Critical appraisal – Randomised controlled trial questions

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Introduction	
Are the aims clearly stated?	Yes – to evaluate safety and efficacy of a new oral preparation of imepitoin for treatment of idiopathic epilepsy under field conditions in dogs and safety up to five time max recommended therapeutic dose over a period of 6 months in healthy dogs under laboratory conditions.
Methods	
Is the study design suitable for the aims?	The study design used is not necessarily constructed for demonstrating non-inferiority (as stated in the methods section), but is focused on the aims stated at the end of the introduction section
Which population was studied?	Dogs > 5kg in weight with a diagnosis of idiopathic epilepsy based on clinical examination, neurological examination +/- MRI that have had at least two seizures in the previous 6 weeks and have not received previous treatment
Were the treatments randomly allocated? If yes, how was the randomisation done?	Yes according to the information reported in the results section, but method not clearly stated in the methods section. In addition, dose escalation was used in both arms in a non-random way. Not described
Were the groups comparable prior to intervention?	According to text yes but supporting data and statistical analysis are not presented
Was the person who administered the interventions blinded?	Not clearly stated; results discuss unblinding but methods do not specifically state how if, or how, blinding was performed.
Is it clear what measurements were carried out in	Not completely clear

the study?	
Were the correct measurements chosen? Do they reflect (or are they strongly related to) the outcome of interest?	Yes
Were previously established validated methods used to make the measurements? (e.g. Glasgow pain score, International Units etc)	No validated methods used
What outcomes were measured?	• Seizure frequency during the baseline period • Seizure frequency during the treatment period • Adverse events as reported by owners • Serum biochemistry for renal and hepatic parameters and electrolytes • Serum concentration of phenobarbital for those dogs allocated to receive this treatment • Seizure data log transformed and converted into a geometric mean monthly seizure frequency for baseline and treatment periods
Are the outcomes clinically relevant?	Yes, though the clinical relevance of log transformed geometric mean monthly seizure frequency is difficult to determine
Were the outcomes assessed blind?	Not clearly stated; dogs receiving phenobarbitone needed more regular blood sampling than those receiving imepitoin so it is difficult to see how blinding was maintained during the study
Are the statistical methods described?	Yes
Was the statistical significance level stated?	No

Was the sample size justified?	No
Was ethical approval obtained?	Not stated
Are the methods described in enough detail that you could repeat them?	No. For example randomization is not described and it is unclear how the date range for the "monthly seizure frequency" intervals on which analyses are based has been determined.
Results	
Were the basic data adequately described?	Summarised in text only.
Do the numbers add up? Are all subjects accounted for?	Yes in Table 1 Yes where numbers are given
Was the statistical significance (p value) stated in the results? Is this consistent with the methods? (It should be stated in the sample size or power calculation)	Yes
Were any side effects of the intervention reported if applicable?	Yes, adverse events reported in 46.6% of dogs in imepitoin group and 57.3% of dogs in phenobarbital group but specific frequencies of different adverse events not given.
What were the main findings/key results?	The authors conclude that imepitoin is non-inferior to phenobarbital in reducing seizure frequency as the percentage of dogs whose monthly seizure frequency decreased by ≥50% was not significantly different between the treatment groups (75% for imepitoin dogs and 83% for phenobarbital treated dogs). Geometric mean monthly seizure frequency for dogs in the imepitoin group that fulfilled all inclusion criteria dropped from 2.060 at baseline to 0.429, whilst the geometric mean monthly seizure frequency for phenobarbital treated dogs that met inclusion criteria fell from 2.208 to 0.332

	(see Table 2) All data are reported in terms of geometric mean monthly seizure frequency; range data for the actual number of seizures experienced by dogs during the trial period would greatly aid interpretation of these data.
Discussion and conclusion	
What do the main findings/key results mean?	Very hard to tell given the complexity of this study design, the lack of sample size calculation, high drop out rates and that the study did not appear to be specifically designed (or reported) to test non-inferiority.
Are the negative findings discussed? How are the negative findings interpreted?	Yes in relation to high drop out number being due to the complexity of the titration regime
Does the discussion reflect the results?	Yes
Interpretation	
What are the clinical implications of this study? Are the subjects in the study similar to those in the BET/your own?	Hard to determine given the very complex and poorly described methodology, the lack of basic data, the high number of drop-outs and the lack of sample size calculation. Both drugs appear to be associated with a high frequency of adverse events Probably but hard to tell from data given.
General	
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