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Randomised clinical trial evaluating the effect of a single preappointment dose of gabapentin on signs of stress in hyperthyroid cats

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SAGE

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Abstract

Objectives The aim of this study was to evaluate the efficacy of gabapentin as an anxiolytic in hyperthyroid cats.

Methods Cats (n = 47) with confirmed hyperthyroidism were successfully enrolled. The cat owner allocated a temperament score and a transport stress score at their first visit. For the second visit the cat owner (blinded to treatment) administered either liquid gabapentin 20 mg/kg (n = 22) or an indistinguishable placebo solution (n = 25) 1 h prior to leaving home. A second transport score was allocated by the cat owner at this visit. Upon admission a compliance score was independently assigned by two veterinary nurses blinded to treatment. Excess blood from routine blood draw was analysed for gabapentin plasma concentration from cats in the gabapentin group.

Results There were no significant differences in baseline transport score between groups ($P = 0.13$), but significant differences were noted in the second visit transport score between cats medicated with gabapentin compared with placebo ($P = 0.018$). Mean compliance scores were significantly different between cats in the treatment group compared with placebo ($P = 0.019$). Further sedation was required to complete the procedures in 24% of cats in the placebo group compared to 9% in the gabapentin group ($P = 0.25$). Mean plasma gabapentin concentrations were 10.1 mg/l (range 1.7–22.7) in the gabapentin group within a 1–3 h time frame post-administration.

Conclusions and relevance Hyperthyroid cats medicated with 20 mg/kg gabapentin 1 h prior to leaving home were more relaxed during transport and more compliant with veterinary procedures than cats administered a placebo solution.

Keywords: Anxiolysis; gabapentin; hyperthyroid; hyperthyroidism; sedation

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Introduction

A study in healthy cats undergoing transportation to a veterinary clinic followed by veterinary examination has documented a positive benefit of gabapentin in reducing stress.[1] That study recommended a dose of 20 mg/kg gabapentin administered 2–3 h prior to the stressful event to provide maximum stress-reducing benefit without adverse sedation. Oral administration of gabapentin has been documented to reduce signs of stress in cats as part of a trap–neuter–return programme,[2] with a dose range of 9.2–47.6 mg/kg. The greatest effect was seen at 2 h post-treatment. Stress is a component of hyperthyroidism[3] and methods to reduce such stress are likely to be advantageous to the patient.

The hypothesis for this study was that hyperthyroid cats medicated with gabapentin at home would show reduced transport stress scores and improved compliance with handling upon arrival at the veterinary clinic vs cats in a placebo group. The aim of this study was to document the safety and efficacy of gabapentin in hyperthyroid cats.

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Materials and methods

This prospective clinical trial was conducted under an Animal Test Certificate (ATC) 49516/0001 obtained from the Veterinary Medicines Directorate (VMD) to enable use of a flavoured gabapentin solution (60 mg/ml; Bova). According to the conditions of the ATC, the study was conducted in compliance with Good Clinical Practice Guidelines. Ethical approval was obtained from the Association of Veterinary Anaesthetists (application number 40).

A sample size calculation was performed using data obtained from the first 20 cats, 10 of which were allocated to each group. The two primary outcome variables assessed were comparison of transport scores (TSs), and mean compliance score (CS). The R package 'pwr' was used to calculate sample size based on two-tailed two sample *t*-tests, a significance level of 0.05 and a power of 0.8. Calculations suggested that a sample size of 21 in each group would be expected to detect a difference of 1.5 in the TS and 1.0 in the CS.

