UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE VETERINÁRIA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS VETERINÁRIAS

AVALIAÇÃO DO EFEITO DA GABAPENTINA SOBRE O EXAME NEUROLÓGICO DE GATOS SAUDÁVEIS

André Fernandes de Azevedo

PORTO ALEGRE

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Dissertação apresentada ao Programa de Pós-graduação em Ciências Veterinárias – UFRGS, como requisito parcial para a obtenção do grau de Mestre em Ciências Veterinárias

Orientadora: Profª. Dra. Fernanda Vieira Amorim da Costa

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AVALIAÇÃO DO EFEITO DA GABAPENTINA SOBRE O EXAME NEUROLÓGICO DE GATOS SAUDÁVEIS

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RESUMO

Fármacos de administração oral pré-consulta, como a gabapentina, estão sendo cada vez mais utilizados como ansiolíticos de curto prazo para reduzir o medo e a ansiedade dos gatos durante as visitas veterinárias. Porém, agentes com efeito sedativo podem influenciar o exame neurológico em humanos, diminuindo ou abolindo respostas específicas, além de afetar a marcha e o equilíbrio. Uma vez que as reações adversas mais comuns da gabapentina em gatos incluem sedação e ataxia, surge a questão se tais efeitos poderiam impactar negativamente o exame neurológico, levando a conclusões errôneas e diagnósticos errados. O objetivo deste estudo foi avaliar a influência de uma dose oral pré-consulta de gabapentina no exame neurológico de gatos saudáveis. Um ensaio clínico prospectivo, duplo-cego, randomizado e controlado por placebo foi realizado com 35 gatos. Os gatos passaram por duas consultas veterinárias e aleatoriamente foram designados para receber placebo ou uma cápsula de 100 mg de gabapentina antes da segunda consulta. O exame neurológico foi realizado durante cada visita, e os resultados foram comparados entre os grupos. A gabapentina alterou significativamente a análise da marcha e as reações posturais neste grupo de gatos saudáveis. A interferência encontrada pode levar a resultados falso-positivos, localização incorreta de lesões neurológicas, aumento dos custos de investigação e postergar o correto diagnóstico. Em compensação, a gabapentina não prejudicou a avaliação dos nervos cranianos e reflexos espinhais, o que nos permite confiar nos resultados desses testes, mesmo em pacientes que receberam o fármaco.

Palavras-chave: atendimento cat-friendly; propriocepção; reações posturais; marcha; ataxia; sedação; ansiolítico

ABSTRACT

Pre-appointment oral drugs such as gabapentin are increasingly being used as a short-term anxiolytic to reduce fear and anxiety of cats during veterinary visits. However, sedative drugs can influence the neurological examination in humans, decreasing or abolishing specific responses in addition to affecting gait and balance. Since the most common adverse reactions of gabapentin in cats are sedation and ataxia, the question arises whether such effects negatively impact the neurological examination, leading to erroneous conclusions and misdiagnosis. The aim of this study was to evaluate the influence of a pre-appointment oral dose of gabapentin on the neurological examination of healthy cats. A prospective, double-blind, randomized, placebo-controlled clinical trial was conducted with 35 client-owned cats. Cats were scheduled two veterinary visits and randomly assigned to receive either a placebo or a 100 mg gabapentin capsule prior to the second veterinary visit. A neurological examination was performed during each visit, and the results were compared between groups. Gabapentin significantly altered gait analysis and postural reactions in this group of healthy cats. The interference found could lead to false-positive results, incorrect localization of neurological lesions, rise in investigation costs, and postponement of a correct diagnosis. In contrast, gabapentin did not impair the assessment of cranial nerves and spinal reflexes, which allows us to be confident about the results of these tests in patients receiving the drug.

Keywords: cat-friendly practice; neuro exam; proprioception; postural reactions; gait; ataxia; sedation; anxiolytic

SUMÁRIO

1 INTRODUÇÃO

Ao deparar-se com qualquer animal apresentando uma possível afecção neurológica, antes da realização de exames complementares, é indicada a realização do exame neurológico (PALUŠ, 2014). Os objetivos do exame neurológico consistem em responder quatro questionamentos. Primeiro, os sinais observados são realmente derivados de uma lesão no sistema nervoso? Problemas ortopédicos, cardiorrespiratórios ou metabólicos, dentre outros, podem mimetizar casos neurológicos, mas alterações específicas no exame podem confirmar a natureza neurológica da afecção (WALKER, 2022). Segundo, qual é a localização da lesão? Estabelecer qual parte do sistema nervoso está afetada ajuda na seleção dos exames complementares mais indicados e em qual região anatômica serão focados; permite também determinar se a doença tem caráter focal ou multifocal – informação que influencia diretamente nos diagnósticos diferenciais (GAROSI, 2009; DEWEY; DA COSTA; THOMAS, 2016). Terceiro, quais os principais processos patológicos que podem justificar os sinais clínicos? Juntando a localização da lesão determinada no exame neurológico com os dados de resenha e histórico, pode-se formular a lista de diagnósticos diferenciais que vai guiar todo o plano diagnóstico (DA COSTA; DEWEY, 2016). E por último, qual é a gravidade da doença? A apresentação mais ou menos acentuada das alterações permite inferir a gravidade do quadro atual do paciente (GAROSI; LOWRIE, 2012).

A avaliação em si consiste numa série de observações e testes realizados pelo médico veterinário, e pode ser executada em sua totalidade em cerca de 10 a 15 minutos (DEWEY; DA COSTA; THOMAS, 2016). O exame divide-se em duas partes. Na primeira etapa, apenas observacional, são avaliados o nível de consciência, conteúdo de consciência e comportamento, postura e marcha do animal. Na segunda parte, de manipulação, o médico veterinário executa vários pequenos testes com o paciente, verificando a resposta dos nervos cranianos, nervos espinais, reações posturais e percepção de dor (GAROSI; LOWRIE, 2012; PALUŠ, 2014; DEWEY; DA COSTA; THOMAS, 2016).

