Gabapentin, melatonin, and acepromazine combination prior to hospital visits decreased stress scores in aggressive and anxious dogs in a prospective clinical trial

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OBJECTIVE
To evaluate sedative and behavioral effects of a client-administered preappointment protocol with PO gabapentin and melatonin and oral-transmucosal acepromazine (GMA protocol).

ANIMALS
45 client-owned dogs between 1 and 12 years old that underwent standardize examinations between February and August 2021.

METHODS
In this clinical trial, dogs with a history of anxiety, fearfulness, and/or aggression during hospital visits were assessed and videotaped before (baseline) and after administration of the GMA protocol. For the second visit, owners administered PO gabapentin (20 to 25 mg/kg) in the evening prior to the next visit and PO gabapentin (20 to 25 mg/kg), PO melatonin (3 to 5 mg/dog), and oral-transmucosal acepromazine (0.05 mg/kg) 90 to 120 minutes prior to the second appointment. Examinations were performed, and behavioral stress and sedation levels were evaluated with semiquantitative rating scales. Randomized videos were analyzed, and a paired t test was used to compare stress and sedation scores between baseline and GMA. A Pearson correlation coefficient was used to evaluate the effect of age on the scores.

RESULTS
Stress scores were significantly lower after the GMA protocol, and sedation scores were significantly higher when compared to baseline (21.84 vs 27.11 and 1.39 vs 0.68, respectively). A significant correlation between increasing age and lower stress scores post-GMA and higher sedation scores post-GMA were observed.

CLINICAL RELEVANCE
Preappointment administration of the GMA protocol reduced signs of stress, fear, and fear-based aggression during hospital visits and provided sedation in this dog population. This protocol could represent an adjunct tool for veterinarians to improve quality of care and reduce animal-related injury.

Veterinarians and technicians often interact with aggressive, fearful, and anxious dogs and are at risk for suffering animal-related physical harm. Historically, forceful restraint has been used to provide care to fearful and aggressive animals. However, repeated use of restraint in a fearful animal increases the patient’s fear and consequent risk of aggression in the future. Dogs may express fear by attempting to escape, hide, or bite. Low-stress handling, behavior modification such as desensitization and counterconditioning, and sedation are management options to prevent patients from experiencing their care as traumatic.

Studies evaluating specific drugs or drug protocols to facilitate procedural management of animals displaying signs of fear and stress have the potential to improve animal welfare, work safety, and client experience. Gabapentin, a gabapentinoid with anticonvulsant and analgesic properties, appears to provide anxiolysis and dose-dependent sedation in veterinary species. A recent study in dogs reported decreased lip-licking, a sign of stress, after 50 mg of gabapentin/kg was administered PO 2 hours prior to the veterinary visits. Exogenous melatonin is another agent that could facilitate management of anxious and fearful animals. In people, PO melatonin has been shown to reduce pre- and postoperative anxiety. In dogs, melatonin provided calming effects during thunderstorms and minimized excitement levels.
Oral melatonin doses of 3 to 9 mg for dogs have been recommended by some authors to decrease anxiety levels in older animals. Studies evaluating anxiolytic and sedative properties of gabapentin and melatonin in dogs are still scarce. Acepromazine is a widely administered drug in veterinary medicine. It elicits behavior-modifying effects such as tranquilization and sedation. Albeit not an anxiolytic agent, acepromazine works synergistically with other sedatives, opioids, and anxiolytics to produce calming effects.

Although an increasing number of veterinary practices are administering PO sedatives or anxiolytics for chemical restraint when dealing with aggressive or anxious dogs, data on treatment reliability and consistency of results are lacking. A case report5 described reliable sedative effects with at-home administration of PO gabapentin, PO melatonin, and oral-transmucosal (OTM) acepromazine. The protocol, known as the chill protocol, was administered by the owners prior to hospital arrival to facilitate the management of a fear-aggressive dog. The authors’ clinical experience suggests that this 3-drug protocol facilitates procedural management of animals that exhibit signs of anxiety and/or aggression. However, no prospective study evaluating the safety and reliability of this protocol has been published.

