Original Article

jfms Journal of Feline Medicine and Surgery

Journal of Feline Medicine and Surgery
1–9
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DOI: 10.1177/1098612X17719399
journals.sagepub.com/home/jfms

This paper was handled and processed by the American Editorial Office (AAFP) for publication in *JFMS*

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Use of single-dose oral gabapentin to attenuate fear responses in cage-trap confined community cats: a double-blind, placebo-controlled field trial

Katherine E Pankratz[1], Kelli K Ferris[1], Emily H Griffith[2] and Barbara L Sherman[1]

Abstract

Objectives This double-blind, placebo-controlled study evaluated the safety and efficacy of single-dose oral gabapentin administered for the attenuation of fear responses in cage-trap confined community cats.

Methods Community cats presented in cage traps for trap–neuter–return (TNR) were recruited and screened for inclusion. Each enrolled cat was randomly assigned and administered one of three equal-volume, single-dose treatments: placebo, low-dose gabapentin (50 mg) or high-dose gabapentin (100 mg). At baseline, 1, 2, 3 and 12 h post-administration, a single, blinded observer scored each cat for signs of fear and sedation using published paradigms, calculated the respiratory rate and documented any observable facial injuries.

Results: Fifty-three cats met the inclusion criteria and completed the study. Cat stress score (a measure of fear) was lower in cats that received gabapentin (50 or 100 mg) than in cats that received placebo (50 mg: $P = 0.027$; 100 mg: $P = 0.029$), with the greatest reduction at 2 h post-treatment ($P = 0.0007$). Respiratory rates did not differ between treatment groups. There was no difference in sedation scores between the groups ($P = 0.86$) at any time point ($P = 0.09$). Cat facial injuries did not vary by treatment group or over time. No adverse effects were detected specific to gabapentin administration. At 1 h, hypersalivation was observed in four cats across all treatment groups. All cats recovered from surgery and anesthesia uneventfully.

Conclusions and relevance This study supports the hypothesis that 50 mg or 100 mg gabapentin (9.2–47.6 mg/kg per cat) reduces fear responses in confined community cats without measurable sedation over 3 h post-administration vs placebo. Gabapentin treatment was well tolerated in this population of cats. Further studies are recommended to investigate the use of oral gabapentin earlier in the TNR process, such as immediately after trapping or prior to transport for the prevention of confinement-related injuries.

Accepted: 12 June 2017

Introduction

As a commonly used method to address overpopulation of unowned community cats, trap–neuter–return (TNR) programs capture, confine and transport cats to a suitable facility for surgical sterilization under anesthesia before returning them to their site of capture.[1] Cats unaccustomed to confinement and close proximity to people may express fear responses.[2] Fear responses, often called 'stress' responses, are expressed through behavioral and physiological signs.[3,4] Behavioral signs may include crouched posture, vocalization and escape attempts with resulting injury.[5,6] Physiological signs may include dilated pupils and elevated respiratory rate.[5,7] Overall, these fear responses negatively affect the welfare and health of community cats in TNR programs.

Administration of a safe, single-dose pharmacologic agent that attenuates cat fear responses during confinement, transport and handling could improve feline welfare.

[1]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, USA
[2]Department of Statistics, College of Agriculture and Life Sciences, North Carolina State University, Raleigh, NC, USA

Corresponding author:
Barbara L Sherman MS, PhD, DVM, DACVB, DACAW, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1060 William Moore Drive, Raleigh, NC 27607, USA
Email: barbara_sherman@ncsu.edu

Currently, there are few safe and effective pharmacologic options available for cats. Acepromazine, a phenothiazine tranquilizer, may produce paradoxical excitation and hypotension. Diazepam, a benzodiazepine anxiolytic, is associated with the risk of fulminant hepatic failure.[8] Recently, trazodone, a serotonin antagonist and reuptake inhibitor, was shown to decrease anxiety in client-owned cats during veterinary examination but caused signs of sedation in laboratory cats.[9,10]

