Canine epilepsy: when to start and when to change treatment

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HOLGER VOLK, JACQUES PENDERIS in part two of their article (part one: *VT* 43.46) consider epilepsy types and suggest tailoring drug treatment to the individual and its underlying condition

Summary

Epilepsy, defined as recurrent seizures, is caused by a heterogeneous group of conditions. The most important step in the management of seizure disorders in dogs is to establish an accurate diagnosis prior to prescribing antiepileptic drugs. The treatment plan needs to incorporate, if possible, the treatment of the underlying condition in addition to standard antiepileptic drug treatments. Epilepsies in which an underlying disease process can be identified are usually more challenging to control. Epilepsies in which an underlying disease process cannot be identified (traditionally defined as idiopathic epilepsy) may also be difficult to manage in dogs that present with a severe seizure phenotype (such as high seizure frequency – for example, cluster seizures) or status epilepticus.

Monotherapy with one of the first choice antiepileptic drugs is successful in the majority of canine cases; however, some dogs with epilepsy that is difficult to control may require more than one standard antiepileptic drug. Consideration should also be given to tailoring the antiepileptic drug treatment regime for the individual dog and underlying condition. Decision-making on which antiepileptic drug or combination of drugs to use in an individual dog is driven not just by the efficacy of the drug (s), but also by the tolerability of the drug (s) and, in some instances, the antiepileptic drugs will need to be changed.

Key words

epilepsy, seizures, status epilepticus

A WIDE range of underlying chronic conditions may cause epilepsy, with recurrent seizures being the main clinical manifestation. While the brain is an incredibly complex structure, it is limited in the ways in which it can display its function and dysfunction, and one of the more common manifestations of forebrain dysfunction is epileptic seizures.

Whether brain dysfunction manifests as seizures is determined in part by the so-called “seizure threshold”. The seizure threshold represents a balance between excitatory and inhibitory processes in the brain and determines the brain’s vulnerability to seizure events. Each brain has a specific seizure threshold, and this can be altered by a variety of factors. The canine epilepsy patient requires a methodical, clinical reasoning approach (Figure 1) to guide the clinician to the most likely underlying disease process and, therefore, to develop an appropriate and adequate treatment plan to reduce the brain’s vulnerability to seizure events.

A seizure is defined by the International League Against Epilepsy (ILAE) as the clinical manifestation of “excessive and hypersynchronous” neuronal discharges, which are fortunately usually self-limiting. Seizures are always a sign of cerebral dysfunction, but vary in their clinical presentation depending on which part of the forebrain they originate from or affect. Seizures can be caused by primary brain disease (intracranial disease) or by brain dysfunction secondary to metabolic disease, alterations in brain perfusion or exogenous or endogenous intoxication (extracranial disease)[1].

Extracranial diseases causing epileptic seizures

Since metabolic and toxic diseases tend to have diffuse, symmetrical effects on the brain, seizures arising from these causes tend to be generalised and symmetrical in onset (Figure 1)[1]. Dogs may present with decreased levels of consciousness, central blindness (absent vision and menace responses, but with normal pupillary light reflexes) and, in more severe cases, may also demonstrate involvement of the brainstem and cerebellum.

Some extracranial conditions can present with acute and rapidly progressive clinical signs (for example, electrolyte abnormalities, exogenous intoxication), while others may have a more waxing and waning clinical course (for example, endogenous intoxication, such as that arising from a portosystemic shunt).

Standard antiepileptic drug therapy will have little efficacy against extracranial seizure disorders and it is imperative an adequate work-up is performed in all canine epilepsy cases to exclude metabolic causes. These seizures can be classified as “reactive seizures” as they can usually be controlled when the primary cause is rectified.

Where seizures arise secondary to exogenous intoxication, long-term (or chronic) antiepileptic drug

treatment is not indicated in most cases[2,3]. However, reactive seizures that continue for more than five minutes, or where the dog has cluster seizures (two or more seizure events in a day), do require treatment with an anticonvulsant in the short term as part of the emergency case management.

Intracranial diseases resulting in epilepsy

Structural forebrain lesions resulting in epileptic seizures include a large array of conditions, with those more commonly identified in clinical canine practice including infection/inflammation, neoplasms, developmental anomalies and cerebral malformations.