This study aimed to evaluate the behavioral and sedative effects of a client-administered preappointment protocol with PO gabapentin (20 to 25 mg/kg), melatonin (3 to 5 mg/dog) and OTM acepromazine (0.05 mg/kg; GMA protocol). On the basis of clinical experience, it was hypothesized that the GMA protocol would reduce stress scores during a hospital visit in over 70% of anxious and aggressive dogs.

Methods

Animals

Forty-five client-owned dogs displaying signs of anxiety (ie, ears pinned back, no eye contact, furrowed brow, tail tucked, or body hunched) or aggression (ie, lunging, growling, snapping, or biting) during hospital visits at the Midwestern University College of Veterinary Medicine and Tufts Cummings School of Veterinary Medicine were included in this study. Enrollment criteria included otherwise healthy dogs (American Society of Anesthesiologists health status I/II) between 1 and 12 years old. This prospective controlled study was approved by Midwestern and Tufts Universities’ Animal Care and Use Committees.

Procedures

This study had 2 cycles with a 2-week washout period between the first (day 1, baseline) and second (day 2, post-GMA) visits to the hospital. On day 1, dogs were placed in a consultation room immediately upon arrival. Animals were videotaped with a stationary camera from when they entered the room until the end of the examination. Animals with a history of severe aggression arrived muzzled prior to the physical examination during both visits to ensure staff safety. To maintain consistency, dogs that arrived muzzled on day 1 also arrived muzzled on day 2, independent of behavioral signs displayed. Physical examination was standardized as follows: placement of the muzzle, if possible (10 seconds); bilateral auscultation of lung sounds with stethoscope (20 seconds); bilateral cardiac auscultation with stethoscope (20 seconds); abdominal palpation (5 seconds); visual inspection of ears (touch ears, if possible, to briefly examine them; 10 seconds); and hold off vein prior to simulated blood collection (apply alcohol, touch skin with a capped needle; 20 seconds). At the end of the first appointment, owners were sent home with gabapentin, melatonin, and acepromazine to be given prior to the second appointment.

Owners were instructed to administer at-home PO gabapentin (20 to 25 mg/kg) in the evening prior to the next visit and PO gabapentin (20 to 25 mg/kg), PO melatonin (3 to 5 mg/dog), and OTM acepromazine (0.05 mg/kg; 10 mg/mL injectable formulation) 90 to 120 minutes prior to the second appointment. Dogs weighing < 10 kg received 3 mg of melatonin and dogs > 10 kg received 5 mg. Drugs were administered 90 to 120 min prior to the veterinary visit to allow onset time for the sedative and anxiolytic effects. In Greyhound dogs, PO gabapentin at 20 mg/kg has been shown to reach maximum plasma concentration in approximately 90 minutes. In a study in which dogs were subjectively characterized as skeptical because they appeared doubtful, slightly suspicious, and timid, calming effects noted following melatonin were observed after 90 minutes of PO administration. No pharmacokinetic or pharmacodynamic studies of OTM injectable acepromazine in dogs were found. However, IM acepromazine may take 30 to 40 minutes to reach peak sedation and PO acepromazine could take up to 60 minutes.

Gabapentin and melatonin were given with a small amount of food, and acepromazine was administered under the tongue with a needleless syringe for mucosal absorption. Owners were advised of the potential for mild-to-heavy sedation, weakness or incoordination, and the need for supervision. Extralabel gabapentin and melatonin and extralabel injectable acepromazine administered was performed with client consent and complied with provisions of AMDUCA and 21 CFR §530.

Dogs were returned for day 2 of the study after receiving the GMA protocol. They were placed in a consultation room upon arrival and videotaped undisturbed at this time and during the standardized examination.