Gabapentin, an antiepileptic medication, has been shown to decrease anxiety in rats and humans,[11–13] but its behavioral effects have not been studied in cats. Although its structure mimics gamma-aminobutyric acid (GABA), gabapentin does not interact with $GABA_A$ and $GABA_B$ receptors, does not inhibit GABA uptake nor does it become a GABA agonist.[14,15] However, gabapentin binds and blocks the effects of the alpha-2-delta subunit of the voltage-dependent calcium channel and results in decreased anxiety.[16] A single-dose of oral gabapentin given to cats demonstrates good bioavailability with no adverse events reported with doses as high as 30 mg/kg.[15,17] Anecdotal use in cats prior to veterinary visits and during TNR programs suggests that gabapentin may also attenuate anxiety and fear responses in cats (KK Ferris, 2016, personal communication).[18]

We hypothesized that cage-trap confined community cats given a single dose of oral gabapentin (50 mg/cat or 100 mg/cat) vs cats given placebo would show: (1) lower fear responses, as quantified using a published feline stress scale; (2) lower respiratory rates; (3) no appreciable sedation; and (4) fewer additional injuries while confined to holding cage traps prior to surgical sterilization. Further, we hypothesized that cats given a higher dose of gabapentin (100 mg/cat) would have a lower cat stress score (CSS) than cats given a lower dose (50 mg/cat). Finally, we aimed to observe all cats for adverse events as a function of 50 mg/cat and 100 mg/cat gabapentin doses vs placebo.

Materials and methods

All study protocols were approved by the North Carolina State University Institutional Animal Care and Use Committee.

Animals

As part of a regional TNR program on Hatteras Island, NC, USA, a local community volunteer group captured community cats in individual humane live cat cage traps. The prior experiences and socialization history of the cats were unknown. The cats were transported by vehicle to a temperature-regulated building for holding prior to surgical sterilization. Cats were confined in their individual cage traps. In order to minimize fear responses in each cat due to a new environment with close proximity to unfamiliar cats and people, volunteers and investigators moved slowly and talked quietly in the room.[19] Each cage trap was covered by a separate piece of lightweight sheeting fabric to reduce visual stimuli. Each cat was left undisturbed unless necessary for the study's procedures and observations. For inclusion in this study, a veterinarian (KEP) visually screened the cats to identify those estimated to be over 4 months of age. Age estimation was based on cat size and was later confirmed under anesthesia by evidence of permanent canine tooth eruption. In addition, the veterinarian evaluated the health of each cat using the American Society of Anesthesiologists' (ASA) categories, including those cats that fell within categories ASA I (normal, healthy patient) and ASA II (patients with mild systemic disease or minor injuries) (https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system). Cats not presented in cage traps, estimated to be younger than 4 months of age or those that fell within categories ASA III–VI (severe systemic illness or severe injuries) were excluded from this study.

Cats were screened between 5 and 6 PM, treated between 6 and 8 PM, and observed subsequently under room lighting, as described below. All cats included in the study were fasted for a minimum of 12 h in preparation for anesthesia and surgery in the NC State College of Veterinary Medicine Mobile Hospital.

Treatments

Another veterinarian (KKF) not involved in study data collection and blind to treatment randomly assigned each cat that met the inclusion criteria to one of three treatment groups (A, B and C). The North Carolina State Pharmacy prepared and randomized the test articles. Treatments were assigned such that within every group of three cats enrolled in the study, each cat was randomly assigned to a different treatment group (A, B or C) using a randomization table. KKF orally administered the designated treatment (A) low-dose gabapentin (50 mg) (gabapentin 50 mg/ml); (B) placebo; or (C) high-dose gabapentin (100 mg) (gabapentin 100 mg/ml) to the assigned cat. These doses were chosen based on prior experience and anecdotal reports of 50 mg or 100 mg doses given orally in cats (KK Ferris, 2016, personal communication).[17,18] Each cat was administered identical total volume (1.0 ml) of test article using a standardized suspension product (50/50 Ora-Plus/Ora-Sweet mix [Ora-Plus suspending vehicle, Ora-Sweet flavored syrup vehicle; Perrigo]). The product was formulated to standardize the volume administered to each cat.

For test article administration, a veterinarian (KKF) drew up into a 3 cc syringe attached to a 5.5" open tom cat catheter the assigned treatment from a bottle labeled A, B or C. Experienced in these techniques, KKF inserted a trap divider (Humaniac Trap Divider; Animal Care Equipment and Services) deliberately and carefully into

Figure 1 Photograph demonstrating oral test article administration using a catheter attached to a dosing syringe to an in-cage confined community cat

each cage trap to direct the cat to one end, thus temporarily restricting the cat's movement. The cat remained immobile with minimal movement. Then, KKF advanced a catheter tip through the wire caging into the cat's oral cavity and administered the test article orally (Figure 1). Then, KKF monitored the cat's response and assured full administration of the test article. The trap divider was removed. The time of treatment administration was defined as t = 0 h.