While these lesions may demonstrate a generalised seizure onset, in many cases there will be a focal seizure onset, often affecting one side of the animal more than the other (Figure 1)[1]. The interictal neurological examination in these animals may also describe asymmetrical neurological deficits, such as hemineglect syndrome, unilateral reduced paw positioning, asymmetrical sensation deficits and menace response deficits.

It needs to be noted seizures themselves can be the first sign of structural brain disease, especially when affecting otherwise “silent” brain areas (for example, the olfactory lobe, which cannot be easily assessed by the neurological examination).

In addition to the interictal neurological examination, the age of onset of seizures is another clinical feature that is useful in the prediction of intracranial disease as a cause of epilepsy. In one study, around a quarter of dogs older than six years of age that were presented for investigation of seizures had significant brain MRI findings, despite having a normal interictal neurological examination[4].

Interestingly, in the same study only 2.2 per cent of dogs with a seizure onset at younger than six years old and a normal interictal neurological examination had identifiable lesions on brain MRI.

Epilepsy resulting from structural forebrain disease is commonly classified as “symptomatic epilepsy”. It is important to not only manage the recurrent seizures in these cases with standard antiepileptic drugs, but to also identify and treat the underlying disease process. Symptomatic epilepsy can be more challenging to treat than other types. The standard treatments available for the management of symptomatic epilepsy include phenobarbital and potassium bromide as the first line treatments of choice.

While the new veterinary licensed antiepileptic medication, imepitoin, is not licensed for the management of symptomatic epilepsy, it may be useful if there is poor control on treatment with phenobarbital.

In general, the main intended target of our current arsenal of veterinary antiepileptic drugs is raising

the seizure threshold and, therefore, reducing the likelihood of recurrent seizures (Figure 2). These medications do not specifically treat the underlying disease process (they are not disease modifying), they do not prevent the development of epilepsy (they are not anti-epileptogenic) and they do not alter the brain's response to drugs.

One example of epileptogenesis in clinical canine practice is the development of seizures following head trauma. Head trauma has been shown to cause acute seizures and induce epileptogenesis leading to post-traumatic epilepsy in 6.6 per cent of dogs[5]. The development of post-traumatic epilepsy is thought to be due to reorganisation of neuronal circuits and changes in ion-channel expression, and these changes may occur over a protracted period of time after the trauma. Newer antiepileptic drugs may have advantages over current medications in that they could prevent epileptogenesis, thereby reducing the number of dogs developing post-traumatic epilepsy. However, there is no clinical or experimental data to suggest any of the antiepileptic drugs used in veterinary medicine prevent epileptogenesis.

Apart from symptomatic epilepsy, recurrent seizures associated with primary brain disease can also be categorised into "idiopathic" or "cryptogenic" (probably symptomatic) epilepsy. The term cryptogenic epilepsy is a descriptive term used for epilepsies where an underlying disease process is suspected, but cannot be identified with the diagnostic tool set that is currently available. Cryptogenic epilepsy is suspected in dogs that have neurological deficits or asymmetrical seizures without detectable pathology (Figure 1).

The term "idiopathic" epilepsy has traditionally been used in veterinary medicine to describe the population of epileptic dogs without interictal neurological deficits and without abnormalities on routine diagnostic tests (Figure 1). Epilepsies without an identifiable cause have a prevalence of 0.6 per cent in first opinion practice[6].

However, many individual breeds have an estimated prevalence higher than 0.6 per cent (up to 33 per cent) and it was therefore proposed a high proportion of these dogs defined as idiopathic epilepsy might have epilepsies caused by genetic defects7. A benign "childhood" epilepsy has been described in the Lagotto Romagnolo dog, which is caused by a truncating mutation in the LG12 gene, causing a dysfunction in brain maturation[8,9]. These dogs "grow out" of their epilepsy after the first couple of months of age as an alternative gene takes over the brain maturation process. Interestingly, a single nucleotide polymorphism was found in the ADAM23 gene, which interacts with LG11 and LG12 in the Belgian shepherd dog[10]. Other canine epileptic syndromes that have been associated with genetic defects include Lafora's disease (EPM2B gene) and neuronal ceroid lipofuscinoses, which also cause visible brain pathology[7,11].

