Effects of gabapentin and trazodone on electroretinographic responses in clinically normal dogs

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OBJECTIVE
To compare electroretinographic (ERG) responses obtained in dogs before and after oral administration of gabapentin, trazodone, and a combination of both medications.

ANIMALS
12 clinically normal dogs.

PROCEDURES
A short-protocol ERG with 20 minutes of dark adaption was recorded for all dogs to establish baseline ERG responses. Dogs then received gabapentin (approx 30 mg/kg), trazodone (approx 20 mg/kg or approx 5 mg/kg), or a combination of gabapentin (approx 20 mg/kg) and trazodone (approx 5 mg/kg) orally, and the same ERG protocol was repeated 2 hours later. Dogs were given a washout period of at least 1 week between treatments.

RESULTS
a-Wave amplitudes were significantly \( P = 0.018 \) decreased after administration of the combination of gabapentin and trazodone. b-Wave amplitudes were significantly decreased after administration of the 20-mg/kg dose of trazodone \( P = 0.006 \) and after administration of the combination of gabapentin and trazodone \( P = 0.002 \). Heavier dogs that received higher total doses of trazodone had decreases in a-wave amplitude after administration of the 20-mg/kg dose of trazodone and in b-wave amplitude after administration of the 5-mg/kg dose of trazodone.

CLINICAL RELEVANCE
High doses of trazodone and the combination of gabapentin and trazodone significantly decreased a-wave and b-wave amplitudes in clinically normal dogs. However, the effects on retinal responses had little clinical importance. Therefore, these medications can be used safely in a clinical setting; however, further studies are needed in dogs with retinal disease.
Little is known about the effects of trazodone or gabapentin on electrical responses of the retina, although their mechanisms of action indicate these medications may impact retinal cell function. Trazodone may affect serotonin signaling between amacrine neurons and bipolar cells in the retina.15 Gabapentin has been shown to have effects on voltage-gated calcium channels in retinal ganglion cells and, potentially, other cells in the retina of laboratory animals.16

The objective of the study reported here was to compare ERG recordings obtained in clinically normal dogs before and after oral administration of gabapentin, trazodone, or a combination of both medications. Specifically, we wanted to determine whether trazodone or gabapentin would have clinically important effects on ERG responses in dogs.

Materials and Methods

Twelve clinically normal client-owned dogs from the veterinary community (ie, dogs owned by staff members and students) were used in the study. Dogs were included only if they did not have any history of vision deficits or ophthalmic disease, weighed between 10 and 40 kg, and were not receiving any medications other than routine parasite preventative and if results of general physical and ophthalmic examinations were normal. The study protocol was approved by the Institutional Animal Care and Use Committee of The Ohio State University, and informed client consent was obtained.

Preliminary ophthalmic diagnostic testing included collecting Schirmer tear test values (Merck Animal Health), measuring intraocular pressure (IOP) with a rebound tonometer (Tono-Vet; Icare), and fluorescein staining of both eyes (I-Glo; JorVet). An ocular examination was normal. The study protocol was conducted that included slit-lamp biomicroscopy (SL-17; Kowa Co) and indirect ophthalmoscopy (Omega 500 LED binocular indirect ophthalmoscope; Heine Optotechnik). Indirect ophthalmoscopy was performed at least 1 hour prior to ERG recording. Pupil diameter (PD) was estimated with a Jameson caliper (Storz Instrument Co) under standard room lighting conditions before and after pupillary dilation.

Experimental protocol

Electroretinograms of both eyes were recorded in each dog before and 2 hours after oral administration of a single dose of the study medication. All dogs were conscious during ERG recordings.

Dogs received the following 4 treatments in the same order with a washout period of at least 1 week between treatments4,7: gabapentin (30 mg/kg), trazodone (20 mg/kg), a combination of gabapentin (20 mg/kg) and trazodone (5 mg/kg), and trazodone (5 mg/kg). Doses were determined on the basis of previously described typical clinical doses and doses on the high end of the clinical dose range.1–6 Doses were calculated to the closest 100-mg (gabapentin) or 25-mg (trazodone) increment and administered as capsules (gabapentin 100-mg capsules; Ascend Laboratories LLC), tablets (trazodone, 50-mg tablets; Teva Pharmaceutical Industries Ltd), or both (Table 1).