A execução do exame neurológico, por si só, é desafiadora para a maioria dos médicos veterinários. Quando o exame é realizado em um gato, a situação torna-se ainda mais complicada. A natureza da espécie felina faz com que os gatos sejam mais susceptíveis ao estresse e menos tolerantes à contenção e manipulação necessárias para a execução da parte interativa da avaliação, quando comparados aos cães (TAYLOR; KERWIN, 2018; TATEO *et al*., 2021). Se o gato for forçado ou completamente contido, as respostas aos testes não serão confiáveis (TAYLOR;

KERWIN, 2018). Em suma, pelo menos metade do exame depende da cooperação do gato. Ajustes no transporte, ambiente e manejo devem ser empregados para reduzir o estresse do paciente felino, mas, ainda assim, em alguns indivíduos mais assustados ou agressivos, a etapa de manipulação da avaliação neurológica pode não ser viável, restando apenas a avaliação indireta a ser realizada (TAYLOR; KERWIN, 2018).

Educação dos proprietários, ambiente exclusivo para os felinos, atenção à linguagem corporal, reforço positivo, manejo delicado, práticas *cat-friendly*, pausas e distrações durante os procedimentos, são algumas das técnicas que vêm sendo empregadas para reduzir o estresse e ansiedade dos gatos durante as visitas à clínica veterinária (RIEMER *et al*., 2021). Fármacos com efeito ansiolítico ou sedativo podem ser administrados pelos proprietários antes da ida à clínica, sendo indicados para os pacientes mais assustados e agressivos. Dentre as opções mais seguras a serem utilizadas, já submetidas a estudos clínicos em gatos, estão a trazodona e a gabapentina (STEVENS, 2016; VAN HAAFTEN *et al*., 2017; PANKRATZ *et al*., 2018; ERICKSON *et al*., 2021).

A gabapentina é um fármaco da classe dos ligantes alpha$_2$delta, juntamente com a pregabalina e a mirogabalina. É um análogo estrutural do ácido gama-aminobutírico (GABA), porém, não age como um GABA-mimético, nem se liga aos receptores GABA. Seu mecanismo de ação é complexo, atuando em diversas vias e receptores (CHENG; CHIOU, 2006), mas acredita-se que seus efeitos se dão principalmente pela sua alta afinidade à subunidade α_2-δ auxiliar dos canais de cálcio voltagem-dependentes pré-sinápticos, bloqueando-os e reduzindo o influxo de cálcio (GEE *et al*., 1996; DOOLEY *et al*., 2007). A redução do influxo de cálcio ocasiona a redução da liberação de neurotransmissores excitatórios, produzindo assim os efeitos antiepilépticos, analgésicos e ansiolíticos (DOOLEY *et al*., 2007; TAYLOR; ANGELOTTI; FAUMAN, 2007).

Em gatos, a gabapentina tem alta biodisponibilidade (90-95%) após a administração oral de uma dose de 10 mg/kg. O pico de concentração plasmática ocorre entre 45 minutos e duas horas, e a meia-vida do fármaco é de três a quatro horas (SIAO; PYPENDOP; ILKIW, 2010; ADRIAN *et al*., 2018). Na medicina felina, a gabapentina tem sido utilizada buscando o efeito antiepiléptico (PAKOZDY; HALASZ; KLANG, 2014; BAKA; POLIZOPOULOU, 2019), como analgésico (VETTORATO; CORLETTO, 2011; LORENZ; COMEFORD; IFF, 2013; STEAGALL *et al*., 2022) e no tratamento da síndrome da hiperestesia felina (AMENGUAL BATLE *et al*., 2019). Mais recentemente, vem sendo bastante empregada como ansiolítico de curto prazo, administrada

no momento pré-consulta, para reduzir o medo e ansiedade durante as visitas à clínica (ERICKSON *et al*., 2021). Um estudo randomizado, duplo-cego, cruzado (*crossover*) e controlado por placebo, demonstrou que a administração de uma cápsula de 100 mg de gabapentina (13 a 29,4 mg/kg) por via oral, 90 minutos antes de colocar o gato na caixa de transporte e levá-lo à clínica, reduziu o estresse e agressividade, além de aumentar a cooperação durante o transporte e exame clínico (VAN HAAFTEN *et al*., 2017). Outro estudo, duplo cego e controlado por placebo, avaliou o uso do fármaco em gatos comunitários durante um programa de captura, castração e devolução. Os animais que receberam doses de 50 mg ou 100 mg de gabapentina (9,2 a 24,4 mg/kg) obtiveram menores escores de estresse (*McCune's Cat stress score* modificado) do que os que receberam placebo, com a maior redução dos escores duas horas após o tratamento (PANKRATZ *et al*., 2018).

Dentre os efeitos adversos que podem ser provocados pela gabapentina em gatos, já foram identificados ataxia, sedação, fraqueza, tremores, vômito e sialorreia (VAN HAAFTEN *et al*., 2017; ADRIAN *et al*., 2018; GUEDES *et al*., 2018). Em cães, sedação e ataxia também foram relatadas com o uso do fármaco (GOVENDIR; PERKINS; MALIK, 2005; PLATT *et al*., 2006). Tontura e sonolência são os efeitos observados com maior frequência na medicina (BOCKBRADER *et al*., 2010; HAN et al., 2016).

Fármacos com efeitos sedativos podem influenciar no exame neurológico em seres humanos, diminuindo ou abolindo certas respostas como o reflexo oculocefálico, reflexo corneano e respostas motoras (MOROW; YOUNG, 2007; SAMANIEGO *et al*., 2011), além de afetar a marcha e o equilíbrio (VAN SEVENTER, 2006), podendo causar erros de diagnóstico e prognóstico. Na medicina veterinária, a interferência de fármacos nos testes neurológicos ainda é pouco estudada, limitada a dois estudos até o momento desta publicação. Fouhety e colaboradores constataram que a morfina não influencia na classificação de lesões medulares em cães com extrusão do disco intervertebral (2020). Outro grupo, de Horsley e colaboradores, verificou que a associação dexmedetomidina/butorfanol não afeta a avaliação dos reflexos de retirada e patelar de cães saudáveis (2021). Até agora nenhum estudo foi realizado em gatos, nem avaliou o exame neurológico por completo. Uma vez que os efeitos adversos mais comuns da gabapentina em gatos são a sedação e ataxia, surge uma questão: poderiam tais efeitos impactar negativamente no exame neurológico, levando a possíveis conclusões errôneas e falhas de diagnóstico?