Assessments

After being screened, cats were left undisturbed in their individual covered cage traps, in a lighted room for 30 mins. Then, a veterinarian (KEP) began observational data collection starting with baseline values, followed by single treatment performed by KKF, as described, above. At each assessment time point, the sheet covering the cage trap was retracted, the observations made and the sheet replaced.

The primary investigator (KEP) assessed fear response, sedation and respiratory rate before treatment (baseline) and 1, 2, 3 and 12 h after treatment. Fear and sedation were based on each cat's response to cage-trap cover removal and posture using a modified McCune's CSS (a measure of fear responses)[5] and a global sedation score (GSS) modified from Hopfensperger et al.[20] The CSS ranged from 1 (fully relaxed) to 7 (terrorized) (Table 1; see supplementary material Appendix 1 for scale description). The GSS ranged from –3 (very excitable) to 3 (very sedated) (Table 1; see supplementary material Appendix 2 for scale description). Respiratory rate was determined by counting chest excursions over 15 s and multiplying by 4 to determine breaths per minute.

In addition, the primary investigator visually assessed each cat's face for fresh injuries and assigned a facial injury score at three time points: baseline, 12 h and while under anesthesia for sterilization surgery. Facial injury score was assigned based on a scale ranging from 1 (superficial injuries) to 4 (severe injuries) defined a priori (Table 1).

Anesthesia and surgery

After 12 h, veterinary students, supervised by the primary investigator (KEP), weighed each cat and induced anesthesia with an intramuscular injection of tiletamine HCl and zolazepam HCl (Telazol; Zoetis) initially at 0.022 mg/kg and then to effect. After anesthesia was induced, it was maintained with a non-rebreathing system of isoflurane (Isoflurane; Pirimal Health Care) in oxygen delivered via a mask (males) or via intubation (females). While under anesthesia, the primary

Table 1 Cat stress score (CSS), global sedation score (GSS) and facial injury score

Score	CSS (adapted from Kessler and Turner)[5]	GSS (adapted from Hopfensperger et al)[21]	Facial injury score
+7	Terrorized		
+6	Very fearful		
+5	Fearful, stiff		
+4	Very tense		Severe active bleeding or 5+ superficial injuries or 2+ deep injuries or tissue loss
+3	Weakly tense	Very sedated	Moderate/slow active bleeding or 3–5 superficial or one deep scratch/laceration/abrasion/puncture
+2	Weakly relaxed	Somewhat sedated	Mild/slow active bleeding or 2–3 superficial scratches/ lacerations/abrasions/punctures
+1	Fully relaxed	Subtle signs of sedation	Superficial scratch/laceration/abrasion/puncture
0		Normal	No injuries observed
–1		Subtle signs of excitation	
–2		Somewhat excitable	
–3		Very excitable	

investigator recorded any abnormal physical examination findings and assigned a facial injury score for each cat. Veterinary students under the direction of a veterinarian (KKF) performed the sterilization surgeries and when recovered sufficiently returned the cats to their cage traps. After postoperative visual examination, the local rescue group volunteers returned the cats to their place of capture for release.

Adverse events

At each time point during the course of the study, cats were observed for any adverse events and these were recorded.

Statistical analysis

Data were stored in a spreadsheet software program (Microsoft Excel 2010) and subsequently analyzed for statistical significance using SAS 9.4 (StatSoft).

A power analysis was performed a priori to determine the minimum sample size needed to ensure adequate power to detect a clinically significant effect. A power analysis was conducted using an ANOVA with three groups and five measurements in G-Power[21] to determine a sufficient sample size; alpha was set at 0.05 and power was set at 0.80. Based on these assumptions, the sample size necessary for detecting a large effect size was 12 ($f = 0.40$), a medium effect size was 27 ($f = 0.25$) and a small effect size was 153 ($f = 0.10$).

Fisher's exact test, appropriate for testing independence between two nominal variables with small sample sizes, was used to test baseline differences in age category and sex between treatment groups. A one-way ANOVA was used to test baseline differences in weight between treatment groups. The ANOVA assumptions include normality and constant variance, and those assumptions were confirmed using residual diagnostics.

