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Does preappointment gabapentin affect neurological examination findings? A prospective, randomized and blinded study in healthy cats

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Abstract

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

Methods A prospective, randomized and blinded clinical trial was conducted in 35 client-owned 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 the test to be performed.

Results Gabapentin was administered to 17 cats. Gait and postural reactions were significantly affected in the gabapentin group. Comparing the gabapentin with the placebo groups, proprioceptive ataxia was identified in 4/17 (23.5%) vs 0/18 cats ($P = 0.0288$); paw placement deficits were seen in 10/11 (90.9%) vs 1/4 (25%) cats; table tactile placement deficits were identified in 13/17 (76.5%) vs 0/18 cats ($P < 0.0001$); hopping deficits were seen in 5/17 (29.4%) vs 0/16 cats ($P = 0.0185$); and abnormalities on wheelbarrowing and extensor postural thrust were reported in 5/17 (29.4%) vs 0/18 cats ($P = 0.0129$). These results had no correlation with age or dose/kg received. No significant difference was noted in the assessment of level and content of consciousness, posture, cranial nerves and spinal nerves. No significant differences were noted in test compliance or examination duration.

Conclusions and relevance Gabapentin significantly altered gait analyses and postural reactions in this group of healthy cats. The administration of gabapentin could lead to false–positive results and, possibly, an incorrect identification of neurological lesions. In contrast, gabapentin did not impair the assessment of cranial nerves and spinal reflexes, which can be assessed in patients receiving the drug.

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

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Introduction

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

Preappointment oral drugs such as trazodone and gabapentin are used as short-term anxiolytics, to reduce fear and anxiety in cats during veterinary visits.[5–7] 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, which could facilitate neurological examination, the drug also has adverse effects. It may cause ataxia, sedation, weakness, tremors, vomiting and hypersalivation in cats.[7–10] Sedation and ataxia have also been reported in dogs.[11,12] Similarly, dizziness and drowsiness are the most frequently observed effects in humans.[13,14]

Sedative drugs can influence neurological examinations 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] There is little information on this topic in veterinary medicine. Since the most common adverse reactions to gabapentin in cats are sedation and ataxia, the following 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 preappointment oral dose of gabapentin on neurological examination in healthy cats. We hypothesized that gabapentin's sedative properties could impair the results of a neurological examination, especially in tests dependent on cortical involvement, such as postural reactions and menace response.

Materials and methods

Study design

This prospective, blinded, randomized clinical trial was performed at the Feline Medicine Service of the Federal University of Rio Grande do Sul Veterinary Clinics Hospital, Brazil, between July and December 2021. The study was approved by the Animal Ethics Committee (approval no. 40478). The owners signed an informed consent form to participate in this study.

Animals

Thirty-eight privately owned healthy cats, aged 6–24 months, with no history or clinical evidence of illness, were initially recruited. Cats underwent physical examination, blood pressure measurement, complete blood count 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, were receiving current medications besides flea preventives or exhibited aggressive behavior, making examination impossible.

Gabapentin administration

A simple randomization table was created in Excel (Microsoft), to divide the cats into two groups and assign them to the corresponding treatment group (19 cats in each group). Each group had the same number of male and female cats. Each cat was scheduled for two veterinary visits, 1–3 weeks apart. No cat was medicated prior to the first visit. Before the second visit, cats received a capsule containing either placebo (composed of magnesium stearate, sodium lauryl sulfate, talc and corn starch) or gabapentin 100 mg fractioned in a veterinary manipulation pharmacy from a commercial human presentation (Gabaneurin; EMS Sigma Pharma). The pharmacy follows rigorous quality-control procedures and standard operating procedures in accordance with the Brazilian Ministry of Agriculture, Livestock and Food Supply (MAPA) and the Brazilian Health Regulatory Agency (ANVISA). The capsules were handed to the owners during the first visit, when they were instructed to administer the capsule orally to the cats, without food, 90 mins before the next scheduled visit. At this time, the owners answered a questionnaire, stating the exact time they had administered the capsule to their cats, as well as the degree of difficulty in doing so, and then returned it to the research team. All investigators and owners were blinded to the study groups.

Neurological examination

The same routine was applied during both veterinary visits. Physical examination, blood pressure measurement and blood collection were carried out first, taking 45–60 mins. Then, the neurological examination was performed, between 135 and 150 mins after gabapentin administration. The same examiner performed the neurological assessment of all cats at both visits.