Dogs were fed normally the morning of each testing day. Prior to ERG recording, preliminary IOP, PD, and Schirmer tear test values were collected. Both eyes were then dilated with 1 drop of tropicamide (Tropicamide ophthalmic solution USP 1%; Akorn Inc) 30 minutes before beginning the ERG protocol; no additional drops were applied during the testing day. After a baseline ERG was obtained, the eyes were irrigated with sterile eye wash (Akorn Animal Health), and IOP and PD measurements were repeated. Dogs were then administered the study medication.

Dogs were monitored for adverse effects, and 2 hours after administration of the study medication,

Table 1—Data on dosing for 12 clinically normal dogs enrolled in a study of the effects of gabapentin and trazodone on electroretinographic (ERG) recordings.

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Weight (kg)</th>
<th>30-mg/kg target dose</th>
<th>20-mg/kg target dose</th>
<th>200-mg/kg target dose</th>
<th>5-mg/kg target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.2</td>
<td>300 (29.4)</td>
<td>200 (19.6)</td>
<td>200 (19.6)</td>
<td>50 (4.9)</td>
</tr>
<tr>
<td>2</td>
<td>12.1</td>
<td>400 (33.1)</td>
<td>200 (16.5)</td>
<td>250 (20.7)</td>
<td>50 (4.1)</td>
</tr>
<tr>
<td>3</td>
<td>13.9</td>
<td>400 (28.8)</td>
<td>300 (21.5)</td>
<td>300 (21.6)</td>
<td>75 (5.4)</td>
</tr>
<tr>
<td>4</td>
<td>16.4</td>
<td>500 (30.5)</td>
<td>300 (18.3)</td>
<td>350 (21.3)</td>
<td>75 (4.6)</td>
</tr>
<tr>
<td>5</td>
<td>16.9</td>
<td>500 (29.6)</td>
<td>300 (17.8)</td>
<td>350 (20.7)</td>
<td>75 (4.4)</td>
</tr>
<tr>
<td>6</td>
<td>17.2</td>
<td>500 (29.1)</td>
<td>300 (17.4)</td>
<td>350 (20.3)</td>
<td>75 (4.4)</td>
</tr>
<tr>
<td>7</td>
<td>18.1</td>
<td>500 (27.6)</td>
<td>400 (22.1)</td>
<td>350 (19.3)</td>
<td>100 (5.5)</td>
</tr>
<tr>
<td>8</td>
<td>19.0</td>
<td>600 (31.5)</td>
<td>400 (21.2)</td>
<td>400 (21.1)</td>
<td>100 (5.3)</td>
</tr>
<tr>
<td>9</td>
<td>27.4</td>
<td>800 (29.2)</td>
<td>500 (18.2)</td>
<td>550 (20.1)</td>
<td>125 (4.6)</td>
</tr>
<tr>
<td>10</td>
<td>31.3</td>
<td>900 (28.8)</td>
<td>600 (19.2)</td>
<td>650 (20.8)</td>
<td>150 (4.8)</td>
</tr>
<tr>
<td>11</td>
<td>31.7</td>
<td>1,000 (31.5)</td>
<td>600 (18.9)</td>
<td>650 (20.5)</td>
<td>150 (4.7)</td>
</tr>
<tr>
<td>12</td>
<td>31.8</td>
<td>1,000 (31.4)</td>
<td>600 (18.9)</td>
<td>650 (20.4)</td>
<td>150 (4.7)</td>
</tr>
</tbody>
</table>

Data represent actual dose administered and are reported as total dose in mg (dose calculated on a mg/kg basis). Dogs received the following 4 treatments in the same order with a washout period of at least 1 week between treatments: gabapentin (30 mg/kg), trazodone (20 mg/kg), a combination of gabapentin (20 mg/kg) and trazodone (5 mg/kg), and trazodone (5 mg/kg). A short-protocol ERG with 20 minutes of dark adaption was recorded before and 2 hours after treatment administration.
the same ERG protocol was applied on both eyes. At the end of the second ERG, posttreatment IOP and PD values were measured, and corneas were stained with fluorescein (I-Glo; JorVet). All dogs were released to their owners within 2 hours after the second ERG recording.

