



## Original Article

# Imepitoin withdrawal in dogs with idiopathic epilepsy well-controlled with imepitoin and phenobarbital and/or potassium bromide does not increase seizure frequency



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## ABSTRACT

Phenobarbital or potassium bromide (KBr) add-on treatment decreases the average monthly seizure frequency in dogs with idiopathic epilepsy resistant to a maximum dose of imepitoin. The importance of continued administration of imepitoin in these dogs is currently unknown. The goal of this study was to assess whether imepitoin withdrawal would destabilize epileptic seizure control. In this prospective clinical trial epileptic seizure control was evaluated by comparing the monthly seizure frequency of 13 dogs with well-controlled idiopathic epilepsy receiving a combination of imepitoin and phenobarbital ( $n=4$ ), imepitoin and KBr ( $n=7$ ), and imepitoin, phenobarbital and KBr ( $n=2$ ) during a period of 3–6 months (pre-withdrawal period), with a follow-up period of 9–12 months after withdrawal of imepitoin (post-withdrawal period). Adverse effects were also recorded before and after withdrawal of imepitoin. Imepitoin was tapered off over 3 months as follows: 20 mg/kg twice daily for 1 month, then 10 mg/kg twice daily for 1 month, then once daily for 1 month.

Withdrawal of imepitoin did not increase monthly seizure frequency ( $P=0.9$ ). Moreover, all owners reported improvement in the adverse effects experienced by their dog after withdrawal of imepitoin. Imepitoin withdrawal in epileptic dogs that were well-controlled with imepitoin and phenobarbital and/or KBr did not worsen epileptic seizure control, and possibly decreased antiepileptic treatment-related adverse effects. However, a worsening of seizure frequency could occur in individual cases.

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## Introduction

Imepitoin is a recently developed antiepileptic drug registered for the treatment of canine idiopathic epilepsy (Pexion EPAR, 2013). Its antiepileptic efficacy has been demonstrated in experimental (Löscher et al., 2013) and clinical trials (Tipold et al., 2014; Rundtfield et al., 2015; Packer et al., 2017) and has been proven to be comparable to phenobarbital (Tipold et al., 2014). Although its efficacy on generalized tonic-clonic and focal epileptic seizures has been demonstrated in dogs with idiopathic epilepsy, imepitoin sole therapy failed to reduce cluster seizure frequency in one study (Rundtfield et al., 2015), but was as effective in reducing seizure frequency in clustering as in non-clustering dogs in another study

(Packer et al., 2017). However, 25% of dogs in one study were considered resistant to imepitoin monotherapy, because epileptic seizure frequency did not decrease by at least 50% (Tipold et al., 2014).

A population of dogs with idiopathic epilepsy resistant to a maximum dose of imepitoin was studied by Royaux et al. (2017). The addition of phenobarbital or potassium bromide (KBr) to imepitoin monotherapy improved seizure control in 79% and 69% of dogs, respectively, and also decreased the number of dogs with cluster seizures.

Currently, there is no evidence-based information available on the importance of continued administration of imepitoin in the seizure management of dogs with well-controlled idiopathic epilepsy. The goal of the current study was to assess if withdrawal of imepitoin in a population of idiopathic epileptic dogs resistant to imepitoin monotherapy, but well-controlled in combination with phenobarbital and/or KBr, would destabilize or worsen epileptic seizure control.

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## Materials and methods

### Study population

The study was conducted as an open-label prospective clinical trial. Informed consent was obtained from all owners. Dogs with idiopathic epilepsy from a previous study by our group (Royaux et al., 2017) were recruited for this study. Dogs were included in this follow-up study if they met the following inclusion criteria: (1) a Tier 1 or Tier 2 confidence level (De Risio et al., 2015) for the diagnosis of idiopathic epilepsy; (2) satisfactory epileptic seizure control for at least 3 months, defined as a reduction of the monthly seizure frequency of at least 50% on combination imepitoin and phenobarbital and/or KBr therapy when compared with the initial monthly seizure frequency on a maximum dose of imepitoin sole therapy; and (3) availability of a seizure diary kept by the owner for the 3–6-month period before withdrawal of imepitoin (pre-withdrawal period), during the 3 months of imepitoin withdrawal, and for 9–12 months of follow-up after imepitoin had been discontinued (post-withdrawal period).

