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International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe

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Abstract

In Europe, the number of antiepileptic drugs (AEDs) licensed for dogs has grown considerably over the last years. Nevertheless, the same questions remain, which include, 1) when to start treatment, 2) which drug is best used initially, 3) which adjunctive AED can be advised if treatment with the initial drug is unsatisfactory, and 4) when treatment changes should be considered. In this consensus proposal, an overview is given on the aim of AED treatment, when to start long-term treatment in canine epilepsy and which veterinary AEDs are currently in use for dogs. The consensus proposal for drug treatment protocols, 1) is based on current published evidence-based literature, 2) considers the current legal framework of the cascade regulation for the prescription of veterinary drugs in Europe, and 3) reflects the authors' experience. With this paper it is aimed to provide a consensus for the management of canine idiopathic epilepsy. Furthermore, for the management of structural epilepsy AEDs are inevitable in addition to treating the underlying cause, if possible.

Keywords: Dog, Epileptic seizure, Epilepsy, Treatment

Background

In Europe, the number of antiepileptic drugs (AEDs) licensed for dogs has grown considerably over the last years. Nevertheless, the same questions remain, which include, 1) when to start treatment, 2) which drug is best used initially, 3) which adjunctive AED can be advised if treatment with the initial drug is unsatisfactory, and 4) when treatment changes should be considered. In this consensus proposal, an overview is given on the aim of AED treatment, when to start long-term treatment in canine epilepsy and which veterinary AEDs are currently in use for dogs. The consensus proposal for drug treatment protocols, 1) is based on current published evidence-based literature [17], 2) considers the current legal framework of the cascade regulation for the prescription of veterinary drugs in Europe, and 3) reflects the authors' experience. With this paper it is aimed to provide a consensus for the management of canine idiopathic epilepsy. Furthermore, for the management of structural epilepsy AEDs are inevitable in addition to treating the underlying cause, if possible.

At present, there is no doubt that the administration of AEDs is the mainstay of therapy. In fact, the term AED is rather inappropriate as the mode of action of most AEDs is to suppress epileptic seizures, not epileptogenesis or the pathophysiological mechanisms of epilepsy. Perhaps, in the future, the term anti-seizure drugs might be more applicable in veterinary neurology, a term that is increasingly used in human epilepsy. Additionally, it is known that epileptic seizure frequency appears to increase over time in a subpopulation of dogs with untreated idiopathic epilepsy, reflecting the need of AED treatment in these patients [63].

In our consensus proposal on classification and terminology we have defined idiopathic epilepsy as a disease in

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its own right, *per se*. A genetic origin of idiopathic epilepsy is supported by genetic testing (when available) and a genetic influence is supported by a high breed prevalence (>2 %), genealogical analysis and /or familial accumulation of epileptic individuals. However in the clinical setting idiopathic epilepsy remains most commonly a diagnosis of exclusion following diagnostic investigations for causes of reactive seizures and structural epilepsy.

Aims of AED treatment

The ideal goal of AED therapy is to balance the ability to eliminate epileptic seizures with the quality of life of the patient. Seizure eradication is often not likely in dogs. More realistic goals are to decrease seizure frequency, duration, severity and the total number of epileptic seizures that occur over a short time span, with no or limited and acceptable AED adverse effects to maximize the dog's and owner's quality of life. Clinicians should approach treatment using the following paradigm [23, 76, 91, 92, 120]:

- **Decide when to start AED treatment**
- **Choose the most appropriate AED and dosage**
- **Know if and when to monitor serum AED concentrations and adjust treatment accordingly**
- **Know when to add or change to a different AED**
- **Promote pet owner compliance**

When to recommend maintenance AED treatment?