Assim sendo, o objetivo do presente trabalho foi avaliar a influência da gabapentina no exame neurológico de gatos saudáveis. Este foi um estudo prospectivo, randomizado e duplo-cego,

onde os animais receberam dose única de 100 mg de gabapentina, ou placebo, por via oral, 1h30min antes do início da consulta veterinária e 2h30min antes do exame neurológico. Nossa hipótese foi que as propriedades sedativas da gabapentina poderiam prejudicar os resultados do exame neurológico, especialmente naqueles testes dependentes de envolvimento cortical, como as reações posturais e a resposta à ameaça.

2 MATERIAIS E MÉTODOS

Os materiais e métodos, assim como os resultados da pesquisa, serão apresentados a seguir no modelo de artigo científico, que está formatado de acordo com as normas do periódico científico *Journal of Feline Medicine and Surgery*.

3 ARTIGO

Journal of Feline Medicine and Surgery

Original Article

Does pre-appointment gabapentin affect the neurological examination findings? A prospective, randomized, double-blind, placebo-controlled study in healthy cats

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Keywords: cat-friendly practice; neuro exam; proprioception; postural reactions; gait; ataxia; sedation; anxiolytic; cutaneous trunci

Abstract

Objectives The aim of this study was to evaluate the influence of a pre-appointment oral dose of gabapentin on the neurological examination of cats.

Methods A prospective, double-blind, randomized, and placebo-controlled clinical trial was conducted with 35 client-owned neurologically healthy cats. Cats were scheduled for two appointments and randomly assigned to receive either a placebo or a 100 mg gabapentin capsule prior to the second veterinary visit. A neurological examination was performed during each visit, and the results were compared between groups. Normal/abnormal response rates for each test were based on the number of cats that allowed that test to be performed.

Results Gabapentin was administered to 17 cats. Gait and postural reactions were significantly affected in the gabapentin group. Comparing gabapentin and placebo groups, respectively, 4/17 cats (23.5%) exhibited proprioceptive ataxia, compared to 0/18 cats ($P = 0.0288$); proprioceptive positioning deficits were seen in 10/11 cats (90.9%) versus 1/4 cats (25%); tactile placing deficits were identified in 13/17 cats (76.5%) versus 0/18 cats ($P < 0.0001$); hopping deficits were seen in 5/17 cats (29.4%) in comparison with 0/16 cats ($P = 0.0185$); and abnormalities on wheelbarrowing and extensor postural thrust were reported in 5/17 cats (29.4%) versus 0/18 cats ($P = 0.0129$). These results had no correlation with age or dose received. No significant difference was noticed in hands-on tests compliance or exam duration.

Conclusions and relevance Gabapentin significantly altered gait analysis and postural reactions in this group of healthy cats. The interference could lead to false-positive results and incorrect localization of neurological lesions. In contrast, gabapentin did not impair the assessment of cranial nerves and spinal reflexes, which allows us to be confident about these tests in patients receiving the drug.

Introduction

The neurological examination is a key step in evaluating any patient presenting with neurologic signs.[1] Performing the test alone is challenging for most veterinarians, but the situation becomes even more complicated when the patient is a cat. The nature of the feline species makes cats more susceptible to stress and less tolerant of restraint and manipulation when compared with dogs.[2] If the cat is forced or completely restrained, test responses may be unreliable.[3] Techniques such as owner education, low-stress transportation, cat-only environment, attention to body language, positive reinforcement, breaks, distractions, and gentle handling have been proposed to minimize the stress of cats during veterinary examinations.[4] But even so, in very frightened or aggressive individuals, the hands-on neurological assessment may not be feasible.

Pre-appointment oral drugs such as trazodone and gabapentin are increasingly being used as a short-term anxiolytic to reduce fear and anxiety of cats during veterinary visits.[5,6,7] Gabapentin, an alpha$_2$delta ligand, has been shown to reduce stress and aggression as well to increase cooperation during transport and clinical examination.[7] Despite these promising effects that could facilitate neurological examination, the drug also has adverse effects. It may cause ataxia, sedation, weakness, tremors, vomiting, and hypersalivation in cats.[7-10] In dogs, sedation and ataxia have also been reported.[11,12] Similarly, dizziness and drowsiness are the most frequent observed effects in humans.[13,14]

Sedative drugs can influence the neurological examination in humans, decreasing or abolishing specific responses such as the oculocephalic reflex, corneal reflex, and motor responses,[15,16] in addition to affecting gait and balance.[17] We have scarce information on this topic in veterinary medicine, with virtually no studies on cats. Since the most common adverse reactions of gabapentin in cats are sedation and ataxia, a question arises: could such effects negatively impact the neurological examination, leading to erroneous conclusions and misdiagnosis? The aim of this study was to evaluate the influence of a pre-appointment oral dose of gabapentin on neurological examination in healthy cats. We hypothesize that gabapentin's sedative properties could impair neurologic examination results, especially in those tests dependent on cortical involvement, such as postural reactions and menace response.

Materials and methods

Study design

This prospective, double-blind, randomized, and placebo-controlled clinical trial was performed at the Feline Medicine Service of the Universidade Federal do Rio Grande do Sul Veterinary Clinics Hospital, Brazil, between July and December 2021. The study was approved by the university's Ethics Committee on the Use of Animals (approval number 40478).

Animals

Thirty-eight privately owned healthy cats, between 6 and 24 months of age, with no history or clinical evidence of illness, were initially recruited. An owner-informed consent form was obtained for all cats prior to enrollment. Cats underwent physical examination, blood pressure measurement, complete blood count (CBC), and serum biochemistry profile. Cats were excluded if abnormalities were detected on any previously cited evaluations; showed signs of neurological disease on the first neurological examination or between appointments; received current medications besides flea preventives; or had aggressive behavior, making the examination impossible to perform.

