Standard Paper

LEVETIRACETAM IN THE MANAGEMENT OF FELINE AUDIOGENIC REFLEX SEIZURES: A RANDOMISED, CONTROLLED, OPEN-LABEL STUDY

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Abstract

Objectives: Currently, there are no published randomised controlled veterinary trials evaluating the efficacy of anti-epileptic medication in the treatment of myoclonic seizures. This study aimed to evaluate the efficacy of phenobarbital and levetiracetam in the management of myoclonic seizures.

Methods: This prospective randomised open-label trial compared the efficacy and tolerability of levetiracetam (20mg/kg q8h) to phenobarbital (3 to 5 mg/kg q12h) in cats with suspected feline audiogenic reflex seizures (FARS), that experienced myoclonic seizures on ≥12 days during a prospective 12-week baseline period. This was followed by a 4-week titration phase (until a therapeutic serum concentration of phenobarbital was achieved) and a 12-week treatment phase.

Results: Of 68 cats randomised, 57 (levetiracetam, n = 28; phenobarbital, n = 29) were evaluable. A reduction of ≥50% in the number of myoclonic seizure days was seen in 100% of patients in the levetiracetam group and in 3% of patients in the phenobarbital group ($P < 0.001$) during the treatment period. Levetiracetam-treated cats were more likely to respond to treatment than those receiving phenobarbital. Levetiracetam-treated cats had higher freedom from myoclonic seizures (50.0% vs 0%; $P < 0.001$) during the treatment period. The most common adverse events were lethargy, inappetance and ataxia, with no difference in incidence between levetiracetam and phenobarbital. Adverse events were mild and transient with levetiracetam but persistent with phenobarbital.

Conclusions: These results suggest that levetiracetam is an effective and well-tolerated treatment for cats with myoclonic seizures and is more effective than phenobarbital.

Whether it will prevent the occurrence of generalised tonic clonic seizures and other behavioural abnormalities if used early in the course of FARS is not yet clear.

270 words

Introduction

Feline audiogenic reflex seizures (FARS) represent a collection of seizure patterns, with the major characteristic being a geriatric-onset (>10 years) of auditory-induced, myoclonic seizures[1]. FARS occurs in pedigree and non-pedigree cats, but among the pedigrees, the Birman breed is over-represented[1]. Avoiding certain sounds can reduce the seizures, although owners reported that it is difficult to avoid noises, and the loudness of the sound also seemed to increase the severity of seizures[1]. A pattern of audiogenic kindling was observed in which myoclonic seizures develop after numerous daily sound exposures and results in the spread of a seizure discharge from brainstem to forebrain structures (i.e. the hippocampus, amygdale, and neocortex) after repetitive stimulation inducing seizures of another type[2,3]. In the case of FARS, these are generalized tonic-clonic seizures (GTCS)[1].

Myoclonus may only be one part of an epilepsy syndrome, and several problems regarding treatment exist. This is also true of FARS, where myoclonic seizures appear to the most common type. Not all antimyoclonic drugs are antiepileptic, and only some antiepileptic drugs (AEDs) are antimyoclonic. In addition, many of the myoclonic epilepsies reported in humans are refractory to drug treatment. No study has investigated treatment response in cats with FARS.

Levetiracetam is a novel AED that was approved at the turn of the century for the treatment of partial epilepsies with or without secondary generalisation. It is structurally related to piracetam, which is commonly used in humans to treat myoclonic seizures. Levetiracetam is efficacious in the treatment of myoclonus and progressive myoclonic epilepsies[4-10].

In the face of availability of newer AEDs such as levetiracetam, there is need to reassess the role of first generation AEDs in the treatment of myoclonic epilepsy. The majority of cats suffering from FARS suffer myoclonic and/or GTCS as part of their syndrome. This provides a unique opportunity to assess the efficacy of antimyoclonic effect of medication. The objective of this study was to explore whether levetiracetam or phenobarbital monotherapy were effective

options in the management of FARS, and hence to determine whether older AEDs, such as phenobarbital, have a role in the treatment of feline myoclonic seizures.