In the past 10 years, many research groups have worked on the identification of genetic mutations in canine epilepsy, but progress has been disappointingly slow. It is thought, as in human medicine, that canine epilepsy is caused by a complex interaction of multiple genetic mutations and the environment[7].

When to start treatment for idiopathic epilepsy

Even if pathology cannot be identified on the extracranial and intracranial investigation, a variety of pathological mechanisms are probably involved for the animal to develop epileptic seizures. In general, it is believed epilepsy is a chronic disease process and that antiepileptic drugs will modify the seizure threshold, but not the disease itself.

Risk factors for epilepsy are an important component of the clinical decisionmaking process – the risk factors determine when and with which drug to initiate treatment. Unfortunately, risk factors for developing epilepsy are not well established in veterinary medicine. In contrast, several drug treatment guidelines have been established in human medicine based on reduction of seizure frequency and also on reducing morbidity, mortality and seizure severity, to improve quality of life, reduce negative social impacts and minimise adverse effects.

An increase in antiepileptic drug dose is mainly restricted by the adverse effects of the drug. More recently, the development of new antiepileptic drugs has focused to a greater extent on improving tolerability, with the hope that improved tolerability will allow higher drug doses and improved efficacy.

When to start chronic treatment for idiopathic epilepsy

While any guide to treatment is a matter of opinion, there is increasing evidence to suggest early instigation of treatment in canine epilepsy is beneficial for patient and owner quality of life. There are also clinical scenarios, particularly those associated with severe seizures or seizure-related adverse effects, where current seizure frequency is less important in deciding whether to start treatment. The authors believe treatment should be initiated in the following situations:

• status epilepticus;

• cluster seizures;

• severe postictal effects;

• identifiable structural lesion present or prior history of brain disease or injury;

• increasing seizure frequency and severity; or

• two or more isolated seizure events in a six-month period.

Risk factors for poor drug responsiveness in canine epilepsy

Genetic risk factors

As previously mentioned, certain dog breeds have a suspected genetic defect, making them more susceptible to develop epileptic seizures; however, genetic factors may also result in differing drug response in the various breeds.

One example of this is that border collies often present with a severe seizure disorder characterised by cluster seizures and, therefore, a high seizure frequency. In a study, nearly three-quarters of border collies were thought to be pharmacoresistant to the antiepileptic medications commonly in use at the time of the study, primarily comprising phenobarbital and potassium bromide[12]. Phenobarbital- resistant border collies with epilepsy had a single nucleotide polymorphism in a promoter region of the multidrug transporter gene encoding for P-glycoprotein, potentially causing an overexpression of P-glycoprotein at the blood brain barrier, which could result in decreased penetration of antiepileptic drugs into the brain[13]. However, the same mutation was not identified in the related Australian shepherd dog[14].

A further five genes were suggested to be associated with drug response to phenobarbital in dogs (KCNQ3 – voltage gated potassium ion channel; SCN2A – sodium ion channel; GABRA2 – GABA receptor; EPOX HYD – phenobarbital metabolism; ABCB4 – drug transportation)[15]. These are interesting preliminary results, but further research is needed to identify the main genetic risk factors.

Clinical risk factors

As a clinician, and until genetic tests for seizure causes are developed, identifying the clinical risk factors associated with refractory epilepsy is usually easier with a more predictable outcome.

It is commonly suspected epilepsy in human patients is better controlled when the antiepileptic medication is started after the first seizure. However, epidemiological studies in developing countries (where antiepileptic drugs are not widely available and treatment is often not initiated or is initiated later in the disease course) suggest remission rates for epilepsy are comparable to those in more developed countries, where treatment is initiated much earlier[16]. In a study examining the effect of the length of treatment on longterm seizure control in Labrador retrievers with epilepsy, no effect of treatment length was evident[17]. However, the length of treatment might not have a direct influence on treatment success; it is recognised in dogs, rodents and humans that increased disease severity (high seizure frequency, cluster seizures and status epilepticus) significantly increases the risk of drug resistance[17]-[20]. Seizure severity will ultimately guide a clinician's reasoning: dogs with more severe epilepsy will in general have treatment initiated earlier than dogs with a less severe seizure disorder. Dogs with a more severe seizure phenotype will therefore be on treatment longer, masking any potential beneficial effect of early treatment initiation on dogs with less severe seizures.

