

## Drug choice and therapeutic drug monitoring in the management of canine primary epilepsy

T Vaughan-Scott<sup>a,c</sup> and J H Taylor<sup>b,d</sup>

### ABSTRACT

Therapeutic drug monitoring is an underutilised resource in the management of canine primary epilepsy. Many of the anti-epileptic drugs, including phenobarbitone, have variable pharmacokinetic profiles in different dogs, with each individual animal showing variable rates of absorption, distribution, metabolism and excretion. This results in variable serum drug concentrations with the same oral dose. Many clinicians interpret this situation as therapeutic failure and classify these patients as refractory to treatment. By measuring blood concentrations of drugs at appropriate times, it is possible to explain the efficacy or failure of treatment, and also to prevent serum concentrations from reaching toxic levels. By analysing paired samples, key pharmacokinetic parameters may be calculated for each patient and a profile for the disposition of the drug obtained. Individual optimal drug dosage can be calculated for each patient at little cost to the pet owner.

**Key words:** canine, drug choice, epilepsy, therapeutic drug monitoring, treatment.

Vaughan-Scott T, Taylor J H **Drug choice and therapeutic drug monitoring in the management of canine primary epilepsy.** *Journal of the South African Veterinary Association* (1999) 70(4): 172–176 (En.). Department of Medicine, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

### INTRODUCTION TO EPILEPSY

#### Terminology

Seizures are the clinical manifestation of a cerebral dysfunction that can have extra-cranial or intra-cranial origins<sup>20</sup>. The terminology used to describe seizures can be confusing, especially the term epilepsy. The term epilepsy has been used to describe recurrent seizures of any cause<sup>20</sup>. For the purposes of this article, primary epilepsy is defined as an imbalance in excitatory and inhibitory neurotransmission with no discernible underlying disease. This is synonymous with cryptogenic, idiopathic, true, genetic or inherited epilepsy<sup>20</sup>. It is essential to exclude other causes of seizures before diagnosing primary epilepsy. A general approach to the diagnosis of seizure disorders in dogs has been well described elsewhere<sup>13,18,19</sup>.

#### Mechanism of primary epilepsy

Epileptic seizures are thought to arise from a group or groups of neurons with an increase in cell membrane excitability

or an imbalance of inhibitory and excitatory neurotransmitters<sup>7</sup>. These defects are currently thought to be hereditary, which accounts for the higher incidence of epilepsy in certain breeds<sup>20,21</sup>. The net result is an imbalance in ionic currents across the affected cell membrane, which spontaneously shifts the cell towards threshold and triggers an action potential<sup>7</sup>. The action potential is propagated through neighbouring neurons and, depending on the locality and extent of the discharge, various clinical signs can result<sup>21</sup>. Recurrent uncontrolled seizures can result in neuronal degeneration and a wide range of clinical consequences<sup>13</sup>. Common consequences in human epileptics are behavioural changes such as psychosis, depression and personality disorders.

#### Kindling and mirror foci

It has been found in experimental models that if epileptogenic discharges are not controlled they can result in 2 important consequences – kindling and mirror foci<sup>7,10</sup>. Kindling is a process whereby abnormal neurons recruit normal neurons into the seizure focus and cause these neurons to become epileptogenic. Abnormal neuron activity can cause kindling even if there are no clinically evident seizures. This can result in independent additional seizure foci and a worsening in the clinical condition and prognosis<sup>7,10</sup>. It has also been found that

an epileptic focus can cause development of a focus on the opposite side of the brain in previously normal neurons. This new contra-lateral lesion is known as a mirror focus. Both kindling and a mirror focus result in additional areas of epileptic neurons. The importance of kindling and mirror foci in epileptic dogs is unknown but until further evidence is available they should be considered as possible causes of deterioration<sup>9</sup>. Both concepts have been challenged in human epileptics, as they have been created experimentally in laboratory animals but not proven clinically in humans<sup>10</sup>. However, epileptic dogs should be treated as soon as possible, as development of additional seizure foci can be prevented by treatment<sup>7,10,20</sup>.