Respiratory rate was modeled using a repeated-measures ANOVA, allowing for effects of treatment group, time, treatment group by time interaction, and day. The repeated-measures ANOVA assumes that the respiratory rates at each time have a common covariance matrix and follow a multivariate normal distribution. Owing to a violation of the sphericity assumption, Huynh–Feldt estimators were used for univariate comparisons. Post-hoc comparisons of statistically significant specific days, times and treatment groups were made using least-squares mean differences, and Tukey's adjustment for multiple testing was used.

CSS and GSS were modeled separately using repeated-measures ordinal logistic regression due to the ordinal nature of the score data, allowing for effects of treatment group, time, treatment group by time interaction and day. In ordinal logistic regression, the response is the probability of moving to a lower score category. The repeated-measures nature of this data means that generalized estimating equations were used to obtain valid tests in the presence of within-subject effects. Post-hoc comparisons of statistically significant specific days, times and treatment groups were made using linear contrasts to test specific treatment effects. The Holm–Sidak adjustment was used to control the family-wise error rate.

Owing to the high frequency of facial injuries at baseline and significant injuries not observed until physical examination under anesthesia, the data obtained on facial injury scores were not used for statistical analysis. A P value of <0.05 was considered significant.

Results

Animals

Fifty-nine community cats were screened for enrollment in this study, conducted 14–17 March 2016. Prior to enrollment, three cats were excluded as they did not meet the inclusion criteria based on age (n = 2) and cage-trap style (n = 1). Of the remaining 56 enrolled cats, three were later withdrawn after examination under anesthesia revealed chronic medical pathologies or severe injuries not visible during examination when awake in their cage traps. Pathologies consisted of multiple abscesses to all four paws (n = 1), severe pododermatitis on all four paw pads (n = 1) and a chronic left hock fracture (n = 1). The remaining 53 cats consisted of 21 intact males, 30 intact females and two spayed females (Table 2). Mean body weight was 3.1 kg (6.8 lb; range 1.4–5.4 kg [3.1–11.9 lb]) and mean estimated age was 15 months (range 4 months to >2 years) (Table 2). The distribution of estimated ages was 4–6 months (n = 3), 6–9 months (n = 10), 9–12 months (n = 14) and >12 months (n = 26) (Table 2). Baseline assessments were performed, on average, 26 mins (SD = 12.24; SE = 1.68) prior to treatment administration.

Treatment groups

The treatment groups consisted of placebo (n = 19), low-dose gabapentin (n = 17) and high-dose gabapentin (n = 17) (Table 2). Cats in the three treatment groups were similar with regard to sex ($P = 0.77$), age ($P = 0.90$) and weight ($P = 0.75$) (Table 2). The test article was successfully administered to all cats. On the basis of body weight determined post-hoc, mean gabapentin doses were 0 mg/kg/dose (placebo), 16.3 mg/kg/dose (low-dose gabapentin) and 35.3 mg/kg/dose (high-dose gabapentin), (Table 2). Gabapentin doses ranged from 9.2–47.6 mg/kg/dose (4.2–21.6 mg/lb/dose) (Table 2).

CSS

There was an overall treatment effect, time effect, treatment by time effect and day effect on CSS. After baseline, cats in both low- and high-dose gabapentin treatment groups overall demonstrated a lower CSS over time than placebo (50 mg: $P = 0.027$; 100 mg: $P = 0.029$). Cats that

Table 2 Demographics and total number of facial injuries observed during physical examination under anesthesia in this double-blind, placebo-controlled study of gabapentin to reduce fear in cage confined community cats