Materials and Methods

Study design

This prospective, multi-centre, randomised, controlled, open-label study was conducted between February 2014 and April 2015 and co-ordinated at Davies Veterinary Specialists. Following a 12-week *baseline* period, cats were randomly allocated to receive levetiracetam or phenobarbital. Directions regarding the dosage (3 – 5 mg/kg q12h PO for phenobarbital and 20 – 25 mg/kg q8h PO for levetiracetam) were given via e-mail or phone to the attending veterinarian. In the case of phenobarbital, a blood sample was collected two weeks after commencing medication to assess the serum concentration of the drug. If the dose was sub-therapeutic the dosage was increased accordingly and a blood sample was collected two weeks later until a mid-range therapeutic concentration was achieved (20 - 35 µg/mL or 86.5 - 151 µmol/l). In both treatment groups, a *titration* period of 4 weeks was included to allow the medication to reach steady-state concentrations. This period was extended in individual cats as required until therapeutic concentrations of phenobarbital were achieved. Following the titration period, a 12-week *treatment* period was observed. Patients were discontinued from the study if their owners withdrew consent, or for lack of efficacy for safety reasons. These were either due to abhorrent adverse effects or a severe increase in seizure frequency as judged by the investigator.

Patients

Cats with a diagnosis of FARS were included. Cats were recruited from the pool of owners that had previously contacted the primary author (ML) regarding a questionnaire-led phenotypic study[1] including new owners that had contacted our centre since completion of the original study.

Diagnosis was achieved by video evidence of audiogenic myoclonic seizures. For inclusion, cats had to have experienced 12 or more days of myoclonic seizures during the prospective 12-week baseline period, have been on no previous anti-epileptic medication and fulfil the criteria of the previously described phenotype for FARS[1]. Patient exclusion criteria included any concurrent disease that could represent a contraindication to the use of levetiracetam or phenobarbital, notably known pre-existing hepatic or renal dysfunction, previous or current treatment with anti-epileptic medication, or signs suggestive of a progressive brain lesion. All owners gave informed consent before participation in the study.

Assessments

Owners were requested to complete a seizure diary during the whole period of the study. They recorded the date, number, and type of seizure (GTCS, myoclonic or absence) on daily record cards. The primary investigator collated and confirmed this information with each owner and recorded it in an electronic spreadsheet. Owners were also instructed to include a record describing any signs of illness, change in activity or attitude. During the study, owners were requested to get on with daily life as normal and to make no attempts to produce the sounds responsible for eliciting their cats' seizures.

The primary efficacy variable was the responder rate for myoclonic seizure days per week. Responders were defined as those experiencing a $\geq 50\%$ decrease in the mean number of myoclonic seizure days per week during the treatment period compared to baseline. Myoclonic seizure frequency was not selected as an efficacy variable as these seizures are frequently difficult to quantify owing to their repetitiveness. Secondary efficacy variables included mean percentage reduction from baseline in myoclonic seizure days/week; rates of seizure freedom from myoclonic seizures; and the total number of myoclonic seizure free days.

Adverse events were also recorded; their intensity and relationship to study medication were judged by the primary investigator (ML) in conjunction with the attending veterinarian.

Seizure Classification

The definition of a GTCS is straightforward but includes variations beginning with a clonic or myoclonic phase. A myoclonic seizure was defined as a sudden, brief, muscular jerk involving the limbs, neck or trunk (singly or in some combination) occurring as a single or irregularly recurrent event. An absence seizure was considered as the occurrence of an abrupt, transient apparent loss of consciousness with no motor activity. These definitions are in accordance with the ILAE classification of epileptic syndromes[11].

Statistical Analysis

On the basis of a two-group continuity corrected χ^2 test, a sample size of 72 cats (36 cats randomly assigned to each treatment group) was considered sufficient to attain a statistical power of 90% for detecting a treatment difference of 40% in responder rate, assuming responder rates of 70% and 30% in the levetiracetam and phenobarbital groups respectively, and using a 5% two-sided significance level.

Two sample t-tests and Fisher's exact tests were used to compare demographics and baseline seizure history between the treatment groups. Patients failing to complete the study were excluded from further analysis.

The treatment OR and 95% CI for the responder rate in myoclonic seizure days per week was calculated using a 2x2 contingency table and Fisher's exact test. Seizure freedom rates were compared between treatment groups using Fisher exact test.