#### Seizure classification

Epileptic seizures are classified as partial, generalised, or partial with secondary generalisation<sup>15,20</sup>.

Generalised seizures result when neurons on both sides of the brain discharge simultaneously to produce symmetrical involvement of the body<sup>13</sup>. The seizure can be triggered initially by a seizure focus, which then spreads *via* the diencephalon to both sides of the brain. This usually causes a tonic (limb extension), clonic (paddling) type of seizure.

Dogs with primary epilepsy most commonly show generalised symmetrical seizures<sup>21</sup>. However, this does not imply that all dogs with generalised seizures have primary epilepsy. Generalised seizures are the most common type of seizures seen in small animal practice and have a wide variety of causes<sup>15</sup>. These seizures can be life-threatening if they occur close together and the patient does not regain consciousness – a condition known as *status epilepticus*<sup>6</sup>. Seizure episodes can be extremely disturbing for the owner and can result in elective euthanasia.

Partial seizures result from a neuronal discharge in a focal area of the cerebral cortex<sup>20</sup>. The clinical signs are dependent on the area involved. Examples of this type of seizure are: muscle jerking, behaviour abnormalities, vomiting, diarrhoea, 'fly biting' and 'star gazing'. Partial seizures usually result from focal or

<sup>a</sup>Department of Medicine, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

<sup>b</sup>Department of Pharmacology and Toxicology, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

<sup>c</sup>Present address: PO Box 22151, Fish Hoek, Cape Town, 7974 South Africa. E-mail: tvs@yebo.co.za

<sup>d</sup>Present address: Animal Health Services Centre, Massey University, Palmerston North, New Zealand.

Received: January 1998. Accepted: October 1999.

multifocal cerebral lesions caused by conditions such as trauma, encephalitis, ischaemia or neoplasia<sup>13,20</sup>.

Partial seizures can spread and result in secondary generalised seizures. The subtle signs of the partial seizure can be missed and result in classification as a generalised seizure.

### Patient management

Pharmacological management of epileptic patients is aimed at controlling seizures and slowing down progression of the disease, resulting in an acceptable pet. There is also a possibility that early treatment can inhibit the process of kindling, the development of mirror foci and neuronal degeneration<sup>7,13,20</sup>.

A small percentage of epileptic cases may prove difficult to control, and many are prematurely classified as refractory to treatment<sup>9</sup>. This may result in the irrational use of multiple anti-epileptic drug combinations, or even unnecessary euthanasia. An epileptic patient should only be classified as resistant to therapy after therapeutic drug monitoring has been undertaken and rational alternative additional treatment has been considered<sup>9</sup>. It must be emphasised that appropriate clinical and laboratory investigations should be completed to rule out other causes of seizures in these cases.

### WHEN TO START ANTICONVULSANT THERAPY

In human patients, anticonvulsant therapy is started early, as it has been found that a delay in treatment worsens the long-term prognosis<sup>12,13</sup>. No similar studies have been performed in dogs. The following is a recommended guide for veterinary patients and treatment should be initiated when one of the following criteria have been met<sup>5,10,12,13</sup>:

1. More than 1 seizure every 6 weeks.
2. More than 1 seizure within a 24-hour period (cluster seizures).
3. *Status epilepticus*.

It is essential to evaluate the haematology and serum chemistry profile before beginning therapy, as these results can be used as a baseline for follow-up evaluations<sup>12</sup>.

### THERAPEUTIC GOALS AND CLIENT EXPECTATIONS

Before initiating treatment, the veterinarian must give the dog owner a realistic expectation of the results of therapy. The ideal goal of therapy is to maintain the patient completely seizure-free with minimal drug side-effects. However, this can only be achieved in about 50 % of cases<sup>13</sup>. Seizure control does not always equal seizure elimination. Realistic treat-

Table 1: Elimination half-lives and dosages of anticonvulsant drugs used in dogs.