	Treatment group			
	Placebo	Low-dose gabapentin	High-dose gabapentin	Total
Gabapentin dose (mg)	0	50	100	
Mean dose (mg/kg)	0	16.3	35.3	
Dose range (mg/kg)	0	9.2–24.4	23.1–47.6	
Sample size	19 (35.8)	17 (32.1)	17 (32.1)	53
Age (months)				$P = 0.90$
4–6	2 (3.8)	0 (0.0)	1 (1.9)	3 (5.7)
6–9	4 (7.5)	2 (3.8)	4 (7.5)	10 (18.9)
9–12	3 (5.7)	6 (11.3)	5 (9.4)	14 (26.4)
>12	10 (18.9)	9 (17.0)	7 (13.2)	26 (49.0)
				mean = 15 months
Mean weight (kg)				$P = 0.75$
	3.0	3.4	3.0	3.1
Sex				$P = 0.77$
Male intact	6 (11.3)	8 (15.1)	8 (15.1)	21 (39.6)
Female intact	12 (22.6)	9 (17.0)	8 (15.1)	30 (56.6)
Female spayed	1 (1.9)	0 (0.0)	1 (1.9)	2 (3.8)
Facial injuries (detected under anesthesia)				
Nasal bridge scratch	1 (1.9)	5 (9.4)	5 (9.4)	11 (20.7)
Nasal bridge abrasion	3 (5.7)	2 (3.8)	0 (0.0)	5 (9.4)
Gingival abrasion	1 (1.9)	0 (0.0)	2 (3.8)	3 (5.7)
Facial scratches	0 (0.0)	3 (5.7)	0 (0.0)	3 (5.7)
Lip scratch	0 (0.0)	1 (1.9)	1 (1.9)	2 (3.8)
Lingual abrasion	0 (0.0)	1 (1.9)	1 (1.9)	2 (3.8)
Fractured tooth	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)
Epistaxis	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.9)
Deep lacerations	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)
Total cats injured per group	7 (13.2)	9 (17.0)	7 (13.2)	23 (43.4)

Data are n (%) unless otherwise indicated

received 50 mg gabapentin vs placebo had a lower CSS at 2 h ($P = 0.035$) and 3 h ($P = 0.029$) (Figure 2). Cats that received 100 mg gabapentin vs placebo had a lower CSS at 2 h ($P = 0.029$) and 3 h ($P = 0.020$) (Figure 2). However, there was no difference between the low-dose and high-dose gabapentin groups ($P = 0.79$).

Across treatment groups over the first 3 h of observation, there was a parallel decline in CSS ($P = 0.0005$) compared with baseline CSS. The lowest CSS overall occurred at 2 h ($P = 0.0007$). CSS at 1 h was significantly lower compared with baseline ($P = 0.005$) and CSS at 2 h was significantly lower than at 1 h ($P = 0.04$). CSS at 2 h and 3 h were not different ($P = 0.97$). CSS at 12 h was not different from 1 h ($P = 0.221$) or from baseline ($P = 0.226$) (Figure 2). There was a difference in CSS between day 1 and day 3 ($P = 0.030$). Cats enrolled on day 3 had a lower CSS overall than cats enrolled on day 1 ($P = 0.012$).

Respiratory rate

There was an overall time effect on respiratory rate. Over the first 3 h of observation in all treatment groups (means: baseline = 66; 1 h = 54; 2 h = 47; 3 h = 45), there was a decline in cats' respiratory rate ($P < 0.0001$). At 1 h in all treatment groups, respiratory rate was lower than at baseline ($P < 0.001$). Respiratory rate did not differ between 1 h and 2 h ($P = 0.50$) and between 2 h and 3 h ($P = 0.09$). At 12 h (mean = 52), cat respiratory rate was higher than at time 3 h ($P = 0.01$) but remained lower than baseline ($P < 0.0001$) (Figure 3).

There was a treatment by time effect on respiratory rate between high-dose gabapentin and placebo. At 1 h, cats that received high-dose gabapentin had lower respiratory rates than cats that received placebo ($P = 0.03$) but not at 2 h ($P = 0.07$) or at 3 h ($P = 0.80$). At no time point, was there a difference in respiratory rate between

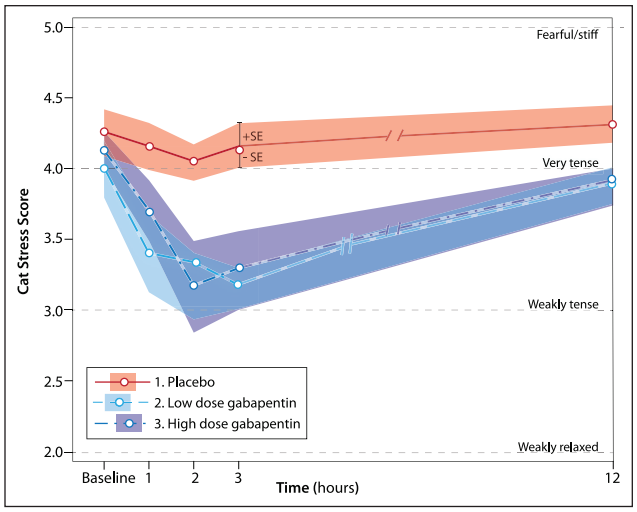

Figure 2 Mean and SE of the cat stress score (CSS) over time of 53 cage-confined community cats that received a single oral dose of either placebo, low-dose gabapentin (50 mg) or high-dose gabapentin (100 mg). Over the first 3 h of treatment administration, cats that received gabapentin showed significantly lower CSS compared with cats that received placebo (50 mg: $P = 0.003$; 100 mg: $P = 0.005$)

