with fluid and oxygen therapy support.

Potassium Bromide: Should there be concerns of hepatic, function, potassium bromide can be used as a first line treatment as the drug is renally excreted.

- Animals can be loaded over five days, with the drug being given orally at a dose of 125mg/kg/day orally (divided am and pm), and then 20mg/kg twice daily (Libromide®); or,
- Animals can be loaded over one day, but this requires hospitalisation. In this case, the dose is given orally at a dose of 100mg/kg, every six hours for 24 hours.

In refractory/resistant SE cases more aggressive treatment such as continuous rate infusions are required, with caution. Ongoing monitoring of the cardiovascular and respiratory system is critical due to the depressive side-effects caused by CRI administration. Intensive care support will be required, including airway maintenance, oxygen supplementation and fluid therapy maintaining hemodynamic support.

Propofol: Has barbiturate and benzodiazepine-like effects and can be administered as a bolus by incremental doses to effect, starting at 1.0mg/kg bodyweight to 6mg/kg.
CRI: for ongoing maintenance, a CRI rate of 0.1mg/kg/min (to 0.6mg/kg/min) can be provided up to a max of 48hrs can be administered.

Diazepam CRI: Dosages of 0.1 – 2.0mg/kg/hr diluted in 0.9% saline and reduced by 50% every 4 to 6 hours, twice before discontinuing (dosages according to Stabile and De Risio (2011, (2012) Chandler K (2011)).
IV Fluids: Appropriate IV Fluids will be determined by the nature of the patient's condition, diagnostics and metabolic imbalances. Discussion of appropriate fluid therapy protocols is not in the remit of this article, however the following fluids maybe required:

- Hypertonic solution in the event of cerebral oedema
- Bicarbonate solution or Compound Sodium Lactate in the event of metabolic acidosis.
- 0.9% Sodium Chloride in the event of fluid losses, toxins etc.

DIAGNOSTICS

According to Stabile and De Risio (2010), diagnosis is often one of exclusion and comprises a full clinical history, neurological exam, normal inter-ictal period and breed predisposition. The following diagnostic tools play significant roles in the exclusion process:

- Neurological exam

Assess the patient for normal or abnormal neurological behaviour in the inter-ictal period. Assess mental status, gait, postural reactions and vision. Facial sensation - are the signs symmetrical or asymmetrical? Also, are there signs of underlying systemic disease?

- Biochemistry & electrolytes

Complete blood work should be performed prior to AED administration to achieve a base line and should be performed on all seizuring patients. It is common for patients on long-term phenobarbital drug therapy to have elevations in the liver enzymes, particularly alkaline phosphatase. This is not a useful indicator for liver dysfunction in isolation, instead measuring pre- and post-prandial bile acids in combination is advisable.
Blood glucose levels must me monitored closely in siezuring and anorectic patients, particularly in suspected cases of insulinoma or diabetic patients.
BUN and creatinine kidney parameters are important in suspected toxin or renal insufficiency cases.
Electrolyte disturbances are common in seizuring animals, whether the seizure is intra or extra-cranial in nature. Therefore, measurement and monitoring of electrolytes such as Sodium, Potassium, acid-base, etc is important for successful treatment.

- Urinalysis

Urinalysis in conjunction with biochemistry findings will help determine renal function by analysing urine, specific gravity, or the abnormal presence of proteins, ketones or glucose.

- Haematology and Serology

Serology is particularly useful in suspected cases of infection. Thyroid function – haematology should be

performed to determine RBC, WBC, platelets, PCV and total protein levels. Measurements of drug serum concentrations are needed in patients currently undergoing AED therapy.

- Radiography/Ultrasound

A study of the abdomen and thorax to identify any primary neoplasia with possible secondary metastasis to the brain or metastatic neoplasia. Abdominal ultrasound can also aid investigation of metabolic disorders (such as insulinoma or portosystemic shunt) causing seizures.

- MRI/CT

MRI to investigate the brain parenchyma should be considered in cases with no extra-cranial cause and is often primarily used in non-responsive cases. It is an excellent tool in intra-cranial diagnostics.

- CSF

CSF analysis is required for cases such as CNS disease, i.e. inflammatory immune-mediated or infectious disease, and should be performed after MRI, as CSF tap is potentially dangerous in cases with increased intra-cranial pressure.

- EEG

Electroencephalography is the recording of spontaneous electrical potentials generated by neurons in the cerebral cortex and can reveal abnormal firing neurons.