The hands-off section of the examination comprised level of consciousness (wakefulness), content of consciousness (awareness), posture and gait. Possible classifications of level of consciousness were alert or depressed (animals inattentive, drowsy, displaying little spontaneous activity). For the assessment of content of consciousness, patients were allowed to explore the consultation room. Content of consciousness was classified as normal

or abnormal based on their spontaneous behavior, the patient's response to the environment and their reactions to the examination/handling itself.

The hands-on examination included assessment of postural reactions (paw placement, table tactile placement, hopping, wheelbarrowing 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 hemostatic forceps, and responses were classified as bilateral, unilateral or absent. Spinal palpation and nociception were not evaluated.

If a cat did not allow the examiner to perform any test after three attempts, that response was registered as 'non-compliant' and was not included in the statistical analysis of that specific test. The duration of the hands-on examination was recorded. Additionally, any time the cat was not compliant during the test procedure, a short pause was made and the total number of pauses registered.

Data analysis and statistics

Results were treated as dichotomous variables. When only two outcomes were observed, data were 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 also grouped, and considered 'normal' if the test was normal on all limbs (or on both sides) and 'abnormal' if the results were abnormal in any limb (or side). If the derived values varied between groups, data were statistically analyzed. Cross 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 with 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, comparison of age and dosing against the number of abnormalities was carried out. Analyses were performed using commercially available software (SPSS version 18 [IBM] and the Art of Stat app). A threshold of 0.05 was used to determine statistical significance.

Results

Of the 38 cats initially recruited, two were excluded due to fear-related aggressive behavior during physical examination (one from the treatment group and one from the placebo group). Another cat (gabapentin group) was excluded because of signs of neurological disease. The remaining 35 were domestic shorthair cats (16 females and 19 males). Median age was 8 months (range 6–24). Median bodyweight was 2.9 kg (range 2.0–4.3) in the placebo group and 3.5 kg (range 2.1–5.3) in the gabapentin group. The median dose of gabapentin was 28.6 mg/kg (range 18.8–46.3).

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 this was not statistically significant ($P = 0.134$). However, gabapentin administration led to a statistically significant number of cats (n = 4) showing proprioceptive ataxia (23.5%; $P = 0.0288$). Content of consciousness and posture were normal in all cats during the second visit. The results of the hands-off evaluation are provided in Table 1.

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

Of the cats that allowed the tests to be performed, after gabapentin, 10/11 (90.9%) had deficits in paw placement, 13/17 (76.5%) in table tactile placement, 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 paw placement, where the comparison could not be performed due to the low number of compliant cats. The complete results of the postural reactions are provided in Table 2.

No absolute difference was observed between the gabapentin and placebo group 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.

Examination duration and compliance

The hands-on examination duration and number of pauses (mean ± SD) are provided in Table 4. There was no statistically significant difference in test timings ($P = 0.303$) or number of pauses ($P = 0.304$) between the gabapentin and placebo groups.

Evaluating the compliance of the cats in the gabapentin group, comparing first and second visits, we could verify

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

Test	Identified outcomes	First visit (unmedicated)		Second visit (medicated)		
		Gabapentin (n = 17)	Placebo (n = 18)	Gabapentin (n = 17)	Placebo (n = 18)	*P* value
Level of consciousness	Normal	17 (100)	18 (100)	15 (88.2)	18 (100)	0.134
	Reduced (drowsy)	0 (0)	0 (0)	2 (11.8)	0 (0)	
Content of consciousness	Normal	17 (100)	18 (100)	17 (100)	18 (100)	–†
Posture	Normal	17 (100)	18 (100)	17 (100)	18 (100)	–†
Gait	Normal	17 (100)	18 (100)	13 (76.5)	18 (100)	0.0288*
	Ataxia	0 (0)	0 (0)	4 (23.5)	0 (0)	

Data are presented as n (%)
*Difference between gabapentin and placebo groups was statistically significant
†No absolute difference between groups

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

Test	Identified outcomes	First visit (unmedicated)		Second visit (medicated)		
		Gabapentin	Placebo	Gabapentin	Placebo	*P* value
Paw placement	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	
Table tactile placement	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	

Data are presented as n (%)
*Difference between gabapentin and placebo groups was statistically significant
†The number of compliant cats in the placebo group was too small to allow a reliable comparison

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

Test	Identified outcomes	First visit (not medicated)		Second visit (medicated)		
		Gabapentin (n = 17)	Placebo (n = 15)	Gabapentin (n = 15)	Placebo (n = 15)	*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)	

Data are presented as n (%)

an increase in the number of cats allowing the proper execution of paw placement (5/17 vs 11/17; +120% relative change). However, this was not statistically significant ($P = 0.07$). Other tests showed only minor variations (Table 5).