### Study design

Dogs with idiopathic epilepsy from a previous study by our group (Royaux et al., 2017) that had achieved a satisfactory seizure control for 6 consecutive months were recruited for the current study (pre-withdrawal period). In dogs that had not yet achieved satisfactory seizure control at the end of the previous study, a third antiepileptic drug (KBr in dogs receiving the combination of imepitoin and phenobarbital, or phenobarbital in dogs receiving the combination of imepitoin and KBr, respectively) was added to the antiepileptic treatment protocol. Phenobarbital was commenced at 3 mg/kg twice daily and KBr was commenced at 20 mg/kg twice daily. The serum concentration of phenobarbital or bromide was then measured after 1 or 2 months, respectively. Phenobarbital and bromide serum concentrations were considered optimal at 25–35 mg/L and 1500–2000 mg/L, respectively (De Risio and Platt, 2014; Bhatti et al., 2015). If the serum concentrations were below these optimal levels, and satisfactory seizure control was not yet achieved, the dose of the add-on drug was increased (Podell, 2013; Bhatti et al., 2015) and the serum concentration was re-measured after 1 or 2 months, respectively. If the dogs did achieve satisfactory seizure control, the dose remained unaltered. Dogs that achieved satisfactory seizure control for 3 consecutive

months with this new antiepileptic drug combination were also recruited for the study (pre-withdrawal period).

A flow diagram of the study design is presented in Fig. 1.

In dogs with satisfactory seizure control, imepitoin was withdrawn by tapering the dose over a 3-month period as follows: 20 mg/kg twice daily for 1 month, then 10 mg/kg twice daily for 1 month and then 10 mg/kg once daily for 1 month. The post-withdrawal period started after imepitoin administration had ceased. Each dog was evaluated clinically and neurologically before withdrawal of imepitoin, immediately after withdrawal of imepitoin, 3 months and 9 months later. At these four appointments, epileptic seizure frequency and adverse effects were recorded, complete blood cell count and serum biochemistry was performed, and phenobarbital and/or bromide serum concentrations were monitored. Additionally, dog owners were contacted by phone at 6 and 12 months during the post-withdrawal period to record epileptic seizure frequency and adverse effects related to the medication. When a dog experienced cluster seizures, each seizure of the cluster was counted as one seizure for the calculation of the epileptic seizure frequency and cluster seizures were noted for that dog.

### Outcome measures

The primary outcome measure was the monthly seizure frequency. For the dogs with satisfactory seizure control after the study by Royaux et al. (2017) ( $n = 11$ ), pre-withdrawal monthly seizure frequency was calculated by dividing the total number of epileptic seizures over the prospective 6-month period by 6. For two dogs that required the addition of a third antiepileptic drug, the monthly seizure frequency was calculated by dividing the total number of epileptic seizures over the prospective 3-month period of satisfactory seizure control by 3. The monthly seizure frequency during the post-withdrawal period was then calculated by dividing the number of seizures that each dog experienced during the available follow-up time (9 months,  $n = 9$ ; 12 months,  $n = 4$ ) by 9 or 12, respectively. Success of imepitoin withdrawal was defined as a post-withdrawal monthly seizure frequency equal to, or lower than the pre-withdrawal monthly seizure frequency, while failure was defined as a post-withdrawal monthly seizure frequency higher than the pre-withdrawal monthly seizure frequency.

The secondary outcome measure was the severity of adverse effects experienced by the dog after the withdrawal of imepitoin, compared with before withdrawal.

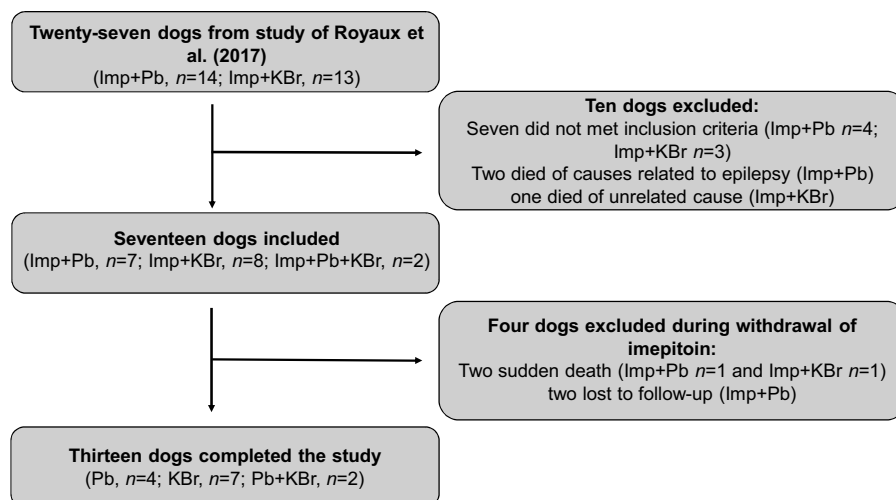


Fig. 1. Flow diagram of the study design. Imp, imepitoin; Pb, phenobarbital; KBr, potassium bromide.

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