Definitive, evidence-based data on when to start AED therapy in dogs based on seizure frequency and type is lacking. As such, extrapolation from human medicine may be possible to provide treatment guidelines. Clinicians should consider the general health of the patient, as well as the owner's lifestyle, financial limitations, and comfort with the proposed therapeutic regimen. Individualized therapy is paramount for choosing a treatment plan. As a general rule, the authors recommend initiation of long-term treatment in dogs with idiopathic epilepsy when any one of the following criteria is present:

- **Interictal period of ≤ 6 months** (i.e. 2 or more epileptic seizures within a 6 month period)
- **Status epilepticus or cluster seizures**
- **The postictal signs are considered especially severe** (e.g. aggression, blindness) **or last longer than 24 hours**
- **The epileptic seizure frequency and/or duration is increasing and/or seizure severity is deteriorating over 3 interictal periods**

In humans, the decision regarding when to recommend AED treatment is based on a number of risk factors (e.g. risk of recurrence, seizure type, tolerability, adverse effects) [42, 115]. In people, clear proof exists that there is no benefit initiating AED treatment after a single unprovoked seizure [42], but there is evidence to support starting treatment after the second seizure [43, 108]. In dogs, long-term seizure management is thought to be most successful when appropriate AED therapy is started early in the course of the disease, especially in dogs with a high seizure density and in dog breeds known to suffer from a severe form of epilepsy [12–14]. A total number of ≥ 10 seizures during the first 6 months of the disease appeared to be correlated with a poor outcome in Australian Shepherds with idiopathic epilepsy [132]. Furthermore, recent evidence exists that seizure density is a crucial risk factor, experiencing cluster seizures, and being male is associated with poor AED response [84].

A strong correlation exists in epileptic people between a high seizure frequency prior to AED treatment and poor AED response [16, 34, 59]. Historically, this has been attributed to kindling, in which seizure activity leads to intensification of subsequent seizures [117]. However, there is little clinical evidence that kindling plays a role in either dogs [54] or humans [111] with recurrent seizures. In humans, a multifactorial pathogenesis is suggested [14, 52]. Recent epidemiologic data suggest that there are differences in the intrinsic severity of epilepsy among individuals, and these differences influence a patient's response to medication and long-term outcome. Additionally, evidence for seizure-associated alterations that affect the pharmacodynamics and pharmacokinetics of AEDs have been suggested [99]. Breed-related differences in epilepsy severity have been described in dogs, with a moderate to severe clinical course reported in Australian Shepherds [132], Border Collies [49, 84], Italian Spinoni [24], German Shepherds and Staffordshire Bull Terriers [84], whereas a less severe form of the disease has been described in a different cohort of Collies (mainly rough coated) [77], Labrador Retrievers [7] and Belgian Shepherds [45]. Consequently, genetics may affect the success of treatment and may explain why some breeds are more predisposed to drug resistant epilepsy [3, 77].

Choice of AED therapy

There are no evidence-based guidelines regarding the choice of AEDs in dogs. When choosing an AED for the management of epilepsy in dogs several factors need to be taken into account (AED-specific factors (e.g. regulatory aspects, safety, tolerability, adverse effects, drug interactions, frequency of administration), dog-related factors (e.g. seizure type, frequency and aetiology, underlying pathologies such as kidney/hepatic/gastrointestinal problems) and owner-related factors (e.g. lifestyle, financial circumstances)) [23]. In the end, however, AED choice is often determined on a case-by-case basis.

Until recently, primary treatment options for dogs with epilepsy have focused mainly on phenobarbital (PB) and potassium bromide (KBr) due to their long standing history, widespread availability, and low cost. While both AEDs are still widely used in veterinary practice, several newer AEDs approved for use in people are also being used for the management of canine idiopathic epilepsy mainly as add-on treatment. Moreover, since early 2013, imepitoin has been introduced in most European countries for the management of recurrent single generalized epileptic seizures in dogs with idiopathic epilepsy.

Several AEDs of the older generation approved for humans have been shown to be unsuitable for use in dogs as most have an elimination half-life that is too short to allow convenient dosing by owners, these include phenytoin, carbamazepine, valproic acid, and ethosuximide [119]. Some are even toxic in dogs such as lamotrigine (the metabolite is cardiotoxic) [26, 136] and vigabatrin (associated with neurotoxicity and haemolytic anemia) [113, 131, 138].