The secondary efficacy variables between treatment arms were tested with a Fisher's exact test for categorical variables and the Wilcoxon rank sums test for continuous variables

A significance level of $P < 0.05$ was established for all analyses.

Results

Patient disposition

Ninety-seven cats underwent baseline assessment, of which 29 were found to be ineligible (12 did not meet the inclusion criteria, 12 cats were lost to follow-up, 3 cats died and 2 owners withdrew consent) and were not randomised (figure 1). Therefore 68 cats were randomised (34 to levetiracetam and 34 to phenobarbital). Baseline demographic characteristics of cats that were randomly assigned to each of the study groups are given in table 1. There was no difference between treatment groups. All cats experienced myoclonic seizures during baseline with 57/68 (84%) experiencing GTCS in addition, during the study period. Only five cats (7%) had a single reported absence seizure during baseline.

The mean age of the cats at seizure onset was 15 years (median 15 years; range, 10-19 years). Thirty-six cats were female (69%; 25/36 neutered) and 32 were male (88%; 28/32 neutered). Breeds comprised of 36 domestic short-haired (DSH), 17 Birman cats, 5 Burmese cats, 3 domestic long-haired (DLH), 2 Bengal cats, and one of each of Maine coon, British Shorthair, European shorthair, Norwegian Forest cat and Birman cross.

A total of 57 cats (84%) completed the study (figure 1). Efficacy analysis therefore included a total of 57 cats (28 receiving levetiracetam; 29 receiving phenobarbital). Daily phenobarbital dose (n=29) was 3.125 mg/kg/day (median; range 1.67 - 7.5 mg/kg/day) with a phenobarbital serum concentration of 27.7 µg/mL (mean; range 20.4 - 33.2 µg/mL). The levetiracetam dose (n=28) was 62.5 mg/kg/day (median; range 60 - 93.75 mg/kg/day).

Four cats died during the course of the treatment period. Two cats in each of the levetiracetam and phenobarbital groups died during the treatment period and were not included in the efficacy analyses. Death was due to euthanasia in all cases with three cats exhibiting progressive non-seizure forebrain signs and one cat in the levetiracetam group having sudden and severe dyspnoea. No post-mortems were performed. Three owners of cats in the levetiracetam group withdrew consent and all cited the frequency with which medication was administered as their reason. One cat was lost to follow-up in the levetiracetam group. Three further cats were excluded

from the phenobarbital group during the treatment period; one owner withdrew consent, one cat was lost to follow-up and one cat developed severe lethargy and was withdrawn.

Baseline parameters

Table 2 summarises the results for the comparisons of baseline myoclonic seizure frequency in both groups. There was no significant difference between the groups.

Efficacy

Table 3 summarises these results. During the 12-week treatment period, all levetiracetam-treated cats (100%) and 1 of 29 phenobarbital-treated cats (3%) exhibited at least a 50% reduction from baseline in the number of myoclonic seizures per week (OR = 0, 95% CI: 0 to 0.0096; $P < 0.001$).

There was a significant difference in those cats experiencing a ≥ 50% decrease in myoclonic seizure days per week compared to baseline between cats receiving levetiracetam and phenobarbital (mean % reduction in seizures [± SD] levetiracetam, 98.8 [4.7]; phenobarbital, 2.8 [23.3], $P < 0.001$).

During the 12-week treatment period, 14/28 cats (50%) receiving levetiracetam were free of myoclonic seizures compared with no cats receiving phenobarbital (OR = 0, 95% CI; 0 to 0.14, $P < 0.001$).

There was a significant difference in the total number of myoclonic seizure free days compared to baseline between treatment groups (mean % increase in seizure free days [± SD] levetiracetam, 95.7 [8.80]; phenobarbital, -57.0 [54.5], $P < 0.001$).