Data analysis

Following complete data collection of baseline and post-GMA of all dogs included in the study, video recordings were assigned a code name and randomly analyzed by 4 observers, including board-certified anesthesiologists and a board-certified behaviorist. Sedation scores were obtained prior to the start of the examination using a semiquantitative rating scale with 4 main categories: general appearance—excitable (0), awake and normal (1), tranquil (2), or stuporous (3); spontaneous posture—standing (0), tired but standing (1), lying but able to rise (2), or unable to rise (3); response to noise stimulus—normal startle reaction/head turn toward noise and
Stress scores were obtained using a semiquantitative rating scale (Supplementary Table S1). Possible scores ranged from 1 (no stress) to 5 (severe stress/aggressive), with a score of 6 (not safe to attempt) assigned if a specific part of the examination could not be performed. A stress score was assigned to each of the 7 predetermined time points of the footage: prephysical examination, during muzzle placement, during thoracic auscultation, during abdominal palpation, during visual inspection of the ears, during simulated blood collection, and postphysical examination. For statistical analysis, behaviors viewed in the highest stress category determined the final stress score. Stress scores during each time point and a final stress score were recorded for each patient.

**Statistical analysis**

This study was powered on the basis of a 2-tailed paired t test for the baseline and postdrug administration comparison. A sample size of 40 dogs was required for 90% power with a significance level of 5%.

Demographic variables for dogs enrolled in this study were summarized with mean and SD or count and percentage, as appropriate. A 2-tailed paired t test was used to compare baseline and post-GMA stress and sedation scores. Stress scores during each time point, total stress score, and sedation scores between baseline and GMA were compared. A 1-way ANOVA was used to compare differences in response by sex. A Pearson correlation coefficient was used to assess the effect of age and sex. A Pearson correlation coefficient, the 2-way random model was selected for a single rater measuring consistency. Statistical significance was assessed at the .05 level. All statistical analysis was performed using R version 4.1.0.

**Results**

Forty-five client-owned dogs were enrolled, and all patients completed the study. Mean (SD) age was 5.34 years (3.17 years) and weight was 17.66 kg (10.43 kg). Four of 45 (9%) dogs were intact females, 9 (20%) spayed females, 10 (22%) intact males, and 22 (49%) neutered males. Sixteen breeds were represented: 2 Chihuahuas, a Miniature Pinscher, an English Pointer, a Labrador Retriever, 2 Papillons, 2 Soft-coated Wheaten Terriers, a Standard Dachshund, a Miniature Dachshund, an English Springer Spaniel, a Sussex Spaniel, a Portuguese Water Dog, an Australian Cattle Dog, a German Shorthair Pointer, a Rottweiler, a Pit Bull Terrier, a Mini Bull Terrier, and 26 mixed-breed dogs.

Stress scores were significantly decreased post-GMA when compared to baseline (Table 1). Forty-one of 45 (91.1%) dogs had a reduction of at least 1 point in stress scores on the drug protocol. Twenty-seven of 45 dogs displayed aggressive behaviors (hair raised, lifted lip, lunging or charging, and barking, growling, snapping, or biting). Dogs with prior aggression had higher baseline scores in the stress categories but a similar statistically significant mean difference post-GMA. The mean (SD) baseline overall stress scores versus post-GMA for aggressive dogs was 28.69 (4.21) and 24.23 (5.93), respectively (P < .001). The difference (95% CI) post-GMA minus baseline was −4.46 (−6.33 to −2.60).

Sedation scores were significantly increased post-GMA when compared to baseline (Table 2).