Cats with confirmed hyperthyroidism referred to the Feline Hyperthyroid Centre (FHC) at Anderson Moores Veterinary Specialists for radioactive iodine therapy (RAI) were eligible for recruitment to this study. Recruitment was conducted at the preassessment attendance appointment in advance of the RAI being scheduled. Randomisation was performed using the random draw method in a 50:50 treatment:placebo ratio by the primary investigator. All cats had ceased antithyroid medication 8 days prior to admission, as per the FHC RAI treatment protocol. At the enrolment stage owners were asked to rate their cat's temperament using a 5-point scale (where 1 is easy to handle and 5 is unable to handle at home), and to rate their cat's level of transport stress using a 7-point scale (1 = fully relaxed, 2 = weakly relaxed, 3 = weakly tense, 4 = very tense, 5 = fearful or stiff, 6 = very fearful, 7 = terrorised). Each of these scales were used by Van Haaften et al.[1] Travel time from the owner's home to the FHC were recorded. Cats were excluded if they were suffering from chronic kidney disease (International Renal Interest Society stage 2 or above), hypertrophic cardiomyopathy American College of Veterinary Internal Medicine grade B2, if the owners were unable to medicate the cat at home, if the cat's existing temperament required treatment with gabapentin for veterinary visits, or if hepatic or neurological disease was diagnosed.

Cats were randomised to receive either gabapentin liquid 20 mg/kg PO (60 mg/ml; Bova) or an equivalent volume of the base ingredient (Bova). The cat owner was instructed to administer the solution 1 h prior to leaving home. Cats were fasted on the morning of the appointment, in accordance with the FHC RAI protocol. Cat owners were blinded to treatment group and the gabapentin or placebo solutions were visually identical.

On arrival at the FHC cats entered a cat-only waiting area, where no other cats were present. Each owner was asked to repeat their assessment of their cat's level of transport stress for this journey using the previous scale.

Upon admission, the cat underwent the following procedures conducted by two registered veterinary nurses (RVNs) in the same set order. Body temperature was evaluated using an aural thermometer (Thermoscan; Braun), pulse rate was assessed by palpation of the femoral artery and respiratory rate was counted by direct observation. Doppler blood pressure (Parkes Doppler; Thames Medical) measurement was then obtained. An area of fur on the back of the neck was clipped ready for radioactive iodine injection. A jugular blood sample was drawn for haematology, biochemistry and total thyroxine (TT4) measurement according to the RAI protocol. The two RVNs involved in these procedures were blinded to the group allocation, and each assigned the cat a CS (0 = no resistance to handling, 1 = minimally resistant to handling, 2 = struggling and difficult to handle, 3 = extreme struggling with or without urination or defaecation) independent of one another, as per Van Haaften et al.[1]

If excess blood was available from the blood draw it was placed in a serum tube, centrifuged at 9500 *g* for 2 mins (Vetspin Duo; VetLab Supplies) and couriered to a laboratory (Synlab, UK) for analysis of plasma gabapentin concentration. Samples were analysed via high-performance liquid chromatography coupled with mass spectrometry (LC-MS/MS; Agilent Technologies 1200 series High-Performance Liquid Chromatograph and 6430 Triple Quadrupole Mass Spectrometer). The LC-MS/MS assay was developed and validated in house with the linear calibration range in serum from 0.5 to 40 mg/l. Plasma gabapentin was not measured in cats in the placebo group. TT4 was measured using an ELISA (Catalyst One; IDEXX).

Once the admission procedures were completed the cat was housed in a feline-only ward awaiting radioactive iodine injection the following day. In this area the cats were observed by an RVN who was instructed to record any adverse effects. At this point the study was deemed to be finished.

Statistical analysis was conducted using Minitab 19. Data for continuous variables were tested for normality using Ryan–Joiner tests. Categorical data were analysed using Fisher's exact tests, ordinal data by Mann–Whitney tests and continuous data by two sample *t*-test if normality was satisfied; otherwise, a Mann–Whitney test was used. All Mann–Whitney tests were adjusted for ties. Correlation between plasma gabapentin levels and assessment scores for compliance and transport were examined using the Spearman rank correlation test. A Wilcoxon signed-rank test was used to compare the two CSs assigned by individual RVNs. All tests were two-tailed.