Regarding GTCS, these were infrequent with 11/68 having no GTCS during baseline (5/34 in the levetiracetam group and 4/34 in the phenobarbital group). The median number of GTCS during baseline for all cats was one (range, 0-3). During treatment, 44/68 cats experienced GTCS (22 cats in each group) and the median number of GTCS during treatment for all cats was 0 (range,

0-1). For levetiracetam-treated cats; 23 had a decrease in the number of GTCS on treatment and 11 were excluded either due to lack of GTCS at baseline or failure to complete the study. Regarding phenobarbital-treated cats; 23 had a decrease in GTCS on treatment, two remained with the same GTCS frequency on treatment, and nine were excluded due to lack of GTCS at baseline or failure to complete the study. No absence seizures were reported during the treatment period in any cat. Consequently, statistical analysis of GTCS and absence seizures was not performed.

Safety Analysis

Safety analysis showed that 24% of cats (16/68) experienced apparent adverse events and that the majority were mild to moderate in nature. Treatment-related adverse events were reported by owners of five cats (5/34; 18%) in the levetiracetam group and included lethargy (4/5), mild inappetance (3/5), ataxia (2/5) and polydipsia (1/5). These signs resolved without any change in dosage after approximately 2 weeks. One cat experienced a serious adverse event (severe lethargy and ataxia) leading to cessation of treatment. Adverse effects were reported in 11/34 cats (32%) receiving phenobarbital, including lethargy (8/11), ataxia (4/11), weakness (1/11) and behavioural changes (1/11). In one case the lethargy was severe enough to warrant withdrawal from the study. These reported signs were relatively persistent in this population, resolving in only 2/11 cats during the treatment period.

In an extension of this study, five patients switched to levetiracetam therapy after receiving phenobarbital because their owners desired improved seizure control. Of these patients, 3/5 have reported no further myoclonic seizures and 2/5 have just one myoclonic seizure per week.

Other Information

Owners of cats in the phenobarbital group perceived no benefit from using the medication with only adverse effects reported (see above). All owners with cats receiving levetiracetam commented on their cat appearing brighter and more responsive during the treatment period

following initial transient effects of sedation and lethargy when reported. Fifteen of 28 owners (54%) had not realised their cat's mentation had altered until observing the effects during treatment.

Discussion

Feline audiogenic reflex seizures (FARS) have provided a unique opportunity to compare the efficacy of phenobarbital and levetiracetam in management of myoclonic seizures. Many owners and veterinarians alike have traditionally considered these seizures to be an age-related finding or potentially that they were associated with concurrent renal or cardiac disease. In making this false assumption this has provided a pool of drug-naïve patients on which to base the grounds of our study. We have therefore been able to evaluate the antimyoclonic efficacy of phenobarbital and levetiracetam in the management of FARS. It has long been suggested that medical management for myoclonic seizures contrasts to that for GTCS. This study provides the first veterinary evidence that levetiracetam is superior to phenobarbital in the management of myoclonic seizures.

The pharmacokinetics of levetiracetam in 10 healthy cats was evaluated following the disposition of a single dose of the drug via oral and intravenous routes[12]. Although limited information on the pharmacokinetics has been published, this study supported the use of levetiracetam at 20mg/kg three times daily. The only efficacy study of levetiracetam in cats reported its use as an adjunct to phenobarbital in 10 epileptic cats with GTCS[13]. The study reported a reduction of more than 50% in seizure frequency in 7/10 cats following administration and the medication appeared well tolerated. Our results support the tolerability, but appear to show a more dramatic response to levetiracetam when used as an anti-myoclonic medication.

Levetiracetam is indicated in people as a monotherapy in the treatment of partial-onset seizures and as adjunctive treatment of myoclonic seizures and GTCS. In a recent double-blind, placebo-controlled trial, levetiracetam (3000 mg/day) was shown to be highly effective as adjunctive therapy in 120 idiopathic generalised epilepsy patients aged 12 to 65 years with

uncontrolled myoclonic seizures. Just over half (58.3%) of these patients achieved a >50% reduction in myoclonic seizure days per week, compared with 23.3% in the placebo group [4]. Another double-blind, placebo-controlled trial has shown adjunctive levetiracetam to be effective in controlling GTCS, myoclonic seizures and all seizures type in patients with idiopathic generalised epilepsy compared with placebo[15]. The median percentage reduction in seizure days per week between the prospective baseline period and treatment period was 62.8% for levetiracetam and 24.7% for placebo. The results of these two double-blind, placebo-controlled studies are in line with the findings of open-label studies in people[16-19], confirming the usefulness of levetiracetam in idiopathic generalised epilepsies with myoclonic seizures.