**Table 1**—Comparison (paired t test) of mean (SD) stress scores for all variables evaluated during an examination and the overall stress score of anxious, fearful, and aggressive dogs before treatment (baseline) and postadministration of 20 to 25 mg/kg of PO gabapentin, 3 to 5 mg/dog PO melatonin, and 0.05 mg/kg of oral-transmucosal acepromazine (GMA protocol).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Post-GMA</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prephysical</td>
<td>3.44 (0.72)</td>
<td>3.07 (0.93)</td>
<td>−0.38 (−0.67 to −0.09)</td>
<td>.0124a</td>
</tr>
<tr>
<td>Muzzle placement</td>
<td>3.36 (1.42)</td>
<td>2.51 (1.35)</td>
<td>−0.85 (−1.16 to −0.54)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Thoracic auscultation</td>
<td>4.06 (0.76)</td>
<td>3.25 (1.07)</td>
<td>−0.81 (−1.03 to −0.58)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Abdominal palpation</td>
<td>4.14 (0.84)</td>
<td>3.42 (1.12)</td>
<td>−0.73 (−0.98 to −0.48)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Visual inspection of the ears</td>
<td>4.08 (0.94)</td>
<td>3.23 (1.17)</td>
<td>−0.85 (−1.11 to −0.58)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Simulated blood collection</td>
<td>4.37 (0.83)</td>
<td>3.38 (1.29)</td>
<td>−0.99 (−1.27 to −0.71)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Postphysical</td>
<td>3.69 (0.68)</td>
<td>3.14 (0.87)</td>
<td>−0.55 (−0.77 to −0.33)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Overall stress score</td>
<td>27.11 (4.16)</td>
<td>21.84 (5.81)</td>
<td>−5.27 (−6.53 to −4.01)</td>
<td>&lt; .0001a</td>
</tr>
</tbody>
</table>

*Values of P < .05 indicate a significant difference between results for baseline versus post-GMA.

**Table 2**—Comparison (paired t test) of mean (SD) sedation scores for all variables evaluated during an examination and the overall sedation score of dogs before treatment (baseline) and postadministration of the GMA protocol.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Post-GMA</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous posture</td>
<td>0.03 (0.11)</td>
<td>0.20 (0.48)</td>
<td>0.17 (0.03 to 0.32)</td>
<td>.0176a</td>
</tr>
<tr>
<td>Eye position</td>
<td>0.01 (0.08)</td>
<td>0.00 (0)</td>
<td>−0.01 (−0.03 to 0.01)</td>
<td>.3229</td>
</tr>
<tr>
<td>Response to noise stimulus</td>
<td>0.05 (0.17)</td>
<td>0.19 (0.35)</td>
<td>0.14 (0.02 to 0.25)</td>
<td>.0184a</td>
</tr>
<tr>
<td>General appearance</td>
<td>0.59 (0.35)</td>
<td>1.02 (0.61)</td>
<td>0.43 (0.26 to 0.60)</td>
<td>&lt; .0001a</td>
</tr>
<tr>
<td>Sedation scale</td>
<td>0.68 (0.43)</td>
<td>1.39 (1.19)</td>
<td>0.71 (0.36 to 1.06)</td>
<td>.0002a</td>
</tr>
</tbody>
</table>

*See Table 1 for key.

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Level of sedation as indicated by spontaneous posture, response to noise stimulus, and general appearance was greater post-GMA, but no difference in eye position was observed. Most dogs were mildly sedated. No other adverse effects were noted during examination or reported by owners following the administration of the GMA protocol. Of the 27 dogs displaying aggressive behaviors, general appearance (P = .008) and overall sedation scores (P = .026) were significantly increased. Overall sedation scores were 0.74 (0.44) at baseline versus 1.34 (1.30) post-GMA. The difference (95% CI) post-GMA minus baseline was –0.60 (0.08 to 1.13).

On day 1, a score of 6 (not safe to attempt) was assigned to 8 of 45 dogs during at least 1 part of the standard examined. Examinations not considered safe to perform were thoracic auscultation (2/8 dogs), abdominal palpation (5/8), visual inspection of ears (7/8), and simulated blood collection (7/8). Post-GMA, the complete standard examined was possible in 5 of the 8 dogs. Thoracic auscultation was possible in all dogs, abdominal palpation in 4 of 5 dogs, and visual inspection of the ears and simulated blood collection in 4 of the 7 dogs in which the examination was previously not performed due to safety concerns.