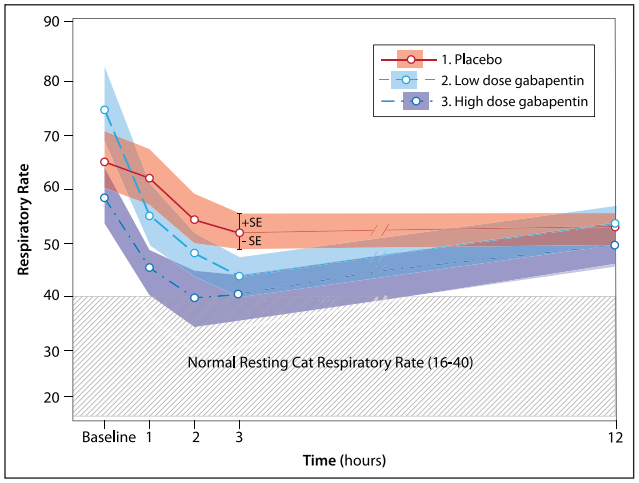

Figure 3 Mean and SE of the respiratory rate (breaths per minute) over time of 53 cage-confined community cats that received a single oral dose of either placebo, low-dose gabapentin (50 mg) or high-dose gabapentin (100 mg). Over the first 3 h of treatment administration, respiratory rate in all cats declined compared with baseline, regardless of treatment group ($P < 0.0001$)

cats that received low-dose gabapentin or placebo (1 h: $P = 0.59$, 2 h: $P = 0.61$, 3 h: $P = 1.000$) (Figure 3). For all treatment groups, no day effect was observed for respiratory rate ($P = 0.120$).

GSS

There was no treatment effect, time effect, treatment by time effect or day effect on the GSS. There was no difference in sedation scores between the three treatment groups at any time point ($P = 0.86$) nor within each group over time ($P = 0.09$) nor day effect ($P = 0.2254$) (Figure 4).

Facial injury score

Twenty cats at baseline and 16 cats at 12 h had visible external facial injuries observed through the cage traps. Facial injuries were observed in all treatment groups at baseline (placebo: n = 9; low-dose gabapentin: n = 6; high-dose gabapentin: n = 5) and at 12 h (n = 5; n = 5; n = 6, respectively). Since evidence of facial injuries was not sensitive to detection over time, the injury scores were not used for statistical analysis.

During physical examination under anesthesia, evidence of fresh (within the prior 24 h) facial injuries was found in cats within each treatment group (placebo: n = 8; low-dose gabapentin: n = 9; high-dose gabapentin: n = 7) (Table 2). Facial injuries included superficial scratches over the nose (n = 11), face (n = 3) and lip (n = 2), abrasion on the nasal bridge (n = 5), gingival abrasion (n = 3) and lingual abrasion (n = 2) (Table 2). Uncommon facial injuries included fractured tooth (n = 1), epistaxis (n = 1) and deep lacerations (n = 1) (Table 2).

Anesthesia and surgery

All 53 cats meeting inclusion criteria underwent anesthesia and surgery within normal expected parameters. All cats recovered uneventfully from anesthesia.

Adverse events

No adverse events specific to gabapentin administration were detected. All cats appeared to tolerate the temporary within-cage restraint required for test article administration without obvious behavioral effects. An adverse event of hypersalivation was noted in four cats (placebo: n = 2; low-dose gabapentin: n = 1; high-dose gabapentin: n = 1) at 1 h post-treatment administration and resolved by 2 h post-treatment. No vomiting, diarrhea, tremors or other side effects were observed in any cat at any dose throughout the course of the study.