It is still not clear how levetiracetam exerts its antiepileptic effect. It does not, like many other AEDs, bind to the $GABA_A$-benzodiazepine receptor complex, does not inhibit voltage-gated sodium channels and does not inhibit low-voltage-activated Ca^{2+}-channels[20]. It has been found to bind to synaptic vesicle glycoprotein SV2A, which is one of three isoforms of the SV2 protein, and the isoform most widely distributed in the brain[20]. SV2A is thought to inhibit presynaptic Ca^{2+} channels, so reducing neurotransmitter release[21]. There is a strong correlation between affinity of levetiracetam for this binding site and the seizure protection given to audiogenic mouse models of epilepsy[20]. Thus, although no molecular mechanisms of action are described for levetiracetam, it is possible that its anti-myoclonic actions are mediated via the SV2A protein.

Two studies have provided evidence that levetiracetam, unlike other AEDs, may have modulatory effects on activity-dependent plasticity and its behavioural consequences. Löscher and colleagues demonstrated that administration of levetiracetam during induction of kindling resulted in a persistent reduction in after-discharge duration, even after discontinuation of treatment in rats[22]. A second study investigated a strain of rats that developed spontaneous seizures in adulthood[23]. They were given long-term levetiracetam before these seizures developed. Even though these seizures continued to develop, a significant decrease in the frequency and duration of both tonic and absence seizures was noted compared with untreated animals. These data suggest that

levetiracetam has a different spectrum of action to other AEDs, which may relate to the novel mechanism of action via SV2A. The observation in our study of cats appearing brighter and more responsive provides tentative evidence to suggest levetiracetam influences behavioural consequences of FARS. However, it cannot be excluded that this change in demeanour may simply be the result of freedom from the myoclonic seizures and hence lack of post-ictal signs.

Rarely, patients have only myoclonic seizures as a manifestation of FARS, but more frequently, the myoclonus may predominate, and GTCS may be infrequent[1]. The predominant seizure type in the cats of our study was myoclonic, while over 80% also had GTCS and less than 10% had absence seizures. Whether a build-up of myoclonic jerks eventually leads to a GTCS is not entirely proven. Many cats are reported to be indifferent to myoclonic jerks with owners frequently electing to monitor their frequency[1]. In some, however, these constitute a concern when owners observe a train of myoclonic jerks culminating in a single GTCS. This observation, combined with the available data suggesting FARS is a progressive disorder[1] infers that early medical intervention is an advantage and when prescribed, owners perceive their cats to be brighter as a result.

Two unanswered questions from these results are, in our view: one, will levetiracetam prevent GTCS in the same way it prevents myoclonus? Potentially the answer to this is 'yes', although statistical evidence in this study is lacking. Two, will levetiracetam prevent progression to GTCS if used as an early interventional therapy? Again, the results here cannot prove this but previous work[22,23] may suggest this is a possibility.

Conclusion

In conclusion, when myoclonus is frequent in cats with FARS and when agreement exists between the owner and the veterinarian that medical treatment is justified, treatment with levetiracetam is likely to be effective. Whether it will prevent the occurrence of GTCS if used early in the course of the disease is not clear.

References

1. Lowrie M, Bessant C, Harvey RJ et al. Audiogenic reflex seizures in cats. Journal of Feline Medicine and Surgery 2015; *In Press*. DOI: 10.1177/1098612X15582080.
2. Kesner RP. Subcortical mechanisms of audiogenic seizures. Exp Neurol 1966;15:192-205.
3. Garcia-Cairasco N. A critical review on the participation of inferior colliculus in acoustic-motor and acoustic-limbic networks involved in the expression of acute and kindled audiogenic seizures. Hear Res 2002;168:208-222.
4. Genton P, Gélisse P. Antimyoclonic effect of levetiracetam. Epileptic Disorders. 2000;2:209-212.
5. Frucht SJ, Louis ED, Chuang C et al. A pilot tolerability and efficacy study of levetiracetam in patients with chronic myoclonus. Neurology. 2001;57:1112-1114.
6. Krauss GL, Bergin A, Kramer RE et al. Suppression of post-hypoxic and post-encephalitic myoclonus with levetiracetam. Neurology. 2001;56:411-412.
7. Kinrions P, Ibrahim N, Murphy K et al. Efficacy of levetiracetam in a patient with Unverricht-Lundborg progressive myoclonic epilepsy. Neurology. 2003;60:1394-1395.
8. Crest C, Dupont S, Leguern E et al. Levetiracetam in progressive myoclonic epilepsy: an exploratory study in 9 patients. Neurology. 2004;62:640-643.
9. Magaudda A, Gelisse P, Genton P. Antimyoclonic effect of Levetiracetam in 13 patients with Unverricht-Lundborg disease: clinical observations. Epilepsia. 2004;45:678-681.
10. Sharpe DV, Patel AD, Abou-Khalil B et al. Levetiracetam monotherapy in juvenile myoclonic epilepsy. Seizure. 2008;17:64–68.

11. ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1989;30:389-399.

12. Carnes MB, Axlund TW, Boothe DM. Pharmacokinetics of levetiracetam after oral and intravenous administration of a single dose to clinically normal cats. American Journal of Veterinary Research 2011;72:1247-1252.

13. Bailey KS, Dewey CW, Boothe DM et al. Levetiracetam as an adjunct to phenobarbital treatment in cats with suspected idiopathic epilepsy. Journal of the American Veterinary Medical Association 2008;15:867-872.

14. Noachtar S, Andermann E, Meyvisch P et al. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology 2008;70:607-616.

15. Berkovic SF, Knowlton RC, Leroy RF et al. Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. Neurology 2007;69:1751–1760.

16. Grünewald R. Levetiracetam in the treatment of idiopathic generalized epilepsies. Epilepsia 2005;46;154–160.

17. Labate A, Colosimo E, Gambardella A et al. Levetiracetam in patients with generalised epilepsy and myoclonic seizures: an open label study. Seizure 2006;15:214–218.

18. Specchio LM, Gambardella A, Giallonardo AT et al. Open label, long-term, pragmatic study on levetiracetam in the treatment of juvenile myoclonic epilepsy. Epilepsy Research. 2006;71:32–39.

19. Specchio N, Boero G, Michelucci R et al. Effects of levetiracetam on EEG abnormalities in juvenile myoclonic epilepsy. Epilepsia 2008;49:663–669.

20. Lynch BA, Lambeng N, Nocka K et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proceedings of the National Academy of Sciences of the United States of America 2004;29:9861-986.

21. Vogl C, Mochida S, Wolff C et al. The synaptic vesicleglycoprotein 2A ligand levetiracetam inhibits presynaptic Ca2+ channels through an intracellular pathway. Molecular Pharmacology 2012;82:199-208.

22. Löscher W, Hönack D, Rundfeldt C. Antiepileptogenic effects of the novel anticonvulsant levetiracetam (ucb L059) in the kindling model of temporal lobe epilepsy. The Journal of Pharamcology and Experimental Therapeutics 1998;284:474-479.

23. Ji-qun C, Ishihara K, Nagayama T et al. Long-lasting antiepileptic effects of levetiracetam against epileptic seizures in the spontaneously epileptic rat (SER): differentiation of levetiracetam from conventional antiepileptic drugs. Epilepsia 2005;46:1362-1370.