It has been demonstrated that dogs with epilepsy can have an increase in seizure frequency over time prior to the initiation of antiepileptic medication[21]. This finding suggests epilepsy may be a progressive disease in dogs, which warrants early treatment.

Age of onset of seizures has also been suggested as a risk factor for developing more severe epilepsy. In the study examining epileptic Labrador retrievers, it was suggested dogs with early onset epilepsy might have a worse outcome than dogs developing idiopathic epilepsy later in life[17]. However, a more recent study could not support this finding, with the age at onset of seizures appearing to have no influence on survival[22]. On the balance of the evidence presented above it can be concluded dogs with epilepsy should be treated sooner in their disease course, rather than later, as long as the effects on the dog and owner's quality of life and the drug tolerability are considered.

Drug resistance: when to change treatment

When seizure control is assessed in dogs with idiopathic epilepsy, more than two-thirds of these dogs will continue to have epileptic seizures[17,22] and around onethird will remain inadequately controlled (less than 50 per cent reduction in seizure frequency)[23-25]. While these dogs may not be fully representative of epileptic dogs seen in non-referral practice – which have a less thorough investigation and some of which may have less severe seizures and therefore not warrant referral – they do highlight the difficulties of achieving good seizure control in dogs with idiopathic epilepsy.

The usual procedure for achieving optimal seizure control is to gradually increase the dose of the first chosen antiepileptic drug until it reaches its maximal tolerated and safe drug level. If this does not improve seizure frequency adequately or to the satisfaction of the owner, additional drugs should be considered. Around onethird of dog owners feel only complete seizure freedom represents acceptable epilepsy control; others tolerate one seizure every three to six months[26]. Phenobarbital and imepitoin are suitable medications for use as first line antiepileptic treatment for the control of idiopathic epilepsy in dogs. Potassium bromide is usually reserved as an add-on, in particular in the UK, where it is only licensed for use in dogs as an adjunctive therapy. Combination therapy of phenobarbital and imepitoin has been successfully reported in dogs[21].

Drug adverse effects: when to change treatment

Phenobarbital and potassium bromide have a similar side effect profile and most dogs will tolerate both drugs well. Potential adverse effects that may be evident (especially initially) include sedation, ataxia, polydipsia and polyuria, polyphagia and weight gain, pancreatitis, and (specifically for phenobarbital) hepatotoxicity (especially if the serum phenobarbital concentration exceeds 35ìg/ml). In some dogs the severity of the potential effects may warrant a change in the antiepileptic medication.

Idiosyncratic reactions (rare, unpredictable and non-dose-dependent reactions) have also been

described for phenobarbital, which necessitate a rapid change to another first line antiepileptic drug. Described idiosyncratic reactions include blood dyscrasias (neutropaenia, thrombocytopaenia and/or anaemia), superficial necrolytic dermatitis, dyskinesias and altered behaviour. Imepitoin appears to cause few side effects, those reported being limited to sedation, polydipsia and polyuria, increased appetite and hyperactivity[27]. Figure 3 details an algorithm describing how to switch treatment from phenobarbital to imepitoin, should the adverse effect profile of phenobarbital warrant a change in the antiepileptic medication. The animal needs to be slowly weaned off phenobarbital to reduce the chance of withdrawal seizures (Figure 3).

Changing treatment from imepitoin to phenobarbital can also be achieved in a relatively short time period, should this be required due to the adverse effect profile of imepitoin. In this instance, the phenobarbital should be rapidly loaded over 24 hours to achieve effective serum phenobarbital concentrations (a loading dose of imepitoin is not required when changing from phenobarbital to imepitoin). Loading doses of phenobarbital are associated with a greater degree of adverse effects (in particular, sedation and ataxia), and this is only performed if there is a clinical requirement to rapidly achieve therapeutic serum concentrations of phenobarbital.