Drug	Elimination half-life	Dose
Phenobarbitone	42–89 hours <sup>12</sup>	2–4 mg/kg p/o bid <sup>2,12</sup>
Potassium bromide	24 days <sup>13</sup>	10 mg/kg p/o bid <sup>13</sup>
Primidone	5–10 hours <sup>4</sup>	5–10 mg/kg p/o bid <sup>4</sup>
Clonazepam	Dose-dependent <sup>4</sup>	0.5 mg/kg p/o tid <sup>4</sup>
Chlorazepate	5 hours <sup>4</sup>	2 mg/kg p/o bid <sup>4</sup>
Valproic acid	1.5–2 hours <sup>4</sup>	10–60 mg/kg p/o tid <sup>4</sup>
Diazepam	1–2 hours <sup>7</sup>	Not applicable
Carbamezapine	1–2 hours <sup>4</sup>	40 mg/kg p/o tid <sup>4</sup>

p/o = *per os*; bid = twice per day; tid = 3 times per day.

ment goals are to decrease the number of seizures and to minimise pre- and post-seizure complications<sup>13</sup>. Clients must be informed that treatment will be lifelong and will probably require administration at least twice a day. Some of the drugs used may have side-effects that cause clinical signs not previously observed in these dogs. Frequent patient evaluations are also essential. Some dogs may still have life-threatening seizure episodes that require emergency therapy. Good client communication will prevent future vet/owner relationships from deteriorating and will ensure continuity in patient treatment and evaluation.

### BASIC PRINCIPLES OF DRUG SELECTION

When selecting an anticonvulsant drug, the veterinarian should consider the following:

1. Has the drug been shown to be beneficial for the treatment of epilepsy in dogs?
2. Do the drug's pharmacokinetics suit the patient in question?
3. Is the drug safe and cost-effective?
4. Can serum concentrations be measured if necessary?

Very few medicines meet these criteria for the treatment of primary epilepsy in dogs<sup>13</sup>. A large number of drugs are available for the treatment of epilepsy in humans, but most of these are ineffective in dogs owing to an unfavourable pharmacokinetic profile. It is the authors' experience that many human drugs are erroneously used owing to pressure being placed on the veterinarian by the client. Dogs metabolise many of these drugs at a very rapid rate, resulting in a very short half-life<sup>5</sup> (Table 1). This makes dosage frequencies unacceptably short and impractical for most pet owners. Certain of the drugs listed in fact have such a short half-life in the dog as to indicate administration by continuous rate infusion. The clinician must be extremely cautious in extrapolating human data to the canine patient, as many human drugs are not effective. Only drugs with proven

efficacy or known pharmacokinetics in the dog should be used.

### DRUG SELECTION IN THE MEDICAL MANAGEMENT OF CANINE PRIMARY EPILEPSY

At present 2 drugs are considered the mainstay of treatment for canine primary epilepsy: phenobarbitone and potassium bromide<sup>3,5,8,12,13</sup>.

#### Phenobarbitone

First synthesised in 1912, phenobarbitone remains the initial drug of choice for the treatment of canine primary epilepsy<sup>13</sup>. It is extremely cheap and its efficacy is proven<sup>5,8</sup>. Its exact mechanism of action is unknown, but some of its effects are mediated mainly *via* the gamma-aminobutyric acid (GABA) membrane receptor. The net result of its action is hyperpolarisation of the neuronal cell membrane, which renders the cell more resistant to the effects of excitatory neurotransmitters<sup>13</sup>.

Phenobarbitone has a favourable pharmacokinetic profile in dogs, with a high oral bioavailability (86–96 %) and a long elimination half-life that ranges between 42 and 89 hours<sup>8,13</sup>. After oral administration the drug is rapidly absorbed, within 2 hours, and reaches maximal serum concentration at 4–8 hours<sup>8,12,13</sup>. It is a potent inducer of hepatic microsomal enzymes, which speeds up its own rate of clearance over time. This often necessitates an increase in dosage.