Correlation of deficits with age and gabapentin dose

Cats were ranked by the percentage of abnormal responses on the neurological examination. Spearman's correlation analysis demonstrated no correlation of deficits with age

Table 4 Total duration of, and the number of pauses in, the hands-on examination of cats in the gabapentin and placebo groups at the first and second veterinary visits

	First visit (not medicated)		Second visit (medicated)		
	Placebo	Gabapentin	Placebo	Gabapentin	*P* value
Duration	8 mins 3 s ± 2 mins 20 s	9 mins 3 s ± 1 mins 48 s	7 mins 35 s ± 2 mins 19 s	9 mins 45 s ± 3 mins 7 s	0.303
Pauses	1.13 ± 1.09	2 ± 1.75	1.32 ± 1.19	2 ± 1.20	0.304

Data are presented as mean ± SD

Table 5 The number of cats compliant with hands-on tests during the first (not medicated) and second (medicated) veterinary visits (gabapentin group only)

	First visit (unmedicated; n = 17)	Second visit (medicated; n = 17)	Relative change (%)	*P* value
Paw placement	5 (29.4)	11 (64.7)	+120	0.07
Table tactile placement	16 (94.1)	17 (100)	+6.25	1.000
Hopping	16 (94.1)	17 (100)	+6.25	1.000
Wheelbarrowing and extensor postural thrust	17 (100)	17 (100)	0	–*
Patellar reflex	16 (94.1)	15 (88.2)	–6.25	1.000
Withdrawal reflex	17 (100)	17 (100)	0	–*
Muscle tone	17 (100)	17 (100)	0	–*
Perineal reflex	15 (88.2)	13 (76.5)	–13.33	0.5
Cutaneous trunci reflex	17 (100)	15 (88.2)	–11.76	0.5

Data are presented as n (%)
*No absolute difference between groups

($r = 0.194$; $P = 0.456$) or dose of gabapentin received (mg/kg [$r = 0.127$; $P = 0.626$]).

Discussion

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

The abnormality seen in gait was proprioceptive ataxia. This adverse effect is frequently reported with the use of gabapentin in cats. Studies have reported that 16% (n = 3/18),[9] 30% (n = 6/20)[7] and even 70% (n = 7/10)[10] of cats exhibit ataxia after receiving gabapentin. Our study found similar results, with 23.5% (n = 4/17) of cats in the gabapentin group showing such clinical signs. Ataxia is a manifestation often seen with sedative agents.[18,19] The presence and severity of ataxia are components used to evaluate the degree of sedation.[20] Hence, the presence of ataxia after the administration of gabapentin – a drug with sedative properties – could be expected. As a clinical sign, proprioceptive ataxia indicates a sensory dysfunction due to the disturbance in transmitting information from the neck, trunk and limbs to the central nervous system (CNS).[21] Ataxia is indicated by an uncoordinated gait, characterized by a wide-based stance, swaying gait abducting or adducting the limb, a long stride and dragging of the digits on the ground.[21,22] It is often associated with lesions affecting proprioceptive pathways in the white matter of the spinal cord.[22] Ataxia induced by the sedative effect of gabapentin could be impossible to distinguish from the ataxia produced by a myelopathy, particularly because – in this group of cats – some that displayed ataxia did not show any other clear signs of sedation. Therefore, evaluation of the gait should be repeated when the sedative effects of gabapentin resolve; this usually happens within 8 h of gabapentin administration.[7]

Another significant influence of gabapentin was seen during postural reaction tests. Deficits in at least one limb were seen in 29.4% of cats (hopping, wheelbarrowing and extensor postural thrust tests) and up to 90.9% (paw placement test) after administration of the drug. Postural reactions have complex pathways in the nervous system, with a sensory pathway extending from the proprioceptive receptors in the limb, passing through the nerve and afferent tracts of the spinal cord, to the brainstem and contralateral cerebral cortex, returning in a similar way via motor pathways to the paw.[1] The sedative and overall CNS inhibitory characteristics of gabapentin may

hinder these complex pathways,[23] generating inadequate responses. Even though postural reaction deficits do not provide specific information on the location of the neurological lesion itself, they are important in identifying neurological dysfunctions and must be interpreted together with other findings.[1] Postural reaction abnormalities are important in deciding whether a patient has a neurological disease. An erroneous postural reaction assessment owing to the administration of gabapentin could lead to incorrect localization of the lesion, unnecessary expense, frustration and delays in diagnosis.