In dogs with well-controlled seizures, where the change from imepitoin to phenobarbital is only required due to the adverse effect profile of the imepitoin, this is performed gradually over 24 hours as follows: 3mg/kg every four hours until a total dose of 20mg/kg to 24mg/ kg is reached (monitor the dog's level of sedation and reduce the dose if the dog is too sedated). As soon as the total "loading" dose is given, the phenobarbital can be provided at a maintenance dose of 3mg/kg twice daily. In dogs with poorly controlled seizures (particularly dogs experiencing cluster seizures or in status epilepticus) the phenobarbital load is performed more quickly (as an infusion over 40 to 60 minutes). As soon as the dog has received its total loading dose of phenobarbital it should be safe to stop the imepitoin.

Conclusion

Canine epilepsy is a chronic disease that requires chronic treatment. Consideration should be given to the underlying cause, and working through the case methodically, combined with an understanding of the current knowledge, will help to tackle the canine epilepsy case successfully.

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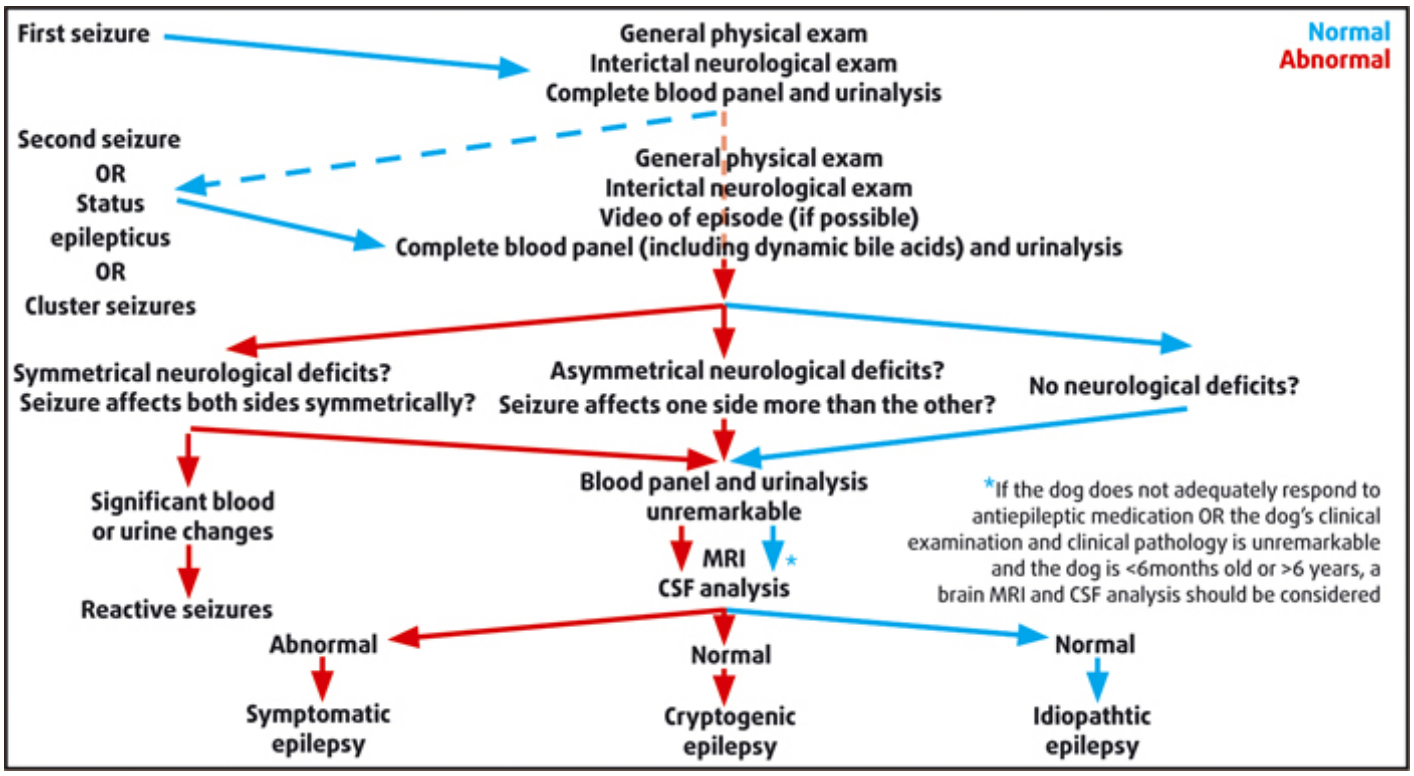

Figure 1. Clinical decision-making in canine epilepsy may appear complicated, but by using a step-by-step approach these cases are relatively straightforward.