Gabapentin administration

Cats were randomly divided into two groups (n = 19 each). Each cat was scheduled for two veterinary visits, one to three weeks apart. No cat was medicated prior to the first visit. Before the second visit, cats in the treatment group received a capsule containing 100 mg of gabapentin (Gabaneurin; EMS Sigma Pharma). Cats in the placebo group received an identical capsule containing 100 mg of white powder. The capsules were handed to the owners during the first visit when they were instructed to orally administer the capsule to the cats, without food, 90 minutes before the scheduled time for the next visit. All investigators and owners were blinded to the study groups.

Neurological examination

The same routine was applied on both veterinary visits. Physical examination, blood pressure measurement, and blood collection were carried out first, taking 45 to 60 minutes. Then,

the neurological examination was performed, between 135 and 150 minutes after gabapentin administration. The same examiner performed the neurological assessment of all cats on both visits.

The hands-off section was comprised of level of consciousness (wakefulness), content of consciousness (awareness), posture, and gait. The hands-on examination included assessment of postural reactions (proprioceptive positioning – Figure 1a; tactile placing – Figure 1b; hopping – Figure 1c; wheelbarrowing – Figure 1d, and extensor postural thrust), cranial nerves (facial symmetry, vision assessment, pupil size, palpebral reflex, menace response, pupillary light reflex, facial sensation, oculocephalic reflex, and tongue symmetry and mobility), and spinal nerves (patellar reflex, withdrawal reflex, muscle tone, perineal reflex, and cutaneous trunci reflex [CTR]). Test responses were classified as absent, reduced, normal, or exaggerated. CTR was tested through a light pinch with a hemostatic forceps, and responses were classified as bilateral, unilateral, or absent. Spinal palpation and nociception were not evaluated during the research.

If a cat did not allow the examiner to perform any test after three attempts, that response would be registered as "non-compliant" and would not be computed for statistical analysis of that specific test. The hands-on examination time length was recorded. Additionally, any time the cat was not complying with the exam, a short pause was made, and the total number of breaks was registered.

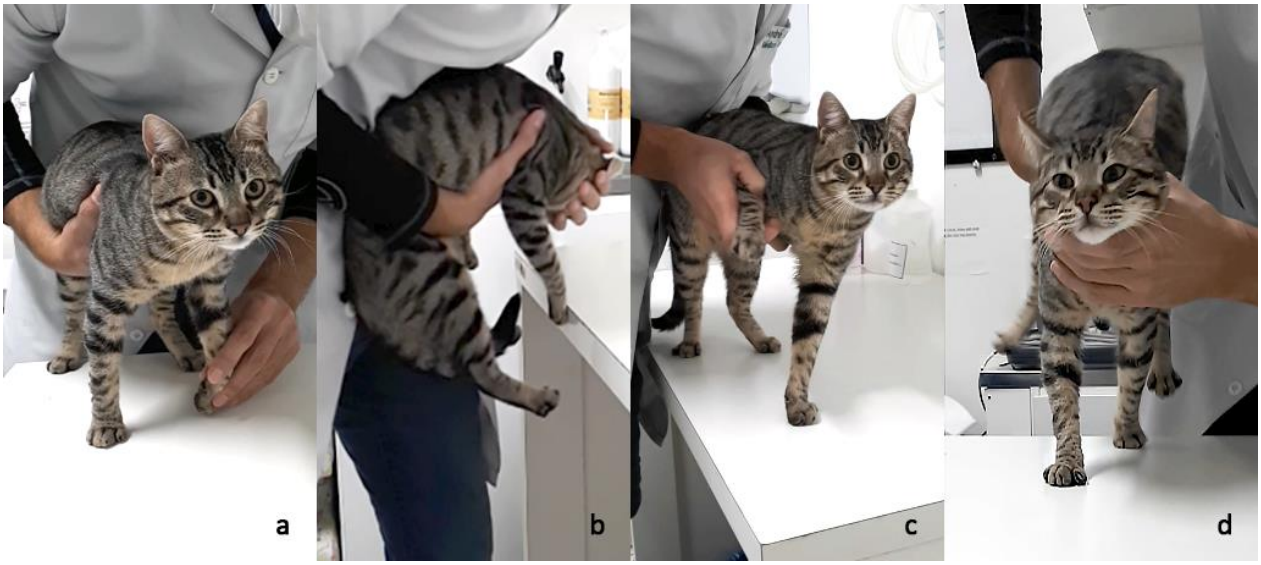

Figure 1 Postural reaction tests on a 1-year-old male domestic shorthair cat: (a) proprioceptive positioning; (b) tactile placing; (c) hopping; (d) wheelbarrowing

Data analysis and statistics

Results were treated as dichotomous variables. When only two outcomes were observed, data was used directly. For tests with several scores, results were grouped in two categories (normal and abnormal). For assessments evaluating two or four limbs separately, or right and left eye (or side), results were grouped as well, deemed "normal" if the test was normal on all limbs (or on both sides), and "abnormal" if any limb (or side) was considered abnormal. If the derived values varied between groups, data were statistically analyzed. Crossed tables were generated, and two-proportions comparison tests were executed whenever possible. Mcnemar's test was applied for compliance comparison of the same group of cats on different occasions. Duration of examination was evaluated under the Shapiro-Wilk test and later compared between groups using the independent samples t test. The Mann-Whitney U test was used to compare the number of breaks. Using Spearman's correlation, confrontation of age and dosing against the number of abnormalities was carried out. Analyses were performed using commercially available software (SPSS version 18 and web application Art of Stat). A threshold of 0.05 was used to determine statistical significance.

Results

Study population

From thirty-eight cats initially recruited, two were excluded due to aggressive behavior (one from treatment group and one from placebo group). Another cat (gabapentin group) was excluded because it started showing signs of neurological disease. The 35 remaining were domestic shorthair cats (16 female entire and 19 male entire). Mean age was 9.7 ± 4.4 months (range 6-24 months). Bodyweight ranged from 2.0-4.3 kg in placebo group and 2.1-5.3 kg in gabapentin group. The mean ± SD dose of gabapentin was 30.9 ± 7.6 mg/kg (range 18.8-46.3 mg/kg).