Common side-effects of phenobarbitone administration include lethargy, sedation, polydipsia, polyphagia and behavioural changes<sup>13</sup>. Many of these side-effects are transient and resolve 1–2 weeks after initiation of treatment<sup>5,8</sup>. It has recently been reported that some dogs may show an idiosyncratic bone marrow reaction characterised by neutropaenia, thrombocytopenia and anaemia<sup>1</sup>. Hepatotoxicity is a serious complication that can occur in some dogs<sup>4</sup>. The diagnosis of hepatotoxicity in patients on phenobarbitone is not easy and cannot depend on a single test<sup>4</sup>. Almost all dogs treated

with phenobarbitone will show an increase in serum alkaline phosphatase activity. This is due to enzyme induction and does not necessarily reflect hepatotoxicity. Eighty-three percent of dogs with phenobarbitone-induced hepatotoxicity showed a concurrent increase in serum alanine transaminase that was disproportionately high when compared to the increase in alkaline phosphatase<sup>4</sup>. Sixty-seven percent of these dogs were hypoalbuminaemic and in 44 % preprandial bile acids were elevated<sup>4</sup>. A diagnosis of hepatotoxicity should be based on liver function tests (e.g. serum bile acids) rather than on raised liver enzymes<sup>1</sup>.

It is interesting to note that in 67 % of dogs in the study, serum trough concentrations of phenobarbitone were above the currently recommended therapeutic range. This may have been due to drug overdosing or decreased hepatic clearance. Therapeutic monitoring could have prevented hepatotoxicity in many of these dogs.

Phenobarbitone treatment should never be withdrawn suddenly in any patient, as this can precipitate severe withdrawal seizures<sup>12,13</sup>. If the drug must be withdrawn, it should be done gradually. The recommended initial dose of phenobarbitone is 2–4 mg/kg twice a day<sup>5,13</sup>. The dose and frequency of administration may have to be increased or decreased according to the results of therapeutic monitoring.

### Potassium bromide

The use of potassium bromide to treat canine epilepsy dates back to the early 1900s<sup>14</sup>. In recent years, interest has centred on the use of potassium bromide together with phenobarbitone in cases that are refractory to phenobarbitone alone<sup>14</sup>. Therefore the main indications for the use of potassium bromide are lack of (or poor) response to phenobarbitone alone or the occurrence of severe adverse effects of phenobarbitone<sup>14,17</sup>.

Potassium bromide therapy is added to the phenobarbitone treatment; it does not replace phenobarbitone.

Bromide's mechanism of action is related to its effects on the post-synaptic chloride channels that are activated by GABA receptors<sup>14</sup>. Bromide is a small molecule and competes with chloride at these channels. The net result is preferential movement of bromide through the receptor, which hyperpolarises the cell membrane. This results in a cell more resistant to excitatory stimuli.

The pharmacokinetics of potassium bromide have been studied in the dog<sup>14</sup>. The drug is well absorbed orally with peak serum concentrations occurring at

90 minutes. Almost all bromide is excreted renally and it has an extremely long half-life of approximately 24 days<sup>14</sup>. A high salt diet will result in greater renal elimination of potassium bromide and can result in treatment failure<sup>17</sup>. An example of this type of diet is a urinary calculolytic diet.

When the serum concentrations of potassium bromide exceed the therapeutic range, toxicity known as bromism can result. Clinical signs of bromism include disorientation, loss of conscious proprioception, hind limb weakness, muscle pain, ataxia, stupor and coma<sup>13,21</sup>.

Potassium bromide is not available as a medicine and the chemical grade of the inorganic salt is used. The drug is not registered for use in dogs and its use is therefore extra-label. The clinician must ensure that these facts are discussed with the owner and the owner is aware of all possible side-effects that the drug may cause.

The chemical grade salt is made up to a solution of 200 mg/ml with double distilled water<sup>3,13</sup>. We have also added cherry-flavoured syrup to the solution to increase the palatability; this has not affected efficacy. The solution is then given at a dose of 10 mg/kg twice a day with food<sup>13,14</sup>. Some authors recommend using the drug at 20 mg/kg once a day<sup>3</sup>. The dose should then be adjusted according to therapeutic monitoring.

