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Phenobarbital or potassium bromide as an add-on antiepileptic drug for the management of canine idiopathic epilepsy refractory to imepitoin

E. Royaux [a,*], L. Van Ham [a], B.J.G. Broeckx [b], I. Van Soens [c,d], I. Gielen [e], D. Deforce [b], S.F.M. Bhatti [a]

[a] Department of Small Animal Medicine and Clinical Biology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium
[b] Laboratory of Pharmaceutical Biotechnology, Faculty of Pharmaceutical Sciences, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium
[c] Companion Animal Internal Medicine Section, Faculty of Veterinary Medicine, Liège University, Quartier Vallée 2, Avenue de Cureghem 3, Sart-Tilman, 4000 Liège, Belgium
[d] Orion Veterinary Clinic, Voortkapelseweg 77, 2200 Noorderwijk, Belgium
[e] Department of Veterinary Medical Imaging and Small Animal Orthopedics, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke, Belgium

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ABSTRACT

Imepitoin has recently been approved in Europe for the management of dogs with idiopathic epilepsy. Currently, there is no evidence-based information available on the efficacy of antiepileptic drugs used as additions to the therapeutic regimen in dogs with idiopathic epilepsy that are not well controlled with imepitoin. The goal of this study was to evaluate the efficacy of phenobarbital or potassium bromide (KBr) as add-on antiepileptic drugs for controlling dogs refractory to a maximum dose of imepitoin (30 mg/kg twice daily). The study was performed as a prospective, randomised, controlled clinical trial. The efficacy of phenobarbital and KBr was evaluated by comparing monthly seizure frequency (MSF), monthly seizure day frequency (MSDF), the presence of cluster seizures during a retrospective 2-month period with a prospective follow-up of 6 months, and the overall responder rate.

Twenty-seven dogs were included in the study, 14 dogs in the phenobarbital group and 13 dogs in the KBr group. Both median MSF and MSDF decreased in the phenobarbital group (both $P = 0.001$) and in the KBr group ($P = 0.004$ and $P = 0.003$, respectively). Overall, the number of dogs with cluster seizures decreased ($P = 0.0005$). The responder rate was 79% vs. 69% in the phenobarbital and KBr groups, respectively. We conclude that phenobarbital or KBr add-on treatment decreases median MSF and MSDF in epileptic dogs refractory to a maximum dose of imepitoin. Combination therapy was generally well tolerated and resulted in an improvement in seizure management in the majority of the dogs.

Introduction

Until recently, primary treatment options for dogs with idiopathic epilepsy mainly focused on phenobarbital and potassium bromide (KBr; Farnbach, 1984; Schwartz-Porsche et al., 1985; Podell and Fenner, 1993; Trepanier et al., 1998; Boothe et al., 2012a). Phenobarbital has the longest history of chronic use of all antiepileptic drugs in veterinary medicine. It appears to decrease seizure frequency in approximately 60–93% of dogs with idiopathic epilepsy when plasma concentrations are maintained within the therapeutic range (25–35 mg/L; Farnbach, 1984; Schwartz-Porsche et al., 1985; Morton and Honhold, 1988; Boothe et al., 2012a). In most EU countries, KBr is approved only for add-on treatment in dogs refractory to first line antiepileptic drug therapy (Bhatti et al., 2015). Phenobarbital and KBr have a synergistic effect and add-on treatment with KBr improves seizure control in dogs that are poorly controlled with phenobarbital alone, or in dogs requiring reduction of phenobarbital dosage due to intolerable adverse effects associated with its use (Podell and Fenner, 1993; Trepanier et al., 1998).

In 2013, imepitoin was approved for the treatment of canine idiopathic epilepsy based on randomised clinical trials in Europe (Rundfeldt et al., 2015; Tipold et al., 2015). In a pseudo-placebo trial, a high dose (30 mg/kg two times daily) of imepitoin was compared to a low dose (1 mg/kg two times daily); the administration of a high dose resulted in significantly greater reduction in monthly seizure frequency (MSF) compared to treatment with the low dose (Rundfeldt et al., 2015). In a recent randomised controlled, blinded study, the efficacy and tolerance of imepitoin was compared with phenobarbital (Tipold et al., 2015). In this study, the administration of imepitoin demonstrated comparable efficacy to phenobarbital in controlling seizures in dogs (Tipold et al., 2015). The frequency of adverse events such as somnolence/sedation, increased appetite,

* Corresponding author.
E-mail address: Emilie.Royaux@vetspecialists.co.uk (E. Royaux).