Neurological examination results

All cats in both groups had a normal neurological examination during the first veterinary visit. Regarding the hands-off evaluation during the second visit, two cats (11.8%) showed reduced level of consciousness (inattention, drowsiness, and reduced activity) after receiving gabapentin, but that value was not statistically significant (P = 0.1340). On the other hand, gabapentin administration led to a significant number of cats showing proprioceptive ataxia (4 cats - 23.5%, P

= 0.0288). Content of consciousness and posture were normal on all cats during the second visit. The results of the hands-off evaluation can be seen in Table 1.

Table 1 Hands-off neurological assessment and outcomes of gabapentin and placebo groups during first and second veterinary visits

Test	**Identified outcomes**	**1st visit (not medicated)**		**2nd visit (medicated)**		
		Gabapentin	**Placebo**	**Gabapentin**	**Placebo**	**P-value**
Level of consciousness	Normal	17 (100%)	18 (100%)	15 (88.2%)	18 (100%)	0.1340
	Reduced (drowsy)	0 (0%)	0 (0%)	2 (11.8%)	0 (0%)	
	Total	17	18	17	18	
Content of consciousness	Normal	17 (100%)	18 (100%)	17 (100%)	18 (100%)	---
	Total	17	18	17	18	
Posture	Normal	17 (100%)	18 (100%)	17 (100%)	18 (100%)	---
	Total	17	18	17	18	
Gait	Normal	17 (100%)	18 (100%)	13 (76.5%)	18 (100%)	0.0288*
	Ataxia	0 (0%)	0 (0%)	4 (23.5%)	0 (0%)	
	Total	17	18	17	18	

--- = Not applicable. No absolute difference between groups
*Difference between gabapentin and placebo groups was statistically significant

The hands-on examination was divided into cranial nerves, postural reactions, and spinal nerves. During the cranial nerves evaluation, no absolute difference was observed between gabapentin and placebo groups (normal responses on all cats), except for the menace response test, where 3/17 (17.6%) of the cats had decreased responses post-gabapentin. However, the results were not statistically different (P = 0.0697).

Postural reactions were the group of tests that presented the most abnormalities. Among the cats that allowed the tests to be performed, after gabapentin, 10/11 (90.9%) had deficits in proprioceptive positioning; 13/17 (76.5%) in table tactile positioning; 5/17 (29.4%) during hopping; and 5/17 (29.4%) in the wheelbarrowing and extensor postural thrust test. In comparison with the placebo group, the difference was statistically significant for all tests but proprioceptive positioning, where the comparison could not be performed due to the low number of compliant cats. The complete results of the postural reactions can be seen in Table 2.

Table 2 Postural reactions evaluation and outcomes of gabapentin and placebo groups during first and second veterinary visits

Test	Identified outcomes	1st visit (not medicated)		2nd visit (medicated)		
		Gabapentin	Placebo	Gabapentin	Placebo	P-value
Proprioceptive positioning	Normal	5 (100%)	4 (100%)	1 (9.1%)	3 (75%)	---
	Abnormal	0 (0%)	0 (0%)	10 (90.9%)	1 (25%)	
	Total (compliant)	5	4	11	4	
Tactile placing	Normal	16 (100%)	18 (100%)	4 (23.5%)	18 (100%)	<0.0001*
	Abnormal	0 (0%)	0 (0%)	13 (76.5%)	0 (0%)	
	Total (compliant)	16	18	17	18	
Hopping	Normal	16 (100%)	18 (100%)	12 (70.6%)	16 (100%)	0.0185*
	Abnormal	0 (0%)	0 (0%)	5 (29.4%)	0 (0%)	
	Total (compliant)	16	18	17	16	
Wheelbarrowing and extensor postural thrust	Normal	17 (100%)	18 (100%)	12 (70.6%)	18 (100%)	0.0129*
	Abnormal	0 (0%)	0 (0%)	5 (29.4%)	0 (0%)	
	Total (compliant)	17	18	17	18	

--- = Not applicable. The number of compliant cats in placebo group was too small to allow a reliable comparison
* Difference between gabapentin and placebo groups was statistically significant

No absolute difference was observed between gabapentin and placebo groups responses during patellar reflex, withdrawal reflex, muscle tone, and perineal reflex evaluation, which were deemed normal on all cats. The overall CTR abnormal (unilateral or absent) response rate was high (48%) but not statistically different between groups (P = 0.464). The results of the CTR tests are shown in Table 3.

Table 3 Cutaneous trunci reflex (CTR) evaluation and outcomes of gabapentin and placebo groups during first and second veterinary visits

Test	Identified outcomes	1st visit (not medicated)		2nd visit (medicated)		
		Gabapentin	Placebo	Gabapentin	Placebo	P-value
Cutaneous trunci reflex	Normal	8 (47.1%)	8 (53.3%)	7 (46.7%)	9 (60%)	0.464
	Abnormal	9 (52.9%)	7 (46.7%)	8 (53.3%)	6 (40%)	
	Total (compliant)	17	15	15	15	

Exam duration and compliance

The hands-on examination duration and number of breaks (mean ± SD) are displayed in Table 4. There was no statistical difference on test timings (P = 0.303) and number of breaks (P = 0.304) between gabapentin and placebo groups.

Table 4 Total duration and number of breaks of hands-on examination of gabapentin and placebo groups during first and second veterinary visits

	1st visit (not medicated)		**2nd visit (medicated)**		
	Placebo	**Gabapentin**	**Placebo**	**Gabapentin**	**P-value**
Duration	8m03s ± 2m20s	9m03s ± 1m48s	7m35s ± 2m19s	9m45s ± 3m07s	0.303
Breaks	1.13 ± 1.09	2 ± 1.75	1.32 ± 1.19	2 ± 1.20	0.304

Data are mean ± SD

Evaluating the compliance of the cats in gabapentin group, comparing first and second visits, we could verify an increase in the number of cats allowing the proper execution of proprioceptive positioning (5/17 vs. 11/17 – a +120% relative change). However, it was not statistically relevant (p = 0.070). Other tests showed only minor variation, as shown in Table 5.