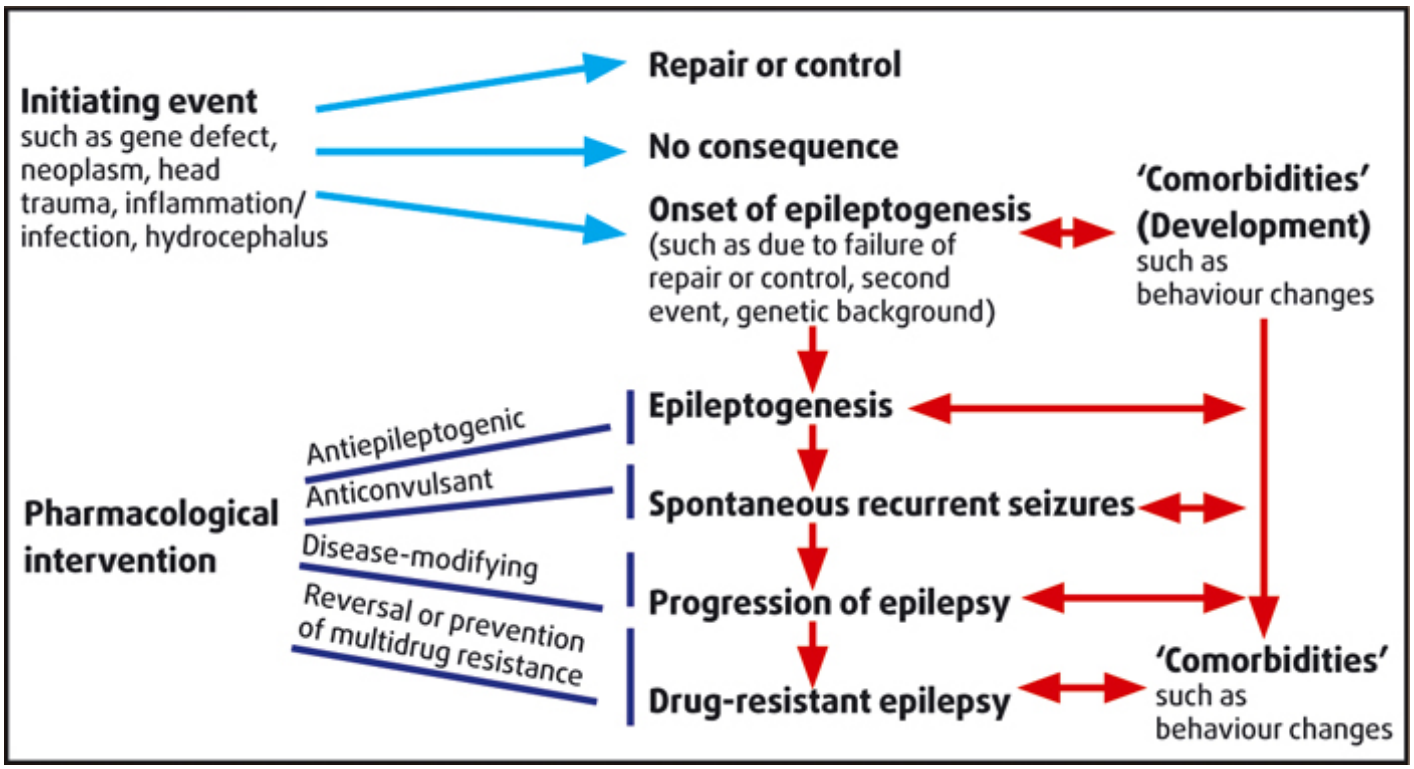

Figure 2. While the majority of the antiepileptic drugs used in veterinary medicine have good anticonvulsant effects, none have reliably been shown to have antiepileptogenic or disease modifying effects. Comorbidities are also common in dogs with epilepsy, in particular, behavioural change28. (Modified from Löscher W (2002), *Trends in Pharmacological Sciences*).