**Electroretinography**

A small, portable ERG unit (RETIport 3S ERG; an-vision) equipped with a 17-mm contact lens monopolar electrode (Kojiman electrode; an-vision) with integrated LED flash was used. Dogs were dark adapted for 20 minutes prior to ERG recording. The right eye was tested first followed by the left eye. Dogs were manually restrained in sternal recumbency, and the eyelids were manually retracted. Proparacaine hydrochloride 0.5% solution (Akorn Inc) and then hydroxypropyl methylcellulose 2.5% gel (Gonak; Akorn Inc) was applied to both eyes prior to contact lens electrode placement. Two subdermal needle electrodes (Genuine Grass platinum subdermal needle electrodes; Natus Neurology) were used as the ground and reference electrodes. The reference electrode was placed approximately 2 cm caudal to the lateral canthus, and the ground electrode was placed on the midline at the dorsal aspect of the skull at the occipital crest. A short Phot.Scot.LED protocol was used to identify the presence of a mixed rod and cone response as described in the RETIport manual. This Phot.Scot.LED protocol was preprogrammed in the device and measured responses to a standard flash (3 cds/m²; 8 flashes; 0.3 Hz). Only dark-adapted results were obtained from both eyes.

**Statistical analysis**

A preliminary power analysis with type I error set at 0.05 and type II error set at 0.15 indicated that 10 dogs would be required to detect a 20% difference in ERG amplitudes and implicit times. Repeated-measures ANOVA was used to evaluate the effect of study treatment on the dependent variables (signal measures). Between PD and study treatments were identified. No interactions with age, weight, and eye (right vs left). Owing to the sample size, age and weight were analyzed for the 6 heavier dogs versus the 6 lighter dogs and for the 6 older dogs versus the 6 younger dogs. All statistical analyses were performed with commercially available statistical software (Stata statistical software, release 13; StataCorp LP). Values of *P* < 0.05 were considered significant.

**Results**

Mean ± SD age of the 12 dogs was 4.1 ± 3.3 years and mean ± SD body weight was 20.5 ± 7.9 kg. There were 7 mixed-breed dogs and 1 of each of the following breeds: Beagle, Dalmatian, Golden Retriever, Labrador Retriever, and Standard Poodle. Six dogs were castrated males, 4 were spayed females, and 2 were sexually intact males. One dog had punctuate superficial corneal fibrosis in 1 eye, 1 dog had faint punctate pigment on the axial anterior lens capsule, and 1 dog had a punctate plaque on its posterior lens capsule; all other dogs had normal physical and ophthalmic examination findings. All Schirmer tear test and IOP measurements were within reference ranges, and IOP was not significantly different from the baseline value at any time. Mean ± SD PD was 7.4 ± 1.0 mm before administration of tropicamide, 12.1 ± 1.0 mm 30 minutes after administration of tropicamide, and 11.4 ± 1.3 mm at the time of the posttreatment measurement. No interactions between PD and study treatments were identified.

Bilateral ERG results for the 12 dogs were summarized (Table 2); representative ERG tracings are shown (Figure 1). For all dogs combined, the mean a-wave amplitude was significantly decreased by 27% after oral administration of the combination of gabapentin (20 mg/kg) and trazodone (5 mg/kg; *P* = 0.018). The mean a-wave amplitude for all dogs combined was decreased by 30% after administration of the 20-mg/kg dose of trazodone; however, this decrease was not significant (*P* = 0.056). The mean b-wave amplitude for all dogs combined was significantly decreased by 23% after administration of the combination of gabapentin (20 mg/kg) and trazodone (5 mg/kg; *P* = 0.002) and by 34% after administration of the 20-mg/kg dose of trazodone (*P* = 0.006).