Table 5 Number of cats compliant to hands-on tests during first (not medicated) and second (medicated) veterinary visits (gabapentin group only)

	1st visit (not medicated) Gabapentin	**2nd visit (medicated) Gabapentin**	**Relative change**	**P-value**
Proprioceptive positioning	5/17 (29.41%)	11/17 (64.71%)	+120%	0.070
Tactile placing	16/17 (94.12%)	17/17 (100%)	+6.25%	1.000
Hopping	16/17 (94.12%)	17/17 (100%)	+6.25%	1.000
Wheelbarrowing and extensor postural thrust	17/17 (100%)	17/17 (100%)	0%	---
Patellar reflex	16/17 (94.12%)	15/17 (88.24%)	- 6.25%	1.000
Withdrawal reflex	17/17 (100%)	17/17 (100%)	0%	---
Muscle tone	17/17 (100%)	17/17 (100%)	0%	---
Perineal reflex	15/17 (88.24%)	13/17 (76.47%)	-13.33%	0.500
Cutaneous trunci reflex	17/17 (100%)	15/17 (88.24%)	-11.76%	0.500

--- = Not applicable. No absolute difference between groups

Correlation of deficits with age and gabapentin dose

For this, cats were ranked by the percentage of abnormal responses through the neurological examination. Spearman's correlation analysis demonstrated no correlation of deficits with age ($R = 0.194$; $P = 0.456$) or dose of gabapentin received (mg/kg) ($R = 0.127$; $P = 0.626$).

Discussion

To the authors' knowledge, this is the first study to describe the effects of gabapentin on the neurological exam of cats. The results demonstrate that gabapentin can significantly affect gait and postural reactions evaluation in healthy cats, compared to placebo. Changes were also noted in level of consciousness and menace response, although those were not statistically relevant. On the other hand, gabapentin did not interfere with the other cranial nerve tests and spinal reflexes evaluation.

A 100 mg oral dose of gabapentin was chosen as this dose has been shown to reduce stress and aggression and increase cooperation during transport and clinical examination.[7] Also, this dose appears to be well tolerated by most cats,[7,10,19] and has increasingly been used by clinicians to deal with fearful or aggressive cats.[5,18] The mean dose was 30.9 mg/kg, similar to other studies with gabapentin in cats, where the mean doses per kg were 20.5, 27.9, and 35.3 mg/kg. [7,10,19]

The capsule was given by the owner at home 90 minutes before the appointment. This timing of 90 minutes before the veterinary visit was the same as used in a previous study.[7] Neurological examination took place between 135 and 150 minutes after gabapentin administration. It was planned in line with the known mean peak serum concentration of gabapentin in cats, from 45 to 120 minutes, and the mean elimination half-life, from 177 to 211 minutes.[8,20] Consequently, the neurological examination was performed after peak concentration was achieved and still within the time range where serum concentration was at the highest levels.

The abnormality seen in gait was proprioceptive ataxia. This adverse effect is frequently reported in cats with the use of gabapentin. Studies have observed values of 16% (3/18)[9], 30% (6/20)[7], and even 70% (7/10)[10] of cats exhibiting ataxia after receiving gabapentin. Our study found similar results, with 23,5% (4/17) of individuals in gabapentin group showing such clinical sign. Ataxia is a manifestation often seen with sedative agents.[21,22] The presence and severity of ataxia are components used to evaluate the degree of sedation, indeed.[23] Hence, the presence of ataxia after the administration of gabapentin, a drug with sedative properties, could be somehow expected.

As a clinical sign, proprioceptive ataxia indicates a disturbance in transmitting information of neck, trunk, and limbs position to the central nervous system (CNS).[24] It is an uncoordinated gait, characterized by wide-based stance, swaying gait abducting or adducting the limb, long stride, and dragging the digits on the ground.[24,25] Usually, it is caused by a lesion affecting proprioceptive pathways in the white matter of the spinal cord.[25] Ataxia induced by gabapentin administration could be impossible to distinguish from the incoordination produced by a real myelopathy, particularly because some cats did not show any other clear sign of sedation, as observed in this work.

Another meaningful gabapentin influence could be detected during the postural reaction tests. Cats displaying deficits on at least one limb ranged from 29.4% (hopping, wheelbarrowing, and extensor postural thrust tests) up to 90.9% (proprioceptive positioning test) after administration of the drug. Postural reactions involve complex pathways in the nervous system, extending from the proprioceptive receptors in the limb, passing through the nerve, afferent tracts of the spinal cord to the contralateral cerebral cortex, returning via efferent pathways to the lower motor neuron in the spinal cord, which will be responsible for stimulating the effector muscle.[1] Sedative and overall CNS inhibitory characteristics of gabapentin[26] may hinder these complex pathways, generating inadequate responses. Even though proprioceptive deficits do not provide specific information regarding the location of the neurological lesion itself, they are important to identify neurological dysfunctions and must be interpreted together with other exam findings.[1] Very often, the postural reactions are the key point in clinical decisions, e.g., deciding whether a patient has peripheral vs. central vestibular disease; or an orthopedic vs. neurologic disorder. A misleading proprioceptive deficit provoked by gabapentin could lead to an erroneous localization of the lesion, unnecessary expenses, frustration, and delays until reaching the final diagnosis.

In a study conducted by van Haaften et al., evaluating the anxiolytic effects of gabapentin, cats that showed the highest degree of sedation were also the ones that received the highest doses.[7] Differently, in the present study, the identified changes in the level of consciousness, gait, menace response, and proprioception did not correlate with the age or dose of gabapentin received. So, at least in this small group of cats, using this dose range (18.8-46.3 mg/kg), we could question if any other inter-individual factor could play a greater role than a dose-related effect. One possible explanation could be different degrees of oral absorption. Previous studies showed slight differences in oral absorption and derived serum concentration of gabapentin between cats.[8,20]

Further investigation correlating gabapentin serum levels with neurological abnormalities is needed to elucidate this. Also, inter-individual variation in pharmacological activity of some drugs can occur, with no linear correlation between plasma concentration and clinical response. For example, this effect was reported with oclacitinib in cats.[27] Maybe a similar mechanism is in place here.