DIFFERENTIAL DIAGNOSIS

Intra-cranial:

(Functional Epilepsy)

- Idiopathic

(Structural Epilepsy)

- Cerebrovascular disease
- Neoplasia i.e. brain lesion, meningiomas
- CNS disease, i.e. immune-mediated encephalitis, granulomatous meningoencephalitis (GME)
- Infectious CNS disease, i.e. FIP, toxoplasmosis, FeLV/FIV, cryptococcus, distemper, neosporosis
- Head trauma
- Congenital, i.e. hydrocephalus

Extra-cranial:

- Toxin, i.e. Carbamates, organophosphates, lead poisoning, ethylene glycol, methaldehyde or strychnine etc.
- Hepatopathy, i.e. Hepatic encephalopathy, porto-systemic shunt (PSS), liver failure. Hepatic encephalopathy secondary to a porto-systemic shunt (PSS) is the most common extra-cranial cause of seizures in young cats.
- Renal disease
- Endocrine, i.e. Hypoglycaemia or Insulinoma
- Metabolic, i.e. Hypocalcaemia, Hyponatraemia or Thiamine deficiency.

Long-Term Management of the Epileptic patient

Depending on the patient status and quality of life, the practitioner will decide on the best course of treatment with the client. Some idiopathic cases will only experience mild, short and intermittent episodes which will not always warrant pharmaceutical treatment as the quality of life is not affected greatly and the AED side-effects pose a greater risk to the animal's long-term health.

Client Education and Compliance

It is crucial that the owner is fully aware of the pet's condition, treatment options and AED side-effects. More importantly, the owner must be fully compliant with the animal's treatment regime, as abruptly stopping treatment can have serious detrimental effects. The aims of anti-epileptic treatment must be discussed and understood as follows:

- To minimise the activity frequency and severity (it is not a cure)
- The potential short and long-term AED side-effects
- Importance of regular health checks, blood tests and costs
- Necessity for regular daily drug administration (same time daily)
- Possibility of SE, home treatment (rectal diazepam) and emergency veterinary care

Pharmaceuticals

Now that you have a blood work base line, the practitioner can establish the most appropriate medication.

Phenobarbital (Phenoleptil®) is usually the first line of treatment for epilepsy and up to 96% is absorbed within two hours post-oral administration, with maximum plasma level concentration reached within four to eight hours in dogs. It takes seven to 14 days to reach a steady state because the elimination half-life is approximately 40 to 90 hours in dogs and 34 to 50 hours in cats. This means that the drug may not start to be effective until that point.
A dose of 2.5-3mg/kg twice daily is sufficient to achieve a therapeutic serum concentration in the majority of dogs and 1.5-2.5mg/kg BID in cats.

KBr (Libromide®) is another first line treatment for epilepsy, particularly if hepatic disease is present as it is renally excreted or if the patient is refractory to Phenobarbital. It is often used in conjunction with other AED for multimodal therapy and it is contraindicated in Hypoadrenocorticism. Most commonly, KBr is used in cases refractory to Phenobarbital and should not be added in to therapy until the Phenobarbital serum concentrations are 25-35µg/ml. KBr has a very long elimination half-life (around 24 days in dogs and 11 days in cats). When changing the dose in order to alter the serum concentration, it can take around three to six months in dogs and six weeks in cats to reach a steady state.
A dose rate of 20 mg/kg twice daily when used as a first-line drug with a dose of 15 mg/kg twice daily when used with Phenobarbital. It should be given with food to avoid vomiting. Renal insufficiency decreases bromide elimination. Therefore, initial dosage should be halved in these cases and monitored closely for toxicity.

(Dosages according to Stabile and De Risio (2011, (2012) Chandler K (2011))

SIDE–EFFECTS

Phenobarbital:
- Sedation, polyuria, polydipsia and polyphagia
- Ataxia and paresis
- Hyperexcitability and aggression
- Neutropenia, lymphopenia and anaemia
- Hepatotoxicity
- Metabolic tolerance

KBr:
- Vomiting
- Ataxia and paresis
- Polyuria, polyphagia and polydipsia
- Acute pancreatitis
- Megaoesophagus
- Worsening of pruritus in atopic patients

MONITORING

Phenobarbital:
Serum concentrations should be checked seven to 14 days after starting therapy or changing the dose. The therapeutic range is 15 to 45 µg/ml, however many dogs need a serum concentration at least 25mg/ml to respond according to Chandler K (2011).
Blood work should be measured every three to six months as a matter of routine and a sample taken at the time of typical seizure activity is advised, if possible.
Dogs with serum concentrations consistently above 35 µg/ml are at risk of hepatic failure. Therefore, if 25 to 35 µg/ml is insufficient to cause acceptable seizure control, a second drug, such as KBr should be added, according to Chandler K (2011). If liver dysfunction is suspected, bile acids should be performed every six to 12 months.