Discussion

Our findings demonstrate that at 2 and 3 h after administration, community cats that received a single oral dose of 50 mg or 100 mg gabapentin displayed significantly lower CSS than cats that received placebo. This finding is consistent with a pharmacokinetic study of single-dose gabapentin in cats that achieved peak plasma concentration at 100 ± 22 mins after oral administration.[15] At 12 h after gabapentin administration, the CSS returned to baseline levels, which is consistent with the significant decline in gabapentin plasma concentration 12 h post-administration.[15] Since cats were not assessed between 3 and 12 h after gabapentin administration, the total duration of the

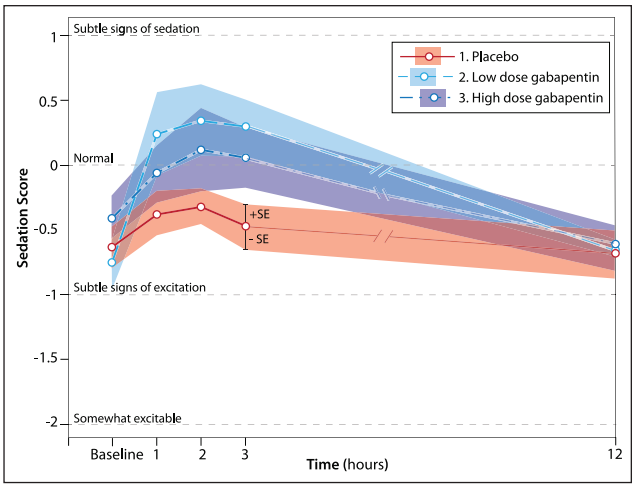

Figure 4 Mean and SE of the global sedation score (GSS) over time of 53 cage-confined community cats that received a single oral dose of either placebo, low-dose gabapentin (50 mg) or high-dose gabapentin (100 mg). There was no difference in the GSS between the treatment groups at any time ($P = 0.86$)

behavioral effects of gabapentin was not identified. Only a single oral dose of gabapentin was used for each cat in our study and the effect of repeated doses was not assessed. While not directly tested, these findings suggest that gabapentin may be beneficial in lowering cat fear responses during procedures performed between 2 to 3 h after administration. Further studies are necessary to determine the duration of gabapentin efficacy between 3 and 12 h post-administration, with repeated doses, and during other procedures such as handling.

Over 1, 2 and 3 h after test article administration, cats across treatment groups showed a parallel decline in respiratory rate, presumably as the holding facility became quieter and cats acclimated to the environment. This study's effort aimed to provide a quiet environment free of other species except people in an effort to minimize additional environmental stressors.[19] The parallel decline in respiratory rate across all treatment groups over time is consistent with reduction in fear responses that could be attributed to acclimation to environmental conditions over time. A cat's normal resting respiratory rate should fall between 16 and 40 breaths per minute. Although not statistically significant, over the first 3 h after test article administration, the mean respiratory rates for the gabapentin-treated cats were lower than the mean respiratory rate for the placebo-treated cats. When comparing our results to another study of respiratory rates in 30 client-owned cats measured at home (mean = 50) compared with the veterinary hospital environment (mean = 58),[7] our findings appear consistent with cats exposed to a change in environment.

All cats enrolled in this study underwent baseline assessments followed by brief temporary in-cage restraint for oral administration of treatment. Although the baseline measurements were collected prior to treatment administration procedures as a measure for comparison and no elevation in CSS or respiratory rate were observed at 1 h, this procedure could have contributed to fear responses in this population of cats. Further studies could evaluate the fear responses of confined community cats that do not undergo additional temporary in-cage restraint and oral treatment administration.

Although variable signs of relaxation were observed, there was no difference in sedation scores at any time or for any treatment. This suggests that under our field confinement conditions with this GSS scheme, gabapentin does not produce a noticeable sedation effect at the doses used in this study. However, with a larger sample size, evidence of sedation may be discovered. Since the cats were not handled, subjected to provocative tests or observed during motor activities, subtle sedation effects could not be detected. The published canine GSS was chosen and applied here as an evaluation of the animal's posture without generating stimuli that could sensitize cats housed in neighboring cage traps. Published feline sedation scales were not used because they require assessment of the cat's responses to environmental stimuli, such as a hand clap, which could disturb and confound evaluation of cats housed nearby.[22–24] In addition, published sedation scales require cat handling. Handling would have imposed distress and risk of escape for these community cats, that may have had limited human contact. In addition, handling the cats would have posed an injury risk to the evaluator. As a result of cage restriction and lack of provocative testing, this study might have underestimated the sedating effects of gabapentin. Further studies that evaluate subtle signs of sedation are recommended.