Although gabapentin has been shown to interfere with some aspects of the neurological examination of cats, it is also necessary to note which tests did not suffer interference from it. Except for the menace response (which showed a minimal absolute but not statistically relevant decrease in response), in this group of cats, the administration of gabapentin did not alter the assessment of cranial nerves and spinal reflexes. This outcome is similar to those found before by Horsley et al., that observed that sedation with dexmedetomidine and butorphanol did not negatively impact the assessment of patellar and withdrawal reflex in dogs.[28] These results may be overlooked at first but also have practical implications. Based on these findings, while examining a cat that received gabapentin, we could be more confident that any abnormality in cranial nerves or spinal reflexes would probably be a true positive caused by neurological dysfunction, not influenced by the drug.

Not only looking for negative interferences in the neurological examination, but we also sought to identify whether the use of gabapentin brought any benefits to it, such as turning the exam faster, reducing the number of breaks, or increasing the cats' compliance with the handling of hands-on tests. There was no consistent difference in exam duration or number of breaks. In fact, we could notice that, in some cases, gabapentin turned the examination longer because it generated artificial abnormalities, and the assessments had to be repeated several times to confirm the deficits. Regarding compliance, the test that showed the highest cooperation increase from cats after gabapentin was proprioceptive positioning. This test is notoriously difficult to perform on cats,[3] and gabapentin appeared to be helpful in this regard. However, here's the caveat: this was also the test where gabapentin generated the most deficits, thus ruling out any advantage in its administration. Furthermore, no important difference in compliance was established in any other hands-on assessment after gabapentin. It is important to remember that this group of cats was composed of young and non-aggressive individuals. Therefore, further studies are needed to verify if a meaningful increase in compliance would be seen if aggressive cats were selected instead.

An additional and curious finding in this research was the low CTR normal (bilateral) response rate. The overall normal response rate was only 52%, with no statistical difference between gabapentin and placebo groups. Commonly, this reflex cannot be elicited in some normal cats and, in the absence of any other deficits, has little relevance.[1,24,25] Previous studies have shown CTR normal response rates varying from 31% to 80% in healthy cats, using hemostat forceps pinching to elicit the reflex.[29, 30] Our results were approximately in the middle of this range. Another investigation with neurologically abnormal cats found similar values, where the CTR was present in 64.8% of the cats.[31] Tsai and Chang also compared CTR responses obtained at the veterinary hospital with responses obtained by the owners at home, finding 100% of cats with normal CTR at home, indicating the possible impact of stress on CTR evaluation.[29] However, despite its anxiolytic properties, gabapentin did not appear to exert any effect on this in the present study.

There were some limitations to this study. Even though some neurological tests were significantly affected, the number of cats was small; an investigation with a larger sample may further demonstrate those abnormalities or even show if the not statistically relevant changes would be significant within a larger group. Also, this research evaluated only healthy cats; it, therefore, cannot conclude that gabapentin would affect cats with neurological or systemic disease in the same manner or to the same extent. Similarly, the results could not be extrapolated to different or repeated doses instead of a single high-dose as used in this investigation. These questions would need further research to be answered. Another limitation was that the examiner was not a board-certified neurologist; nevertheless, the clinician executing the tests has vast experience in performing the neurological examination, working exclusively with small animal neurology for several years. Additionally, having had only one examiner could lead to bias; a second examiner would increase the overall confidence in the outcomes, especially with a solid inter-observer agreement. Finally, there was the inherent difficulty to assess slight variations on the level of consciousness of cats assertively; while prominent alterations can be easily identified, subtle changes in the state of arousal may be hard to notice and subject to interference from environmental factors and behavioral characteristics of the species itself.

Conclusions

A pre-appointment single oral dose of 100mg of gabapentin significantly altered gait analysis and postural reactions in this group of healthy cats. Even though gabapentin administration appears to increase compliance of cats with some hands-on tests, the interference could lead to false-positive results, incorrect localization of neurological lesions, rise in investigation costs, and postponement of a correct diagnosis. In contrast, gabapentin did not impair the assessment of cranial nerves and spinal reflexes, which allows us to be more confident about these tests. Therefore, upon identification of ataxia or postural reaction deficits in a cat that received pre-appointment gabapentin, the authors recommend, if possible, repeating the neurological evaluation on another occasion to confirm the findings without the influence of the drug.

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

This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognized high standards (‘best practice’) of individual veterinary clinical patient care were followed. Ethical approval from a committee, while not specifically required for publication in JFMS, was nonetheless obtained, as stated in the manuscript.

Informed consent

Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or nonexperimental animals) for the

procedure(s) undertaken (either prospective or retrospective studies). For any animals or humans individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved.

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4 CONCLUSÕES

O estudo avaliou a influência de uma dose única de gabapentina oral no exame neurológico de gatos saudáveis. Foram identificadas alterações estatisticamente significativas nos gatos que receberam a medicação, com interferência importante na avaliação da marcha e das reações posturais. Tais alterações não foram notadas nos animais que receberam placebo. Ainda que o uso da gabapentina possa aumentar a tolerância dos gatos a alguns testes executados no exame neurológico, a interferência encontrada pode levar a resultados falso-positivos, localização incorreta de lesões neurológicas, aumento dos custos de investigação e adiamento do correto diagnóstico. Em compensação, outro dado importante obtido pelo estudo foi que a gabapentina não prejudicou a avaliação dos nervos cranianos e reflexos espinhais, o que nos permite confiar nos resultados desses testes, mesmo em pacientes em uso do medicamento. Os resultados ressaltam a importância de saber se o paciente foi previamente medicado e, ao identificar ataxia proprioceptiva ou déficits nas reações posturais em um gato que recebeu gabapentina pré-consulta, repetir a avaliação neurológica em outra ocasião para confirmar os achados sem a influência do fármaco.