Results

A total of 67 cats were enrolled in the study. Thirty other owners did not consent to the study for a variety of reasons which, where stated, included the following: already treated with gabapentin (n = 8), owner was unable to medicate the cat (n = 8), increased alanine aminotransferase (n = 1), chronic kidney disease (n = 2) and epilepsy (n = 1). Twenty enrolled cats did not subsequently participate for a variety of reasons, including a diagnosis of neoplasia (n = 1), owner consented then did not book treatment (n = 3), owner did not collect medication (n = 1), cat was euthanased (n = 2), cat unable to be medicated owing to stress (n = 1), owner did not give the medication (n = 5), treatment cancelled by owner (n = 6) and one cat vomited after administration of the solution. This resulted in 22 cats in the gabapentin group (10/22 male neutered; 12/22 female neutered) and 25 in the placebo group (9/25 male neutered; 16/25 female neutered), and data were obtained for all 47 cats. All owners were able to administer the liquid provided. All cats were confirmed as hyperthyroid upon admission. The mean TT4 values in the gabapentin group were 174.1 nmol/l (range 73–257) and 171 nmol/l (range 80–257) in the placebo group (reference interval 0–60 nmol/l). The cats had previously been treated with carbimazole (three per group), methimazole (seven per group), thiamazole (12 in the gabapentin group, 14 in the placebo group) and one cat in the placebo group was on no medication.

Results are detailed in Table 1. There were no significant differences in age ($P = 0.79$), body mass ($P = 0.28$) or sex ($P = 0.56$) between groups. Baseline temperament scores between groups were not significantly different ($P = 0.50$). The journey times (in minutes) from the owner's home to the FHC were not significantly different ($P = 0.30$). There were no significant differences in baseline TSs ($P = 0.13$), but significant differences were noted in the TS between cats following medication with gabapentin vs placebo ($P = 0.018$). Perfect agreement between the RVNs was achieved for 94% of CSs, and there was no significant difference between the RVNs ($P = 0.79$). The mean of their CSs were significantly different between cats in the treatment group compared with placebo ($P = 0.019$). Further sedation was required to complete the procedures in 24% of cats in the placebo group compared with 9% in the gabapentin group ($P = 0.25$). The temperament score of all cats requiring sedation to enable procedures in the placebo group were 1 or 2 on a scale of 1–5, where 5 indicates the cat is unable to be handled. No adverse effects were reported in the cats following admission procedures and compliance scoring with all cats undergoing RAI.

Excess blood was available from all but two cats in the gabapentin group, as these cats were administered further gabapentin to complete procedures. Mean plasma gabapentin levels from 19 cats was 10.1 mg/l (range 1.7–22.7). The correlation between plasma gabapentin levels and TS was $r_s = -0.494$ ($P = 0.032$). The correlation between plasma gabapentin levels and mean CS was $r_s = -0.492$ ($P = 0.038$).

Discussion

Hyperthyroid cats medicated with 20 mg/kg gabapentin 1 h prior to leaving home were more relaxed during transport and more compliant with veterinary procedures than cats administered a placebo solution. These findings are in agreement with work in healthy cats.[1,2] In the gabapentin group 2/22 (9%) cats were classified as a treatment failure requiring further sedation vs 6/25 (24%) in the placebo group.

This study was conducted to assess whether the physiological changes associated with hyperthyroidism altered the pharmacodynamics of gabapentin. According to the

Table 1 Demographics and outcome measures in cats administered gabapentin 20 mg/kg or placebo 1 h prior to transport to a veterinary hospital

	Mean (median) placebo (n = 25)	Mean (median) gabapentin (n = 22)	*P* value
Age (years)	11.78	11.59	0.791
Body mass (kg)	3.89	4.15	0.280
Sex (MN)*	9 (36)	10 (45)	0.562
Temperament score	1.68 (1)	1.86 (1)	0.497
Journey time from home (mins)	58 (45)	68 (60)	0.302
Transport score visit 1	4.12 (4)	3.50 (3)	0.133
Transport score visit 2	3.08 (3)	2.27 (2)	0.018
Compliance score first RVN	1.72 (2)	0.91 (1)	0.016
Compliance score second RVN	1.68 (2)	0.91 (1)	0.026
Mean compliance score	1.70 (2)	0.91 (0.75)	0.019
Additional sedation required*	6 (24%)	2 (9%)	0.253

*Data are n (%)
MN = male neutered; RVN = registered veterinary nurse

RAI treatment protocol, all cats had stopped oral antithyroid medications 8 days prior to admission and were confirmed as being hyperthyroid. Gabapentin was chosen for this study as a result of clinical experience based on the work of Van Haaften et al,[1] and in the absence of a licensed product for this purpose in cats or another non-licensed medicine with documented efficacy at the time of study design.