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] This dose also appears to be well tolerated by most cats,[7,10,24] and has increasingly been used by clinicians to deal with fearful or fear-related aggressive cats.[5] The mean dose was 30.9 mg/kg, which is similar to that used in other studies in cats, where the mean doses were 20.5, 27.9 and 35.3 mg/kg, respectively.[7,10,24]

The capsule was given to the cat by the owner, at home, 90 mins before the appointment. This timing was the same as used in a previous study.[7] Neurological examination took place between 135 and 150 mins after the administration of gabapentin, and was planned in line with the known mean peak serum concentration of gabapentin in cats (45–120 mins) and its mean elimination half-life, (177–211 mins).[8,25] Consequently, the neurological examination was performed after the peak concentration was achieved and within the range when serum concentration was at its highest levels.

In a study conducted by van Haaften et al,[7] who evaluated the anxiolytic effects of gabapentin, cats that showed the highest degree of sedation were also the ones that received the highest doses. In contrast, in the present study, similarly to what is reported in humans,[26] the identified changes in the level of consciousness, gait, menace response and postural reactions did not correlate with the age of the cat or the dose of gabapentin received. Therefore, at least in this small group of cats, using this dose range (18.8–46.3 mg/kg), whether other inter-individual factors could have played a greater role than a dose-related one could be questioned. One possible explanation could be different degrees of oral absorption, or even non-linear absorption. Previous studies have shown slight differences in the oral absorption and derived serum concentration of gabapentin between cats.[8,25] Further investigation correlating gabapentin serum levels with these neurological abnormalities is needed to elucidate this.

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. Except for the menace response (which showed a minimal absolute but not statistically significant decrease in response), in this group of cats, the administration of gabapentin did not alter the assessment of cranial nerve and spinal reflexes. These results may be overlooked at first; however, they also have practical implications. Based on these findings, while examining a cat that has received gabapentin, we can be more confident that any abnormality in cranial nerve or spinal reflexes would probably be a true positive caused by neurological dysfunction, and not influenced by the drug. Other sedative drugs did not alter the assessment of patellar and withdrawal reflex in dogs.[27]

We not only looked for negative interferences of gabapentin in the neurological examination; we also sought to identify whether the use of gabapentin brought any benefits, such as increasing the speed of the neurological examination, reducing the number of breaks or increasing cats' compliance with hands-on tests. There was no consistent difference in examination duration or the number of breaks. In fact, we did notice that, in some cases, gabapentin administration resulted in longer examination times 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 paw placement. Paw placement is notoriously difficult to perform on cats,[3] and gabapentin appeared to be helpful in this regard. However, this was also the test in which gabapentin generated the most deficits, thus ruling out any advantage in its administration. Furthermore, after gabapentin administration, no important difference in compliance was established in any other hands-on assessment. It is important to remember that this group of cats was composed of young and friendly individuals. Therefore, further studies are needed to verify if a meaningful increase in compliance would be seen if cats with fear-related aggression were selected instead. Additionally, it is important to mention that the administration of a sedative/anxiolytic drug should not replace the correct handling of a cat during an examination, in order to minimize stress and fear behavioral responses, and increase the cat's compliance with the examination.

An additional and curious finding of this research was the low CTR normal (bilateral) response rate. The overall normal response rate was only 52%, with no statistically significant difference seen between cats in the gabapentin and placebo groups. CTR is, in general, an unreliable test and often it cannot be elicited in some normal cats; therefore, in the absence of any other deficits, it has little relevance.[1,21,22] Previous studies have shown CTR normal response rates varying from 31% to 80% in healthy cats, using hemostat forceps pinching to elicit the reflex.[28,29] Our results were approximately in the middle of this range. Tsai and Chang[28] also compared CTR responses obtained at a veterinary hospital with responses obtained by owners at home, finding that 100% of cats had a normal

CTR at home, indicating the possible impact of stress on CTR evaluation. However, in the present study, despite its anxiolytic properties, gabapentin did not appear to exert any effect on eliciting this reflex.

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 whether the changes that were not statistically significant could be significant within a larger group. This research also evaluated only healthy cats; therefore, we 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 consideration was that the examiner was not a board-certified neurologist; nevertheless, the clinician executing the tests has been working in small animal neurology for 7 years. Additionally, having 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 in confidently assessing slight variations in the level of consciousness of cats; 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 the behavioral characteristics of the species itself.

Conclusions

A preappointment single oral dose of 100 mg gabapentin significantly altered gait analysis and postural reactions in a group of healthy cats. Even though gabapentin administration appears to increase the compliance of cats with some hands-on tests, the interference could lead to false–positive results, potentially incorrect identification of neurological deficits, a 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 the results of these tests. Therefore, upon identification of ataxia or postural reaction deficits in a cat that received preappointment 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 The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognized high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS*. Although not required, where ethical approval was still obtained, it is 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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