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ANEXO 1

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado(a) a participar, como voluntário, em uma pesquisa. Após ser esclarecido(a) sobre as informações a seguir, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que está em duas vias. Uma delas é sua e a outra é do pesquisador responsável. Na sua cópia consta o telefone e endereço institucional do pesquisador principal, de modo que você poderá tirar suas dúvidas sobre o projeto e a participação do seu gato, agora ou a qualquer momento. Em caso de recusa ou desistência você não será penalizado(a) de forma alguma. Em caso de dúvida você pode procurar o Comitê de Ética em Uso de Animais (CEUA) da Universidade Federal do Rio Grande do Sul (UFRGS) pelo telefone (51) 3308 – 3738 ou pelo e-mail ceua@propesq.ufrgs.br.

INFORMAÇÕES SOBRE A PESQUISA

Título do projeto: Avaliação do efeito da gabapentina sobre a frequência cardíaca, frequência respiratória, pressão arterial, exame neurológico, parâmetros ecocardiográficos e escore de estresse em felinos saudáveis

Pesquisador responsável: Prof. Dra. Fernanda Vieira Amorim da Costa

Endereço: Av. Bento Gonçalves, 9090 – Agronomia, Porto Alegre, CEP: 91540-000, Telefone: 51 3308-6922

Aluna responsável: Tayná Mayer Veronezi – Médica Veterinária, aluna de mestrado no Programa de Pós-Graduação em Ciências Veterinárias – Universidade Federal do Rio Grande do Sul (PPGCV-UFRGS).

Telefone para contato: (51) 99273-8540

E-mail: taynaveronezivet@gmail.com

Seu gato foi selecionado para participar da pesquisa “Avaliação do efeito da gabapentina sobre a frequência cardíaca, frequência respiratória, pressão arterial, exame neurológico, parâmetros ecocardiográficos e escore de estresse em felinos saudáveis”. A participação não é obrigatória, a qualquer momento você pode desistir e retirar seu consentimento em fazer parte da pesquisa. Sua recusa não trará nenhum prejuízo na relação do seu animal com o pesquisador ou com a instituição. O objetivo deste projeto é avaliar o uso da gabapentina nos parâmetros

ecocardiográficos, nos parâmetros fisiológicos, como frequência cardíaca, frequência respiratória e pressão arterial não invasiva, exame neurológico e se a medicação será eficaz na redução dos sinais de estresse em gatos saudáveis.

Você terá a garantia de sigilo das informações obtidas bem como o direito de retirar o consentimento a qualquer tempo.

CONSENTIMENTO LIVRE E ESCLARECIDO

Eu,_____,RG _____, CPF _____, abaixo assinado, proprietário do felino da raça _____, sexo _____, idade _____, denominado de _____, ficha HCV _____, concordo em ceder meu animal para participar do projeto "Avaliação do efeito da gabapentina sobre a frequência cardíaca, frequência respiratória, pressão arterial, exame neurológico, parâmetros ecocardiográficos e escore de estresse em felinos saudáveis", bem como o registro fotográfico do mesmo.

Declaro que entendi os objetivos, riscos e benefícios da participação do meu gato e que fui devidamente informado e esclarecido pela mestranda pesquisadora TAYNÁ MAYER VERONEZI sobre a pesquisa e os procedimentos nela envolvidos. Foi-me garantido que posso retirar o meu consentimento a qualquer momento, sem que isto leve a qualquer penalidade ou interrupção do acompanhamento do meu animal.

Porto Alegre, _____ de _____ de 202_.

_____ _____

Assinatura do tutor Assinatura do aluno (mestrando)

_____

Assinatura do orientador (pesquisador responsável)

U F R G S
UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PRÓ-REITORIA DE PESQUISA

Comissão De Ética No Uso De Animais

CEUA UFRGS

CARTA DE APROVAÇÃO

Comissão De Ética No Uso De Animais analisou o projeto:

Número: 40478
Titulo: AVALIACAO DO EFEITO DA GABAPENTINA SOBRE A FREQUENCIA CARDIACA, FREQUENCIA RESPIRATORIA, PRESSAO ARTERIAL, EXAME NEUROLOGICO, PARAMETROS ECOCARDIOGRAFICOS E ESCORE DE ESTRESSE EM FELINOS SAUDAVEIS

Vigência: 01/06/2021 à 31/08/2022

Pesquisadores:

Equipe UFRGS:

FERNANDA VIEIRA AMORIM DA COSTA - coordenador desde 01/06/2021
Daniela Jardim Lopes - desde 01/06/2021
MARCELO MARCHETTI TROJAN - desde 01/06/2021
TAYNÁ MAYER VERONEZI - desde 01/06/2021
JOÃO VICTOR BARBIERI FERRONATTO - desde 01/06/2021
KIRIAN RENATA FRANCK - desde 01/06/2021
Izadora Loeff Zardo - desde 01/06/2021
André Fernandes de Azevedo - desde 01/06/2021
LUCIANA NEVES NUNES - pesquisador desde 01/06/2021

Comissão De Ética No Uso De Animais aprovou o mesmo , em reunião realizada em 17/05/2021 - Reunião via webconferência - Mconf UFRGS, em seus aspectos éticos e metodológicos, para a utilização de 40 gatos (Felis silvestris catus) saudáveis, com idades entre 6 meses a 2 anos, atendidos no Hospital de Clínicas Veterinárias da UFRGS de acordo com os preceitos das Diretrizes e Normas Nacionais e Internacionais, especialmente a Lei 11.794 de 08 de novembro de 2008, o Decreto 6899 de 15 de julho de 2009, e as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), que disciplinam a produção, manutenção e/ou utilização de animais do filo Chordata, subfilo Vertebrata (exceto o homem) em atividade de ensino ou pesquisa.

Porto Alegre, Sexta-Feira, 28 de Maio de 2021

ALEXANDRE TAVARES DUARTE DE OLIVEIRA
Coordenador da comissão de ética