Since the 1990s, new AEDs with improved tolerability, fewer side effects and reduced drug interaction potential have been approved for the management of epilepsy in humans. Many of these novel drugs appear to be relatively safe in dogs, these include levetiracetam, zonisamide, felbamate, topiramate, gabapentin, and pregabalin. Pharmacokinetic studies on lacosamide [68] and rufinamide [137] support the potential use of these drugs in dogs, but they have not been evaluated in the clinical setting. Although these newer drugs have gained considerable popularity in the management of canine epilepsy, scientific data on their safety and efficacy are very limited and cost is often prohibitive.

Phenobarbital

Efficacy

PB has the longest history of chronic use of all AEDs in veterinary medicine. After decades of use, it has been approved in 2009 for the prevention of seizures caused by generalized epilepsy in dogs. PB has a favourable pharmacokinetic profile and is relatively safe [2, 87, 97]. PB seems to be effective in decreasing seizure frequency in approximately 60–93 % of dogs with idiopathic epilepsy when plasma concentrations are maintained within the therapeutic range of 25–35 mg/l [10, 31, 74, 105]. According to Charalambous et al. (2014) [17], there is overall good evidence for recommending the use of PB as a monotherapy AED in dogs with idiopathic epilepsy. Moreover, the superior efficacy of PB was demonstrated in a randomized clinical trial comparing PB to bromide (Br) as first-line AED in dogs, in which 85 % of dogs administered PB became seizure-free for 6 months compared with 52 % of dogs administered Br [10]. This study demonstrated a higher efficacy of PB compared to Br as a monotherapy, providing better seizure control and showing fewer side effects.

Pharmacokinetics

PB is rapidly (within 2h) absorbed after oral administration in dogs, with a reported bioavailability of approximately 90 % [2, 87]. Peak serum concentrations are achieved approximately 4–8h after oral administration in dogs [2, 97]. The initial elimination half-life in normal dogs has been reported to range from 37–73h after multiple oral dosing [96]. Plasma protein binding is approximately 45 % in dogs [36]. PB crosses the placenta and can be teratogenic.

PB is metabolized primarily by hepatic microsomal enzymes and approximately 25 % is excreted unchanged in the urine. There is individual variability in PB absorption, excretion and elimination half-life [2, 87, 97]. In dogs, PB is a potent inducer of cytochrome P450 enzyme activity in the liver [48], and this significantly increases hepatic production of reactive oxygen species, thus increasing the risk of hepatic injury [107]. Therefore PB is contraindicated in dogs with hepatic dysfunction. The induction of cytochrome P450 activity in the liver can lead to autoinduction or accelerated clearance of itself over time, also known as metabolic tolerance, as well as endogenous compounds (such as thyroid hormones) [40, 48]. As a result, with chronic PB administration in dogs, its total body clearance increases and elimination half-life decreases progressively which stabilizes between 30–45 days after starting therapy [97]. This can result in reduction of PB serum concentrations and therapeutic failure and therefore, monitoring of serum PB concentrations is very important for dose modulation over time.

A parenteral form of PB is available for intramuscular (IM) or intravenous (IV) administration. Different PB formulations are available in different countries, it should be emphasized, however, that IM formulations cannot be used IV and *vice versa*. Parenteral administration of PB is useful for administering maintenance therapy in hospitalized patients that are unable to take oral medication. The pharmacokinetics of IM PB have not been explored in dogs, however, studies in humans have shown a similar absorption after IM administration compared to oral administration [135]. The elimination half-life in dogs after a single IV dose is approximately 93h [87].

Pharmacokinetic interactions

In dogs, chronic PB administration can affect the disposition of other co-administered medications which are metabolized by cytochrome P450 subfamilies and/or bound to plasma proteins [48]. PB can alter the pharmacokinetics and as a consequence may decrease the therapeutic effect of other AEDs (levetiracetam, zonisamide, and benzodiazepines) as well as corticosteroids, cyclosporine,

metronidazole, voriconazole, digoxin, digitoxin, phenylbutazone and some anaesthetics (e.g. thiopental) [23, 33, 72, 82, 130]. As diazepam is used as first-line medicine for emergency use (e.g. status epilepticus) in practice it should be emphasized to double the IV or rectal dose of diazepam in dogs treated chronically with PB [130]. Concurrent administration of PB and medications that inhibit hepatic microsomal cytochrome P450 enzymes such as cimetidine, omeprazole, lansoprazole, chloramphenicol, trimethoprim, fluoroquinolones, tetracyclines, ketoconazole, fluconazole, itraconazole, fluoxetine, felbamate and topiramate may inhibit PB metabolism, increase serum concentration and can result in toxicity [10].