Figures

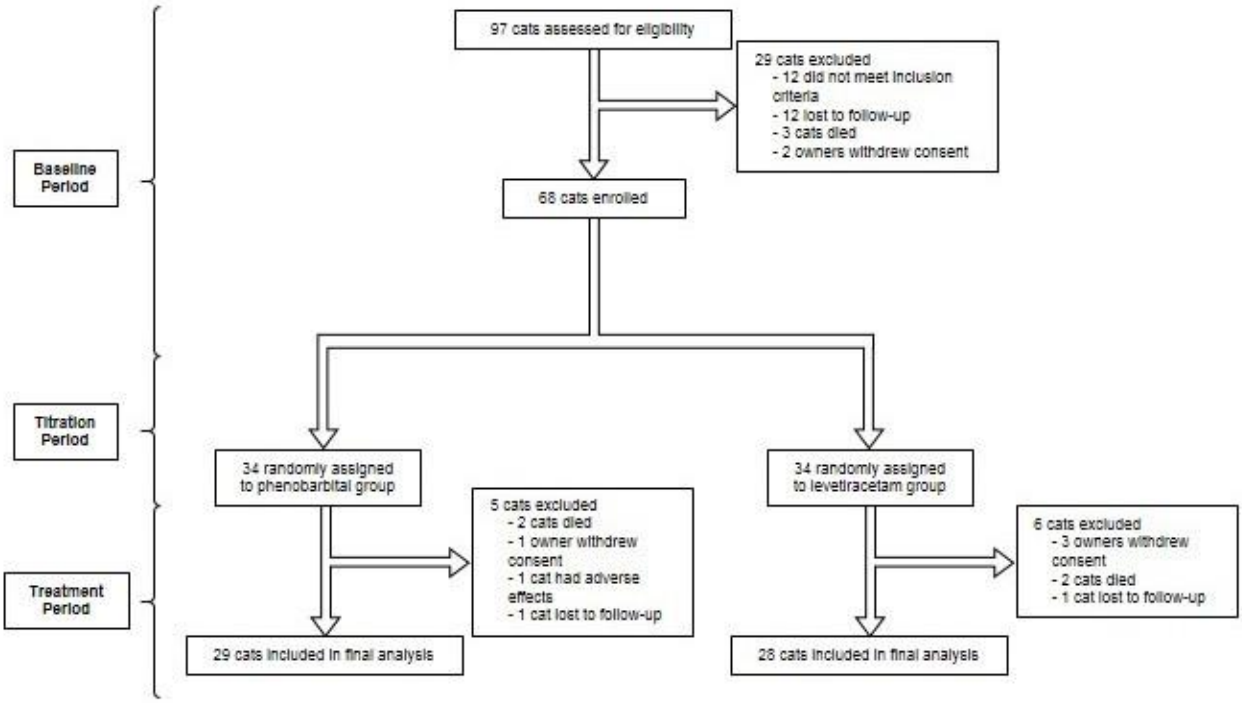

Figure 1: Trial profile.

Tables

		Levetiracetam (n= 34)	Phenobarbital (n=34)	*P*-value
Age, years		18 (12-23)	19 (13-22)	0.09
Weight, kg		4 (2-8)	4 (1-10)	0.29
Breed				0.97
	DSH	17	19	
	DLH	2	1	
	Birman	8	9	
	Other	34	34	
Sex				0.70
	F	17	15	
	FN	13	9	
	M	17	19	
	MN	11	14	
Age at onset of seizures, years		15 (10-19)	16 (10-19)	0.10
Seizure duration, years		3 (2-4)	3 (2-4)	1.00

Table 1: Baseline characteristics of cats allocated to each treatment group. Median (range). DLH, domestic long-hair; DSH, domestic short-hair; F, female; kg, kilograms; M, male; N, neutered.

	Levetiracetam Group (n=34)	Phenobarbital Group (n=34)	*P* Value
Myoclonic seizure frequency per day	2.52 (0-18)	2.3 (0-17)	0.248
Total myoclonic seizure free days	33.4 (22-53)	35 (21-43)	0.348
Myoclonic seizures per week	2.5 (0-57)	2.3 (0-51)	0.248
Myoclonic seizure days per week	4.2 (0-7)	4.1 (0-7)	0.348

Table 2: Frequency of myoclonic seizures at baseline in both treatment groups. Median (range).

	Levetiracetam Group (n=28)	Phenobarbital Group (n=29)	*P* Value
Number of cats achieving ≥50% reduction from baseline in the number of myoclonic seizures per week	28 (100%)	1 (3%)	<0.001
Mean percentage reduction from baseline in the number of myoclonic seizures per week	98.8 (±4.7)	2.8 (±23.3)	<0.001
Number of cats achieving myoclonic seizure freedom	14 (50%)	0 (0)	<0.001
Mean percentage increase in myoclonic seizure free days	95.7 (±8.8)	-57 (±54.5)	<0.001

Table 3: Efficacy of levetiracetam and phenobarbital in the management of feline audiogenic reflex myoclonic seizures. Number (percentage); mean (±standard deviation).