### WHY PERFORM THERAPEUTIC DRUG MONITORING?

Therapeutic drug monitoring has become an important tool for the individualisation of drug dosages. By measuring serum drug concentrations at appropriate times, the optimal dosage and frequency of drug administration can be calculated. Monitoring also prevents serum concentrations from reaching toxic concentrations. From a clinical perspective it can inform the clinician whether treatment failure is due to inappropriate drug dosages or due to incorrect drug choice.

Therapeutic monitoring is especially useful in the following circumstances<sup>11</sup>:

1. Drug has a narrow therapeutic range.
2. To determine therapeutically effective concentrations.
3. To confirm or prevent toxicity.
4. Poor relationship between dose and serum concentrations.
5. Lack of a therapeutic effect.
6. To determine owner compliance with treatment.

All of these factors are relevant in the treatment of primary epilepsy with phenobarbitone and potassium bromide. Point 4 is especially applicable to pheno-

barbitone treatment. It has been found that the oral dose of phenobarbitone has a poor relationship to serum concentrations in dogs<sup>12</sup>. In our experience only 46 % of dogs being treated with appropriate doses of phenobarbitone have serum drug concentrations within the therapeutic range. This demonstrates the varying bioavailability of the drug amongst individuals. Treatment with the correct dose does not always ensure adequate blood concentrations.

To understand when to perform therapeutic monitoring, a few basic pharmacokinetic principles must be considered. The first is the elimination half-life of a drug. This is the time taken to reduce the drug concentration in serum by half. With a drug that is rapidly metabolised and eliminated, the half-life will be short. A good example is diazepam, which has an elimination half-life of 2–4 hours in the dog<sup>8</sup>. Phenobarbitone, however, is slowly metabolised and excreted in the dog, and therefore has a long half-life of 42–89 hours.

The second concept is the steady state. When a drug is repeatedly given to a dog at a frequency that closely approximates its half-life, the serum concentrations will gradually increase, as the rate of administration will initially be greater than the rate of excretion<sup>16</sup>. Eventually the rate of drug administration and drug excretion reach an equilibrium, which is known as the steady state. Before steady state is reached, serum drug concentrations undergo wide variations.

The serum concentration of the drug at steady state is determined by the dose and frequency of the drug administered, and the time required to reach steady state is determined by the drug's half-life. A practical guideline is that steady state is achieved after approximately 5 half-lives<sup>11</sup>. Serum concentrations of the drug do not remain absolutely constant at steady state. Soon after drug administration, concentrations will reach a peak, and just before the next dose, the concentrations will drop to a trough. As long as the peak concentrations achieved after dosing are not toxic, and as long as the trough concentrations are not so low as to be ineffective, fluctuations in serum concentration are not detrimental.

### GUIDELINES FOR THERAPEUTIC MONITORING OF PHENOBARBITONE AND POTASSIUM BROMIDE

#### The importance of reaching steady state before sampling

For reasons given above, it is obvious that measuring serum concentrations of an anti-epileptic drug before the steady-

Table 2: Guidelines for therapeutic monitoring of phenobarbitone and potassium bromide.

Drug	Time to steady state	Monitoring intervals	Peak serum concentration <sup>b</sup>	Therapeutic serum concentration
Phenobarbitone	15 days <sup>10</sup>	15, 45, 90, 180, 360 days <sup>a</sup> and then every 6 months <sup>12</sup>	4–8 hours <sup>7,11,12</sup>	20–40 µg/ml <sup>4,7,9,12</sup>
Potassium bromide	150 days <sup>13</sup>	30, 120 days <sup>a</sup> and then every 6 months <sup>13</sup>	Not applicable	0.7–2 mg/ml <sup>2,12,21</sup>

<sup>a</sup>After starting treatment.