Common adverse effects

Most of the adverse effects due to PB are dose dependent, occur early after treatment initiation or dose increase and generally disappear or decrease in the subsequent weeks due to development of pharmacokinetic and pharmacodynamic tolerance [35, 121] (Table 1). The adverse effects include sedation, ataxia, polyphagia, polydipsia and polyuria. For an in-depth review on the adverse effects of PB, the reader is referred to comprehensive book chapters [23, 32, 91].

Idiosyncratic adverse effects

These effects occur uncommonly in dogs and include hepatotoxicity [13, 22, 39, 75], haematologic abnormalities (anaemia, and/or thrombocytopenia, and/or neutropenia) [51, 56]), superficial necrolytic dermatitis [66], potential risk for pancreatitis [38, 46], dyskinesia [58], anxiety [58], and hypoalbuminaemia [41] (Table 1). Most of these idiosyncratic reactions are potentially reversible with discontinuation of PB. For an in-depth review on the idiosyncratic adverse effects of PB the reader is referred to comprehensive book chapters [23, 32, 91].

Laboratory changes

Laboratory changes related to chronic PB administration in dogs include elevation in serum liver enzyme activities [39, 41, 75], cholesterol and triglyceride concentrations [41]. Alterations in some endocrine function testing may occur (thyroid and adrenal function, pituitary-adrenal axis) [21, 41, 128]. For an in-depth review on these laboratory changes the reader is referred to comprehensive book chapters [23, 32, 91].

Dose and monitoring (Fig. 1)

The recommended oral starting dose of PB in dogs is 2.5–3 mg/kg BID. Subsequently, the oral dosage is tailored

Table 1 Most common reported adverse effects seen in dogs treated with PB, imepitoin and KBr (rarely reported and/or idiosyncratic adverse effects are indicated in grey

AED	Adverse effects in dogs
PB	Sedation
	Ataxia
	Polyphagia
	Polydipsia/polyuria
	Hepatotoxicity
	Haematologic abnormalities
	Superficial necrolytic dermatitis
	Potential risk of pancreatitis
	Dyskinesia and anxiousness
	Hypoalbuminaemie
Imepitoin	Polyphagia (often transient)
	Hyperactivity, apathy, polyuria, polydipsia, hypersalivation, somnolence,
	vomiting, ataxia, apathy, diarrhoea, prolapsed nictitating membrane,
	decreased sight and sensitivity to sound
KBr	Sedation
	Ataxia and pelvic limb weakness
	Polydipsia/polyuria
	Polyphagia
	Nausea, vomiting and/or diarrhea
	Personality changes (aggression, irritability, hyperactivity)
	Megaoesophagus
	Persistent cough
	Increased risk of pancreatitis