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polydipsia and polyuria was significantly higher in the phenobarbital group compared to the imepitoin group (Tipold et al., 2015).

At present, scientific data and evidence-based guidelines on which antiepileptic drug can best be combined with imepitoin in dogs with poor seizure control are lacking. Therefore, we evaluated and compared the efficacy of phenobarbital or KBr as an add-on treatment for dogs with idiopathic epilepsy refractory to a maximum dose of imepitoin to provide guidance for clinicians.

Materials and methods

Study population

The study was conducted as a prospective, randomised, controlled clinical trial, approved by the ethical committee of the Ghent University Faculty of Veterinary Medicine (Approval number EC2014/82; 6 August 2014). Informed consent was obtained from all owners. Dogs presented at the neurology service of the Small Animal Department between November 2014 and July 2015 with a history of epileptic seizures were screened for study entry. The inclusion criteria were: (1) a suspected diagnosis of idiopathic epilepsy based on the onset of epileptic seizures between 6 months and 6 years of age, normal physical and neurological examination during the inter-ictal period; and complete blood count, comprehensive serum biochemistry profile and routine urine examination results in the reference ranges (De Risio et al., 2015). Additional, optional, criteria included unremarkable magnetic resonance imaging of the brain or cerebrospinal fluid analysis, if performed (De Risio et al., 2015); (2) generalised epileptic seizures; (3) poor seizure control, defined as at least four seizures over a period of 2 months while treated with the maximum dose of imepitoin (30 mg/kg twice daily); and (4) a seizure log kept by the owner for at least 2 months before the start of the study (i.e. the defined pre-study period) and during the entire study period (6 months).

Study design

Dogs were randomly divided into two groups using a computer-generated randomisation list: one group received phenobarbital (phenobarbital group) and the other received KBr (KBr group) as add-on to a maximum dose of imepitoin.

Dogs in the phenobarbital group received phenobarbital at a dose of 2 mg/kg two times daily initially (De Risio, 2014a). The serum phenobarbital concentration was measured after 1, 2 and 6 months. We considered the optimal therapeutic phenobarbital serum concentration to be between 25 and 35 mg/L (De Risio, 2014a; Bhatti et al., 2015). If the serum phenobarbital concentration was below 25 mg/L and the MSF did not decrease by at least 50%, the dose of phenobarbital was recalculated and increased (Podell, 2004). If the serum phenobarbital concentration was below 25 mg/L and the MSF decreased by at least 50%, the dose of phenobarbital was not adjusted unless there were two or more seizures per month. If the serum phenobarbital concentration was above 35 mg/L, the dose of phenobarbital was recalculated and decreased (Podell, 2004), regardless of the MSF.

Dogs in the KBr group received an initial loading dose without hospitalisation. Over the first 6 days, the dogs received 52 mg/kg two times daily (adapted from De Risio, 2014b; Bhatti et al., 2015); thereafter, a maintenance dose of 20 mg/kg two times daily was administered. The serum KBr concentration was measured after 1, 2 and 6 months. We considered the optimal therapeutic KBr serum concentration to be between 1500 mg/L and 2000 mg/L (De Risio, 2014b; Bhatti et al., 2015). If the serum KBr concentration was below 1500 mg/L and the MSF did not decrease by at least 50%, the dose of KBr was recalculated and increased (De Risio, 2014b). If the serum KBr concentration was below 1500 mg/L and the MSF decreased by at least 50%, the dose of KBr was not adjusted unless there were two or more seizures per month. If the serum KBr concentration was above 2000 mg/L, the dose of KBr was recalculated and decreased (De Risio, 2014b), regardless of MSF.