<sup>b</sup>Time taken after oral drug administration for the drug to reach peak serum concentrations.

state plateau is reached will be both unreliable and a waste of money. Therapeutic drug monitoring should only be performed when the drug has been administered for at least 5 half-lives, and peak and trough fluctuations have become constant. Considering the half-life of phenobarbitone, monitoring should only begin 15 days after starting treatment<sup>11</sup>. Potassium bromide has a very long half-life and in theory should take 150 days to reach steady state<sup>14</sup>. However, by using statistical modelling it has been found that monitoring can begin 30 days after starting therapy<sup>14</sup>. The recommended monitoring intervals and procedures for both drugs are shown in Table 3.

### Single or paired samples

After the drug has reached steady state, the clinician must decide whether to take single or paired samples. A single sample is taken to determine trough concentrations only, whereas paired samples are used to determine trough and peak concentrations. The advantage of paired sampling cannot be overemphasised, as the half-life of the drug can be estimated from peak and trough concentrations. This allows the laboratory to recommend not only the dosage but also the frequency of administration.

Should a single sample be measured, it is important to measure the trough level, as most failures with antiepileptic drug administration occur as a result of too low trough concentrations<sup>15</sup>.

It is best to draw serum for trough level determination just before administration of the drug. For example, if the dog is on twice-a-day treatment with phenobarbitone, at 07:00 and 19:00, the sample should be drawn a few minutes before dosing at 19:00.

Should paired samples be drawn, the same example can be used. The peak sample should be drawn 4–8 hours after dosing and the trough level just before dosing at 19:00. Time of sampling must be marked accurately, as this is required to determine the serum half-life of the drug. The laboratory should also be informed of the dose administered, the mass of the dog and the dosing interval. Samples should be taken into ordinary serum

tubes, and not serum separation tubes, as these tubes can falsely reduce the phenobarbitone level<sup>2</sup>.

### Recommendations

We recommend using paired samples for phenobarbitone to calculate pharmacokinetic parameters but only trough samples for potassium bromide. The data that have been collected for potassium bromide rely mainly on trough values which will therefore permit comparison of data<sup>14</sup>.

### Therapeutic range

The therapeutic range is the range of serum drug concentration that is therapeutically effective without causing toxicity. Most of the published therapeutic ranges refer to the trough concentration only. The clinician must therefore adjust the drug dosage to achieve a trough concentration within the therapeutic range. If the concentration is below the lower limit of the therapeutic range, treatment can fail. If the concentration is above the upper limit, toxicity can result. The therapeutic range for phenobarbitone is 20–40 µg/ml<sup>5,8,10,13</sup> and for potassium bromide 0.7–2 mg/ml<sup>13</sup> (Table 2)<sup>3,22</sup>.

### Elimination half-life

The benefit of taking paired samples is to allow the laboratory to calculate the half-life of the drug in that specific patient<sup>1</sup>.

Current recommendations indicate that if the half-life is greater than 36 hours, twice-a-day administration can be used<sup>1</sup>. If the half-life is shorter than 36 hours, the same total daily dose or 15 % higher dose is divided and given 3 times per day<sup>1</sup>. This ensures that serum drug concentrations remain constant and do not fall below the therapeutic range.

### CONCLUSION

Canine primary epilepsy is a common disease in dogs<sup>15</sup>. Only 50–70 % of dogs respond well to treatment and are maintained seizure-free in the long term. Therapeutic drug monitoring is a very useful aid in the management of these cases, as it can guide the clinician towards the correct dosage regimen and also

prevent toxicity from occurring.

Collection of paired serum samples at peak and trough times allows calculation of useful pharmacokinetic data, which can be used to calculate the exact dosage requirements and dosage frequency for a particular patient. This is important, as no two patients have exactly the same pharmacokinetic profile. A good example of this phenomenon is phenobarbitone, where drug dosage concentrations have been shown to correlate poorly with serum concentrations.

We recommend using paired-sample collection (peak and trough) for the monitoring of phenobarbitone concentrations, but only trough sample collection for the monitoring of potassium bromide.

Therapeutic monitoring is indispensable in cases that appear to be refractory to treatment. A case should only be considered refractory if serum trough concentrations are at the upper limit of the reported therapeutic range and the patient is still showing clinical signs of seizures. Alternative therapies can then be attempted.