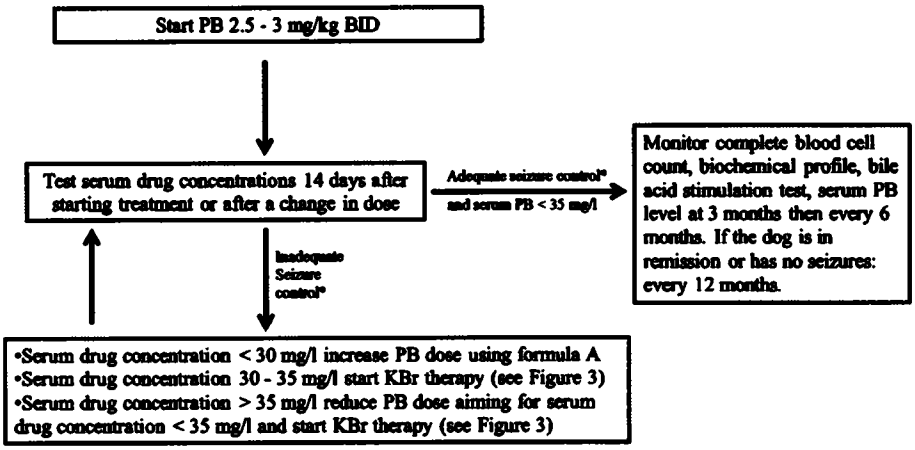

Fig. 1 PB treatment flow diagram for decision making during seizure management in an otherwise healthy dog. The authors advise to start with PB (and add KBr if inadequate seizure control after optimal use of PB (Fig. 3)): in dogs with idiopathic epilepsy experiencing recurrent single generalised epileptic seizures; in dogs with idiopathic epilepsy experiencing cluster seizures or status epilepticus; in dogs with other epilepsy types. *Criteria for (in)adequate seizure control with regard to efficacy and tolerability (see Consensus proposal: Outcome of therapeutic interventions in canine and feline epilepsy [94]). 1. Treatment efficacious: a: Achievement of complete treatment success (i.e. seizure freedom or extension of the interseizure interval to three times the longest pretreatment interseizure interval and for a minimum of three months (ideally > 1 year); b: Achievement of partial treatment success (i.e. a reduction in seizure frequency including information on seizure incidence (usually at least 50 % or more reduction defines a drug responder), a reduction in seizure severity, or a reduction in frequency of seizure clusters and/or status epilepticus). 2. Treatment not tolerated i.e. appearance of severe adverse effects necessitating discontinuation of the AED

to the individual patient based on seizure control, adverse effects and serum concentration monitoring.

Because of considerable variability in the pharmacokinetics of PB among individuals, the serum concentration should be measured 14 days after starting therapy (baseline concentration for future adjustments) or after a change in dose. To evaluate the effect of metabolic tolerance, a second PB serum concentration can be measured 6 weeks after initiation of therapy. Recommendations on optimal timing of blood collection for serum PB concentration monitoring in dogs vary among studies [23]. Generally, serum concentrations can be checked at any time in the dosing cycle as the change in PB concentrations through a daily dosing interval is not therapeutically relevant once steady-state has been achieved [62, 70]. However, in dogs receiving a dose of 5 mg/kg BID or higher, trough concentrations were significantly lower than non-trough concentrations and serum PB concentration monitoring at the same time post-drug dosing was recommended, in order to allow accurate comparison of results in these dogs [70]. Another study recommended performing serum PB concentration monitoring on a trough sample as a significant difference between peak and trough PB concentration was identified in individual dogs [10]. The therapeutic range of PB in serum is 15 mg/l to 40 mg/l in dogs. However, it is the authors' opinion that in the majority of dogs a serum PB concentration between 25–30 mg/l is required for optimal seizure control. Serum concentrations of more than 35 mg/l are associated with an increased risk of hepatotoxicity and should be avoided [22, 75]. In case of inadequate seizure control, serum PB concentrations must be used to guide increases in drug dose. Dose adjustments can be calculated according to the following formula (Formula A):

New PB total daily dosage in mg
= (desired serum PB concentration/actual serum PB concentration)
× actual PB total daily dosage in mg

A dog with adequate seizure control, but serum drug concentrations below the reported therapeutic range, does not require alteration of the drug dose, as this serum concentration may be sufficient for that individual. Generally, the desired serum AED concentration for individual patients should be the lowest possible concentration associated with >50 % reduction in seizure frequency or seizure-freedom and absence of intolerable adverse effects [23].

In animals with cluster seizures, status epilepticus or high seizure frequency, PB can be administered at a loading dose of 15–20 mg/kg IV, IM or PO divided in multiple doses of 3–5 mg/kg over 24–48h to obtain a therapeutic brain concentration quickly and then sustain it [10]. Serum PB concentrations can be measured 1–3 days after loading. Some authors load as soon as possible (over 40 to 60 min) and start with a loading dose of 10 to 12 mg/kg IV followed by two further boluses of 4 to 6 mg/kg 20 min apart.

Complete blood cell count, biochemical profile (including cholesterol and triglycerides), and bile acid stimulation

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