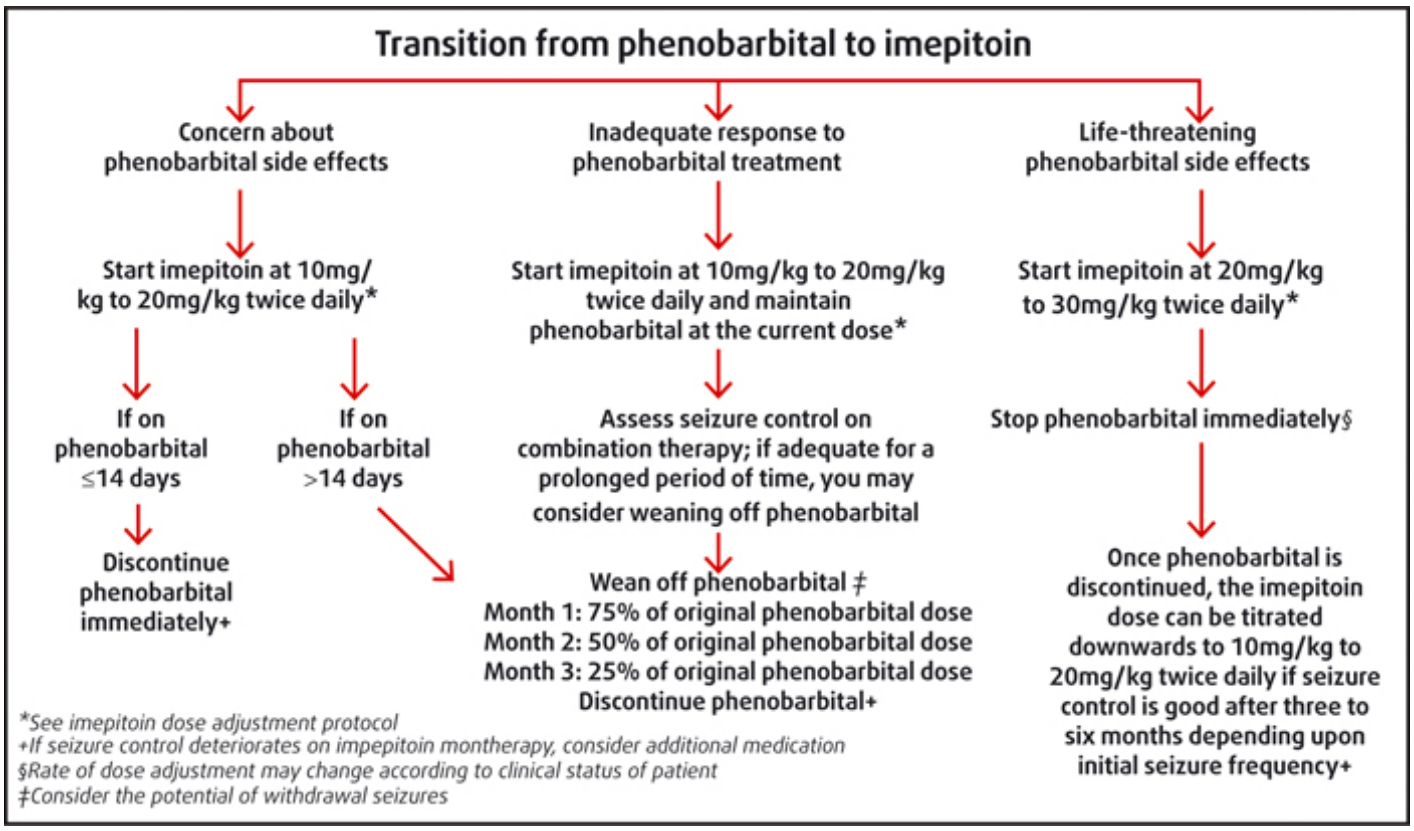

Figure 3. Transition from phenobarbital to imepitoin should be carefully considered and should only be done when there is a significant reason. Should a change of treatment be required, then gradual weaning off the phenobarbital dose is important to avoid withdrawal effects[29]. Prepared by the canine epilepsy advisory group: Sigitas Cizinauskas, Robyn Farquar, Gualtiero Gandini, Jacques Penderis, Kai Rentmeister, Jean Laurent Thibaud, Sandra Tyler and Holger Volk.