**Table 2**—Mean ± SD ERG responses measured bilaterally in the 12 dogs in Table 1.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Amplitude (µV)</th>
<th>Implicit time (ms)</th>
<th>Amplitude (µV)</th>
<th>Implicit time (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>a-wave</td>
<td></td>
</tr>
<tr>
<td>Gabapentin (30 mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>52.2 ± 33.4</td>
<td>13.9 ± 3.4</td>
<td>127.6 ± 54.7</td>
<td>29.5 ± 4.5</td>
</tr>
<tr>
<td>After medication</td>
<td>52.0 ± 38.0</td>
<td>13.5 ± 2.4</td>
<td>111.7 ± 61.7</td>
<td>30.6 ± 5.0</td>
</tr>
<tr>
<td>Trazodone (20 mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>61.4 ± 36.3</td>
<td>14.5 ± 2.7</td>
<td>141.9 ± 70.9</td>
<td>31.8 ± 4.1</td>
</tr>
<tr>
<td>After medication</td>
<td>43.0 ± 23.9</td>
<td>13.7 ± 3.0</td>
<td>93.9 ± 36.7e</td>
<td>31.0 ± 4.7</td>
</tr>
<tr>
<td>Gabapentin (20 mg/kg) and trazodone (5 mg/kg)</td>
<td>62.7 ± 31.0</td>
<td>13.1 ± 2.2</td>
<td>145.2 ± 43.3</td>
<td>30.1 ± 4.3</td>
</tr>
<tr>
<td>Baseline</td>
<td>45.7 ± 24.3a</td>
<td>13.6 ± 2.8</td>
<td>111.1 ± 53.0a</td>
<td>32.0 ± 5.9</td>
</tr>
<tr>
<td>After medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone (5 mg/kg)</td>
<td>68.6 ± 31.8</td>
<td>13.6 ± 1.8</td>
<td>148.0 ± 43.0</td>
<td>32.1 ± 4.4</td>
</tr>
<tr>
<td>After medication</td>
<td>61.7 ± 29.6</td>
<td>12.8 ± 2.0</td>
<td>133.7 ± 54.5</td>
<td>31.1 ± 3.7</td>
</tr>
</tbody>
</table>

*Significantly (*P* < 0.05) different from baseline value.
Trazodone may also affect the retina by blocking calcium channels and by additional mechanisms that have not yet been elucidated.

The combination of a 5-mg/kg dose of trazodone and a 20-mg/kg dose of gabapentin significantly decreased both a-wave and b-wave amplitudes in the present study. Gabapentin alone led to minor decreases in b-wave amplitude, but a significant difference was not detected. Furthermore, b-wave implicit times were only slightly prolonged after gabapentin administration, and again, a significant difference was not detected. To our knowledge, there have been no previous investigations on the effect of gabapentin on canine retinal function; however, this drug has been reported to affect rat ganglion cells in vitro in purified cell culture. In dogs, gabapentin may act to decrease the release of excitatory neurotransmitters in the retina by presynaptically binding voltage-gated calcium channels.

Multiple reports of humans receiving gabapentin for epilepsy have described abnormalities in vision and retinal function on the basis of visual field and electrophysiologic testing; however, no exact mechanism of action was found. One human patient was reported to have an abnormal ERG pattern following gabapentin administration, and the authors of that report suggested that an individual predisposition to toxic effects on retinal function might have been responsible. To our knowledge, there are no other reports of gabapentin or any reports of trazodone affecting ERG recordings in any species.

Gabapentin and trazodone may have a synergistic effect on decreasing ERG signal amplitudes. Although administration of a 5-mg/kg dose of trazodone alone had no significant effect on all dogs combined, with the addition of gabapentin, the a-wave and b-wave amplitudes were decreased in the present study. A previous report describes enhanced anxiolytic and sedative effects with concurrent use of gabapentin and trazodone in dogs. Humans treated with gabapentin had clinical pain improvement and had a trend toward improved pain control with the addition of trazodone, suggesting a possible synergistic mechanism.

Intraocular pressure and PD were measured to control for possible effects on ERG results and effects of treatments. There was no change in IOP with dilation or administration of any of the study treatments. Following tropicamide administration, PD increased as expected and decreased by < 1 mm after 2 hours elapsed following administration of study treatments. This slight decrease in PD was expected and not clinically important.

No adverse effects of ERG or the study treatments were noted. On the basis of the authors’ subjective observation, the dogs had variable change in behavior after oral administration of the treatments.

**Figure 1**—Representative ERG tracings obtained before (baseline; left) and after (right) oral administration of gabapentin (20 mg/kg) and trazodone (5 mg/kg) in a clinically normal (N) dog. The trough of the a-wave (a) and peak of the b-wave (b) are indicated. Notice the decrease in amplitude of both waves following administration of gabapentin and trazodone. OD = Right eye.