Therapeutic monitoring should be performed in all cases of primary epilepsy, as it is cost-effective and can guide rational decision-making in these often difficult cases.

### ACKNOWLEDGEMENTS

Dr L S Jacobson and Professor R J Milner are thanked for their helpful comments.

### REFERENCES

- Boothe D 1998 Anticonvulsant therapy in small animals. *Veterinary Clinics of North America: Small Animal Practice* 28: 411–449
- Boothe D, Simpson G, Foster T 1996 Effects of serum separation tubes on serum benzodiazepine and phenobarbitol concentrations in clinically normal and epileptic dogs. *American Journal of Veterinary Research* 57: 1299–1301
- Chrisman C 1995 Seizures. In Ettinger S, Feldman E (eds) *Textbook of veterinary internal medicine* (4th edn). W B Saunders, Philadelphia: 152–158
- Dayrell-Hart B, Steinberg S, Van Winkle T, Farnbach G 1991 Hepatotoxicity of phenobarbitol in dogs: 18 cases (1985–1989). *Journal of the American Veterinary Medical Association* 199: 1060–1066
- Dyer K, Shell L 1993 Anticonvulsant therapy: a practical guide to medical management of epilepsy in pets. *Veterinary*

- Medicine* 88: 647–653
6. Dyer K, Shell L 1993 Managing patients with status epilepticus. *Veterinary Medicine* 88: 654–659
  7. Fenner W, Hass J 1989 Mechanisms of seizure disorders. *Problems in Veterinary Medicine* 1: 501–515
  8. Frey H 1989 Anticonvulsant drugs used in the treatment of epilepsy. *Problems in Veterinary Medicine* 1: 558–577
  9. Hass J, Fenner W 1989 Epilepsy resistant to anticonvulsant therapy. *Problems in Veterinary Medicine* 1: 596–605
  10. Lane S, Bunch S 1990 Medical management of recurrent seizures in dogs and cats. *Journal of Veterinary Internal Medicine* 4: 26–39
  11. Neff-Davis C 1988 Therapeutic drug monitoring in veterinary medicine. *Veterinary Clinics of North America: Small Animal Practice* 18: 1287–1307
  12. Parent J 1988 Clinical management of canine seizures. *Veterinary Clinics of North America: Small Animal Practice* 18: 605–622
  13. Podell M 1996 Seizures in dogs. *Veterinary Clinics of North America: Small Animal Practice* 26: 779–809
  14. Podell M, Fenner W 1994 Use of bromide as an antiepileptic drug in dogs. *Compendium on Continuing Educating for the Practicing Veterinarian* 16: 767–773
  15. Podell M, Fenner W, Powers J 1995 Seizure classification in dogs from a nonreferral-based population. *Journal of the American Veterinary Medical Association* 206: 1721–1728
  16. Riviere J 1988 Veterinary clinical pharmacokinetics Part II. Modeling. *Compendium on Continuing Educating for the Practicing Veterinarian* 10: 314–328
  17. Shaw N, Trepanier L, Center S, Garland S 1996 High dietary chloride content associated with loss of therapeutic serum bromide concentrations in an epileptic dog. *Journal of the American Veterinary Medical Association* 208: 234–236
  18. Shell L 1993 The diagnostic approach to seizures. *Veterinary Medicine* 88: 641–646
  19. Shell L 1993 The differential diagnosis of seizures. *Veterinary Medicine* 88: 629–640
  20. Shell L 1993 Understanding the fundamentals of seizures. *Veterinary Medicine* 88: 622–628
  21. Shwartz-Porsche D 1994 Seizures. In Braund K (ed.) *Clinical syndromes in veterinary neurology* (2nd edn). Mosby, St Louis: 234–251
  22. Yohn S, Morrison W, Sharp P 1992 Bromide toxicosis (bromism) in a dog treated with potassium bromide for refractory seizures. *Journal of the American Veterinary Medical Association* 201: 468–470