Each dog in the study was clinically and neurologically evaluated at the beginning of the study and after 1, 2, 4 and 6 months. Two and 6 months after the start of the study, complete blood count and serum biochemistry were performed. In addition, dog owners reported their dog's seizure history in a questionnaire.

Outcome measures

MSF and monthly seizure day frequency (MSDF) were the primary outcome measures. To determine the MSF of each dog, the number of seizures during the 2 months before and during the 6 months after the start of the study was divided by 2 and 6, respectively. The monthly seizure day frequency (MSDF), meaning the number of days with seizures per month, was also estimated to avoid bias due to clusters with a high number of seizures. To determine the MSDF, the number of days with seizures during the 2 months before and during the 6 months after the start of the study was divided by 2 and 6, respectively.

Secondary outcome measures were the responder rate, occurrence of cluster seizures, cessation of seizures and adverse effects during the study period. A dog was considered a responder if the MSF during the study period decreased by at least 50%, compared to the pre-study MSF. Non-responders experienced either a reduction in MSF less than 50% or an increase in MSF. The responder rate was calculated as the percentage of dogs that were responders.

Criteria for withdrawal of the study

Dog owners and the investigator could withdraw a dog from the study at any time for any reason. If withdrawal occurred after 2 months of the study period, all data were included and the dog was considered to have completed the study with the ending month being the month of withdrawal. If withdrawal occurred prior to 2 months of the study period, data were not used for the study.

Statistical analysis

Statistical analysis was performed in R (version 3.1.2). Due to non-normality of the data, non-parametric tests were used and results are reported as median and range. The effect of the add-on treatment on MSF and MSDF was assessed overall and for the phenobarbital or the KBr group separately with the Wilcoxon signed-rank test. The McNemar's chi-square test was used to evaluate the effect of add-on therapy on the presence of cluster seizures (yes/no) overall and separately for the phenobarbital and KBr groups. A cluster of seizures was defined as more than one seizure within 24 h and was counted as the true number of individual seizures.

To assess potential population stratification, the MSF and MSDF, and whether cluster seizures were present or absent, were compared between the phenobarbital and KBr groups in the 2-month period prior to add-on using the Wilcoxon rank sum test and Fisher's exact test, respectively. During the 6-month follow-up, the effect of KBr and phenobarbital on the MSF, MSDF and the MSF values per month and MSDF values per month was also compared with the Wilcoxon rank sum test, and the presence/absence of cluster seizure data was analysed using Fisher's exact test. *P* values of ≤0.05 were considered significant.

Results

Study population

In total, 30 dogs met the inclusion criteria. Three owners decided not to participate in the study. Reasons given for not participating were lack of time and living too far away from the clinic to come for regular visits. Twenty-seven dogs were included in the study, 14 dogs in the PB group and 13 dogs in the KBr group. Breeds in the phenobarbital and KBr groups are presented in Table 1. The median age at study entry and at onset of the first seizure in each group is presented in Table 2. The median weight at study entry and at the end of the study is presented in Table 2. A seizure log of 2 months or more was available for all dogs. Five dogs received the maximum dose of imepitoin for <2 months and were enrolled earlier in the study because of high MSF. Both MRI of the brain and examination of the CSF were performed in 12/27 (44%) of the dogs (6/14 in the phenobarbital group and 6/13 in the KBr group) and considered unremarkable. Six dogs had been treated with phenobarbital monotherapy prior to imepitoin monotherapy. From this

Table 1
Breeds represented in the phenobarbital and potassium bromide (KBr) groups.

Breed	Phenobarbital group	KBr group
Australian Kelpie	0	1
Beagle	2	2
Belgian shepherd	0	1
Border collie	1	1
Caucasian shepherd	0	1
Chihuahua	0	1
Cocker spaniel	2	2
Cross breed	0	1
Dalmatian	1	0
Golden retriever	1	1
Labrador retriever	1	1
Miniature pinscher	1	0
Miniature schnauzer	0	1
Greyhound	1	0
Labradoodle	1	0
English bulldog	1	0
Bordeaux dog	1	0
Spanish water dog	1	0