Multivariable analysis indicated that there was a significant interaction between weight and treatment with administration of trazodone. In the 6 heavier dogs (mean ± SD weight, 26.6 ± 6.4 kg), mean a-wave amplitude was significantly (P = 0.018) decreased by 47% after administration of the 20-mg/kg dose of trazodone and mean b-wave amplitude was significantly (P = 0.004) decreased by 23% after administration of the 5-mg/kg dose of trazodone. The 6 heavier dogs received a total trazodone dose ≥ 350 mg in the 20-mg/kg trial and a total trazodone dose ≥ 100 mg in the 5-mg/kg dose trial (Table 1).

No other comparisons of a-wave or b-wave amplitudes or interactions with age, weight, or eye (right vs left) were significant. The a-wave and b-wave implicit times were not significantly altered with administration of any of the treatments, and significant interactions with age, weight, and eye were not identified. Baseline measurements did not differ significantly across study treatments.

**Discussion**

Trazodone, alone and in combination with gabapentin, significantly decreased ERG wave amplitudes in clinically normal dogs in the present study. However, the magnitude of this decrease was small and likely would not be clinically important when evaluating the results of a short-protocol ERG for the presence or absence of overall retinal function. A total dose of trazodone ≥ 100 mg significantly decreased b-wave amplitude and a total dose ≥ 350 mg significantly decreased a-wave amplitude. These findings indicate a likely dose-dependent effect of trazodone on retinal function. The exact mechanism of action that trazodone may have on canine retinal function is unknown. One possibility is that trazodone may alter serotonin signaling in the retina. Serotonin is released by amacrine neurons and accumulates in bipolar cells in the vertebrate retina, which likely affects photoreceptor signals. Trazodone may also affect the retina by blocking calcium channels and by additional mechanisms that have not yet been elucidated.

The combination of a 5-mg/kg dose of trazodone and a 20-mg/kg dose of gabapentin significantly decreased both a-wave and b-wave amplitudes in the present study. Gabapentin alone led to minor decreases in b-wave amplitude, but a significant difference was not detected. Furthermore, b-wave implicit times were only slightly prolonged after gabapentin administration, and again, a significant difference was not detected. To our knowledge, there have been no previous investigations on the effect of gabapentin on canine retinal function; however, this drug has been reported to affect rat ganglion cells in vitro in purified cell culture. In dogs, gabapentin may act to decrease the release of excitatory neurotransmitters in the retina by presynaptically binding voltage-gated calcium channels. Multiple reports of humans receiving gabapentin for epilepsy have described abnormalities in vision and retinal function on the basis of visual field and electrophysiologic testing; however, no exact mechanism of action was found. One human patient was reported to have an abnormal ERG pattern following gabapentin administration, and the authors of that report suggested that an individual predisposition to toxic effects on retinal function might have been responsible. To our knowledge, there are no other reports of gabapentin or any reports of trazodone affecting ERG recordings in any species.

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No adverse effects of ERG or the study treatments were noted. On the basis of the authors’ subjective observation, the dogs had variable change in behavior after oral administration of the treatments.
Some dogs seemed to require less manual restraint and be less reactive to placement of electrodes after treatment administration; however, this change was not objectively assessed and may warrant future study. All dogs were ambulatory and alert when released to owners within 2 hours after each treatment protocol. A previous report\textsuperscript{23} emphasized the need for sedation to obtain reliable, reproducible ERG recordings in dogs, but a study by Freeman et al\textsuperscript{23} did not find sedation necessary to minimize electrical noise induced by patient movement and produce high-quality ERG recordings. In the present study, the presence of electrical noise was not assessed and doing so might be beneficial in future investigations.

Results of the present study indicate that oral administration of gabapentin and trazodone can be used in the clinical setting to treat anxiety in hospitalized dogs as needed before performing ERG. However, the present study evaluated clinically normal dogs, and it is possible that the effects of these medications on ERG wave amplitudes may become clinically relevant in dogs with abnormal retinal function. Nonetheless, clinicians can use these findings to roughly estimate the effects that these medications may have on wave amplitudes in their clinical patients. Future research directions include age- and breed-matched studies, evaluation of dogs with known or suspected retinal dysfunction, various ERG protocols to evaluate different populations of retinal cells, and specific effects of the medications on retinal physiology.

Acknowledgments

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References