KBr:
Serum concentration should be measured at one month and three months to gauge if the animal is on approximately the right dose. The therapeutic range is 1000 to 3000 µg/ml and timing of sampling is not important according to Chandler K (2011). Renal parameters should also be measured routinely.

REFRACTORY CASES

Cases which do not respond to Phenobarbital and/or KBr therapy or were the first line treatment dosages need to be reduced or discontinued due to unwanted side-effects are candidates for a second line treatment regime.
In the refractory case, an additional drug therapy should only be considered when the serum concentration of Phenobarbital and/or potassium bromide are at the high ends of the recommended ranges in order to really classify them as resistant to Phenobarbital and/or Potassium Bromide.

The following AED can be added as 2nd line treatment:
- Levetiracetam: Add on 10-20mg/kg, three or four times daily in cats and dogs
- Gabapentin: Add on 10-20mg/kg in dogs and 5 to 10mg/kg in cats, three times daily
- Pregabalin: Add on 3-4mg/kg, two/three times daily in dogs
- Zonisamide: Add on 10mg/kg, twice daily in dogs and 5-10mg/kg once daily in cats.

(Dosages according to Stabile and De Risio (2011, (2012) Chandler K (2011)).

DIET

Protein: In the case of PSS, reduce the production and absorption of seizure-inducing substances such as amino acids, ammonia and short chain fatty acids by providing a low protein diet and the addition of Lactulose.
Thiamine: deficiencies can be seen in cats with high dietary levels of Thiaminase from exclusive fresh fish diets.
Sodium: a sudden change in salt content in the diet may affect Potassium Bromide excretion. If a high salt diet is introduced Potassium Bromide elimination will increase, serum concentrations may drop and breakthrough seizures may occur. Drinking excessive sea water may have a similar effect. Equally, a decrease in sodium intake can lead to an increase in serum concentrations leading to toxicity.

CAVM

Complimentary and alternative medicine alongside pharmaceuticals can have benefits in the treatment and management of epilepsy, with specific supplements designed for the epileptic patient.

As well as adding a complete vitamin and mineral supplement to the diet, including EFA to help support the central nervous system, Valerian root is reported to have beneficial effects in epileptic cases.

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Reader Questions and Answers

1. WHAT IS THE MOST COMMON TYPE OF SEIZURE IN CATS?
(a) Generalised Seizures
(b) Structural Seizures
(c) Focal Seizures
(d) Functional Seizures

2. DEFINE THE TERM 'STATUS EPILEPTICUS'
(a) Seizure duration of 10 minutes
(b) Seizure duration of 15 minutes
(c) Multiple seizures of short duration within a 12-hour period
(d) Seizure duration of 5 minutes or longer

3. WHAT ANTICONVULSANT DOSAGE OF DIAZEPAM CAN BE ADMINISTERED IV AS A FIRST LINE OF TREATMENT DURING STATUS EPILEPTICUS?
(a) 0.2mg/kg – 0.5mg/kg
(b) 0.5mg/kg – 1mg/kg
(c) 1mg/kg – 2mg/kg
(d) 2mg/kg – 3mg/kg

4. WHICH ANTI-EPILEPTIC DRUG IS EXCRETED RENALLY AND SHOULD THEREFORE BE MONITORED VERY CLOSELY IN PATIENTS WITH RENAL INSUFFICIENCY?
(a) Phenobarbital
(b) Potassium Bromide
(c) Pregabalin
(d) Levetiracetam

5. PATIENTS RECEIVING LONG-TERM PHENOBARBITAL THERAPY SHOULD HAVE ROUTINE BIOCHEMISTRY SAMPLING EVERY THREE TO SIX MONTHS. WHAT CONSISTENT SERUM CONCENTRATION LEVELS COULD POTENTIALLY CAUSE HEPATIC FAILURE?
(a) 5 - 10 μg/ml
(b) 10 - 20 μg/ml
(c) 25 - 30 μg/ml
(d) >35 μg/ml

ANSWERS: 1. C, 2. D, 3. B, 4. B, 5. D.