The aforementioned study[1] reached these conclusions without consideration to a sample size calculation. Those authors studied 20 pet cats, 11 in the gabapentin group and nine in the placebo group. We recruited 10 cats per group in the initial phase of the study and these results were used for a sample size calculation. Our effect size was determined based on the results of Van Haaften et al[1] and clinical experience – using a difference of 1.5 points on a 7-point scale for TS and difference of 1 point on a 4-point scale for CS.

In the present study, temperament was assessed by cat owners at the recruitment stage to verify if there were differences between groups that could affect the results and this question was asked again at admission for RAI treatment. There were no significant differences in temperament between groups. The temperament of all cats requiring sedation to enable procedures in the placebo group were 1 or 2 on a scale of 1–5, where 5 indicates that the cat cannot be handled, demonstrating that apparently calm cats become stressed in a veterinary environment. This could also be related to the fact that temperament scores were assigned at the preassessment appointment, and at the admission appointment when cats were no longer receiving antithyroid medication but the cat owner still scored their cat according to their previous perception. Initial scores were not made available to clients at this stage.

Gabapentin 100 mg capsules were used by Van Haaften et al[1] with one capsule per cat, which led to some inaccuracy in dosing and a dose range of 13.0–29.4 mg/kg. Those authors concluded that 20 mg/kg gave the best balance of sedation for the desired purpose, without excessive or long-duration sedation. To dose accurately, a liquid preparation was selected for the present study and it was a compounded formulation with a roast chicken flavour. Despite the flavouring, the bitterness of gabapentin is difficult to disguise. The solution was well tolerated by the majority of cats. One cat vomited after administration of the solution and was removed from the study. Initially, the VMD determined that a human preparation of gabapentin should be used, in close accordance with the prescribing cascade where a human medicine should be used before a compounded formulation where a veterinary licensed product is not available. Experience demonstrates that this human formulation is highly unpalatable, and we were concerned that this would affect recruitment to the study. Although the palatability of human gabapentin for cats is poorly documented in the literature, the VMD accepted our argument for the flavoured compounded preparation when presented with quality-assurance data from the manufacturer.

The RVNs who assessed the CSs were experienced nurses familiar with working in a cat-only environment using low-stress handling techniques. A score of 3 was assigned to any cat that struggled and according to standard practice no attempts were made to inappropriately restrain any cats. The CS assigned by each RVN was examined statistically and significant differences between RVNs were not observed.

Gabapentin plasma concentrations demonstrated correlation with both TSs and CSs, our measures of stress reduction. The timing of gabapentin administration to achieve peak plasma levels at a 2–3 h point after administration was based on the recommendations of Van Haaften et al[1] and supported by pharmacokinetic data in healthy cats,[4] in the absence of pharmacokinetic data for hyperthyroid cats. After administration of 10 or 30 mg/kg PO, peak plasma gabapentin concentration was detected at 120 and 90 mins, respectively.[4] We could therefore suggest that 20 mg/kg might achieve peak concentration within this time range, because those authors documented a dose-related effect. However, we should note there could be differences in pharmacokinetics in euthyroid and hyperthyroid cats. In the present study plasma concentrations within a 1.5–3 h post-administration window ranged from 1.7 to 22.7 mg/l (mean 10.1). In the previous pharmacokinetic study[4] values of 10 mg/l 120 mins after 10 mg/kg PO and 25 mg/l 90 mins after 30 mg/kg were documented in healthy cats. The laboratory reference interval is 2–20 mg/l, although this reference interval is not specific to anxiolysis, as no such work has been conducted to date.

Conclusions

Gabapentin liquid 20 mg/kg PO administered 1 h prior to leaving home and 2 h prior to veterinary treatment is a safe and effective option for reducing stress in hyperthyroid cats requiring veterinary treatment.

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Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned)

animals and procedures that differed from established internationally recognised high standards ('best practice') of veterinary clinical care *for the individual patient*. The study therefore had prior ethical approval from an established (or ad hoc) committee as stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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