Overall, this study's findings are consistent with veterinary clinical recommendations that gabapentin doses of 50 mg and 100 mg per cat attenuate anxiety in cats. These recommendations also include gabapentin doses as high as 150 mg per cat as a means to reduce anxiety in the veterinary clinic, a dose not assessed in the present study.[18] Further studies could be performed to determine the effect of gabapentin on cat anxiety, including client-owned cats, prior to transport as a pretreatment to crate confinement, travel and clinical evaluation for low-stress veterinary visits.

Although this study aimed to evaluate the effect gabapentin had on fear responses in confined community cats, the influence of environmental measures cannot be neglected. Throughout the study, all efforts were made to minimize exposure to people, maintain a calm and quiet environment, and to leave the cats undisturbed whenever possible.[19]

At the baseline assessment post-capture and transport, facial injury assessment visualized through the cage traps discovered fresh facial injuries in all groups,

but no additional injuries were observed during the study. Since many cats displayed fresh facial injuries at the baseline assessment, these recent injuries are likely to have resulted from fear responses and escape attempts during the trapping, confinement and transport phases, prior to this study. While deserving of further research, the peak time of effect for gabapentin in this study suggests that gabapentin may be most beneficial if administered earlier in the trap, confine, transport, hold sequence of the TNR program. For example, gabapentin administration immediately after trapping or prior to transport may reduce cat fear responses in their cage traps during confinement and transport and decrease resulting confinement-associated injuries.

This study supports the safety of a single oral dose of gabapentin to community cats. All cats tolerated gabapentin at a wide dose range (9.2–47.6 mg/kg per cat). The only observed adverse event was hypersalivation, noted in four cats (<1% of the study population), 1 h after test article administration. This phenomenon was observed across treatment groups. Hypersalivation could have been a consequence of fear associated with temporary restraint, irritation associated with insertion of the catheter tip into the cat's mouth or a reaction to the taste of the oral suspension. After treatment, all 53 cats successfully underwent anesthesia and recovered uneventfully. With a larger sample size, additional adverse events may be discovered.

As an additional point of interest, cats in our study received the test article orally via protected contact and without direct handling (Figure 1). To our knowledge, this is the first study to use a minimally invasive catheter attached to a syringe to administer oral medication to cage-trap confined community cats. Cats that received the test article appeared to swallow the entire dose; no test article waste was observed in any cat. This field technique has been utilized by a veterinarian (KKF) to effectively administer oral gabapentin to over 200 cage-trap confined community cats over a 2 year period. With some training and experience, the process of oral administration with this technique is an efficient and low cost procedure to provide an effective and safe route to administer liquid oral medications to awake undomesticated cats.

Conclusions

This study supports the hypothesis that gabapentin attenuates fear responses in confined community cats during the first 3 h of a holding period without producing sedation. A single oral gabapentin dose of 50 mg or 100 mg, up to 47.6 mg/kg per cat, was safe and did not cause serious adverse events in this population of cats. There was no difference in sedation scores between treatment and placebo groups. This study suggests that a single 50 mg dose of gabapentin could be used to attenuate community cat fear responses at other times in the TNR process. Future work should investigate the use of oral gabapentin to explore the optimal time for repeat dosing and the use in other cat populations, such as client-owned cats, prior to transport and veterinary examination.

Acknowledgements The authors thank Friends of Felines Cape Hatteras Island community volunteers and Christinia B Hicks, DVM, of Coastal Animal Hospital for their assistance with the cats. We thank Dan Aber and the North Carolina State Veterinary Pharmacy for the test article preparation and randomization scheme; Kenneth Royal, PhD, MSEd, of the North Carolina State College of Veterinary Medicine performed the power analysis; and John Joyner and Alice Harvey of the North Carolina State Veterinary Media and Design Services produced Figure 1 and Figures 2–4, respectively. We thank Margaret Gruen, DVM, PhD, DACVB, for her constructive suggestions.

Supplementary material The following files are available:
Appendix 1. Cat stress score.
Appendix 2. Global sedation score.

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

Funding This study was supported by the Animal Behavior Fund of the North Carolina Veterinary Medical Foundation.

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