No difference between sex and stress (P = .9) or sedation (P = .54) scores was found. A larger change in stress and sedation levels occurred with increasing age. A significant correlation between increasing age and lower stress scores post-GMA (r = 0.43; P = .005) and higher sedation scores post-GMA (r = –0.43; P = .004) was observed. No difference was found between weight and stress (P = .22) and sedation (P = .45) scores.

Intraclass correlation coefficient for final stress score was 0.61 (0.47, 0.73) for baseline and 0.66 (0.53, 0.78) for post-GMA scores indicating moderate interrater reliability. Individual sedation scale scores had very little variation in values and saw upwards of 70% raw percentage agreement between the raters for the subscales.

Discussion

This study showed that client preappointment administration of gabapentin PO, melatonin PO, and acepromazine OTM significantly decreased stress and increased sedation scores in anxious and aggressive dogs during a veterinary visit. The GMA protocol reduced signs of stress in 91.1% (41/45) of dogs, which was higher than hypothesized. Post-GMA, complete examination was possible in 5 of 8 aggressive dogs. The ability to perform the examination and/or portions of the examination previously not performed due to safety reasons indicated clinical improvement post-treatment. Although there are no previous studies assessing the GMA protocol, data on the effects of administration of each individual drug appear to corroborate the findings of the present study.1,12,13,15,19,24

A decrease in behavioral indicators of stress occurred following administration of PO gabapentin (20 to 25 mg/kg, 90 to 120 minutes prior to the consult), acepromazine, and melatonin. In a previous study of dogs with storm-phobia, fear scores were significantly decreased following administration of 25 to 30 mg/kg of PO gabapentin 90 minutes prior to the storm.2,3 In contrast, Stollar et al4 reported that administration of 50 mg/kg of PO gabapentin 120 minutes prior to a veterinary visit decreased the frequency of lip-licking but did not significantly decrease other anxiety-related behaviors in dogs. Due to significant differences in study design and drug protocol, a direct comparison between that study and our study cannot be performed. However, a possible explanation for the different results is that the synergistic effect of the other agents included in the GMA protocol may be necessary to ensure there is a decrease in stress signs in anxious dogs receiving PO gabapentin.

The addition of PO melatonin to the GMA protocol may have helped reduce the stress response observed in this dog population. Oral melatonin has been shown to minimize excitement and provide calming effects in dogs.15,16,17 In a recent study,18 significant perioperative calming effects were observed in dogs characterized as “skeptical” (doubtful, slightly suspicious, and timid) that received 5 mg/kg of PO melatonin 90 minutes prior to induction of anesthesia. Additionally, vital parameters after drug administration were within physiologic ranges, supporting its safety in dogs. In our study, the dose of PO melatonin was lower at 3 mg (dogs < 10 kg) and 5 mg (dogs > 10 kg). Similarly to gabapentin, the synergistic effect of the drug combination could have resulted in a significant decrease in stress signs in anxious and aggressive dogs.

When combined with gabapentin and melatonin, acepromazine, a reliable tranquilizer, likely decreased struggle and fear during the examination, resulting in less fear-inducing restraint needed. This may have contributed to the overall less stressful experience for the dogs following the GMA protocol. Acepromazine is currently thought to have minimal or no anxiolytic effect; therefore, it should not be used as a sole agent to manage fear or phobic states.25 Although acepromazine has been associated with an increase in noise sensitivity and a disinhibition of aggression,25,26 no dogs in our study were found to be more sensitive to noise, as indicated by the response to noise stimulus scores, or became more aggressive.

Although there was an increase in sedation score post-GMA protocol, most dogs were only mildly sedated, making this effect of minimal clinical concern. Increased sedation levels may be partly due to the use of PO gabapentin. Previous studies have reported sedation as a common effect following administration of PO gabapentin in dogs and cats.6,24 A recent study6 reported that 7 of 22 dogs became mildly sedated 2.5 to 3.5 hours following administration of 50 mg of gabapentin/kg, but the effects resolved within 1.5 to 4 hours. The effects of the GMA protocol on sedation levels may also be partly explained by the inclusion of OTM acepromazine. Although sedation was noted, other possible effects of acepromazine such as paroxysmal arousal,
disinhibition, or heightened startle response to noise did not occur. It is possible that these potential adverse effects of acepromazine were mitigated by its combination with gabapentin and melatonin. Oral melatonin is unlikely to be the cause of the increased sedation levels observed. A recent study reported no sedation in dogs receiving 3 mg (dogs < 15 kg) and 6 mg (dogs > 15 kg) of melatonin PO. A correlation between increasing age and greater reduction in stress scores and greater increase in sedation scores was found. This finding may be partly explained by age-related decrease in hepatic function affecting the plasma half-life of drugs such as acepromazine, melatonin, and possibly gabapentin. The effective dose of drugs in older dogs may have been greater, thus resulting in more profound effects. In dogs, gabapentin is metabolized to N-methylgabapentin (around 34% of the dose) and excreted in urine; therefore, it requires a functional renal system for excretion of the drug. In cats, the presence of chronic kidney disease resulted in higher dose-normalized gabapentin serum concentrations than in normal cats. Although none of the dogs included in our study had clinical signs of renal disease, blood work to assess kidney values was not obtained. Therefore, the greater effects observed with increasing age could have been due to a possible undiagnosed renal dysfunction that resulted in higher serum concentrations in older dogs.

This study had limitations such as the lack of control groups receiving only 1 of the 3 agents or combinations of 2 agents instead of all 3 agents. However, the aim of the study was to prospectively evaluate a specific drug protocol widely administered in veterinary practices. Another limitation was the lack of a placebo control group. All dogs received the GMA protocol on day 2, and they could have been more habituated to the environment in this subsequent visit. Future studies with a randomized placebo-controlled design can minimize any possible bias or influence of previous experience on study results. Dogs that are fearful, anxious, or aggressive often need systematic desensitization or counterconditioning, which is a lengthy process requiring several appointments before decreases in stress, anxiety, or aggression are noted. In fact, Stellato et al reported that even a 4-week training program was only mildly effective at reducing fear in dogs with preexisting fear during veterinary appointments. Therefore, the influence on the follow-up visit is unlikely to have significantly affected the results of the present study. There are no data reporting improvements in behavior after a single positive veterinary visit, but the contrary appears to be true. Even 1 negative prior experience increased stress-related behavior at future veterinary visits, and these dogs were found to be more fearful than dogs with positive prior experience. The observed reduction in stress signs after preappointment administration of medication(s) such as the GMA or trazodone reinforces the benefits of this practice. Another limitation of the study was the stationary camera used to videotape the dogs. The distance and inability to evaluate the animals from different angles may explain the lack of evidence of change in eye position, the only indicator of sedation level that was not statistically different before and after the GMA. However, heavy sedation is required for a rolled eye to be observed. The mild sedation observed with this protocol may be another reason eye position did not differ compared to pre-GMA scores.

In conclusion, PO gabapentin (20 to 25 mg/kg) administered the night before a hospital visit and PO gabapentin (20 to 25 mg/kg), PO melatonin (3 to 5 mg), and OTM acepromazine (0.05 mg/kg) administered 90 to 120 minutes prior to the visit reduced stress scores and increased sedation scores in this population of anxious and aggressive dogs. Improvement in handleability and increased compliance during the examination were noted, with many severely stressed dogs displaying mild to moderate stress post-GMA. The GMA protocol may be a reliable and safe tool for veterinarians in their work with fearful, stressed, and aggressive dogs.

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org